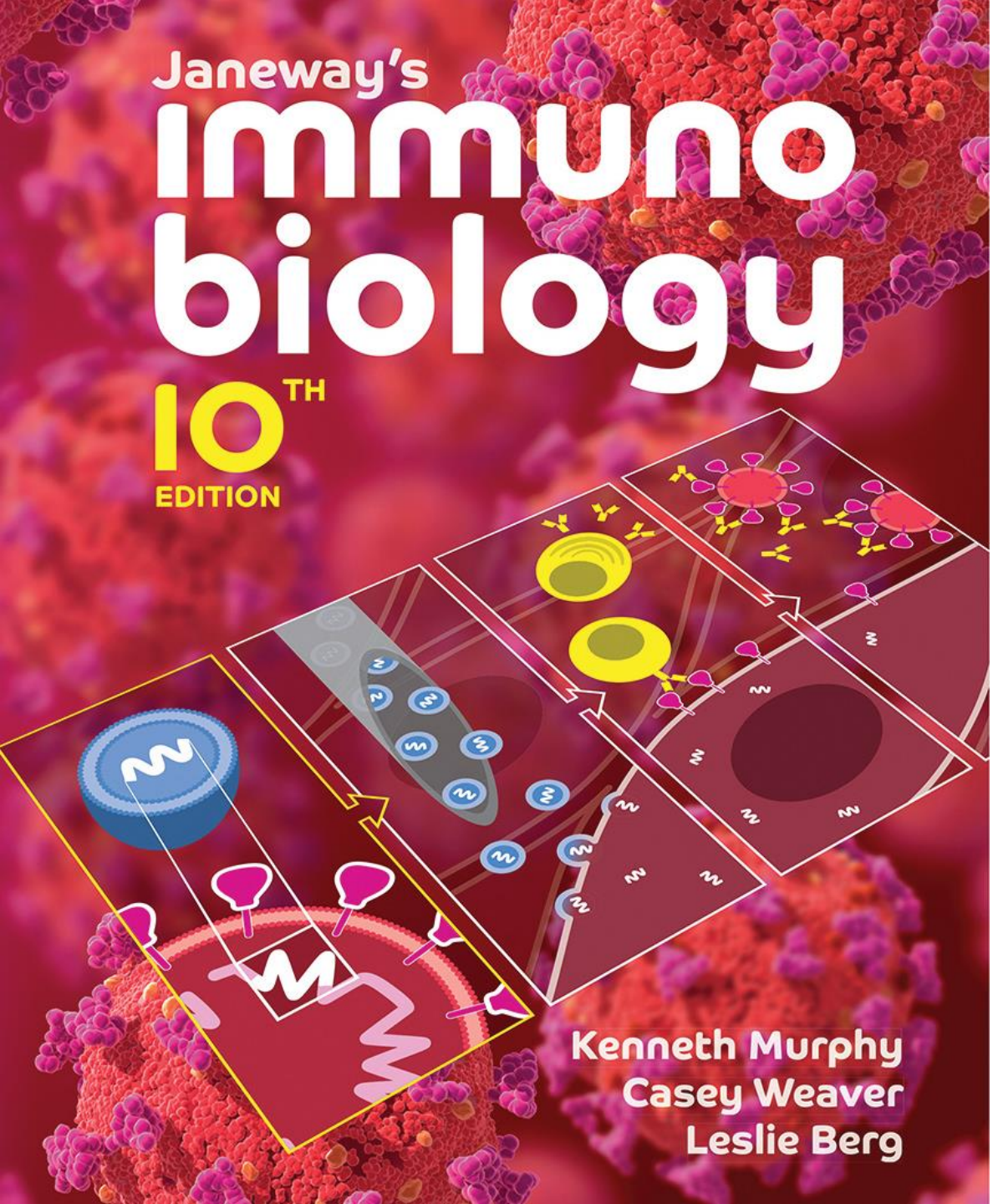


Basic Concepts in Immunology

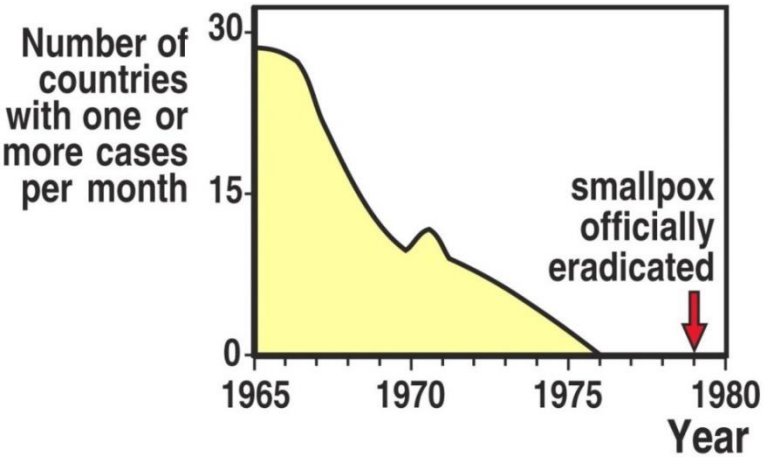
Innate Immunity

Hsi-Hsien Lin
(Molecular Immunology Laboratory)
Email: hhlin@mail.cgu.edu.tw

The eradication of smallpox by vaccination

Figure 1.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Sir Edward Jenner
(1749-1823)
Vaccinia (cowpox)

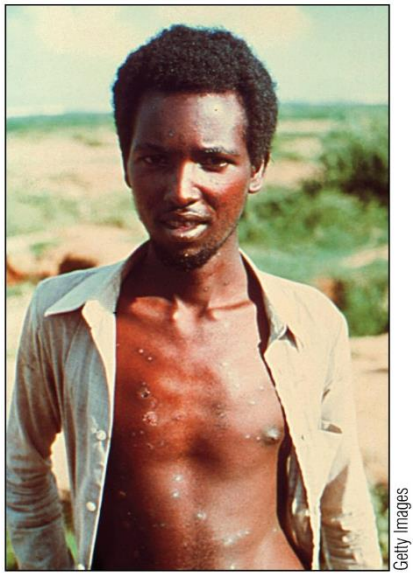


Vaccine

In 1979, WHO announce officially the eradication of smallpox

Louis Pasteur
(1822-1895)

Cholera,
Anthrax, Rabies



Getty Images

Immunity

Host ⟷ **Microorganisms**

Innate Immunity:
Non-specific,
No Memory.

Adaptive Immunity:
Specific with
Memory.

Virus
Bacteria
Protozoans
Helminths
(parasitic worms)

Phases of the immune response			
Response		**Typical time after infection to start of response**	**Duration of response**
Innate immune response	Inflammation, complement activation, phagocytosis, and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Elimination of pathogen by effector cells and antibody	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Figure 1.7 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Innate and Adaptive Immunity

- Pathogens (Antigens)
- Immune responses (innate vs. adaptive)
- Life-long protective immunity (Antibodies)
- Immunological recognition, immune effector functions, immune regulation, immunological memory.
- Immune cells (leukocytes, myeloid, lymphoid)
- Cell-mediated immunity, humoral immunity

Principles of innate immunity

Anatomic and **chemical** barriers are the first defense against pathogens

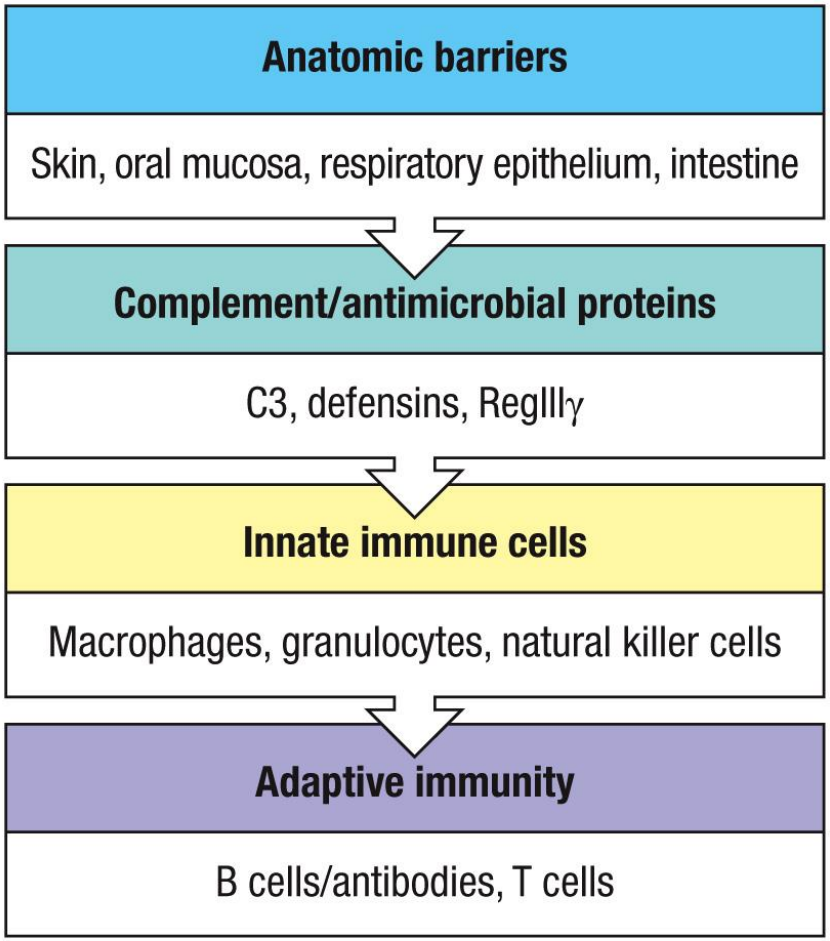


Figure 1.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Principles of innate immunity

The immune system is activated by **inflammatory inducers** that indicate the presence of pathogens or tissue damage.

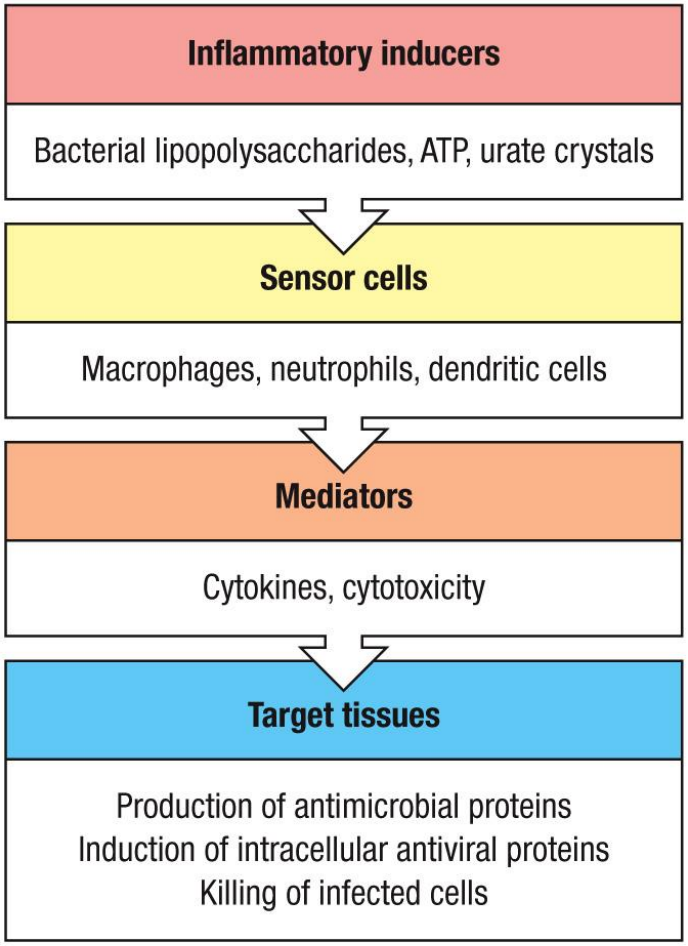
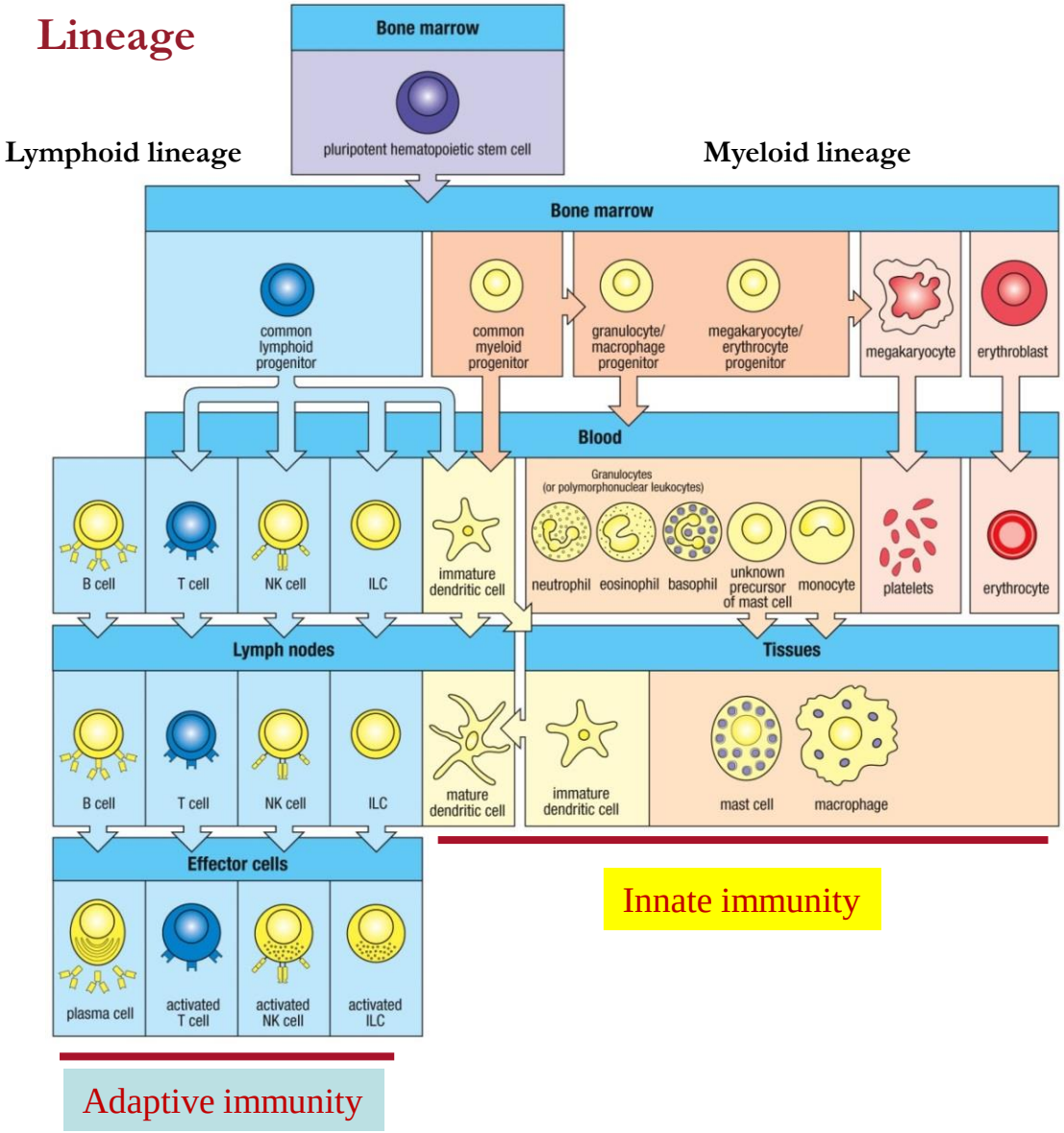


Figure 1.6 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

The cellular components of the immune system

Lineage



Hematopoietic stem cell (HSC)
Pluripotency
Progenitor cell (HPC)
Differentiation
Maturation

Questions:

1. How to define HSC?
2. How to define HPC?
3. How to define mature immune cells?

Immune cell subtypes:
Th1, Th2, Th17, Treg, …
M1/M2 macrophage
N1/N2 neutrophils
ILC-1, ILC-2, etc.

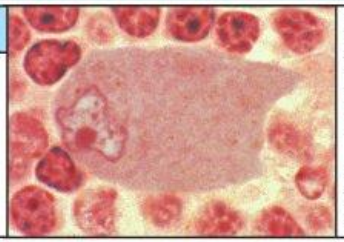
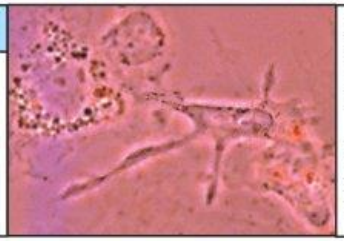
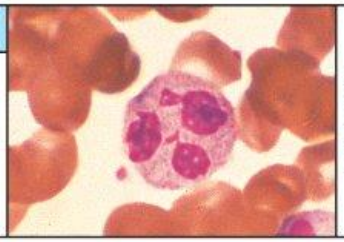
Principles of innate immunity

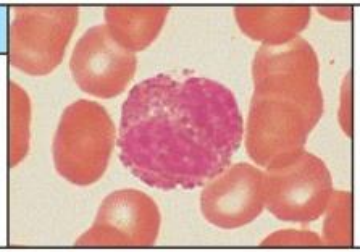
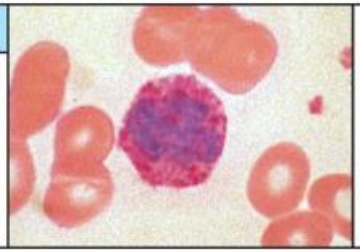
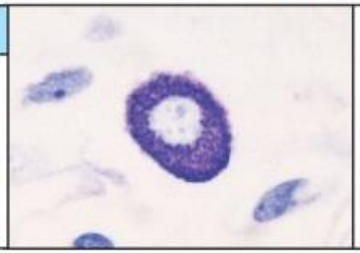
The **myeloid lineage** comprises most of the cells of the **innate immune system**

Myeloid Cells

Innate Immunity: Phagocytes, inflammatory cytokines

Adaptive immunity: Ag-presentation cells (APCs)

Cell		Activated function
Macrophage		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell		Antigen uptake in peripheral sites Antigen presentation in lymph nodes
Neutrophil		Phagocytosis and activation of bactericidal mechanisms

Eosinophil		Killing of antibody-coated parasites
Basophil		Unknown
Mast cell		Release of granules containing histamine and other active agents

Principles of innate immunity

Sensor cells express **pattern-recognition receptors** that provide an initial discrimination between self and nonself.

Innate immune Recognition

Pattern-recognition Receptors (PRRs)

Pathogen-associated Molecular Patterns (PAMPs)

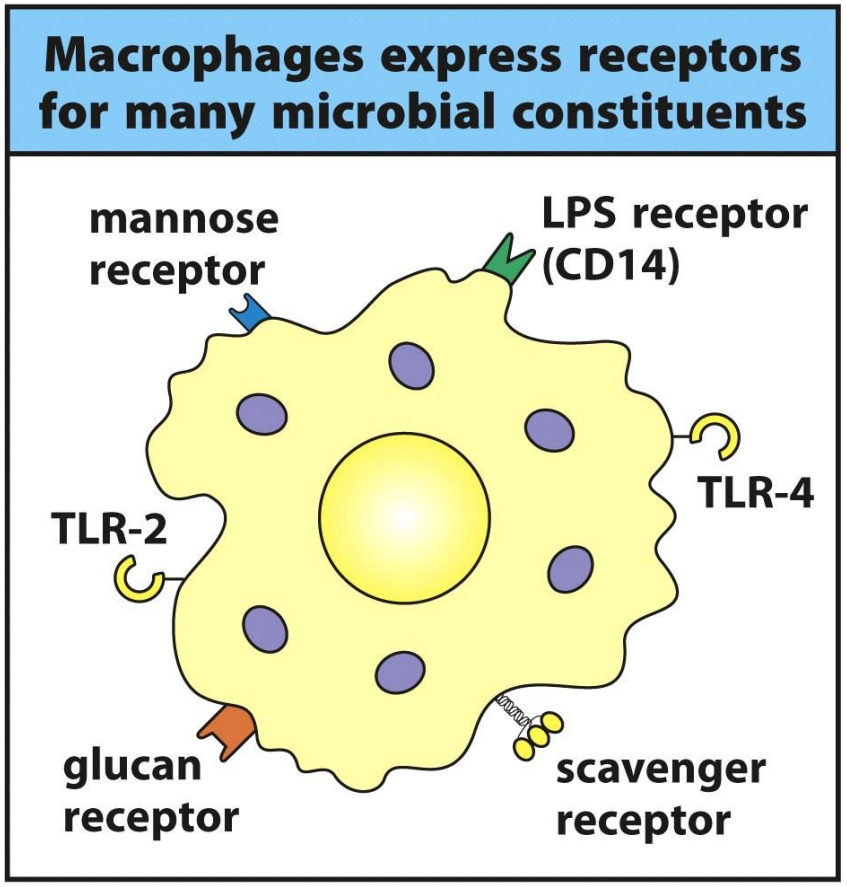


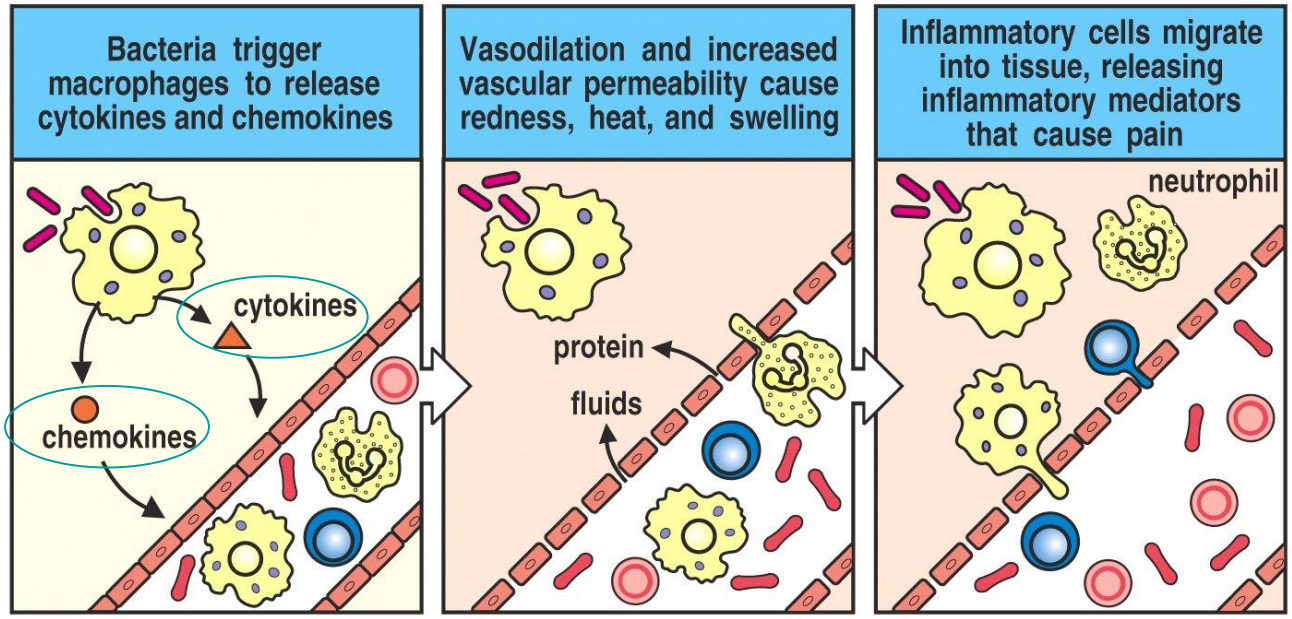
Figure 1.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Principles of innate immunity

Sensor cells induce an inflammatory response by producing mediators such as **chemokines** and **cytokines**

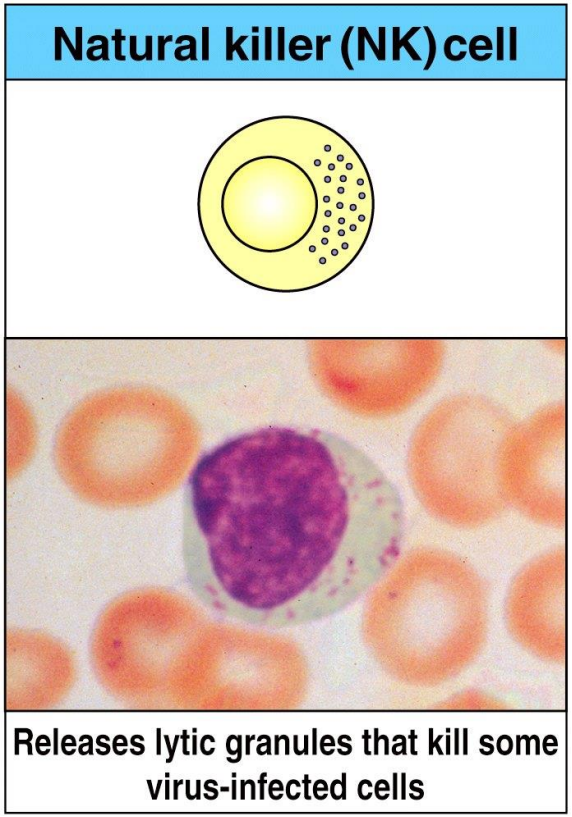
Inflammation

rubor (redness), tumor (swelling), calor (heat), and dolor (pain)



Principles of innate immunity

Innate lymphoid cells and natural killer cells are effector cells that share similarities with lymphoid lineages of the adaptive immune system.



Innate lymphoid cells (ILCs): Cytokine-producing lymphoid cells important in the innate immune responses.

Natural killer (NK) cells:
Innate immunity (virus-infected cells).
Adaptive immunity (Cytokine-producing cells).

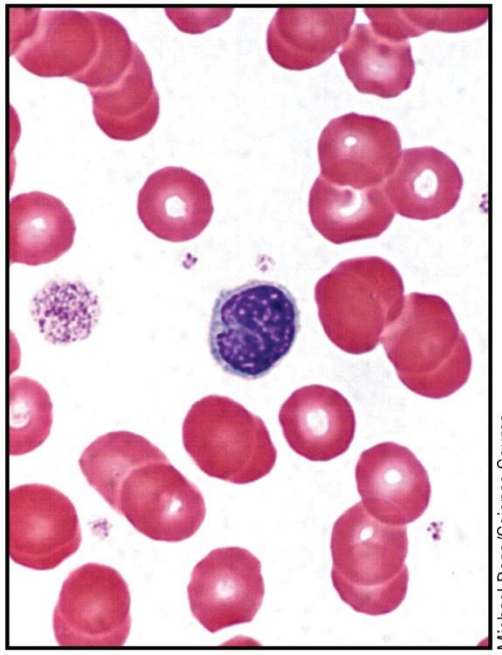
Principles of adaptive immunity

The interaction of antigens with antigen receptors induces lymphocytes to acquire **effector** and **memory** activity.

Adaptive immunity: Lymphoid Cells (lymphoid lineage)

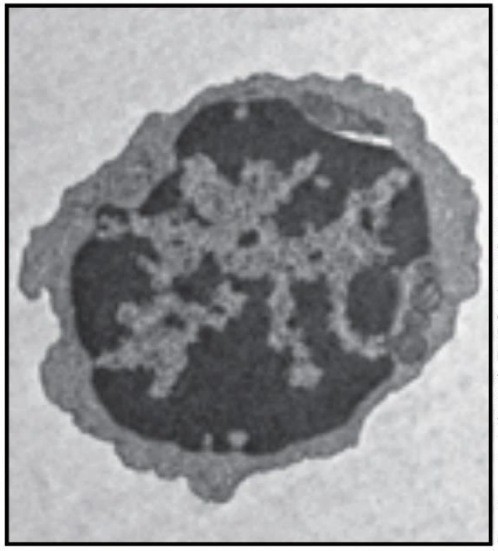
B lymphoid cells, plasma cells. Immunoglobulins (Ig)/Antibody (Ab)

T lymphoid cells, T helper (Th) cells, cytotoxic T (Tc) cells



Michael Ross/Science Source

Lymphocytes are mostly small and inactive cells



Rawlings et al. (2011) *EMBO J* (2011) 30: 263–276. Reprinted with permission © Wiley

Schematic structure of antigen receptors

Ag recognition

B cell: Ab **T cell: TCR (T cell receptor)**

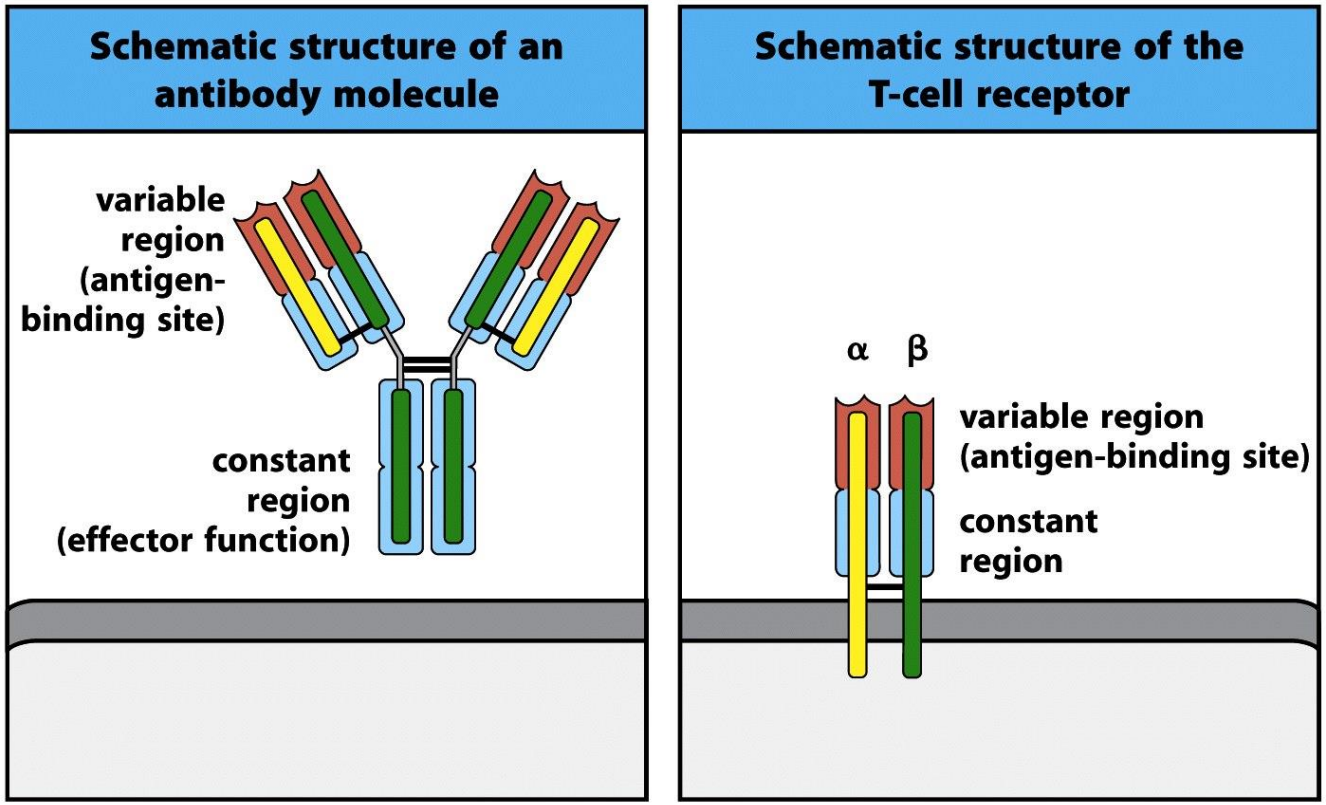
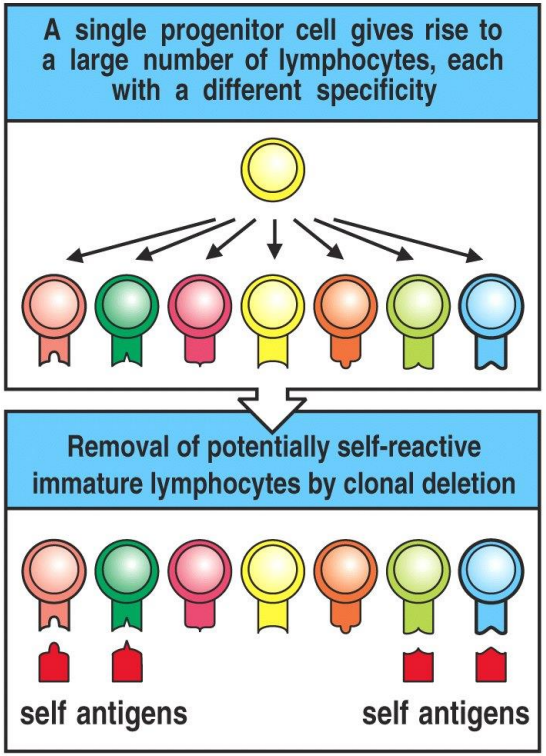


Figure 1-13 Immunobiology, 7ed. (© Garland Science 2008)

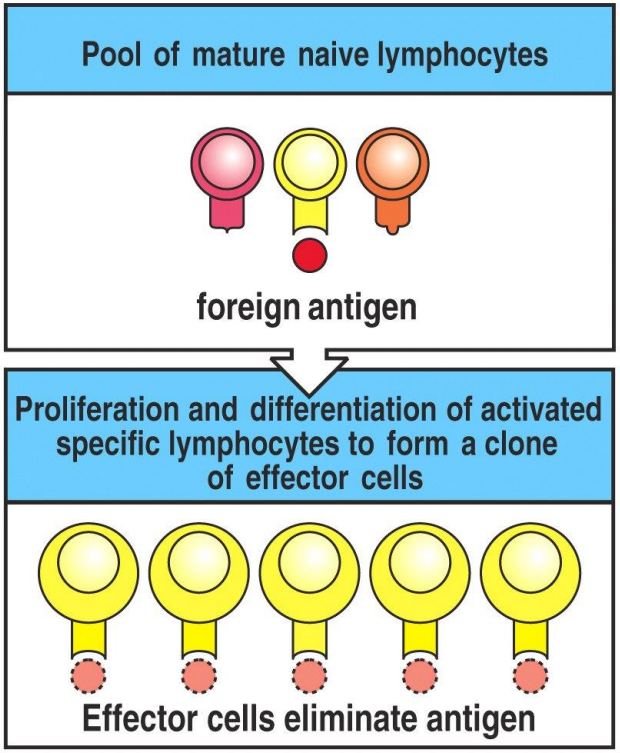
Principles of adaptive immunity

Antigen-receptor genes are assembled by somatic gene rearrangements of incomplete receptor gene segments.

Clonal Selection: Lymphocytes that were activated by Ag give rise to clones of Ag-specific cells

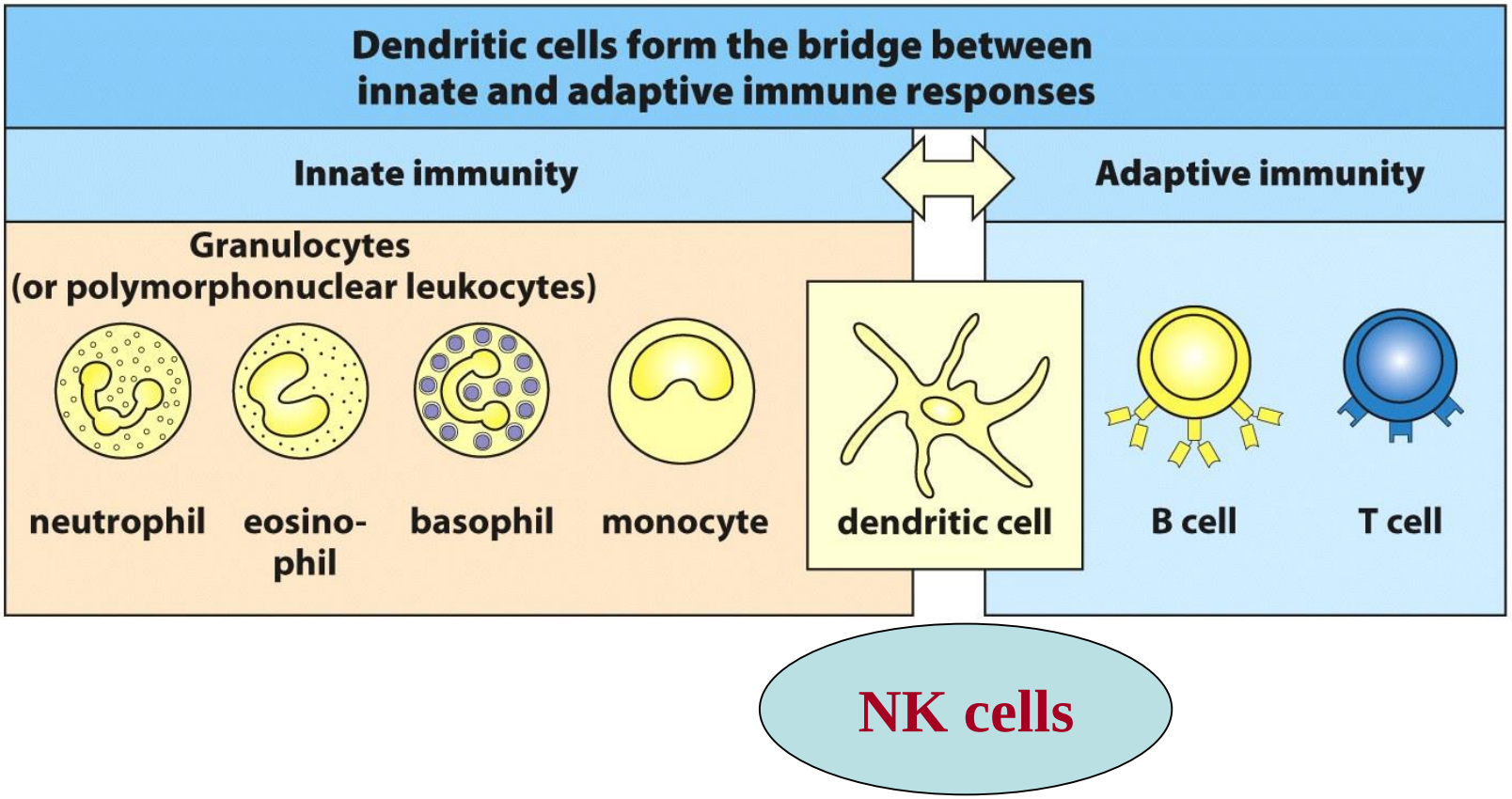


Clonal Deletion



Immunological Tolerance

Coordination between innate and adaptive immunities



Principles of adaptive immunity

Adaptive immune responses are initiated by antigen and antigen-presenting cells in peripheral lymphoid tissues.

Dendritic cells (DCs) are the most potent Ag-presenting cells (APCs)

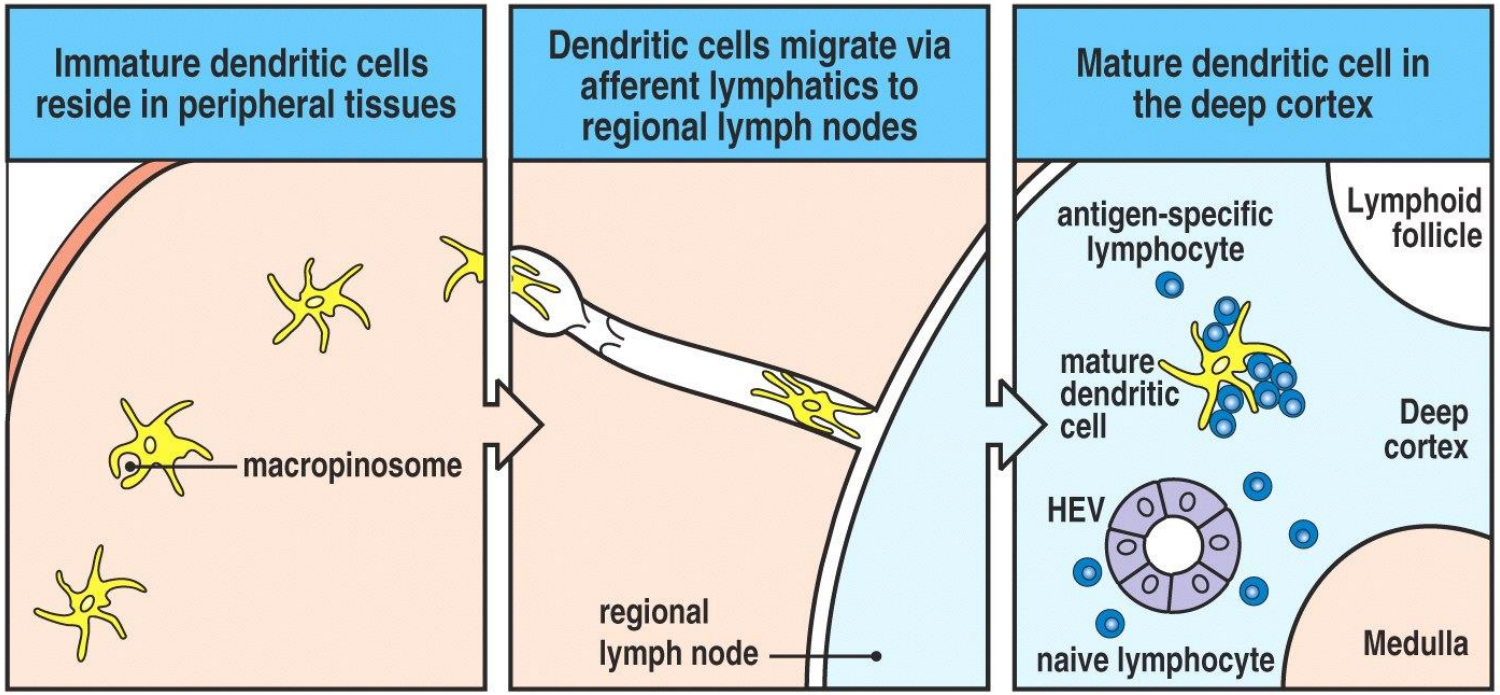


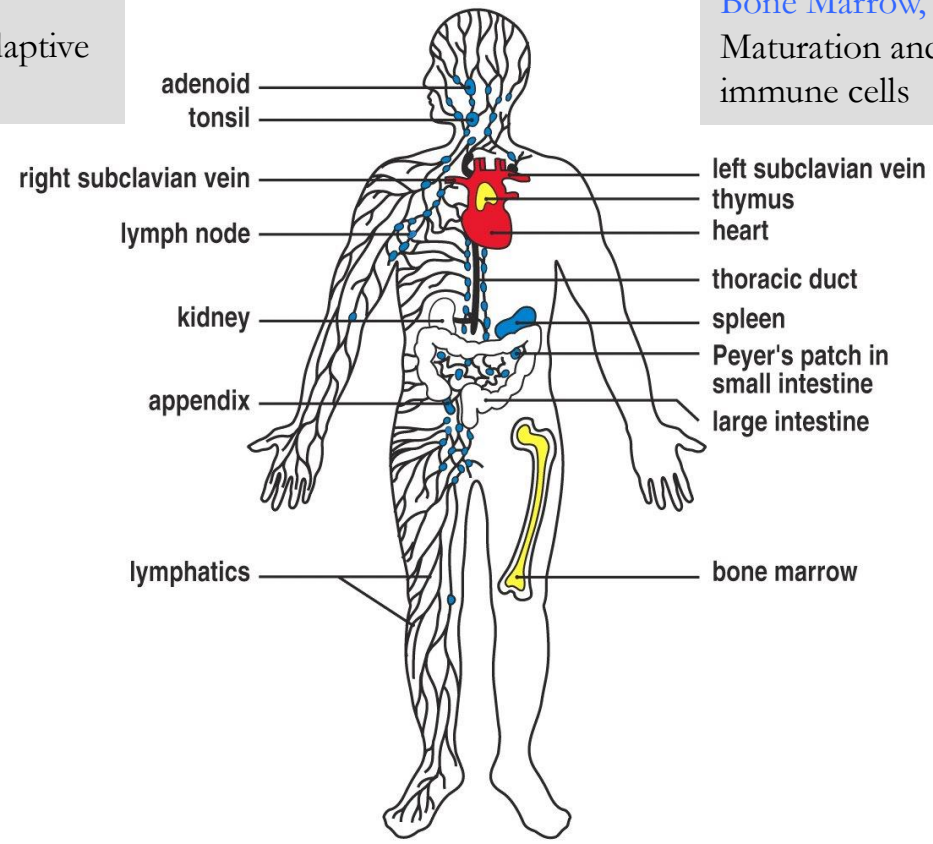
Figure 1-13 Immunobiology, 6/e. (© Garland Science 2005)

The lymphoid tissues/organs

Lymphocytes mature in the bone marrow or the thymus and then congregate in lymphoid tissues throughout the body

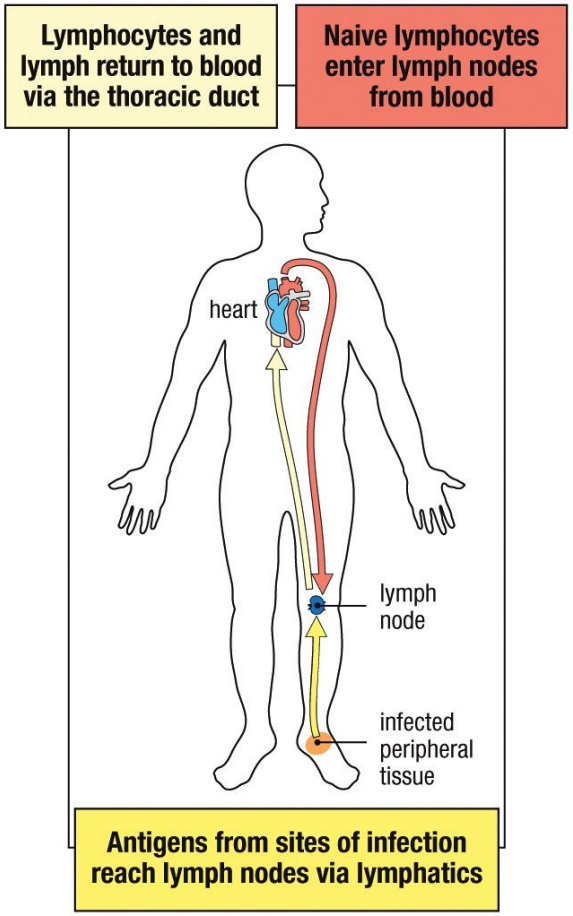
Peripheral (Secondary) Lymphoid Organs: Lymph nodes, Spleen, Gut-associated lymphoid tissues (GALT)
Presentation of Ag, Initiation of adaptive Immune responses

Central (Primary) Lymphoid Organs: Bone Marrow, Thymus
Maturation and differentiation of immune cells



Principles of adaptive immunity

Lymphocytes encounter and respond to antigen in the peripheral lymphoid organs



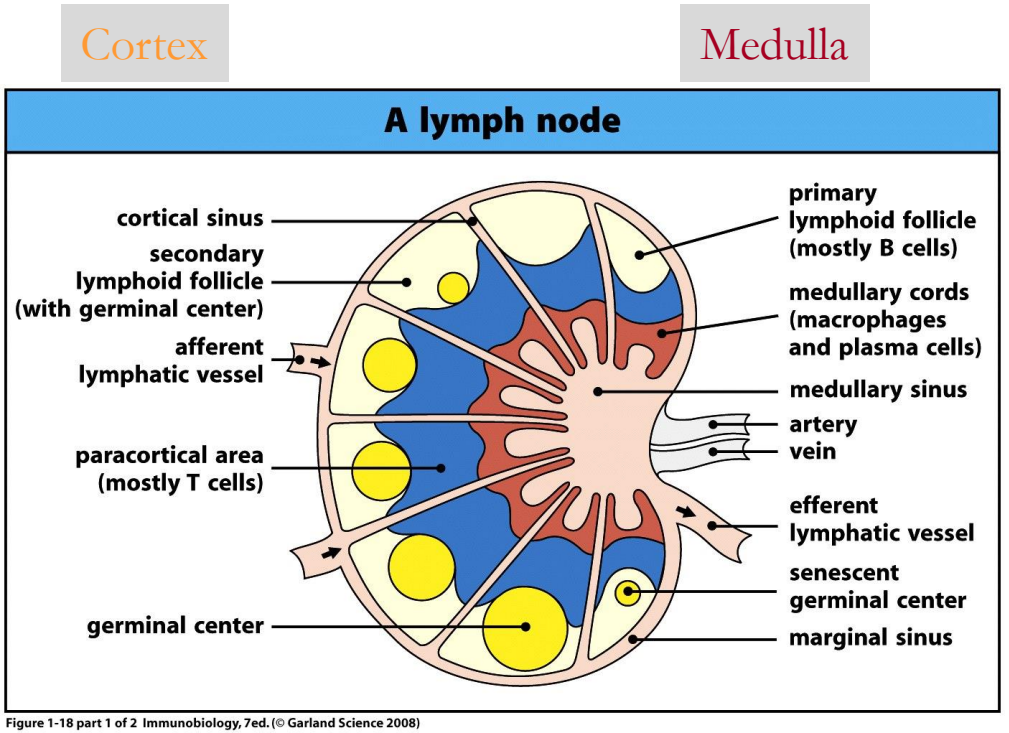
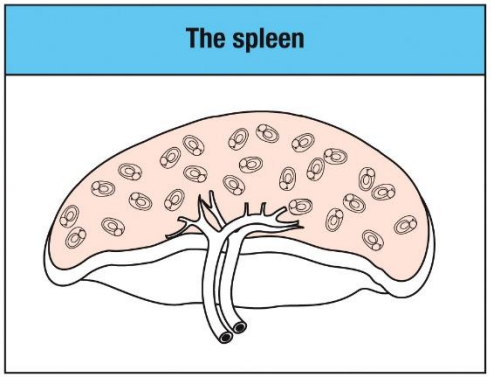
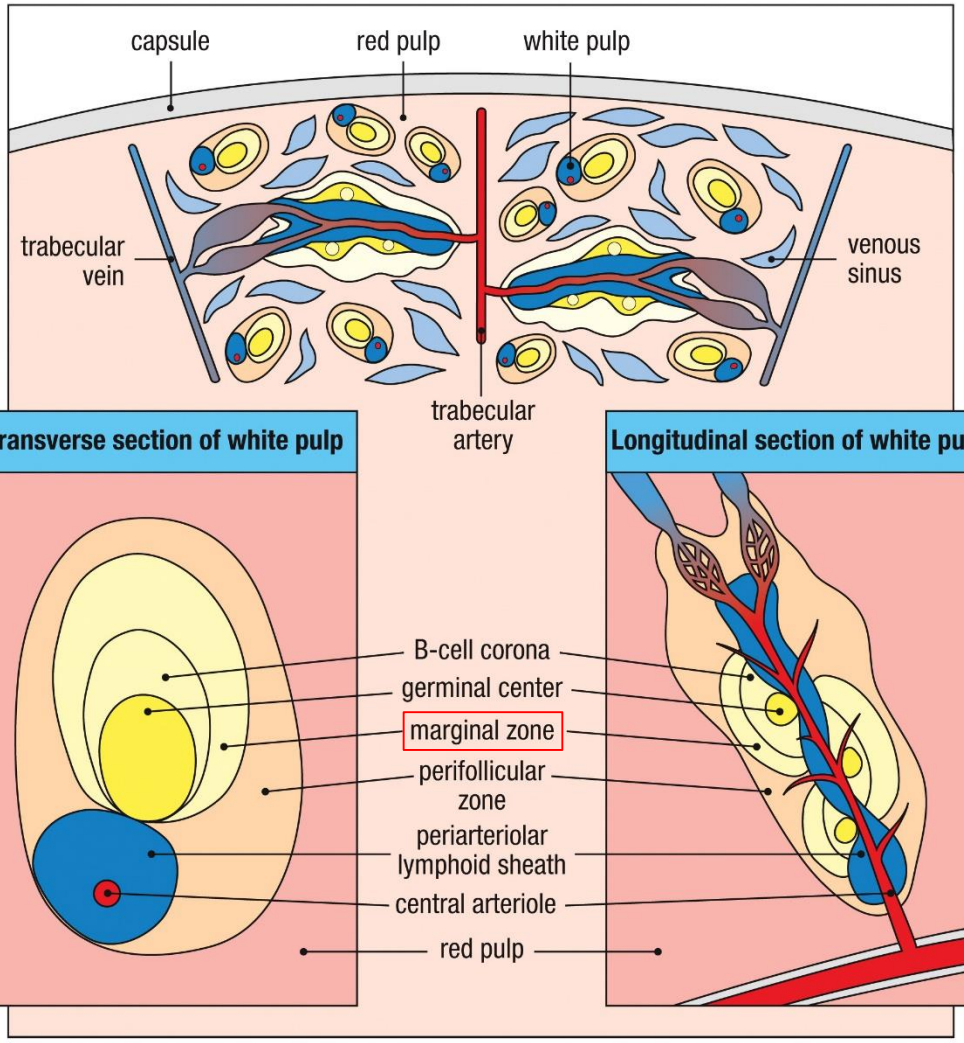
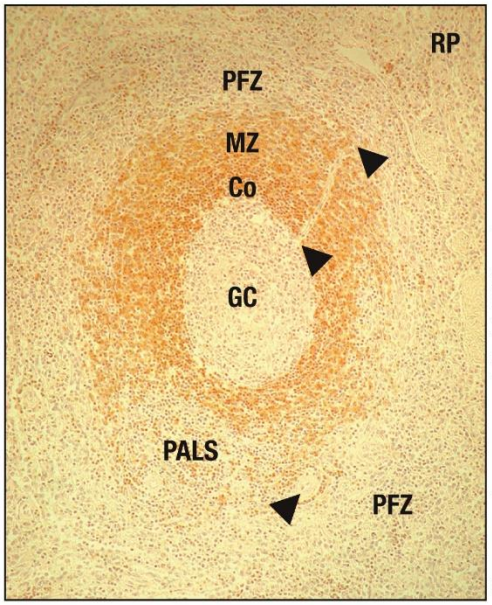


Figure 1-18 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Organization of the lymphoid tissues of the spleen







Photograph courtesy of N. M. Milicevic

Principles of adaptive immunity

Mucosal surfaces have specialized immune structures that orchestrate responses to environmental microbial encounters

Gut-Associated Lymphoid Tissues

70-75% peripheral lymphoid cells

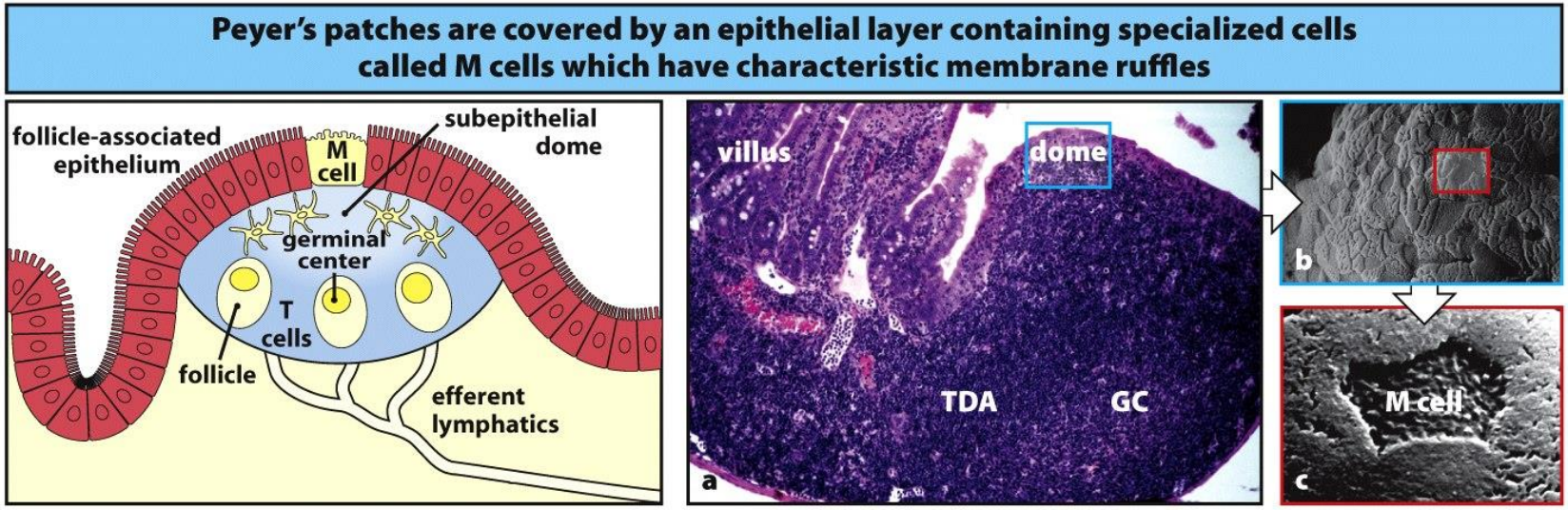
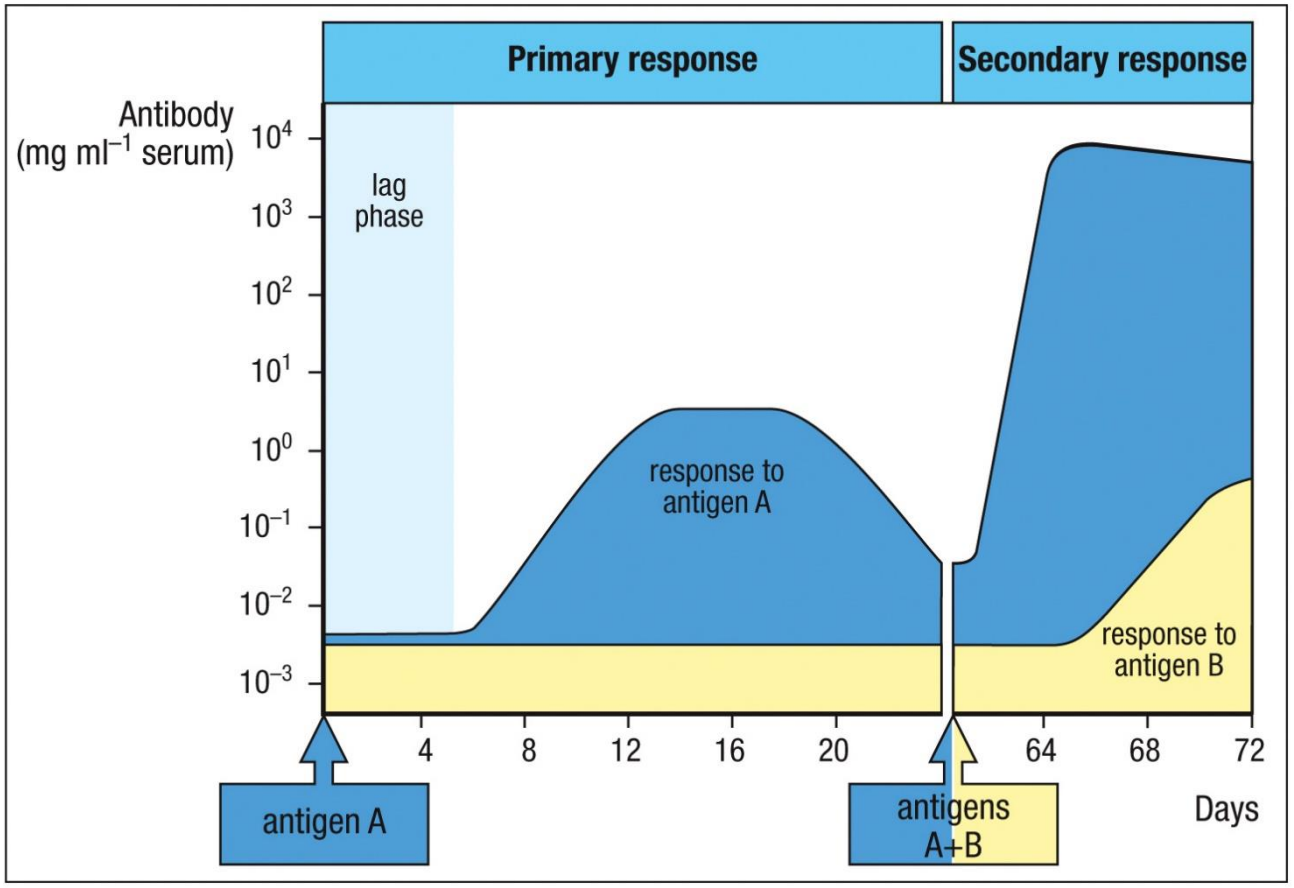


Figure 1-20 Immunobiology, 7ed. (© Garland Science 2008)

Principles of adaptive immunity

Lymphocytes activated by antigen proliferate in the peripheral lymphoid organs, generating **effector cells** and **immunological memory**

Primary immunization Secondary (booster) immunization



Immune balance

control of allergies, autoimmune disease, tumor, and the rejection of transplanted organs

Antigen	Effect of response to antigen	
	Normal response	Deficient response
Infectious agent	Protective immunity	Recurrent infection
Innocuous substance	Allergy	No response
Grafted organ	Rejection	Acceptance
Self organ	Autoimmunity	Self tolerance
Tumor	Tumor immunity	Cancer

Figure 1-32 Immunobiology, 6/e. (© Garland Science 2005)

The response to an initial infection occurs in three phases

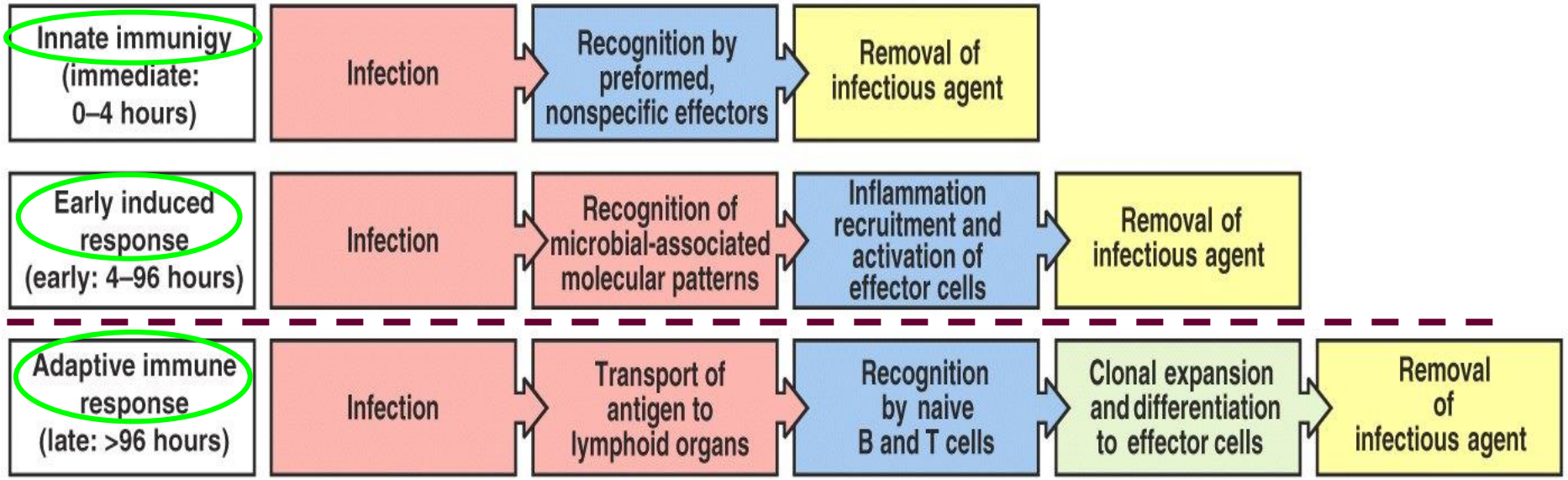


Table 12–3. Components of Innate Immunity

Components	Principal functions
Barriers	
Epithelial layers	Prevent microbial entry
Defensins	Microbial killing
Intraepithelial lymphocytes	Microbial killing
Circulating effector cells	
Neutrophils	Early phagocytosis and killing of microbes
Macrophages	Efficient phagocytosis and killing of microbes, secretion of cytokines that stimulate inflammation
NK cells	Lysis of infected cells, activation of macrophages
Circulating effector proteins	
Complement	Killing of microbes, opsonization of microbes, activation of leukocytes
Mannose-binding lectin (collectin)	Opsonization of microbes, activation of complement (lectin pathway)
C-reactive protein (pentraxin)	Opsonization of microbes, activation of complement
Coagulation factors	Walling off infected tissues
Cytokines	
TNF, IL-1, chemokines	Inflammation
IFN-α, -β	Resistance to viral infection
IFN-γ	Macrophage activation
IL-12	IFN-γ production by NK cells and T cells
IL-15	Proliferation of NK cells
IL-10, TGF-β	Control of inflammation

Anatomic barriers and initial chemical defenses

Epithelial surfaces of the body provide the first barrier against infection

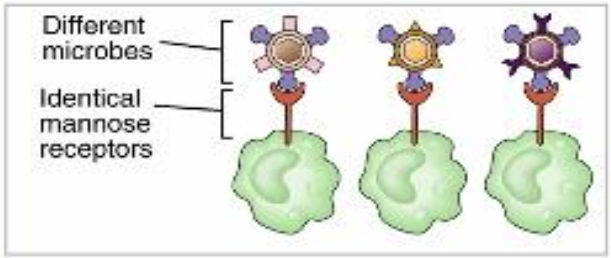
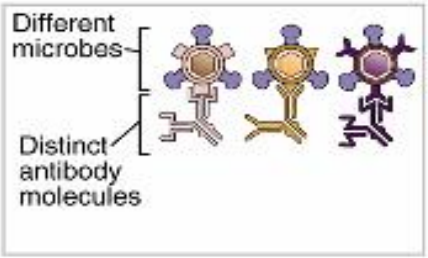
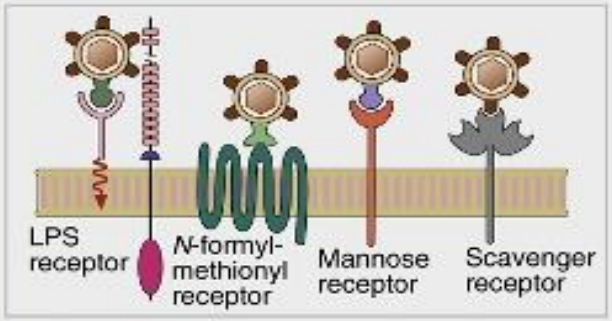
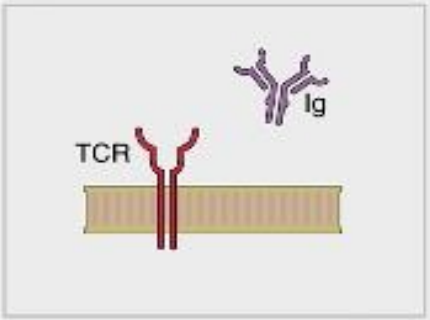
Mucosal immune system

Mucosal epithelia Mucin glycoproteins

	Skin	Gut	Lungs	Eyes/nose/oral cavity
	Stratified epithelium	Single cell layer of columnar epithelium	Upper airway: pseudostratified columnar epithelium Lower airway: single cell layer of columnar epithelium	Pseudostratified columnar epithelium
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid	Longitudinal flow of air or fluid	Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
		Enzymes (pepsin)		
	β-defensins Lamellar bodies Cathelicidin	α-defensins (cryptdins) RegIII (lecticidins) Cathelicidin	α-defensins Cathelicidin	Histatins β-defensins
Microbiological	Normal microbiota			

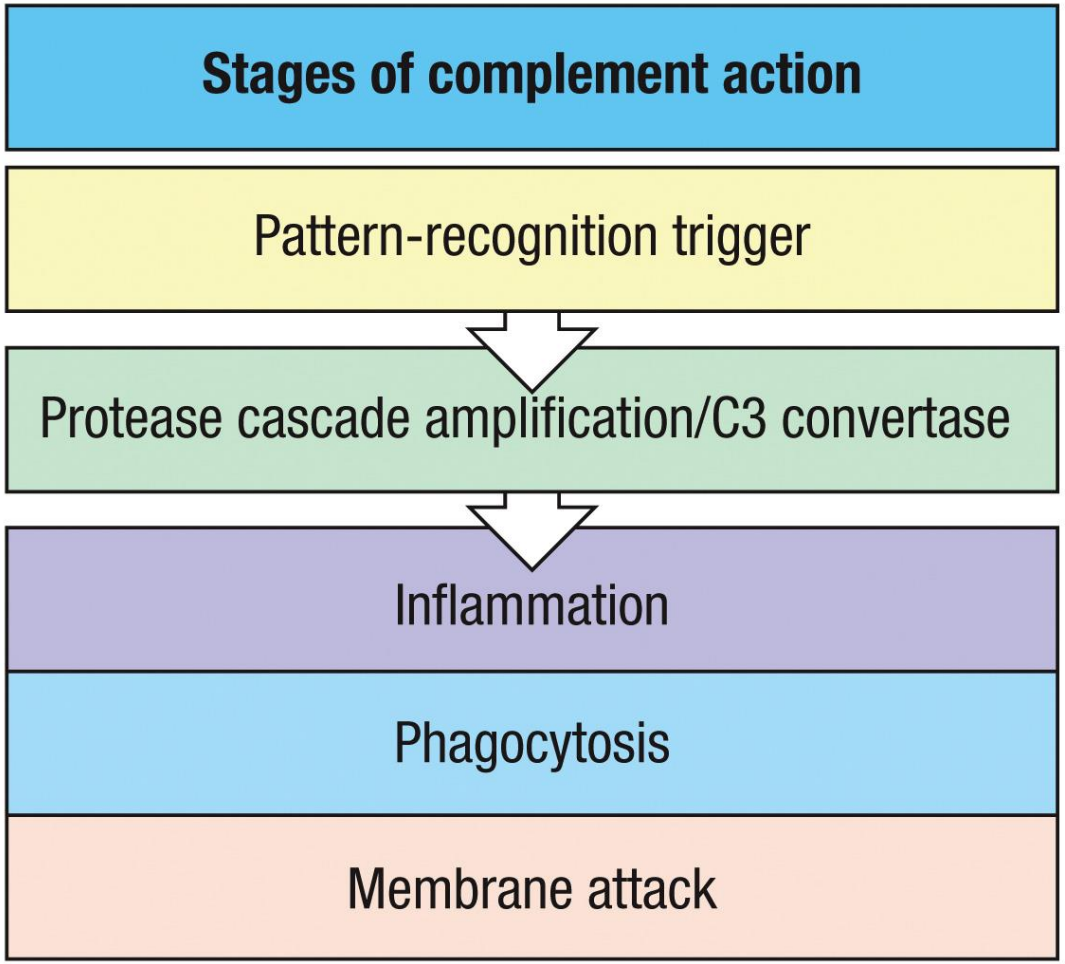
Pattern recognition by the immune system

Table 12–1. Specificity of Innate and Adaptive Immunity

	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes ("molecular patterns") 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Receptors	Encoded in germline; limited diversity 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and nonself	Yes; host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on selection against self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

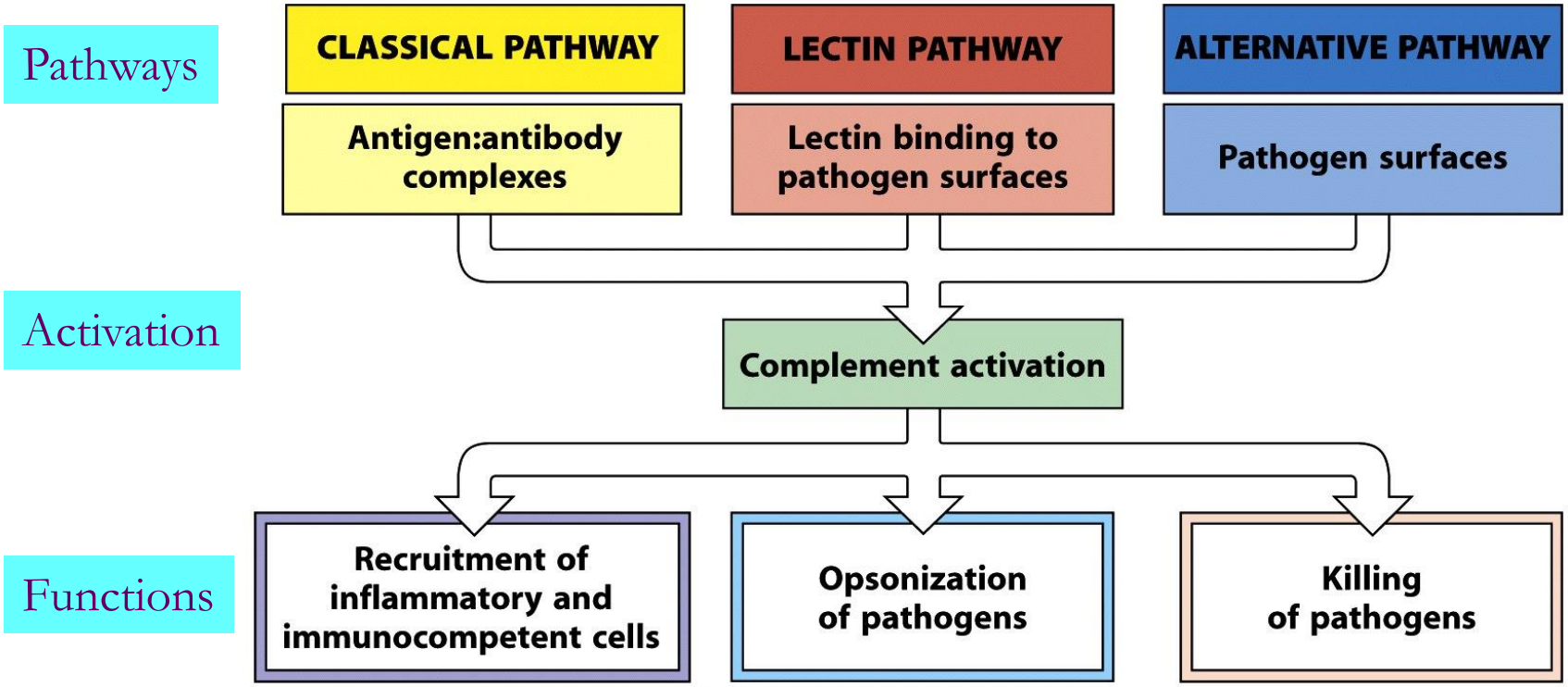
The complement system and innate immunity

Jules Bordet
The Nobel Prize in
Physiology or Medicine
1919



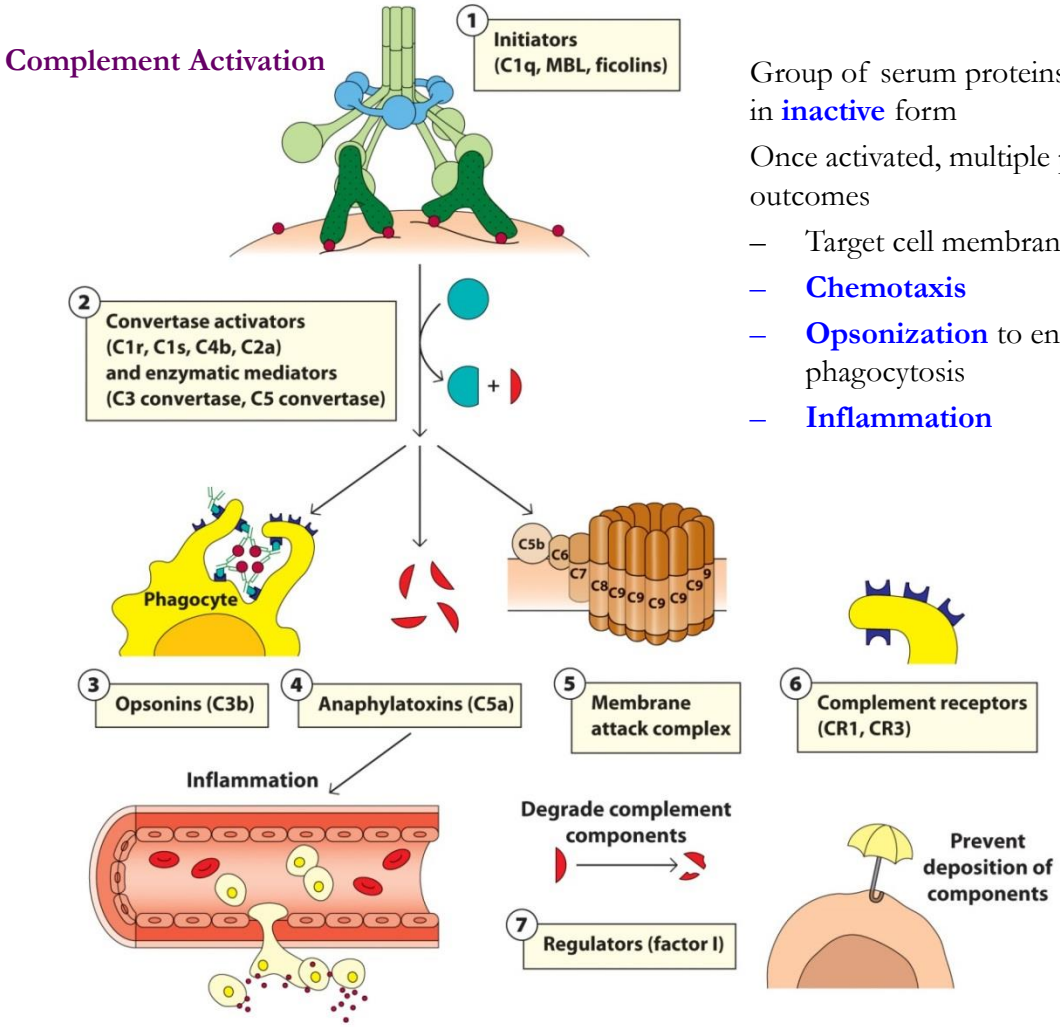
The complement system and innate immunity

The complement system recognizes features of microbial surfaces and marks them for destruction by coating them with C3b



The Complement System

The protein members of the complement system



Group of serum proteins circulating in **inactive** form

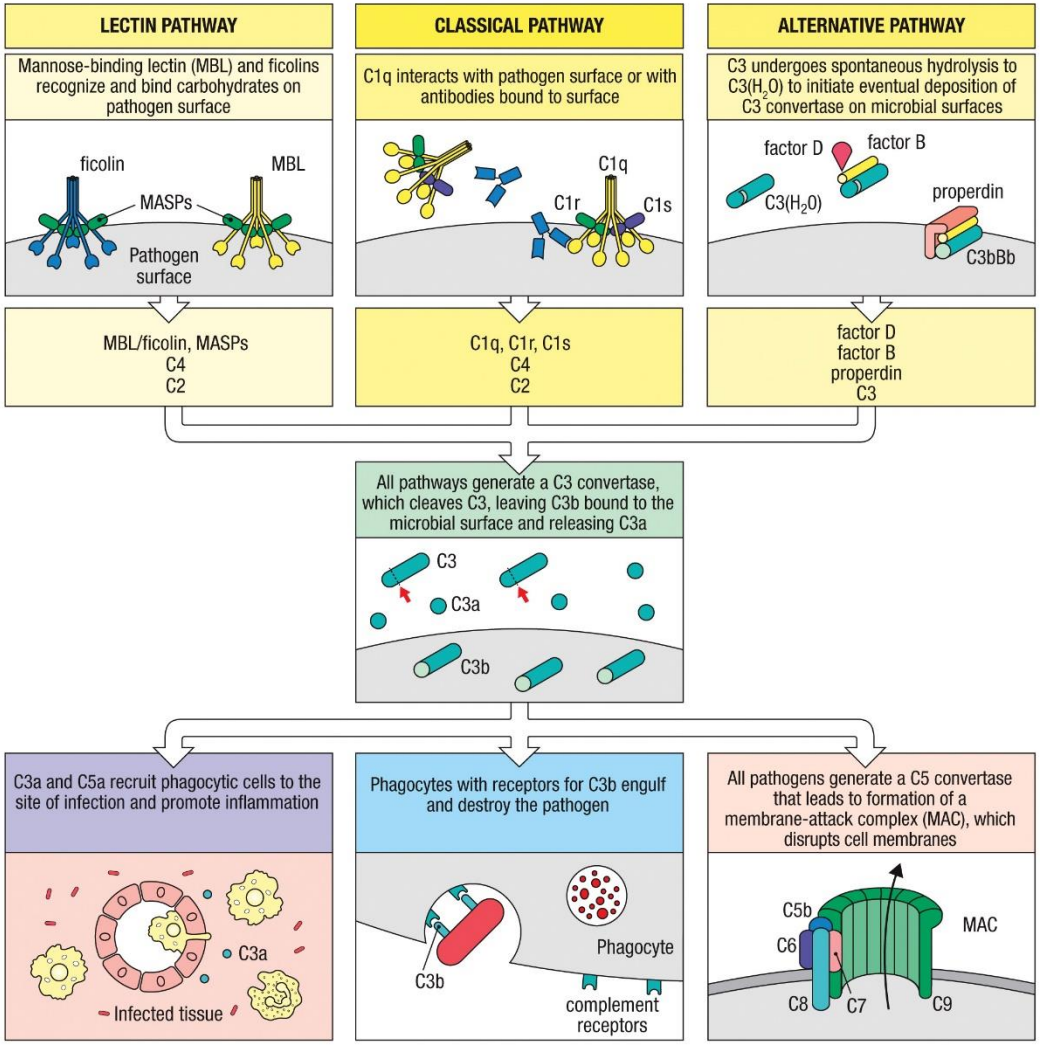
Once activated, multiple possible outcomes

- Target cell membrane **lysis**
- **Chemotaxis**
- **Opsonization** to enhance phagocytosis
- **Inflammation**

Functional protein classes in the complement system	
Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to mannose on bacteria	MBL
Activating enzymes	C1r C1s C2b Bb D MASP-1 MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a
Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 C1qR
Complement-regulatory proteins	C1INH C4bp CR1 MCP DAF H I P CD59

The complement system and innate immunity

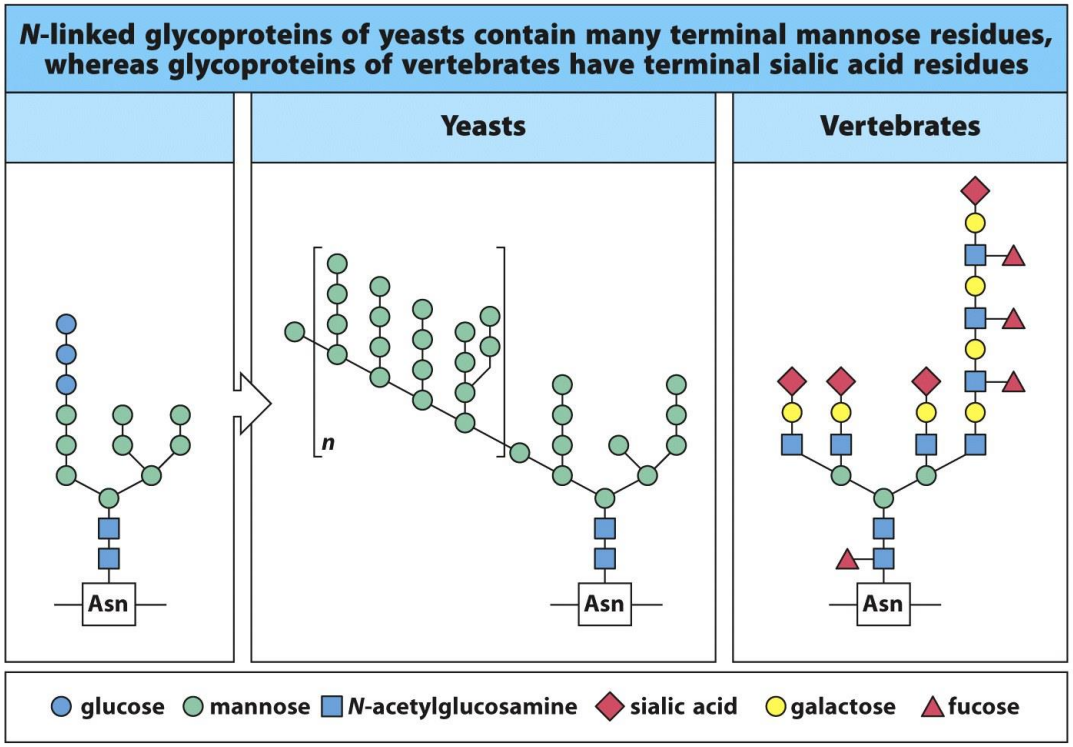
The complement system recognizes features of microbial surfaces and marks them for destruction by coating them with C3b



Lectin pathway

Pathogen-associated molecular patterns (PAMPs)
Pattern-recognition molecules (PRMs)
Mannose-binding lectin, Collectins, Ficollins

Do you know of any other type of lectin molecules? and their functions?



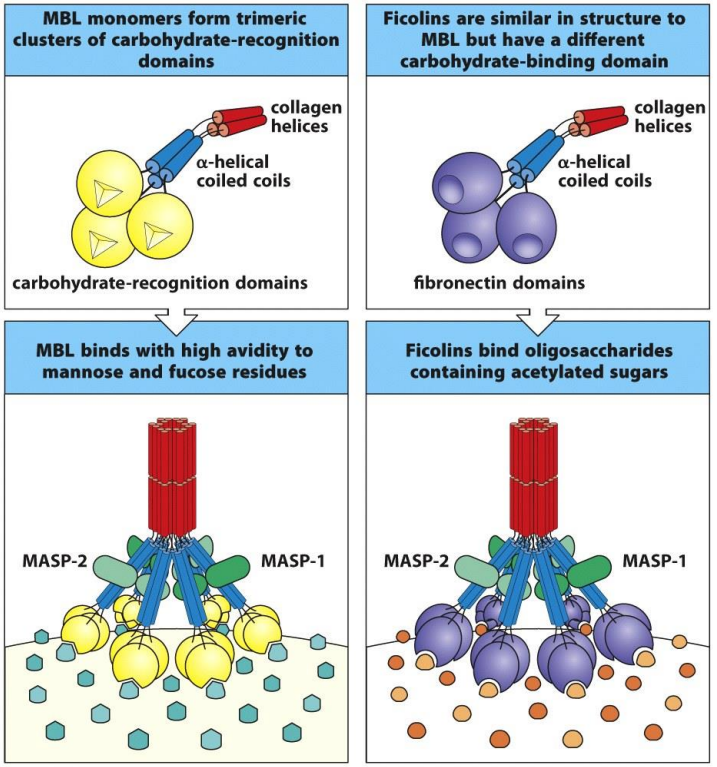
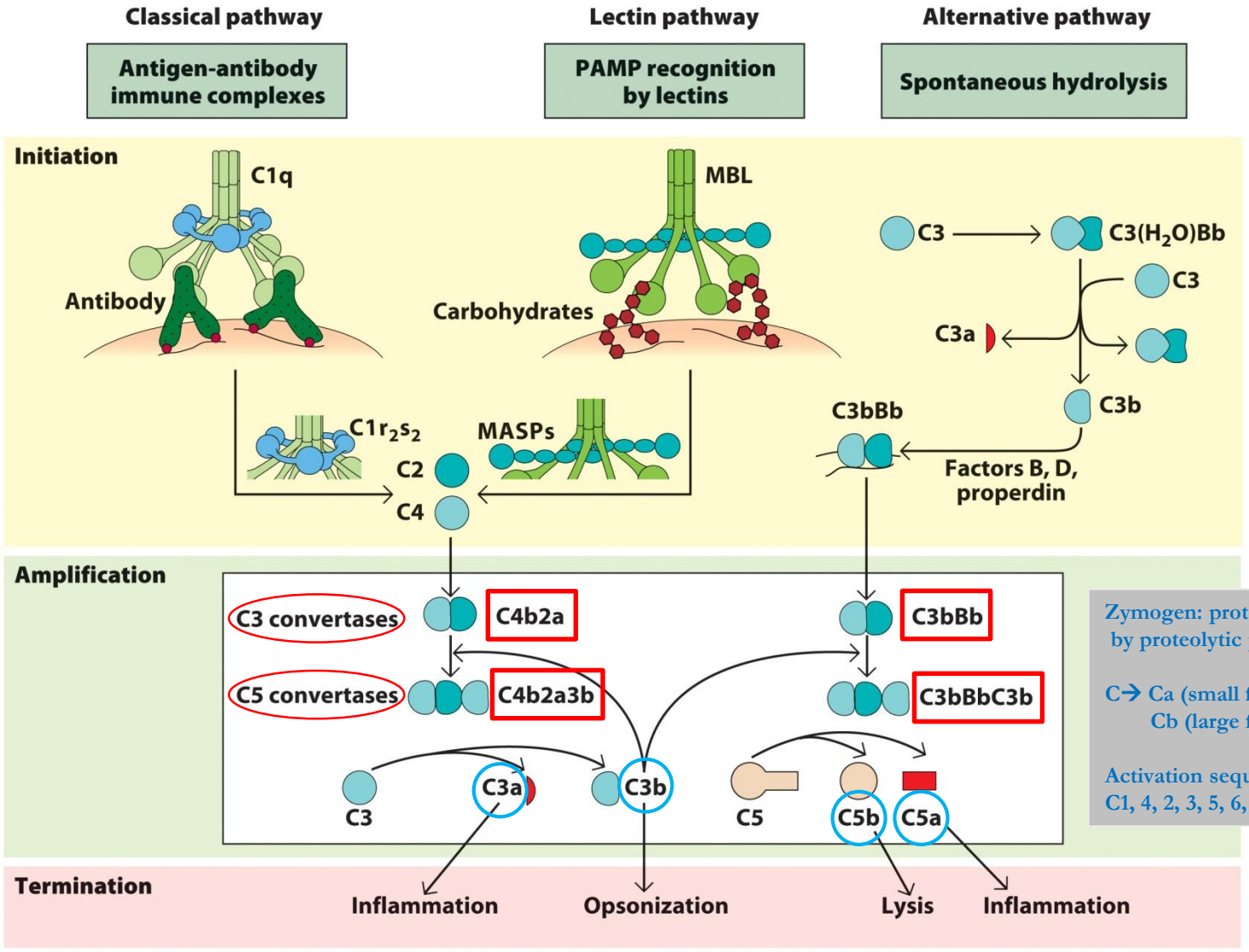


Figure 2.15 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Three major **activation pathways** of the complement system

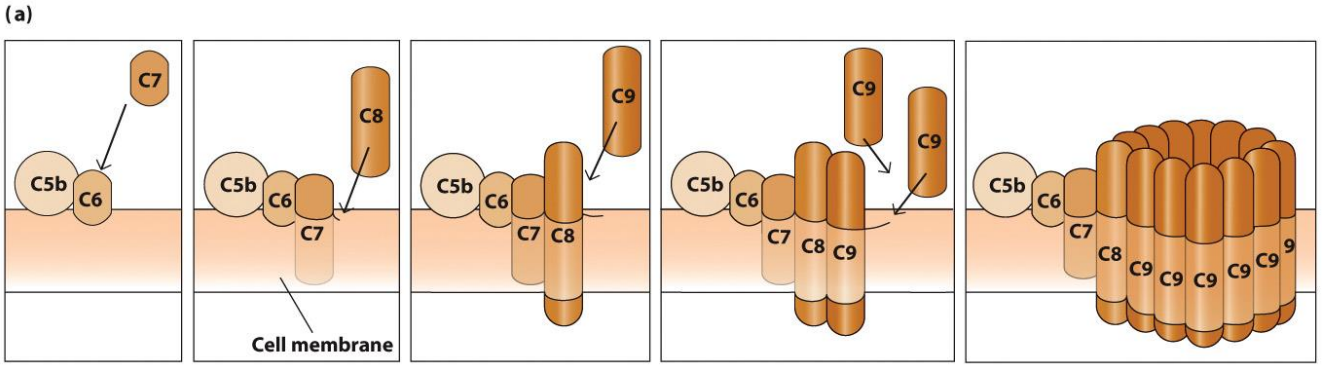


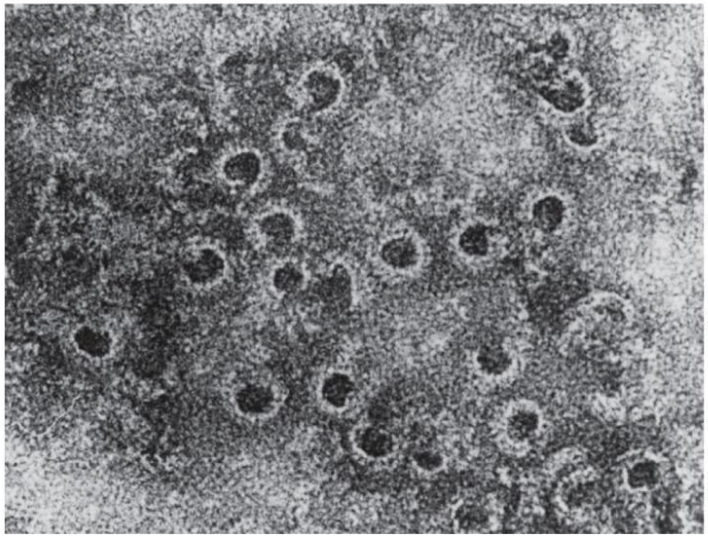
Zymogen: proteins activated by proteolytic processing.

C→ Ca (small fragment), Cb (large fragment).

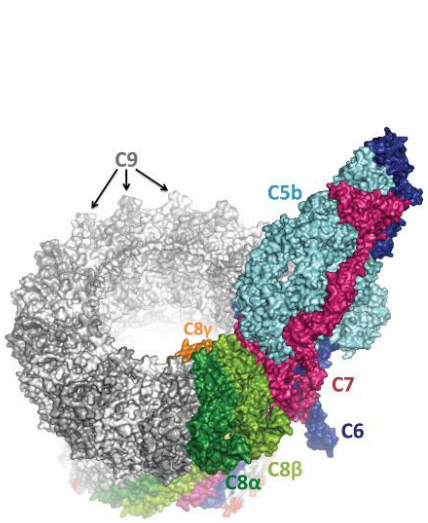
Activation sequence: C1, 4, 2, 3, 5, 6, 7, 8, 9

Assembly of the membrane-attack complex (MAC) generates a pore in the membrane

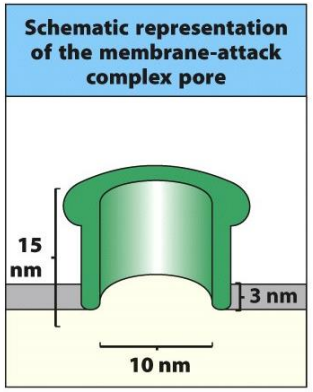




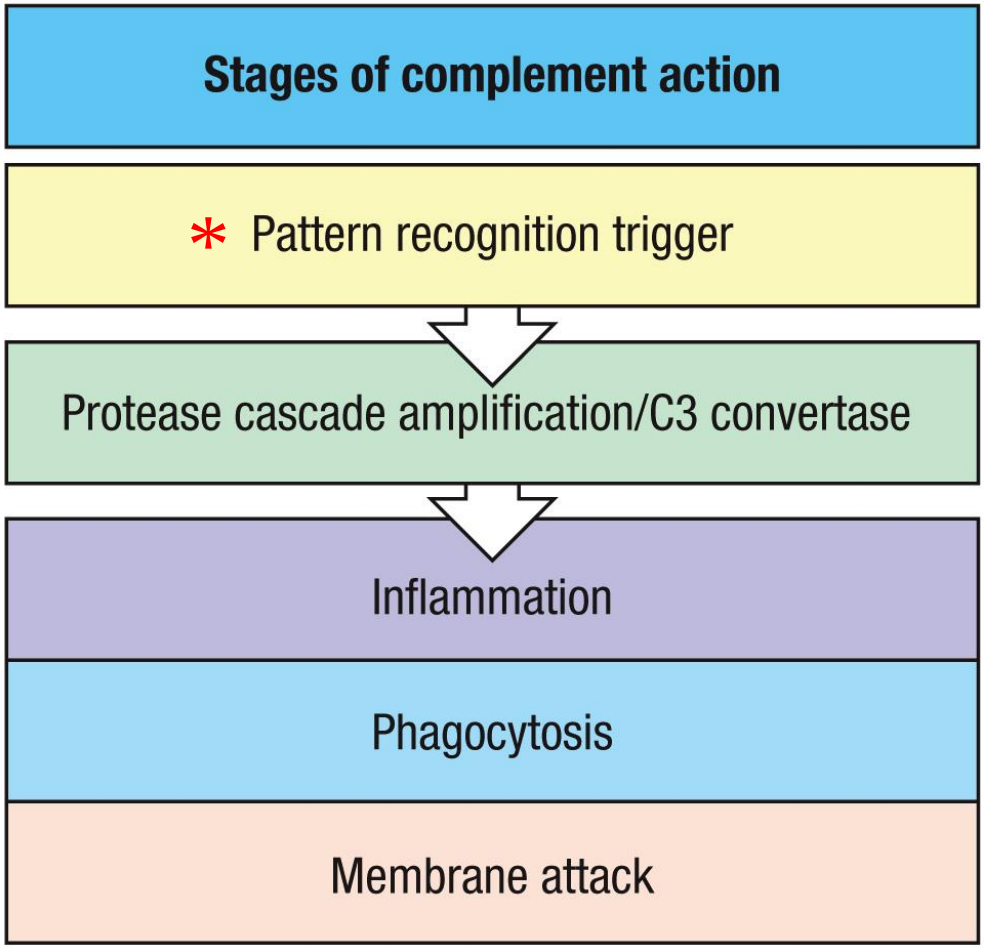
Republished with permission of Elsevier, from Humphrey, J. and Dourmashkin, R., 1969, The lesions in cell membranes caused by complement. Reprinted from *Advances in Immunology*, Volume 11, Copyright 1969, 75–115.



Drs. Robert Liddington and Alex Aleshin, SBP Medical Discovery Institute, La Jolla, CA.

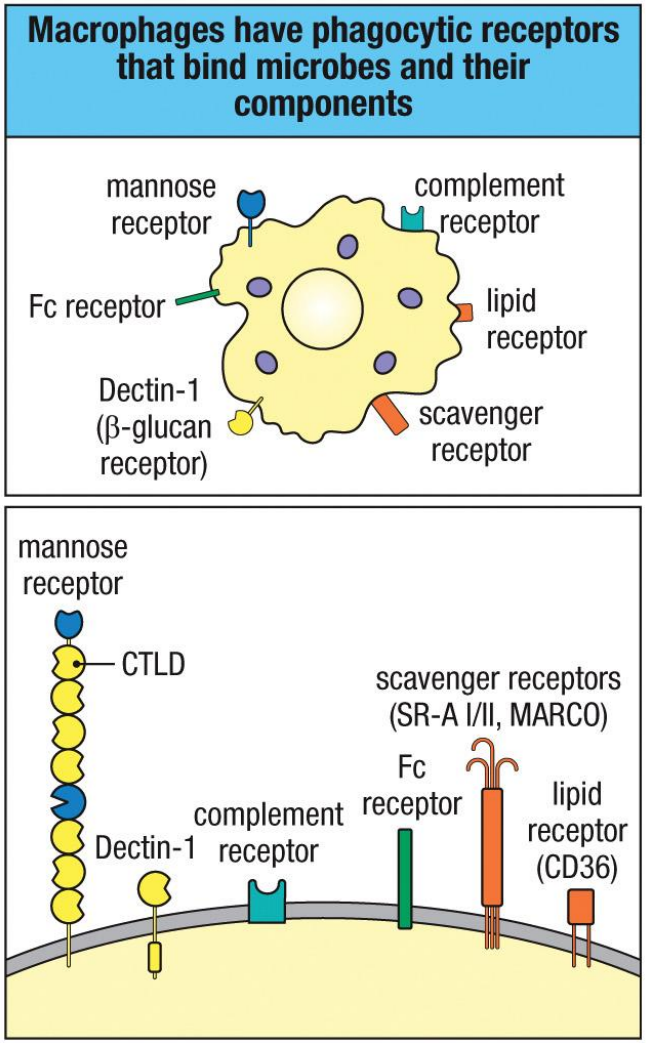


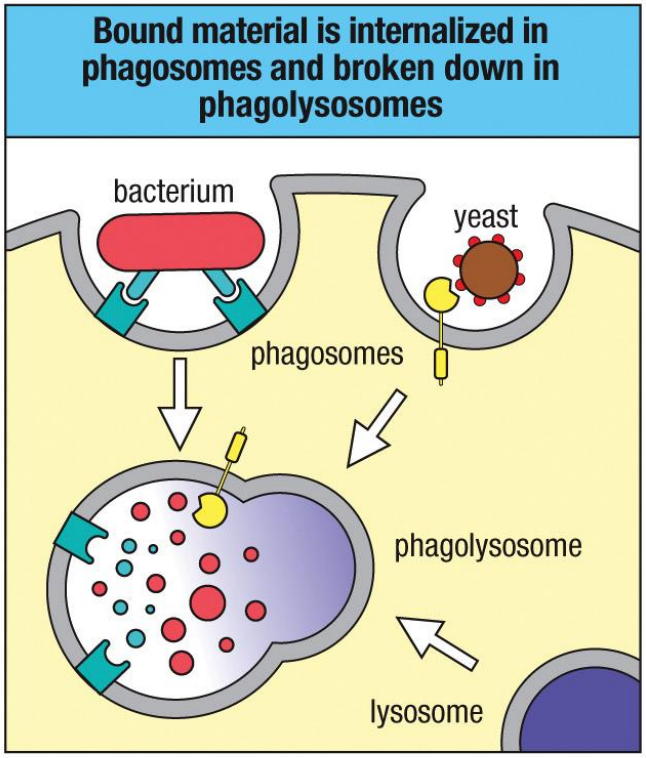
The complement system and innate immunity



Pathogen recognition by cells of the innate immune system

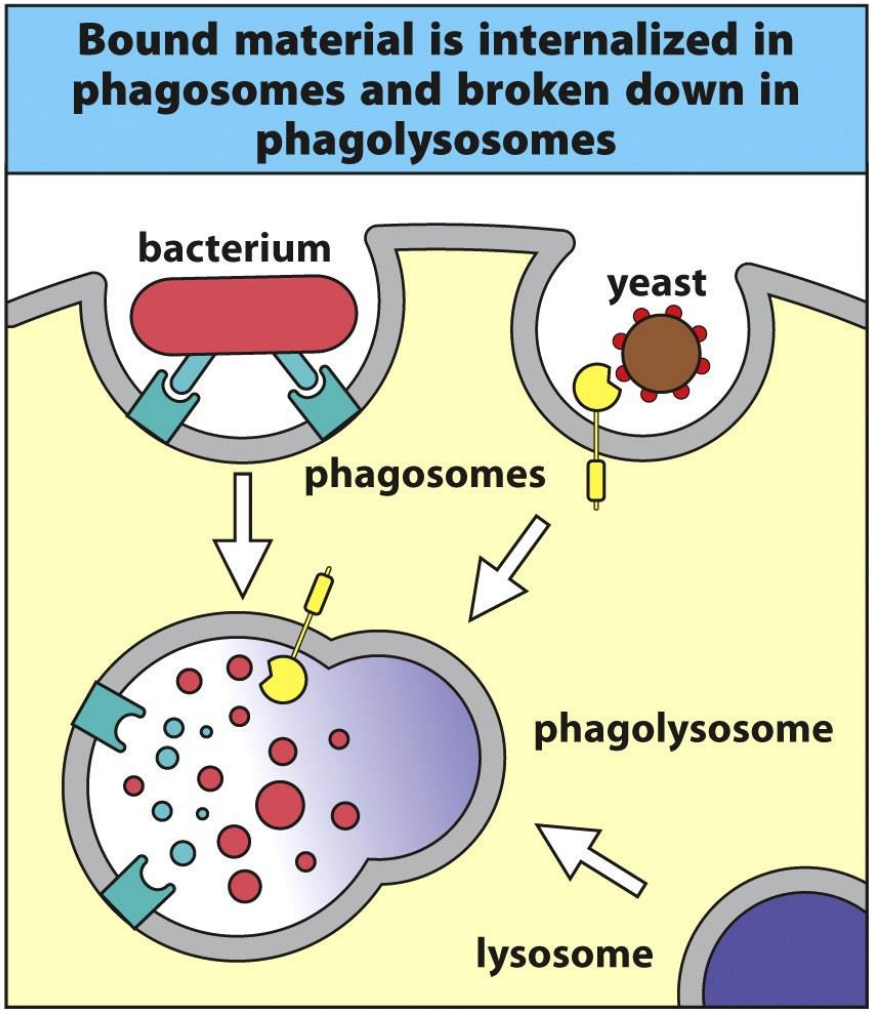
After entering tissues, many microbes are recognized, ingested, and killed by phagocytes





CTLD: C-type lectin–like domain

CRD: carbohydrate-recognition domain



Macropinocytosis: uptake of fluids and soluble molecules.

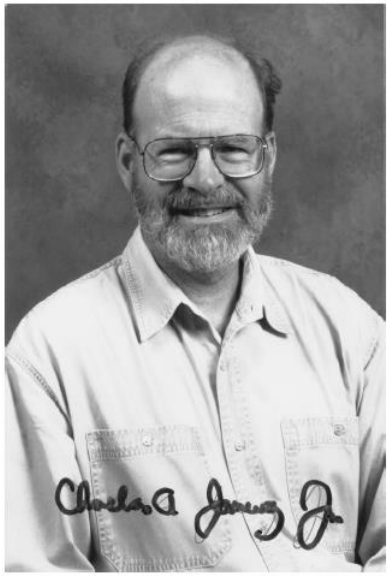
Phagocytosis: receptor-mediated endocytosis. Opsonin mediated, Non-opsonin mediated.

Phagosome: endosome.

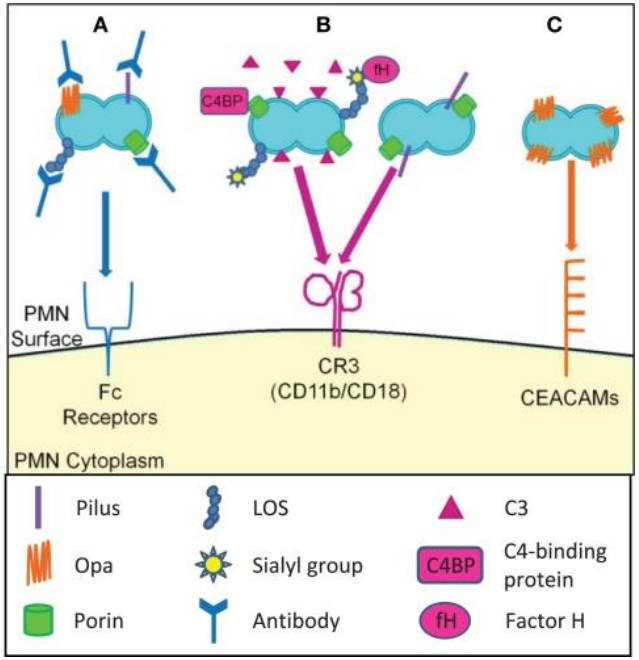
Phagolysosome: fusion of phagosome and lysosome. Microbial killing mechanism.

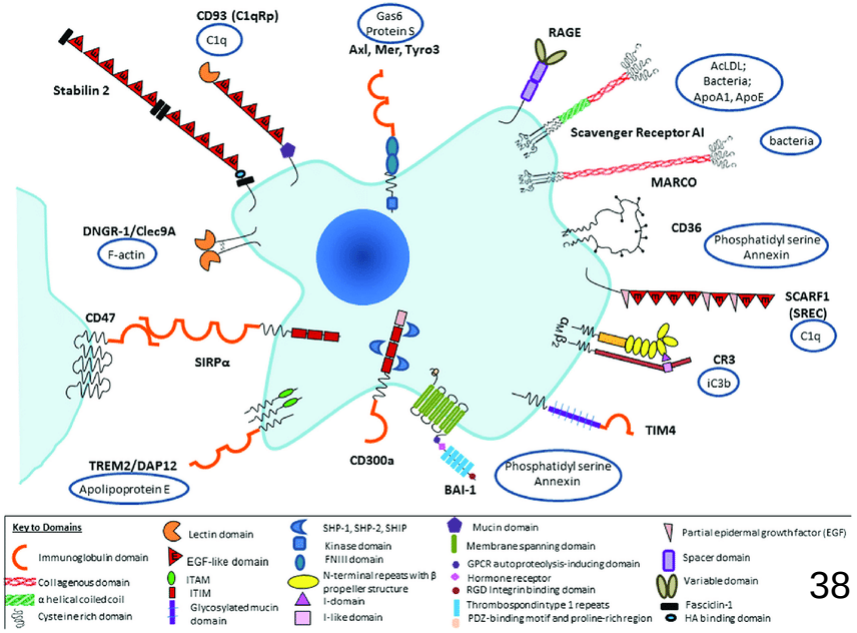
Phagocytosis

- FcR and complementR-mediated phagocytosis (Opsonin-dependent).
- Opsonin-independent.
- Distinction and Recognition of self and non-self /altered self.
- Pathogen Associated Molecular Patterns (PAMPs).
- Pattern Recognition Receptors (PRRs).
- Clearance of pathogens and apoptotic cells
- Phagocytic synapse.

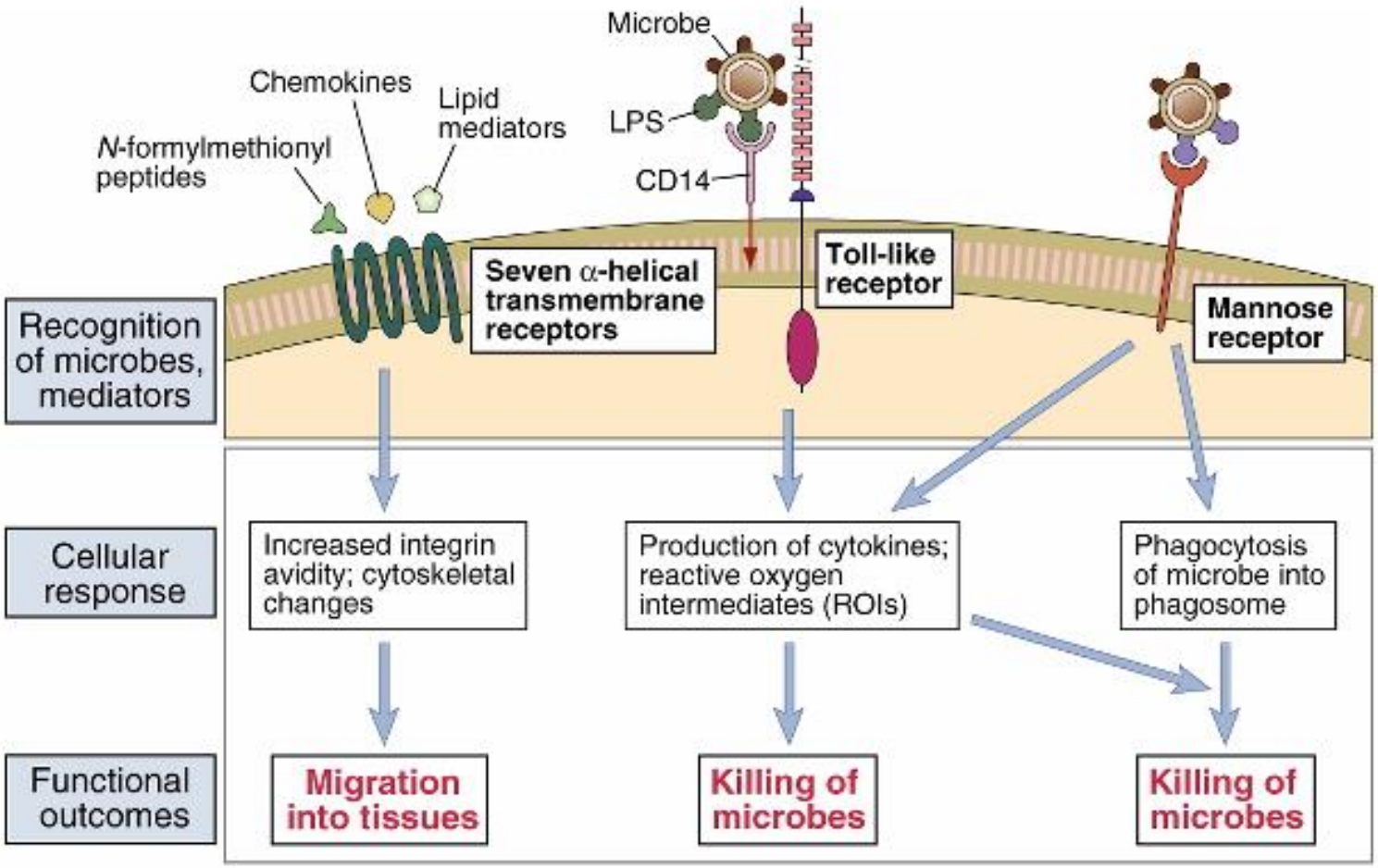


E. Metchnikoff





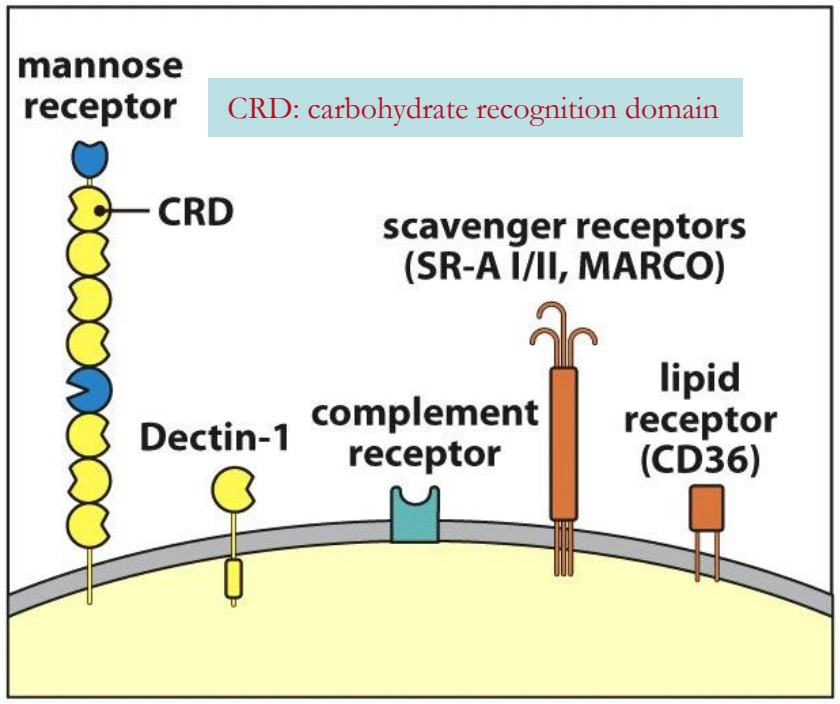
Recognition of pathogens



Pathogen recognition by cells of the innate immune system

Pattern Recognition Receptors (PRRs)

Microbial ligands: Pathogen-associated molecular patterns (PAMPs)



- C-type Lectins: Mannose Receptor (MR), Dectin-1, DC-SIGN.
- Scavenger Receptors: SR-A I/II, MARCO, CD36.
- Complement Receptors: CR-1, CR3.
- Toll-like receptors
- Intracellular microbial sensors

Pathogen recognition by cells of the innate immune system

Toll is required for anti-fungal responses in *Drosophila*

Toll-like receptors (TLRs) represent an ancient and evolutionary conserved pathogen-recognition system

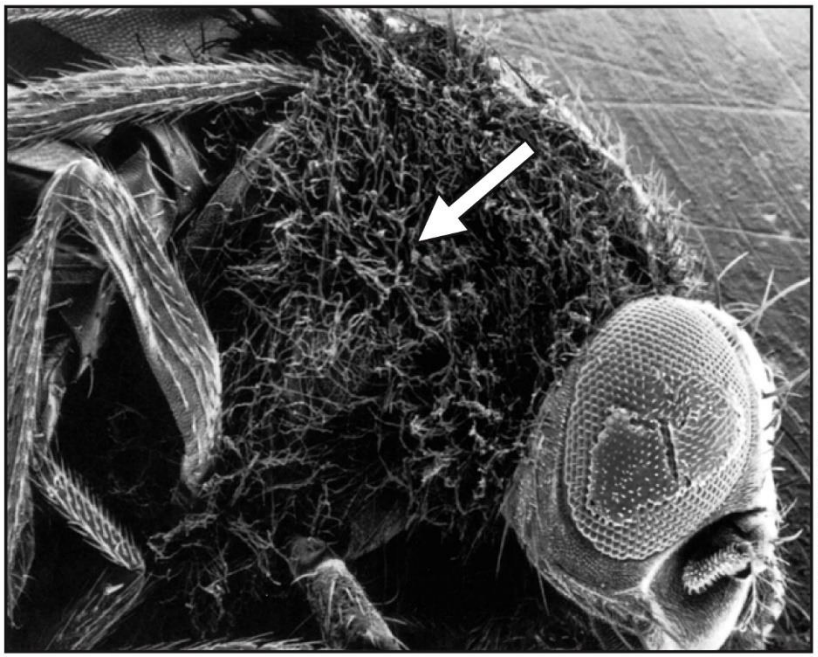
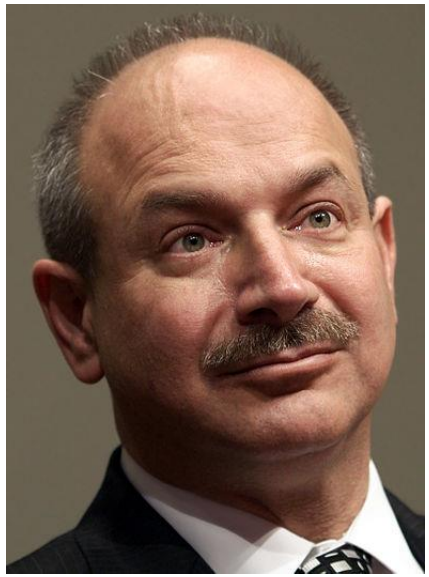


Photo courtesy of J.A. Hoffmann

Cell, 1996

Jules A. Hoffmann



Bruce A. Beutler

2011 Nobel Prize Physiology/Medicine

Mammalian **Toll-like receptors (TLRs)** are activated by many different pathogen-associated molecular patterns

Innate immune recognition by mammalian Toll-like receptors	
Toll-like receptor	**Ligand**
TLR-1:TLR-2 heterodimer	Lipomannans (mycobacteria) Diacyl and triacyl lipopeptides (bacteria) Lipoteichoic acids (Gram-positive bacteria) Cell-wall β-glucans (fungi)
TLR-2:TLR-6 heterodimer	
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)

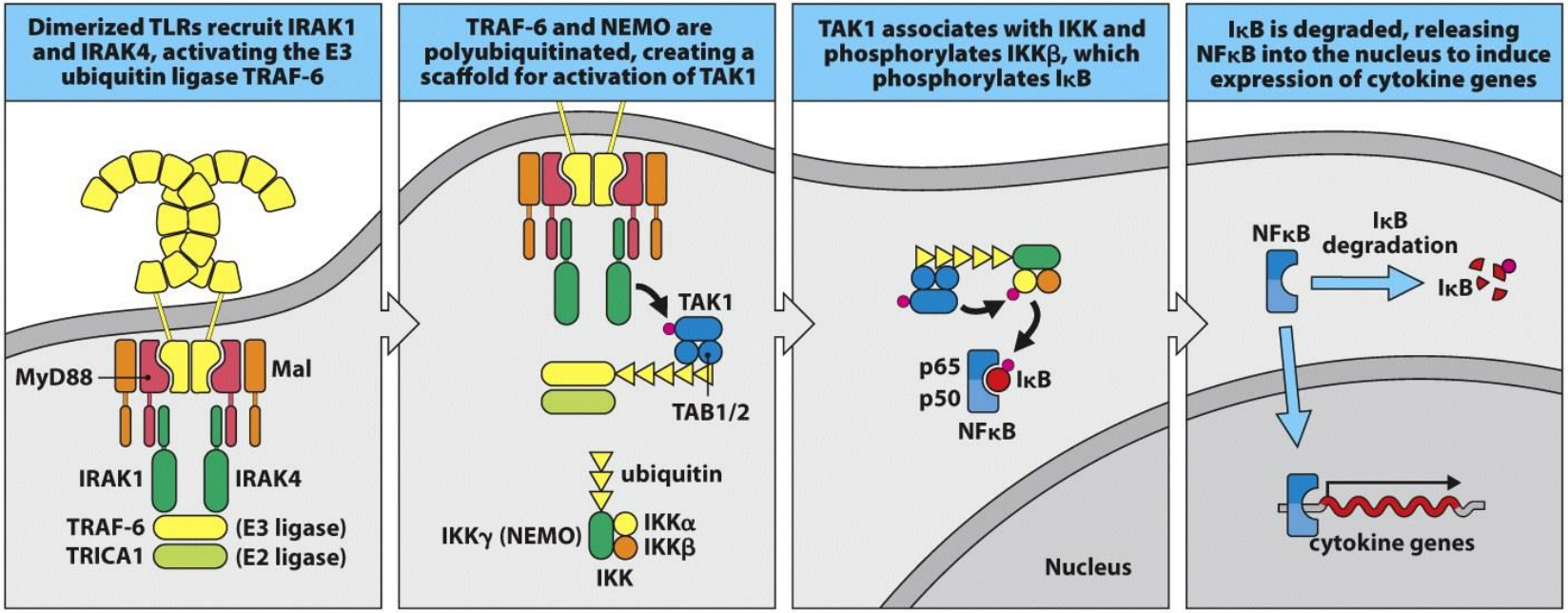
LPS: lipopolysaccharide (only present in Gram-negative bacteria cell wall)

Table 12–2. Examples of Molecular Patterns of Microbes and Pattern Recognition Receptors of Innate Immunity

Molecular pattern of microbe	Source	Pattern recognition receptor of innate immunity	Principal innate immune response
dsRNA	Replicating viruses	Toll-like receptor?	Type I interferon production by infected cells
LPS	Gram-negative bacterial cell wall	Toll-like receptor/CD14	Macrophage activation
Unmethylated CpG nucleotides	Bacterial DNA	Toll-like receptor	Macrophage activation
N-formylmethionyl peptides	Bacterial proteins	*N*-formylmethionyl peptide receptors	Neutrophil and macrophage activation
Mannose-rich glycans	Microbial glycoproteins or glycolipids	1. Macrophage mannose receptor 2. Plasma mannose-binding lectin	1. Phagocytosis 2. Opsonization, complement activation
Phosphorylcholine and related molecules	Microbial membranes	Plasma C-reactive protein	Opsonization, complement activation

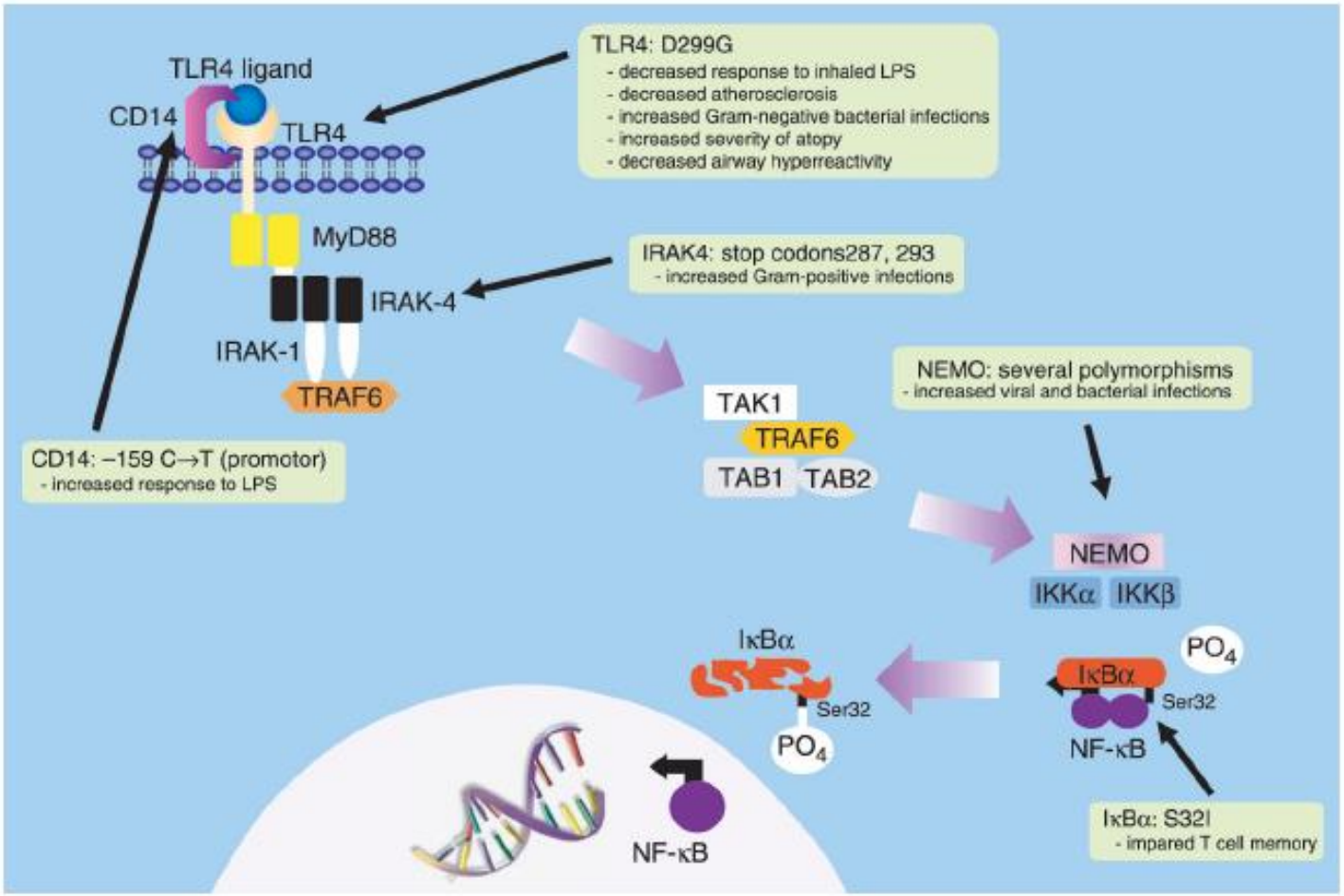
Abbreviations: dsRNA, double-stranded RNA; LPS, lipopolysaccharide.

TLR signaling can activate transcription factors (NFκB, AP-1, IRF) to induce the expression of Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and type I interferons (IFNs)



Adapters: MyD88, MAL, TRIF, TRAM (TIR, Death domains)
Signaling intermediates: IRAK1, IRAK4, TRAF-6, TAK1, TAB1/2 NEMO (IKK), NFκB.
Pro-inflammatory cytokines: Type-I interferons, IL-1, IL-6, TNF-α

TLRs and Human Diseases

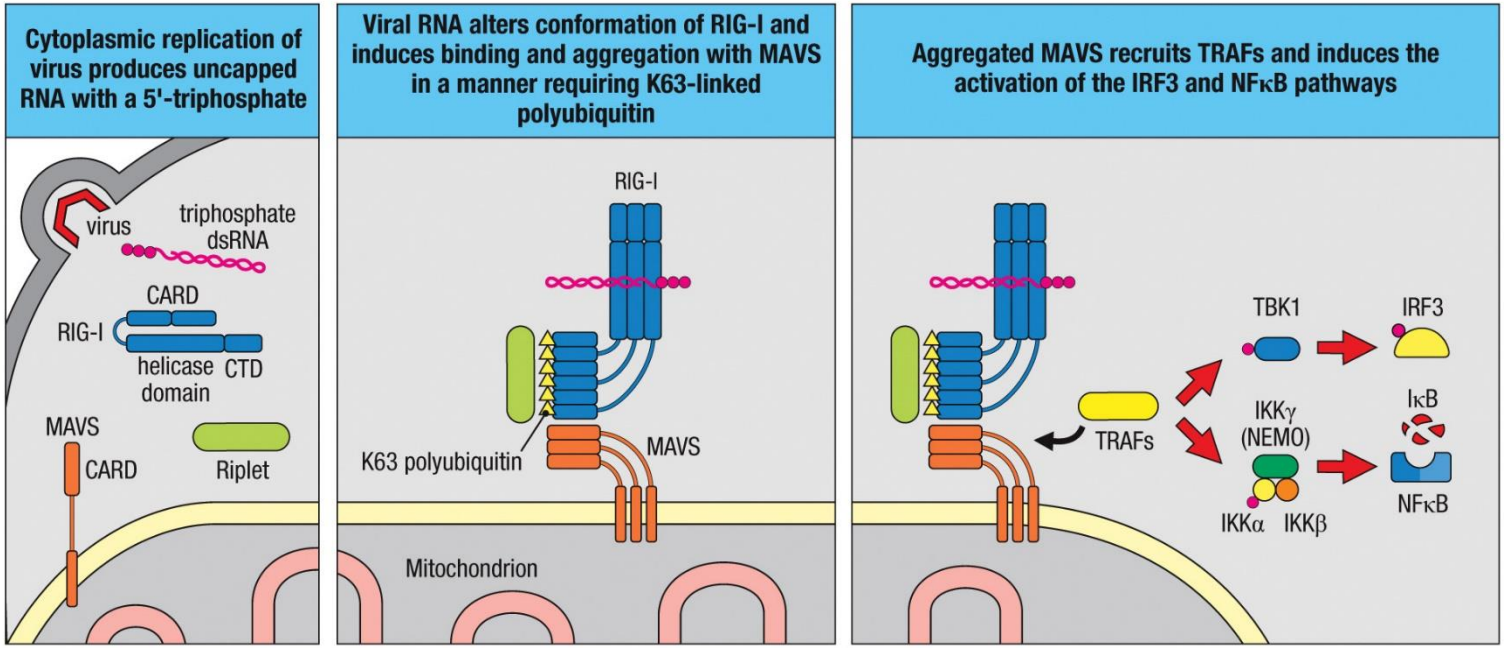


Nat Immunol. 5: 975-979, 2004

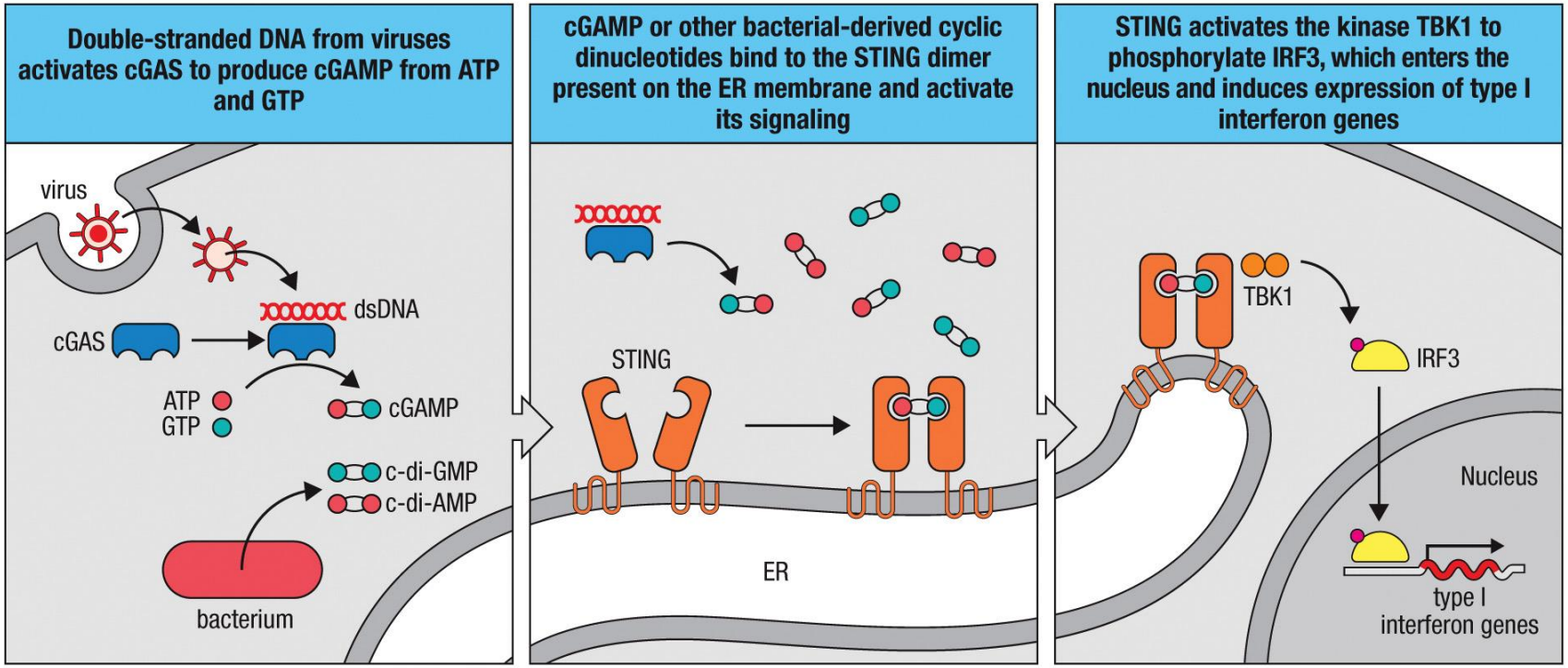
The **RIG-I–like** receptors detect cytoplasmic viral RNAs and activate MAVS to induce **type I interferon** production and pro-inflammatory cytokines

RIG-I: retinoic acid-inducible gene I.
RNA helicase-like domain
and CARD domain.

MDA-5 (helicard): dsRNA.
Type I interferons production.



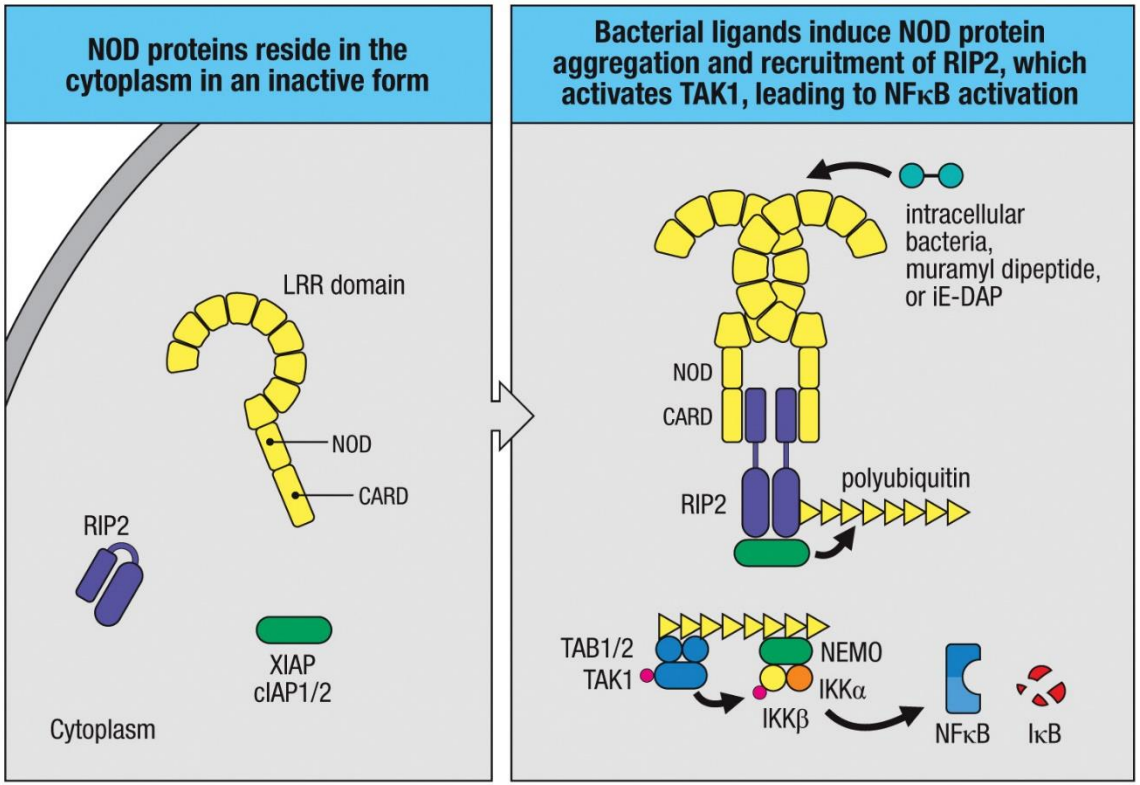
cGAS is a cytosolic sensor of DNA and signals through **STING** to activate type I interferon production



The **NOD-like receptors** (NLRs) act as intracellular sensors of bacterial infection

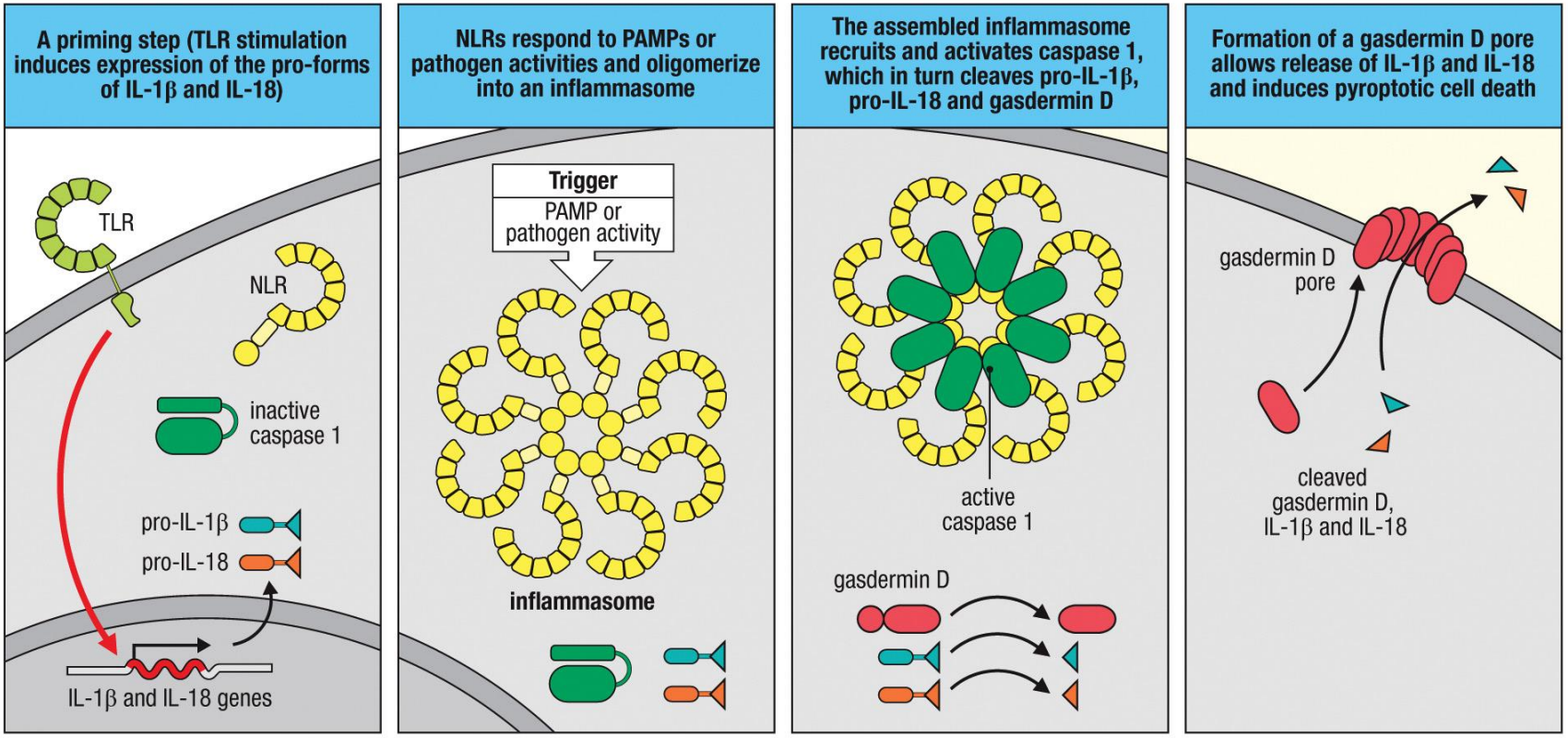
NLRs comprise a large family of intracellular sensors with diverse functions

NOD: Nucleotide-binding oligomerization domain
CARD: caspase recruitment domain. LRRs.
NOD1: iE-DAP (Gram-). NOD2: muramyl dipeptide.
Crohn's disease (NOD2 loss-of-function)
Blau syndrome (Gain-of-function)



Certain NLR proteins react to infection or cellular damage by forming an **inflammasome** that induces cell death and secretion of inflammatory cytokines

NLR, ASC, pro-caspase 1, IL-1β, IL-18, gasdermin D



NALP3 (NLRP3, cryopyrin): pyrin domain (CARD-like domain)
Sensors of cellular stress/damages.
Activation of caspase-1→ Inflammasome → pro-inflammatory Cytokines (IL-1, IL-18).
Gout. Familial cold inflammatory syndrome. Muckle-Wells syndrome

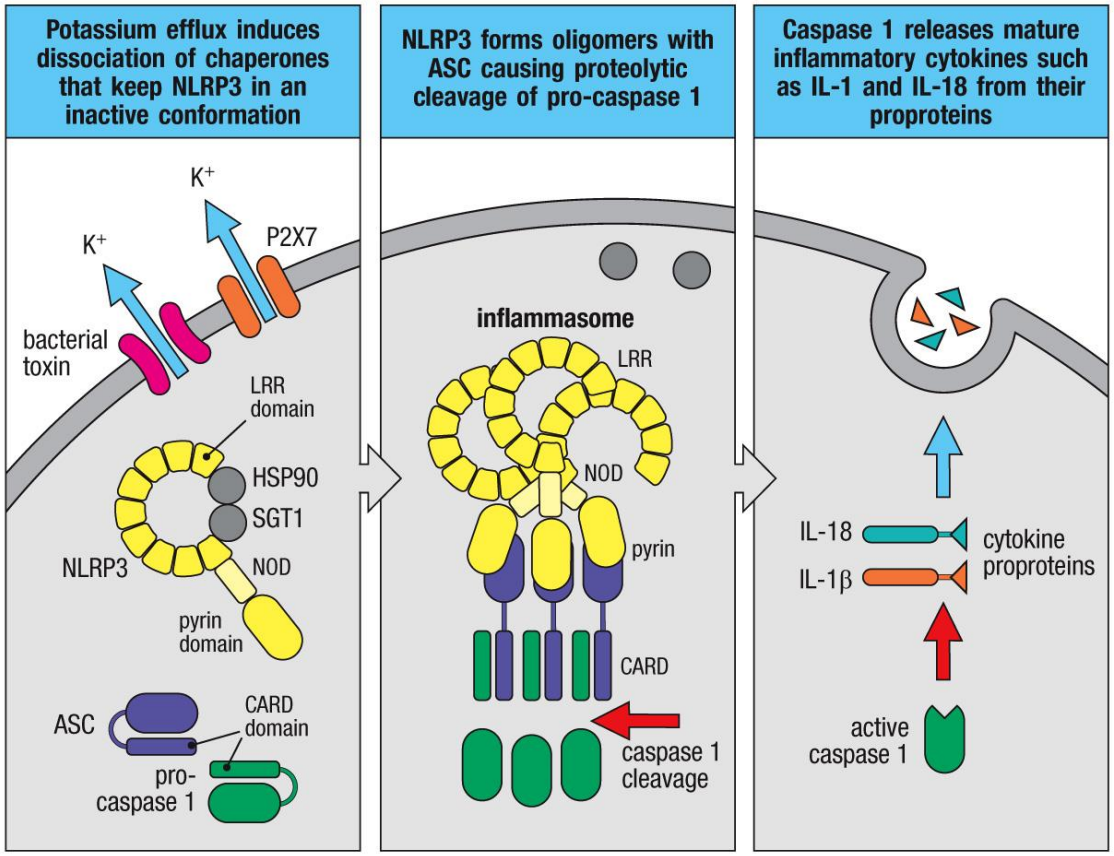
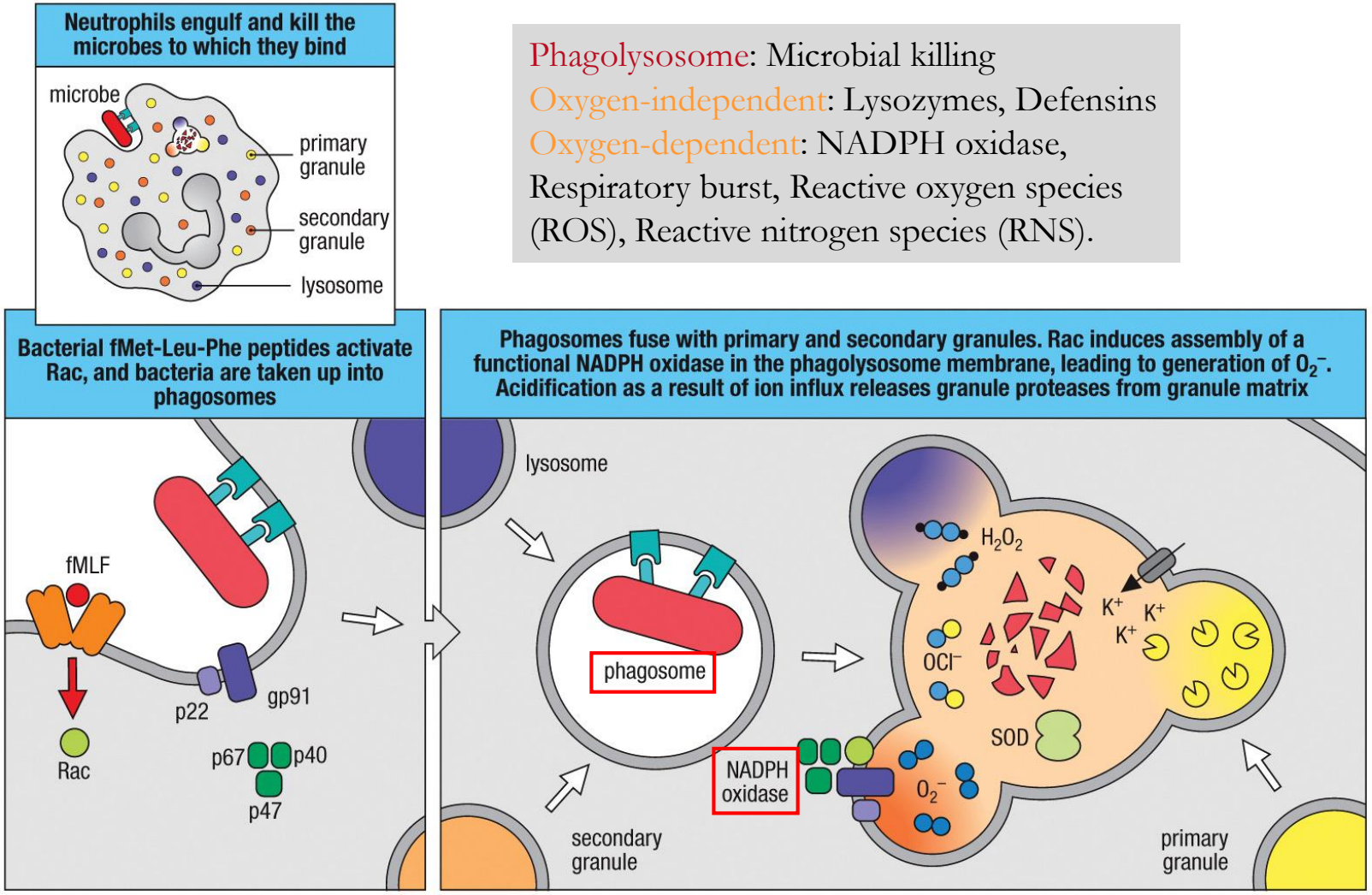


Figure 3.19 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Pathogen recognition by cells of the innate immune system

The microbicidal respiratory burst in phagocytes is initiated by activation-induced assembly of the phagocyte NADPH oxidase

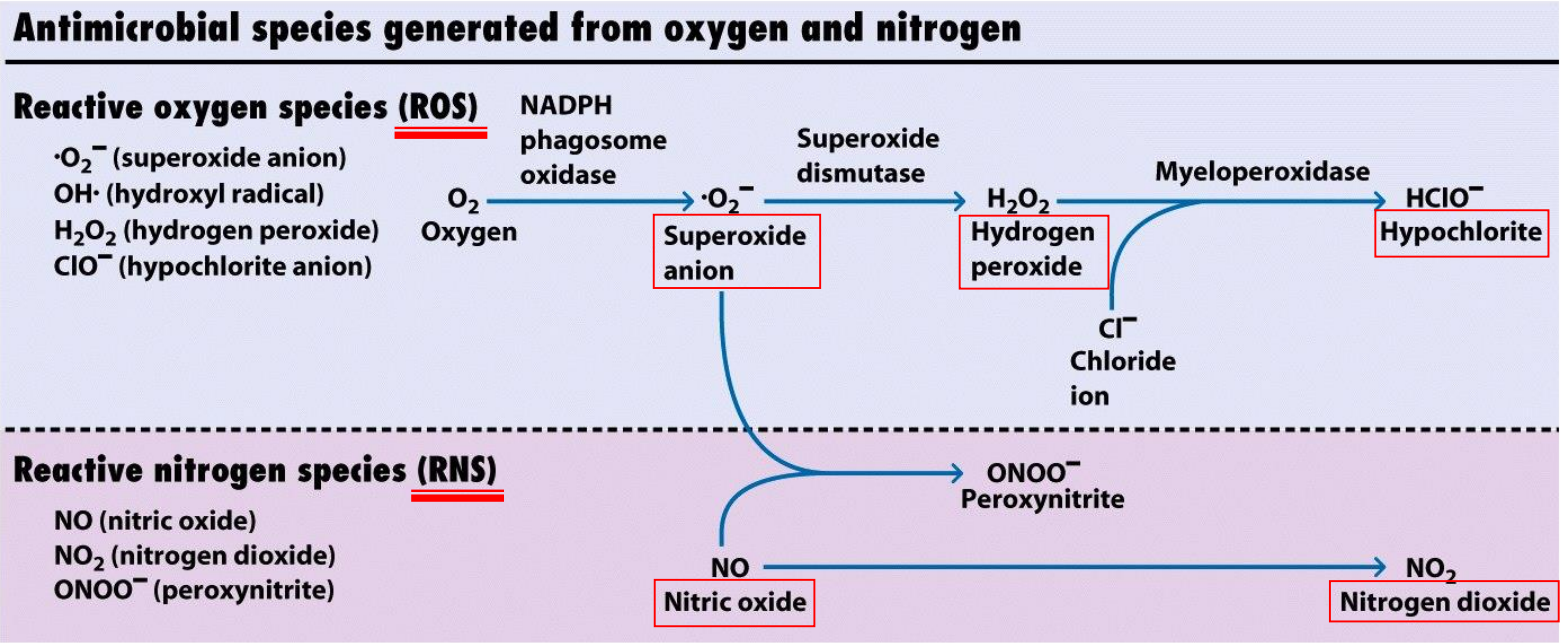
Phagolysosome: Microbial killing
Oxygen-independent: Lysozymes, Defensins
Oxygen-dependent: NADPH oxidase, Respiratory burst, Reactive oxygen species (ROS), Reactive nitrogen species (RNS).



Antimicrobial mechanisms of phagocytes		
Class of mechanism	**Macrophage products**	**Neutrophil products**
Acidification	pH ≈ 3.5–4.0, bacteriostatic or bactericidal	
Toxic oxygen–derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^\bullet$, hydroxyl radical $^\bullet OH$, hypochlorite OCl^-	
Toxic nitrogen oxides	Nitric oxide NO	
Antimicrobial peptides	Cathelicidin, macrophage elastase–derived peptide	α-Defensins (HNP1–4), β-defensin HBD4, cathelicidin, azurocidin, bacterial permeability inducing protein (BPI), lactoferricin
Enzymes	Lysozyme: digests cell walls of some Gram-positive bacteria Acid hydrolases (e.g., elastase and other proteases): break down ingested microbes	
Competitors		Lactoferrin (sequesters Fe^{2+}), vitamin B_{12}–binding protein

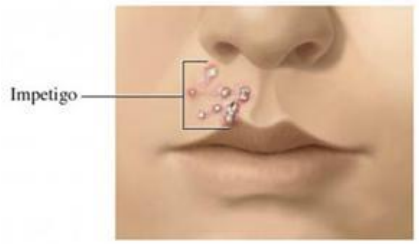
Oxygen-independent

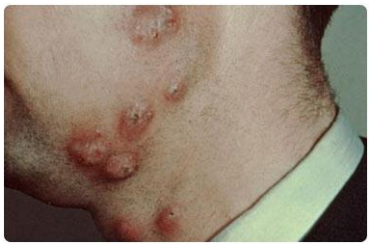
Oxygen-dependent

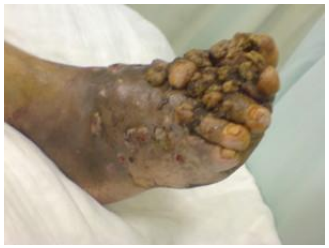


Nitric oxide is produced by nitric oxide synthase, iNOS2. Superoxide is produced by a multicomponent, membrane-associated NADPH oxidase. The activation of NADPH oxidase is accompanied by a transient increase in oxygen consumption (respiratory burst).

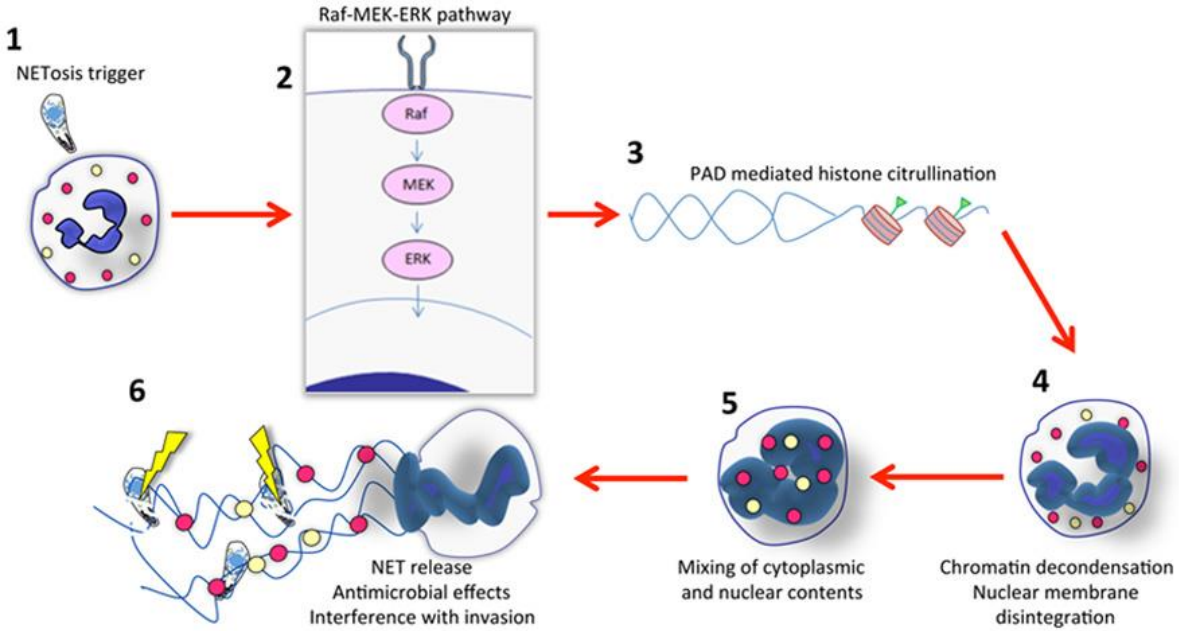
Chronic Granulomatous Disease (CGD). Defects in Cyt gp91^{phox}, Cyt gp67^{phox}, or Cyt gp22^{phox}.







Neutrophil Extracellular Traps (NETs)



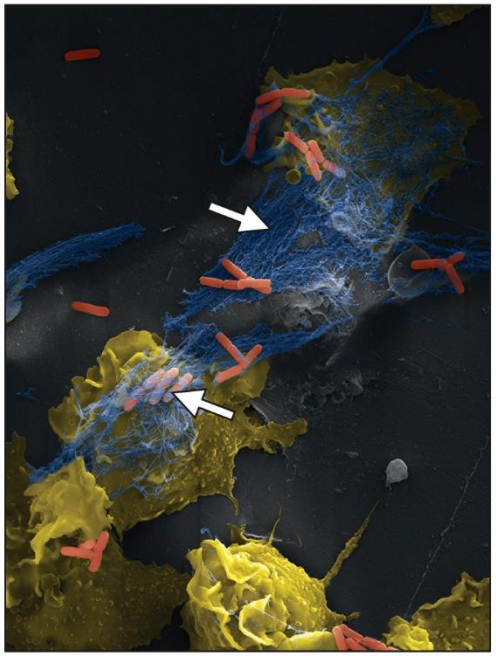
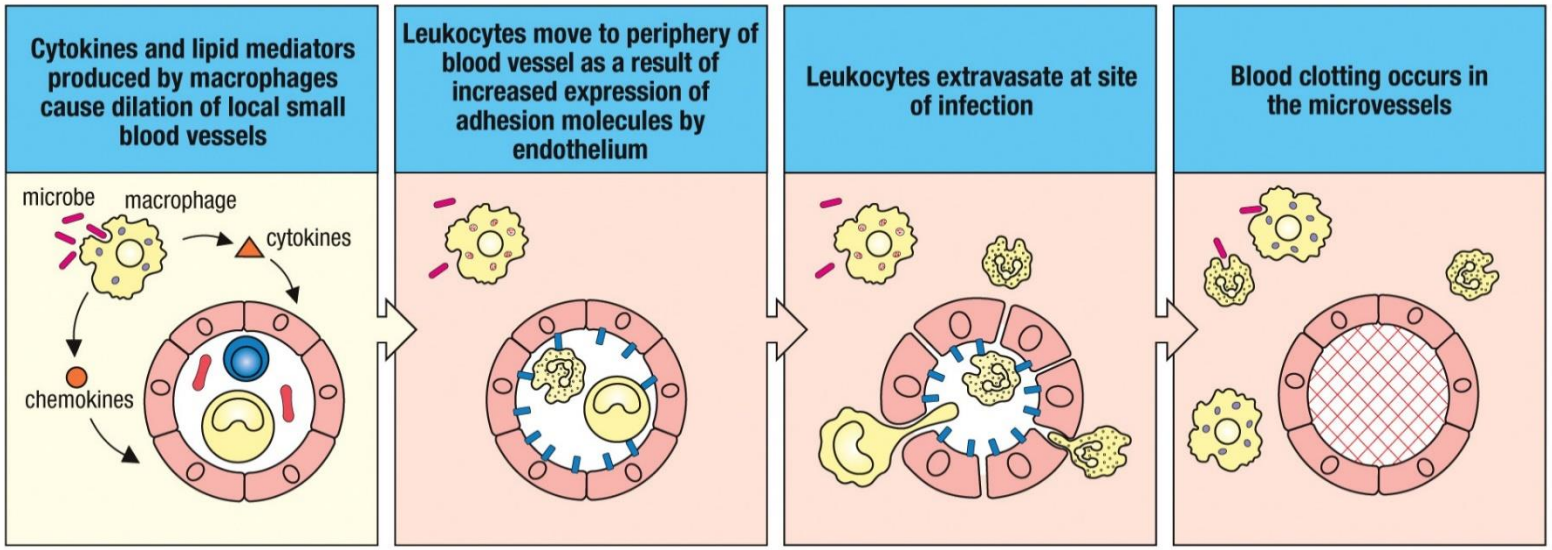


Photo courtesy of Arturo Zychlinsky

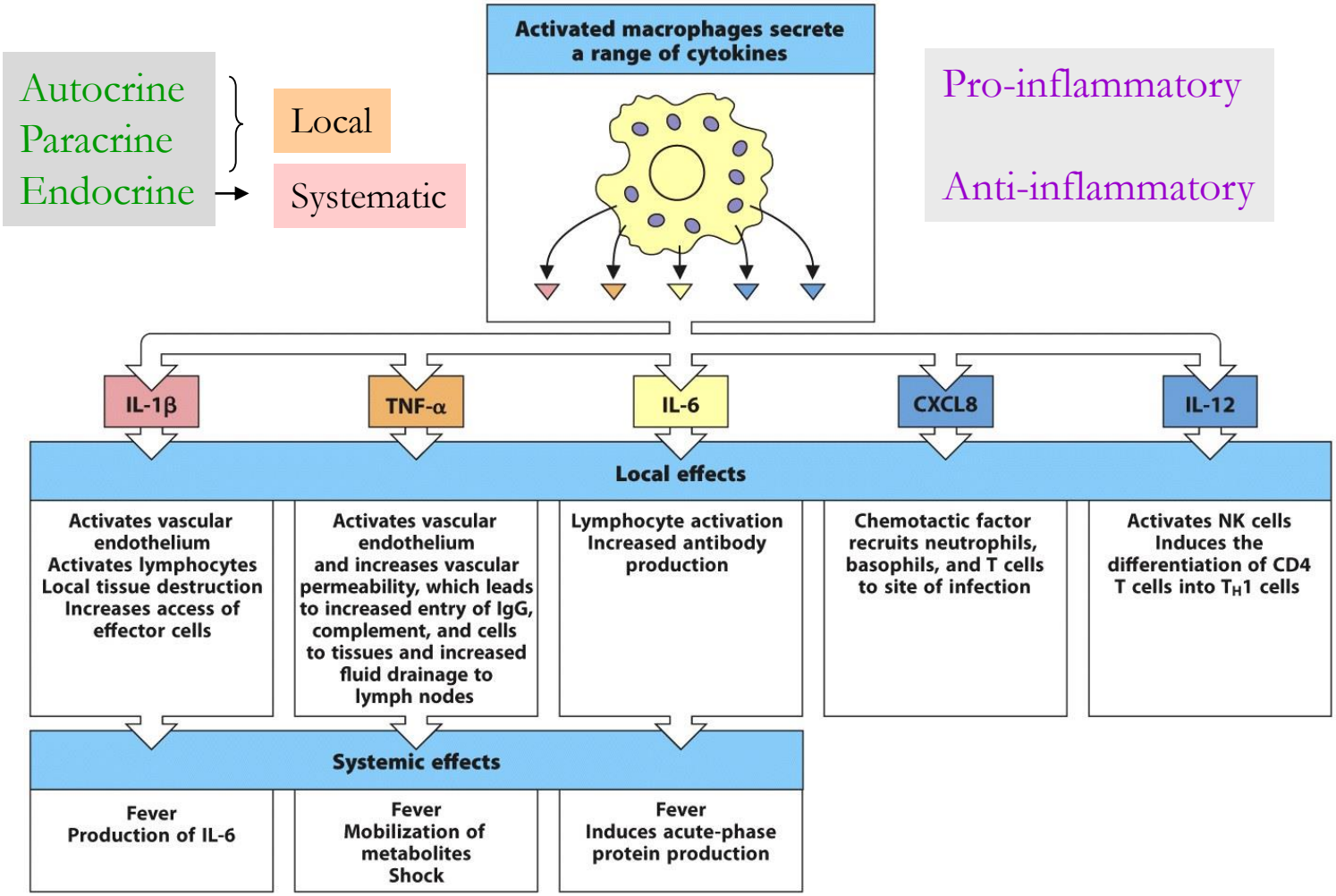
Microbial recognition and tissue damage initiate an **inflammatory response**

Inflammation:
Redness (Rubor), Swelling (Tumor), Heat (Calor), and Pain (Dolor).

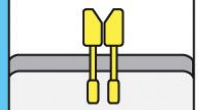
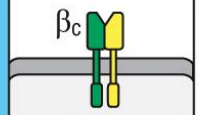
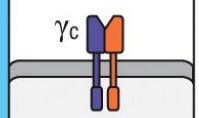
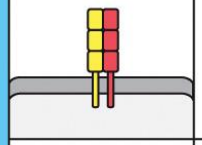
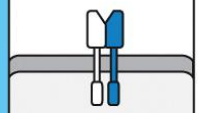
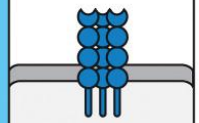
Activated Phagocytes: Cytokines (pro-inflammatory), Chemokines.
Vascular permeability, activation of leukocytes and endothelium, cell adhesion molecules, extravasation, edma, coagulation system.
Prostaglandins, leukotrienes, TNF-α



Macrophages and DCs activated by pathogens secrete a range of **cytokines** that have a variety of local and distant effects



Important cytokine and chemokine receptors in innate immunity

Homodimeric receptors		Receptors for erythropoietin and growth hormone
Heterodimeric receptors with a common chain		Receptors for IL-3, IL-5, GM-CSF share a common chain, CD131 or β_c (common β chain)
		Receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 share a common chain, CD132 or γ_c (common γ chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2Rα (CD25)
Heterodimeric receptors (no common chain)		IL-1 family receptors
		Receptors for IL-13, IFN-α, IFN-β, IFN-γ, IL-10
TNF receptor family		Tumor necrosis factor (TNF) receptors I and II, CD40, Fas (Apo1, CD95), CD30, CD27, nerve growth factor receptor
Chemokine receptor family		CCR1–10, CXCR1–5, XCR1, CX3CR1

2020
TANG PRIZE

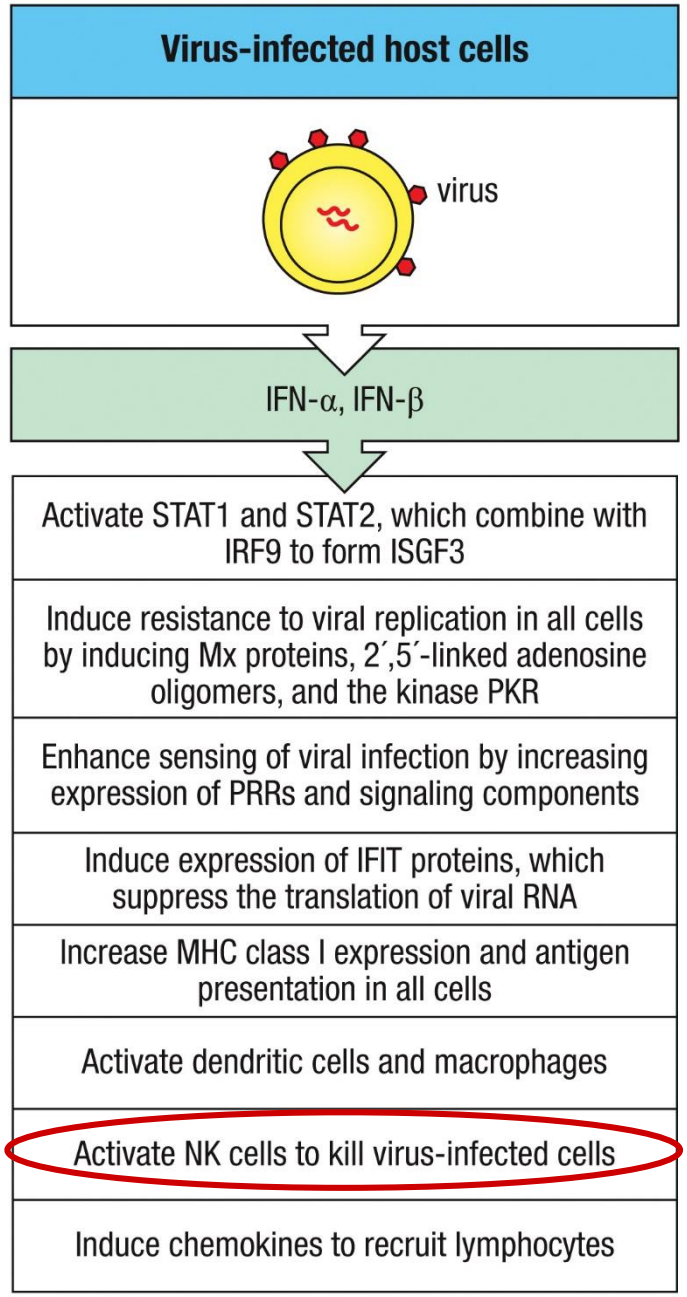
Charles Dinarello/IL-1

Marc Feldman/TNF

Tadamitsu Kishimoto/IL-6

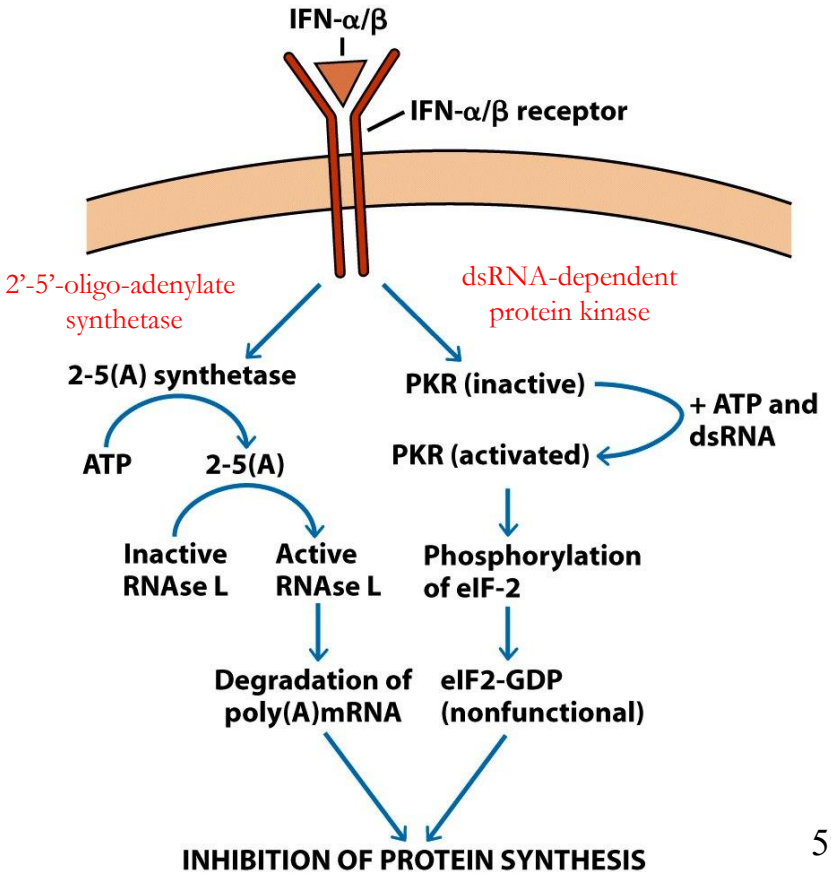
Innate lymphoid cells (**ILCs**) provide protection in early infection

The major categories of innate lymphoid cells (ILCs) and their properties			
Innate lymphoid subgroup	**Inducing cytokines**	**Effector molecules produced**	**Function**
NK cells	IL-12, IL-18, type I IFN	IFN-γ, perforin, granzyme	Immunity against viruses, intracellular pathogens
ILC1	IL-12, IL-18	IFN-γ	Defense against viruses, intracellular pathogens
ILC2	IL-25, IL-33, TSLP	IL-5, IL-13, amphiregulin, IL-4	Expulsion of extracellular parasites, tissue repair
ILC3 (LTi cells)	IL-1β, IL-23	IL-17, IL-22	Immunity to extracellular bacteria



Type I interferons induced by viral infection make several contributions to host defense

Interferons are antiviral proteins produced by cells in response to viral infection



NK cells are activated by interferons and macrophage-derived cytokines for early defense against intracellular infections