Innate Immunity

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Overview of Innate Immunity

The term *innate immunity* refers to defense mechanisms that are always present, ready to combat microbes and other offending agents.

The major components of innate immunity are:

- Surface epithelia
- Tissue sentinel cells
- White blood cells
- Soluble plasma proteins

Introduction

Three phases of the host response to infection, reflects the distinct layers of innate immunity:

Anatomic barriers

Epithelia that line the internal and external surfaces of an organism (intimately linked to preformed effectors).

Preformed effectors

Cells (e.g., phagocytes beneath epithelial layer) and *chemical fluids* (e.g., antimicrobial peptides) acting locally or systemically (e.g., complement system).

Recruitment of effector cells

Involves the recognition of pathogens by PRRs and lead to a local *inflammatory reaction*. Also bridges innate with the adaptive immune system.

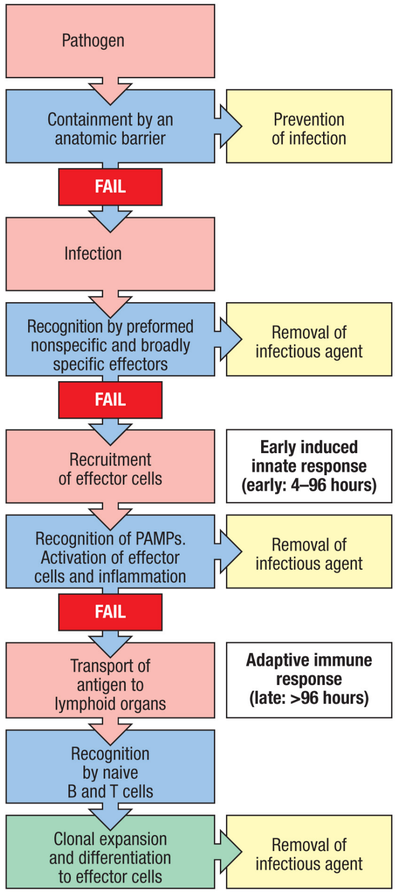


Figure 2.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Pathogen versus microbe

Definition of a **pathogen:** a microorganism that *makes us sick*

➔ has evolved strategies to overcome the body's defense system and thereby cause disease.

Definition of a pathogen linked to the status of an individual's immune system

➔ from the perspective of an individual with a reduced immune system:
more microorganisms can be dangerous
= « *opportunistic* » pathogens

Routes of infection for pathogens				
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**	**Type of pathogen**
Mucosal surfaces				
Mouth and respiratory tract	Inhalation or ingestion of infective material (e.g., saliva droplets)	Measles virus	Measles	Paramyxovirus
		Influenza virus	Influenza	Orthomyxovirus
		Varicella-zoster	Chickenpox	Herpesvirus
		Epstein–Barr virus	Mononucleosis	Herpesvirus
		Streptococcus pyogenes	Tonsillitis	Gram-positive bacterium
		Haemophilus influenzae	Pneumonia, meningitis	Gram-negative bacterium
		Neisseria meningitidis	Meningococcal meningitis	Gram-negative bacterium
	Spores	*Bacillus anthracis*	Inhalation anthrax	Gram-positive bacterium
Gastrointestinal tract	Contaminated water or food	Rotavirus	Diarrhea	Rotavirus
		Hepatitis A	Jaundice	Picornavirus
		Salmonella enteritidis, S. typhimurium	Food poisoning	Gram-negative bacterium
		Vibrio cholerae	Cholera	Gram-negative bacterium
		Salmonella typhi	Typhoid fever	Gram-negative bacterium
		Trichuris trichiura	Trichuriasis	Helminth
Reproductive tract and other routes	Sexual transmission/ infected blood	Hepatitis B virus	Hepatitis B	Hepadnavirus
		Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Retrovirus
	Sexual transmission	*Neisseria gonorrhoeae*	Gonorrhea	Gram-negative bacterium
		Treponema pallidum	Syphilis	Bacterium (spirochete)
Opportunistic infections	Resident microbiota	*Candida albicans*	Candidiasis, thrush	Fungus
	Resident lung microbiota	*Pneumocystis jirovecii*	Pneumonia	Fungus
External epithelia				
External surface	Physical contact	*Trichophyton*	Athlete's foot	Fungus
Wounds and abrasions	Minor skin abrasions	*Bacillus anthracis*	Cutaneous anthrax	Gram-positive bacterium
	Puncture wounds	*Clostridium tetani*	Tetanus	Gram-positive bacterium
	Handling infected animals	*Francisella tularensis*	Tularemia	Gram-negative bacterium
Insect bites	Mosquito bites (*Aedes aegypti*)	Flavivirus	Yellow fever	Virus
	Deer tick bites	*Borrelia burgdorferi*	Lyme disease	Bacterium (spirochete)
	Mosquito bites (*Anopheles*)	*Plasmodium* spp.	Malaria	Protozoan

Replication of living agent in their hosts that causes infection

Means to cause disease

- *Exotoxin production*: secreted toxins from pathogens
- *Endotoxin production*: tissue damage by non-secreted constituents of pathogens - LPS - via the host
- *Direct cytopathic effect*
- Indirectly via *immune-mediated tissue damage*

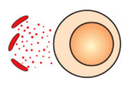
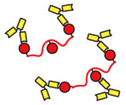
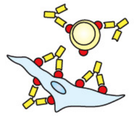
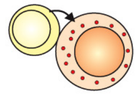
	Direct mechanisms of tissue damage by pathogens			Indirect mechanisms of tissue damage by pathogens		
	Exotoxin production	Endotoxin	Direct cytopathic effect	Immune complexes	Anti-host antibody	Cell-mediated immunity
Pathogenic mechanism						
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridium tetani* *Vibrio cholerae*	*Escherichia coli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)	Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*	Lymphocytic choriomeningitis virus Herpes simplex virus *Mycobacterium tuberculosis* *Mycobacterium leprae* *Borrelia burgdorferi* *Schistosoma mansoni*
Disease	Tonsillitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid fever Bacillarydysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles, subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma	Kidney disease Vascular deposits Glomerulonephritis Kidney damage in secondary syphilis Transient renal deposits	Rheumatic fever Hemolytic anemia	Aseptic meningitis Herpes stromal keratitis Tuberculosis Tuberculoid leprosy Lyme arthritis Schistosomiasis

Figure 2.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Overcoming innate host defenses to establish disease

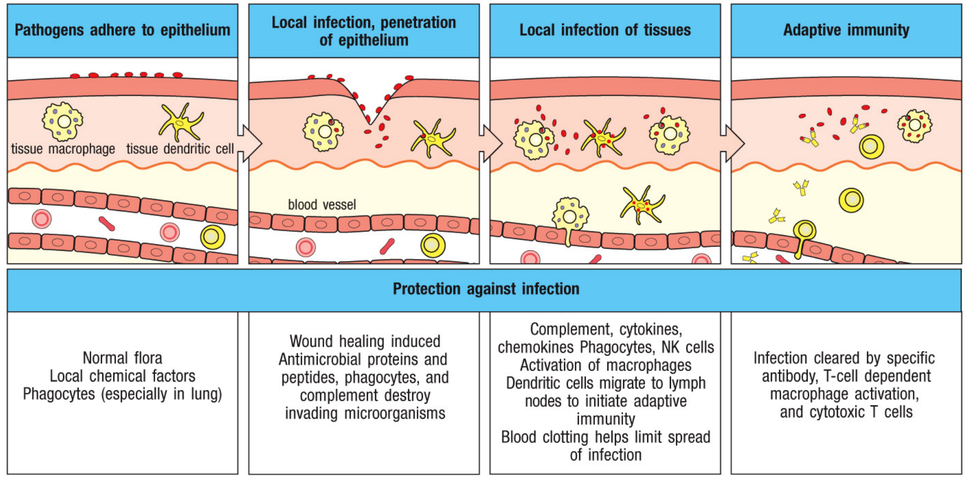
Checkpoints that microbes must overcome to cause disease

- ☑ Attachment of pathogen to epithelium
- ☑ Crossing the epithelium (burns, wounds, insect bites can facilitate this step)
- ☑ Overcoming immediate defense mechanisms (e.g., resistance to chemical destruction)

➔ Pathogenic bacteria distinguished from others by their ability to having evolved special adaptions strategies that evade innate immune mechanisms

1st happening in a tissue:

local infection focus from where the pathogen further spread



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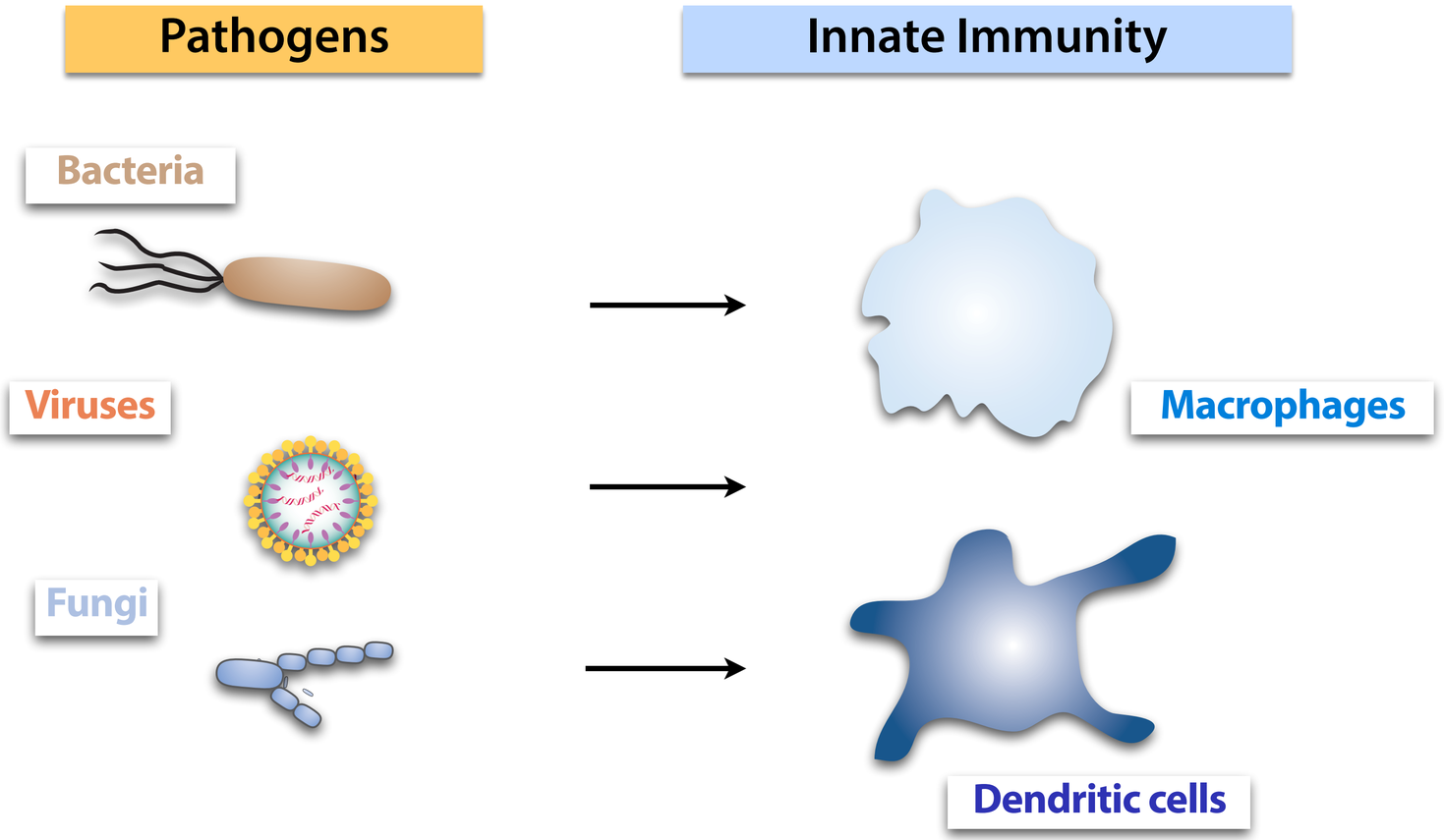
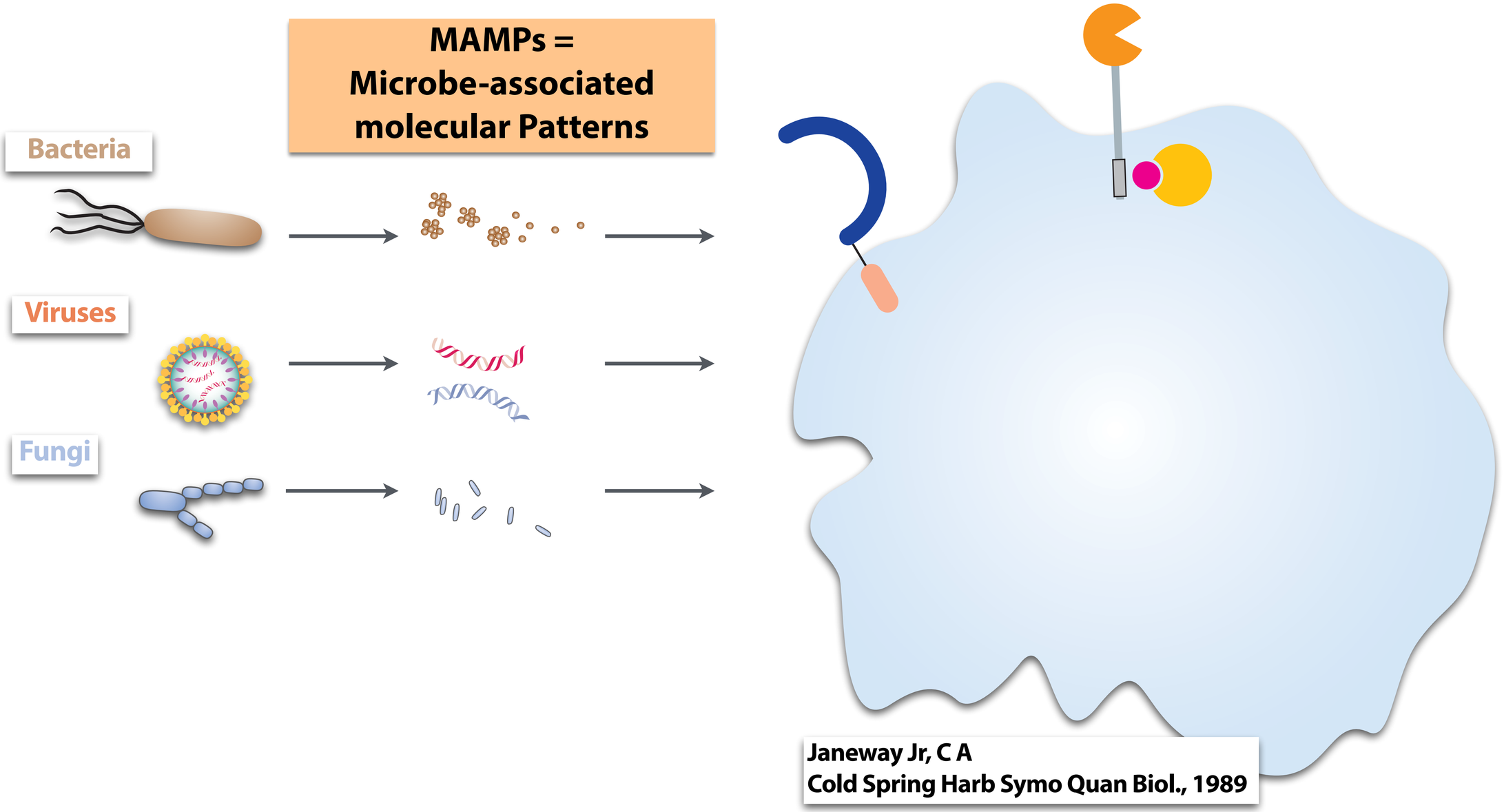
Innate Immune Recognition of Pathogens

Pattern recognition receptors



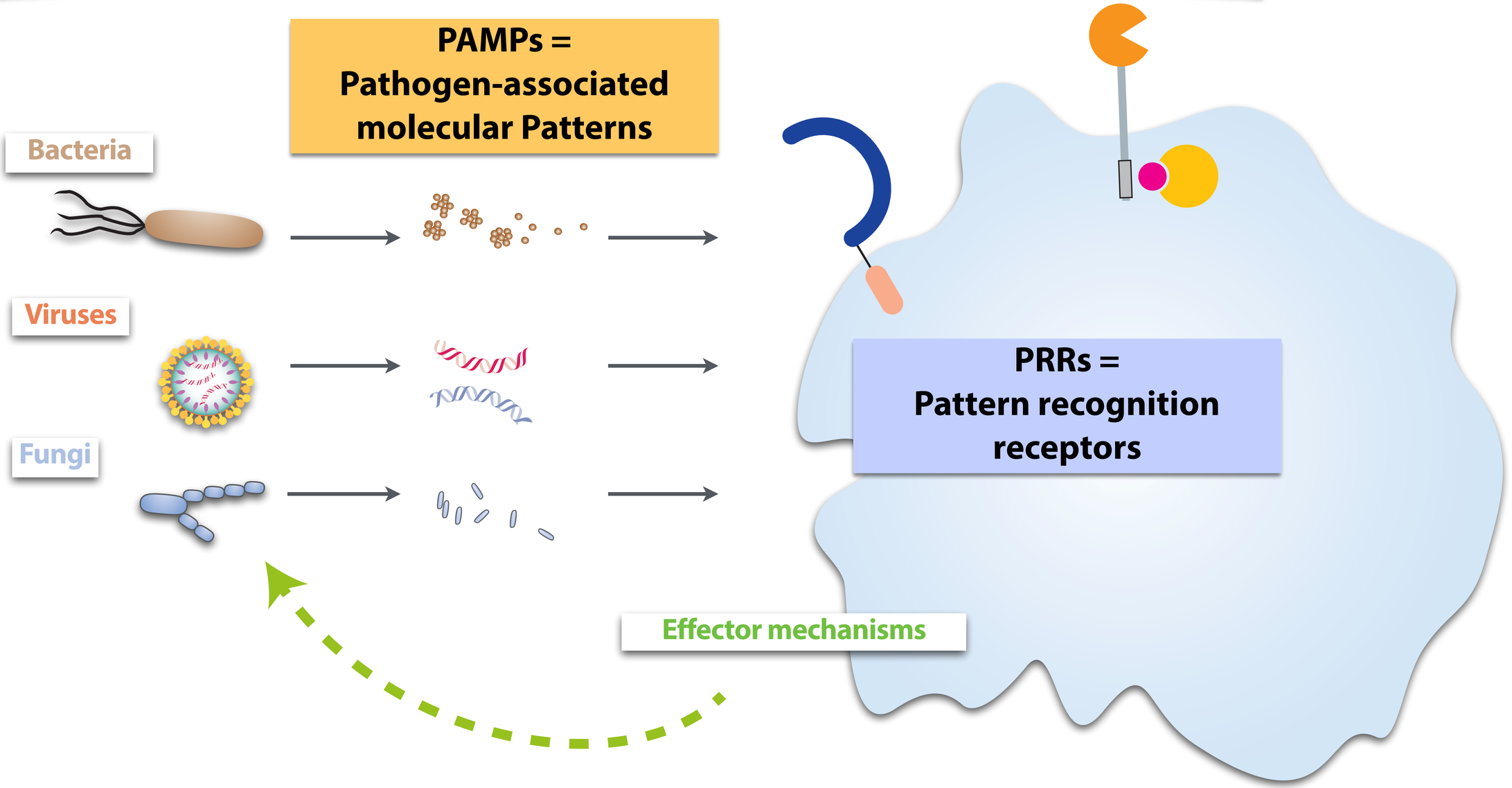
Pattern recognition receptors

MAMPs =
Microbe-associated molecular Patterns

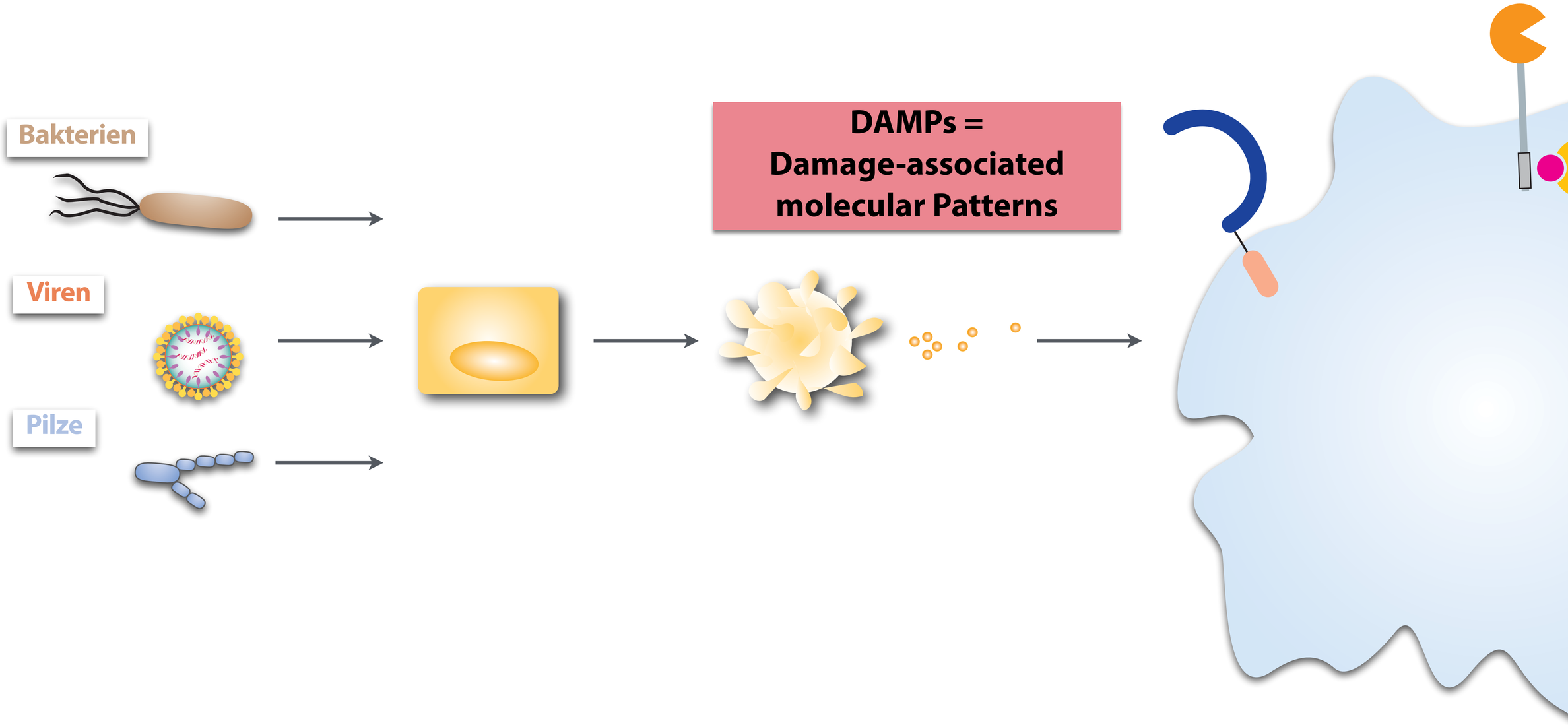


Janeway Jr, C A
Cold Spring Harb Symo Quan Biol., 1989

Pattern recognition receptors



Pattern recognition receptors



Principles of innate immune recognition (1)

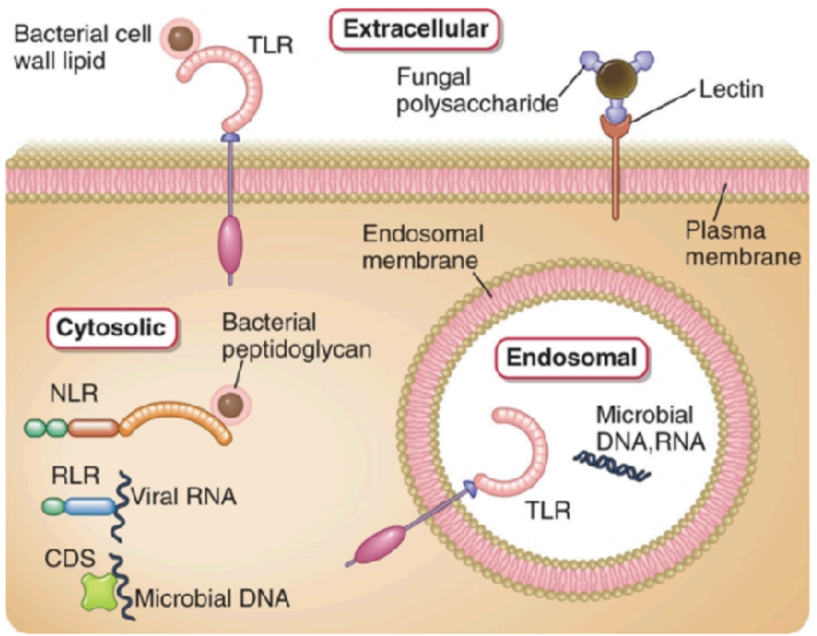
- The innate immune system recognizes microbial products that are often <u>essential</u> for survival of the microbes.
- The innate immune system also recognizes endogenous molecules that are produced by or released from damaged and dying cells.

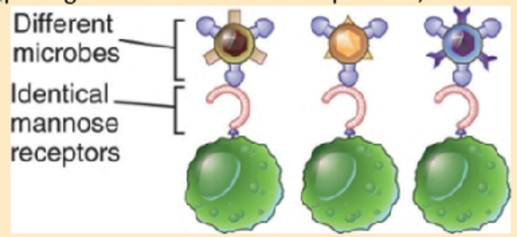
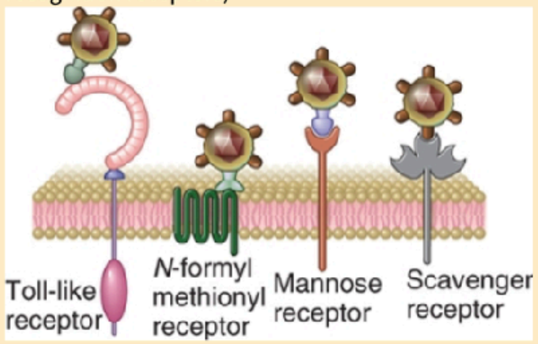
		Microbe Type
Pathogen-Associated Molecular Patterns		
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	—
Crystals	Monosodium urate	—
Proteolytically cleaved extracellular matrix	Proteoglycan peptides	—
Mitochondria and mitochondrial components	Formylated peptides and ATP	—
Nuclear proteins	HMGB1, histones	—

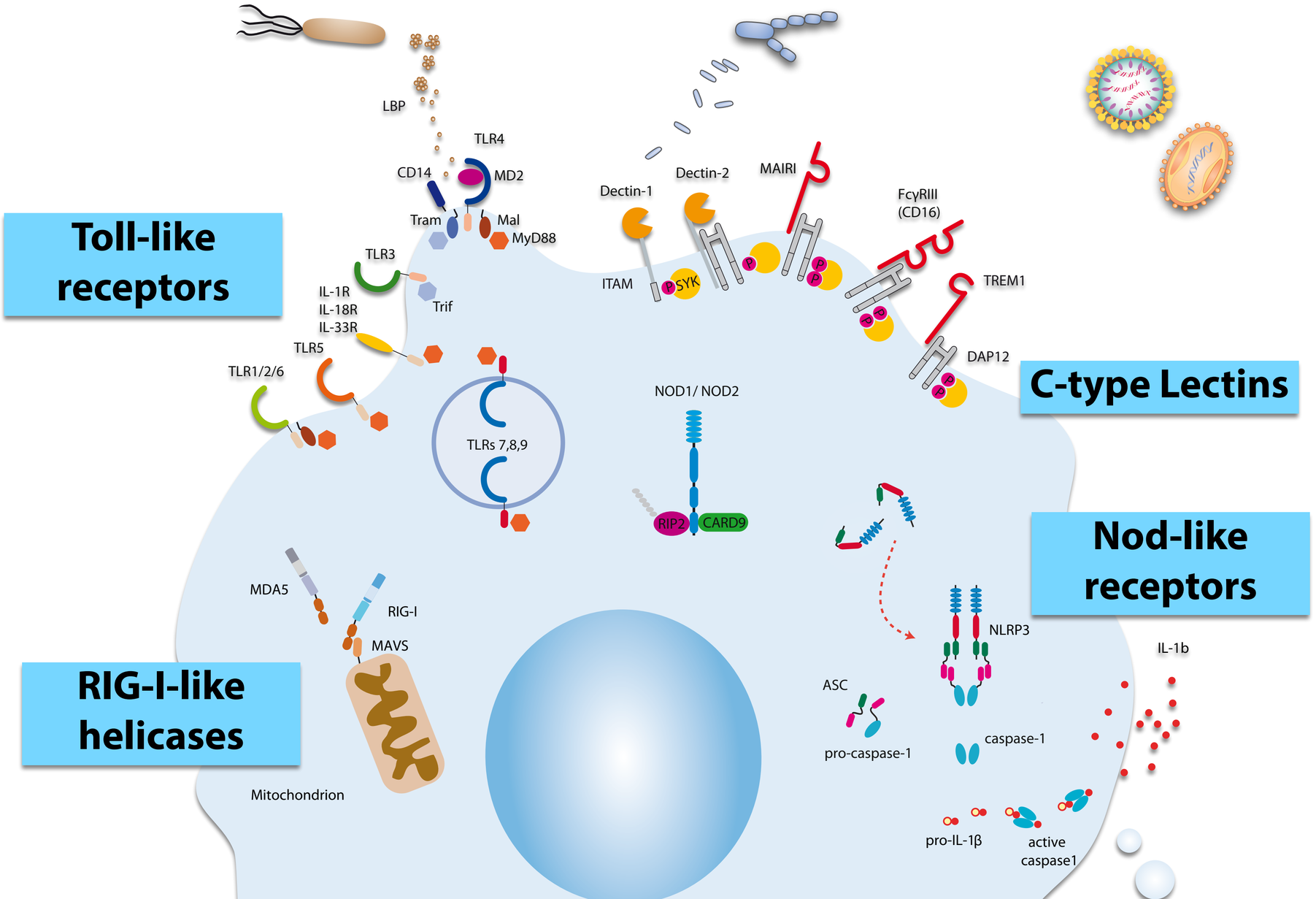
ATP, Adenosine triphosphate; *CpG*, cytosine-guanine–rich oligonucleotide; *dsRNA*, double-stranded RNA; *HMGB1*, high-mobility group box 1; *HSP*, heat shock protein; *LPS*, lipopolysaccharide; *ssRNA*, single-stranded RNA.

Principles of innate immune recognition (2)

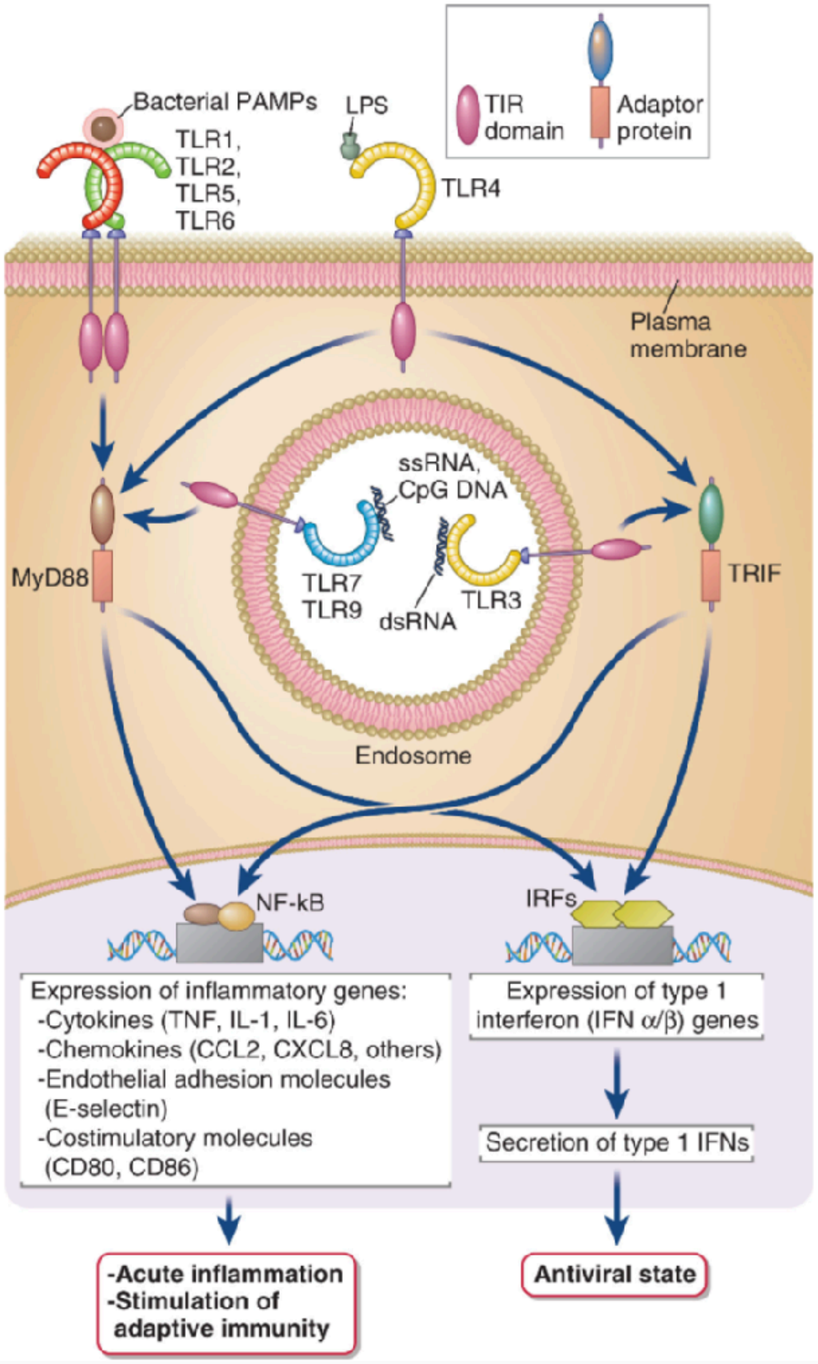
- The innate immune system uses **several types of cellular receptors**, present in different locations in cells, and soluble molecules in the blood and mucosal secretions, to recognize PAMPs and DAMPs.
- The receptors of the innate immune system are encoded by inherited (**germline**) genes, whereas the genes encoding receptors of adaptive immunity are generated by somatic recombination of gene segments in the precursors of mature lymphocytes.
- The innate immune system does not react against normal, healthy cells and tissues.



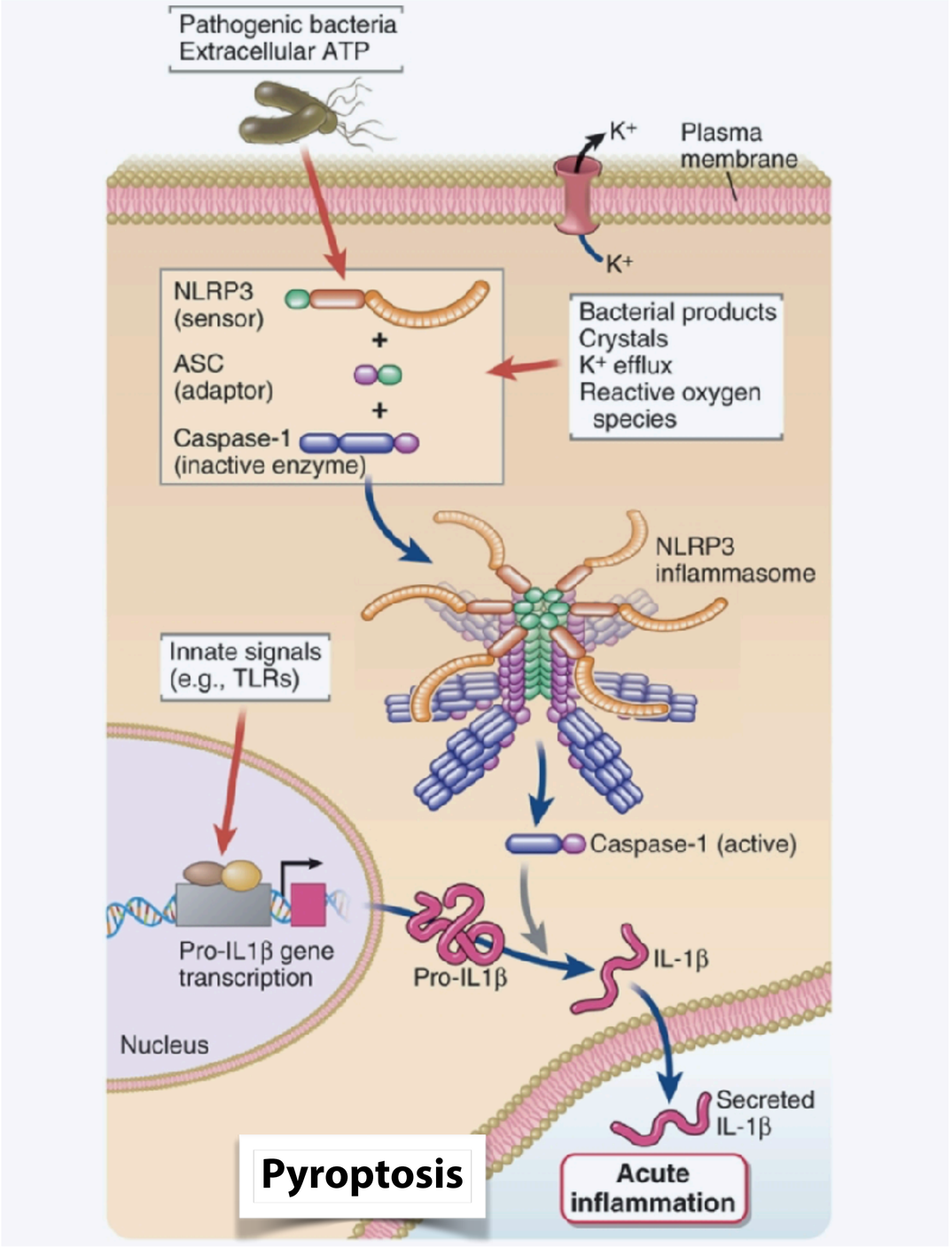
	Innate Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) 
Number of microbial molecules recognized	About 1000 molecular patterns (estimated)
Receptors	Encoded in germline; limited diversity (pattern recognition receptors) 
Number and types of receptors	<100 different types of invariant receptors
Distribution of receptors	Nonclonal: Identical receptors on all cells of the same lineage
Genes encoding receptors	Germline encoded, in all cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions


Toll-like receptors
LBP
TLR4
CD14
MD2
Tram
Mal
MyD88
TLR3
Trif
IL-1R
IL-18R
IL-33R
TLR5
TLR1/2/6
TLRs 7,8,9
Dectin-1
Dectin-2
MAIRI
ITAM
SYK
FcγRIII
(CD16)
TREM1
DAP12
C-type Lectins
NOD1/ NOD2
RIP2
CARD9
Nod-like receptors
NLRP3
ASC
pro-caspase-1
caspase-1
IL-1b
pro-IL-1β
active
caspase1
MDA5
RIG-I
MAVS
Mitochondrion
RIG-I-like helicases

Toll-like receptors

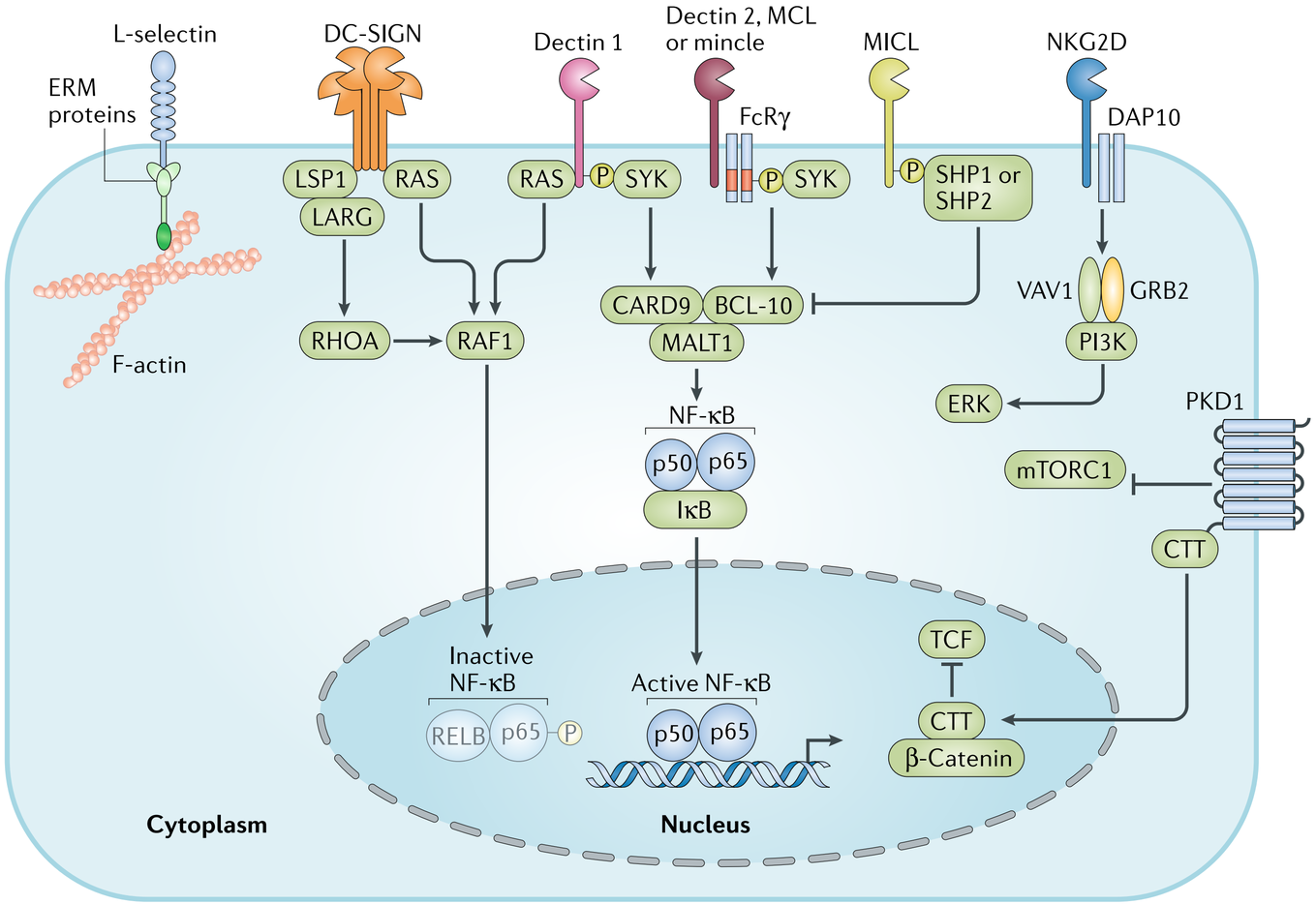


The inflammasome

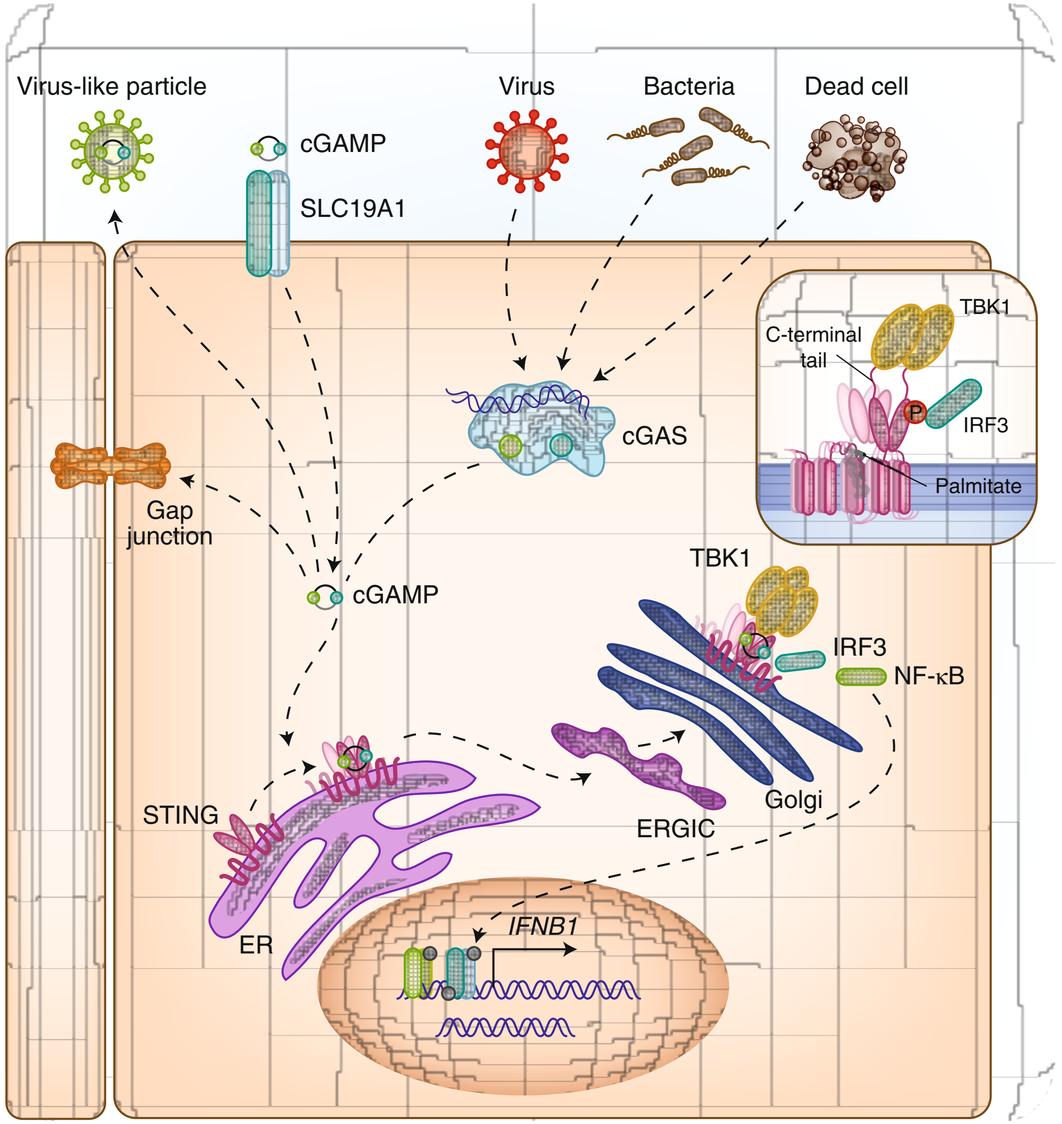


The C-type lectins

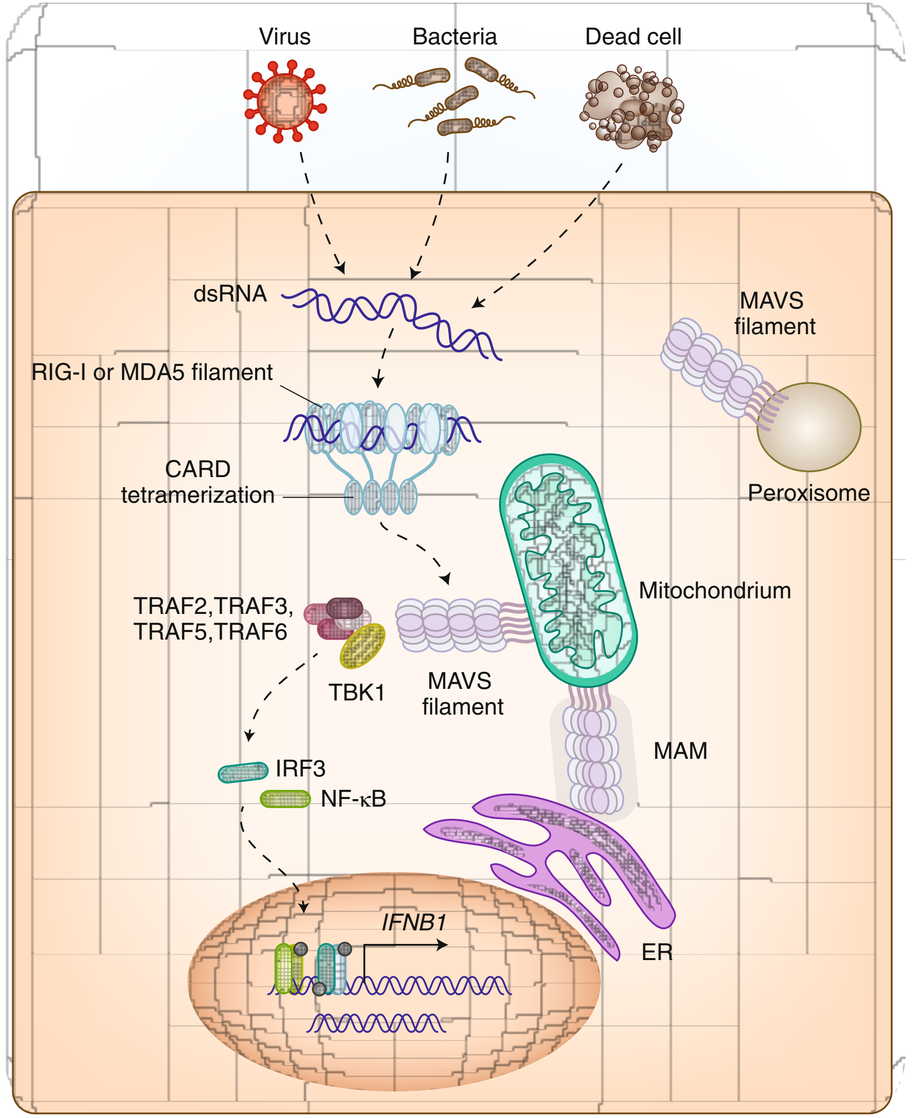
Bind carbohydrates in a Ca^{++} dependent manner



Cytosolic DNA sensors



Cytosolic RNA sensors



Cellular components of the innate immune system

Epithelial surfaces: the first line of defense

Three categories of antimicrobial functions of epithelia

1) **Mechanical / Physical**

- *Tight junctions*
- Production of *mucus*, composed of glycoproteins called mucins, that prevents the adhesion of pathogen to epithelial surface

defect in mucus production: cystic fibrosis

- *Peristalsis* (e.g., in the gut)

2) **Chemical**

3) **Microbiological**
(commensal bacteria / microbiota)

- Production of *antimicrobial substance*
(e.g., lactic acid by some lactobacilli)
- Induction of *responses*
(e.g., antimicrobial peptide production)

	Skin	Gut	Lungs	Eyes/nose/oral cavity
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			

Figure 2.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Antimicrobial proteins

Different antimicrobial proteins are produced by *epithelial cells and phagocytes*.

General substances: acid pH (stomach), digestive enzyme, bile, fatty acids

Antibacterial enzymes:

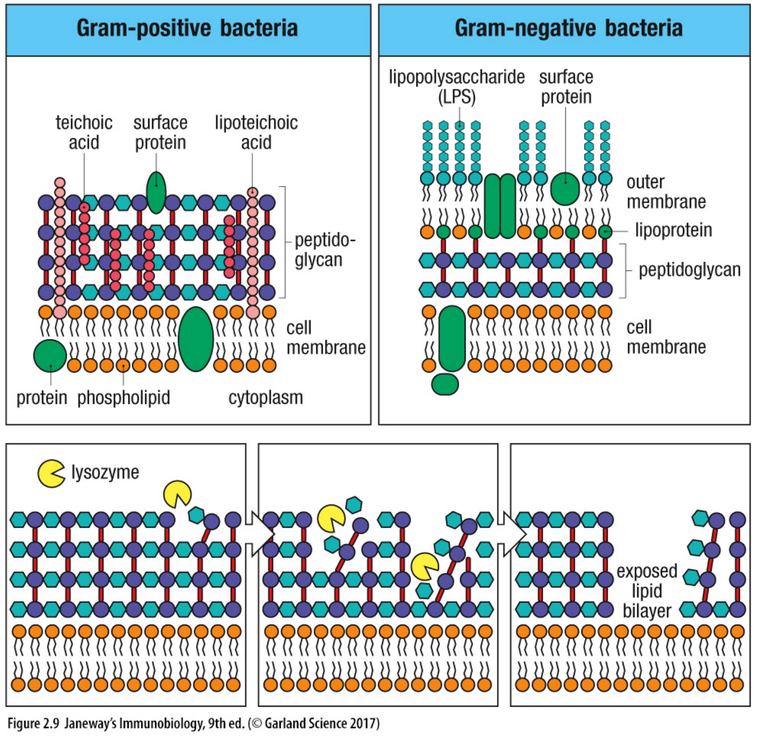
1) Lysozyme

- Secreted in tears, saliva and by phagocytes and Paneth cells
- Selectively cleaves *peptidoglycan*

  ➔ More effective against Gram-positive bacteria

2) Secretory phospholipase A_2

- Basic enzyme
- enters bacterial cell walls to cleave *phospholipids*



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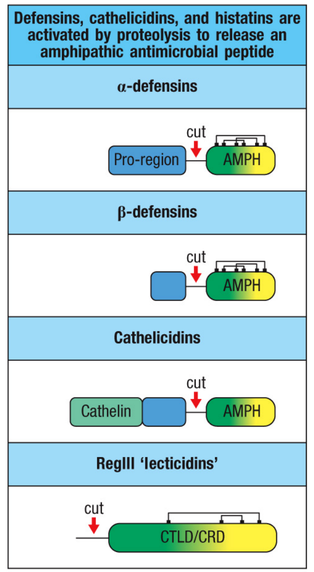
Antimicrobial peptides

Antimicrobial peptides: huge class of evolutionary highly conserved substances (conserved in plants, drosophila), classified in 3 major types ➔ *defensins, cathelicidins, histatins*

- Short cationic peptides, which derive from an inactive propeptide through being processed by cellular proteases
- Common *amphipathic* structure (two separate regions: one positively charged, the other hydrophobic) ➔ functionally important!
- Act within minutes to disrupt the membrane of bacteria, fungi and also certain viruses involving the formation of a *membrane pore*



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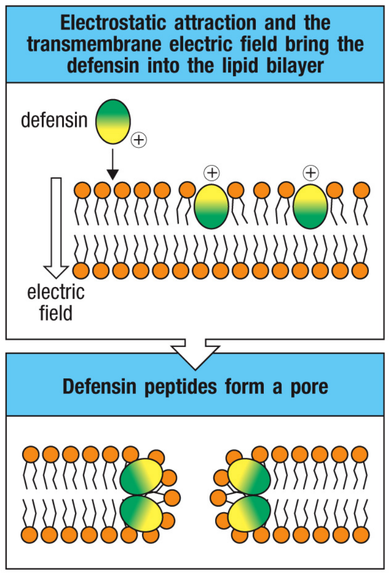
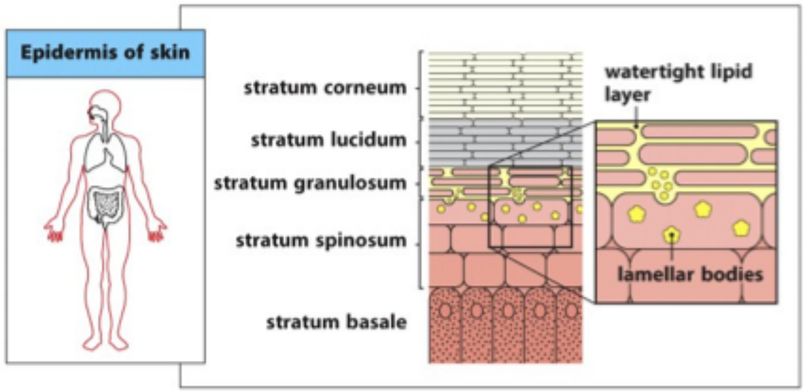
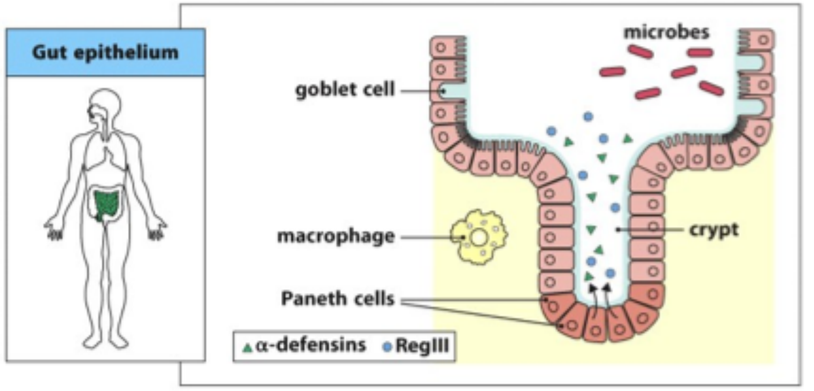


Figure 2.10 (part 2 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Antimicrobial peptides storage

Neutrophils store α-defensins in primary granules, which can fuse with phagosomes
Paneth cells constantly secret crypticidins (processed by trypsin)
β-defensins produced in response to certain stimuli or can be stored in *lamellar bodies* of kerationcytes or type II pneumocytes in the lung



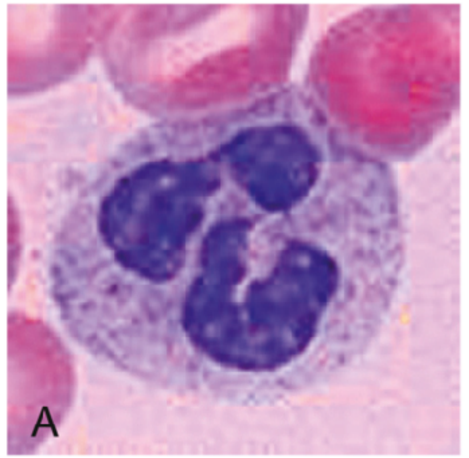


Phagocytes (1)

Phagocytes, including neutrophils and macrophages, are cells whose primary function is to ingest and destroy microbes and remove damaged tissues.

Neutrophils (polymorphonuclear leukocytes (PMNs)):

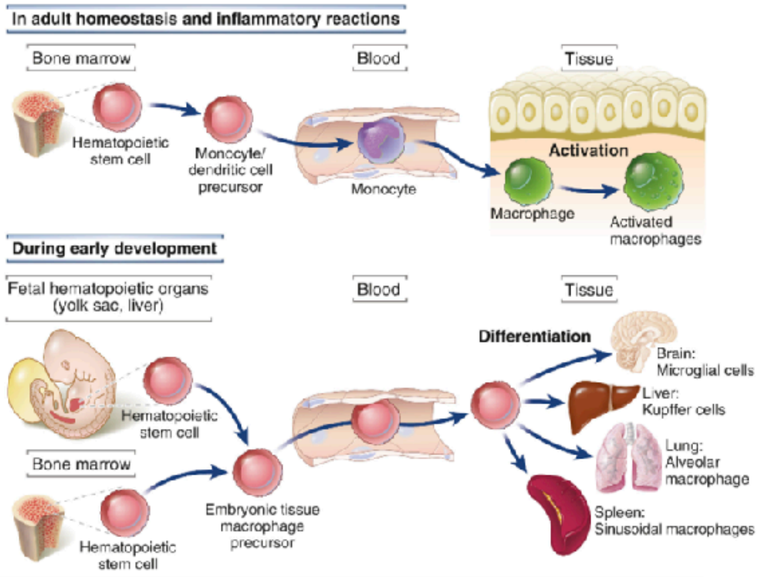
- produced in the bone marrow
- most abundant population of circulating white blood cells (more than 1×10^{11} neutrophils per day produced in an adult)
- contains two types of membrane-bound granules
- principal cell type in acute inflammatory reactions
- major function: phagocytose microbes and destroy these in phagolysosomes, killing of extracellular microbes through release of granular content

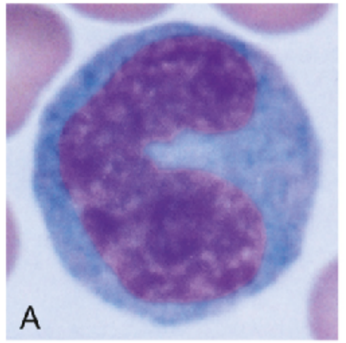


Phagocytes (2)

Mononuclear phagocytes:

- includes circulating cells called monocytes, which become macrophages when they migrate into tissues, and tissue resident macrophages, which are derived mostly from hematopoietic precursors during fetal life (see figure)
- Monocytes: produce inflammatory mediators, are phagocytic, and are rapidly recruited to sites of infection or tissue injury
- Macrophages: ingest and kill microbes, dispose of apoptotic cells, APCs, tissue repair after injury





Dendritic cells (DCs) (1)

- arise from both myeloid and lymphoid progenitors in the bone marrow
- migrate through the blood to peripheral lymphoid organs and tissues
- most potent Antigen-presenting cells (APCs)

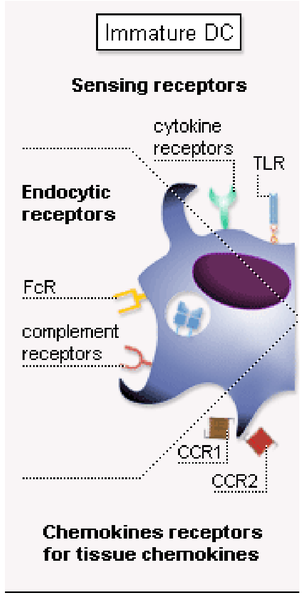
Feature	Classical dendritic cells	Plasmacytoid dendritic cells
Surface markers	CD11c high CD11b high	CD11c low CD11b negative B220 high
Major location	Tissues	Blood and tissue
Expression of Toll-like receptors	TLRs 4, 5, 8 high	TLRs 7, 9 high
Major cytokines produced	TNF, IL-6, IL-12	Type I interferons
Postulated major functions	Induction of T cell responses against most antigens	Antiviral innate immunity and induction of T cell responses against viruses

Dendritic cells (DCs) (2)

DCs exist in two different states: immature and mature

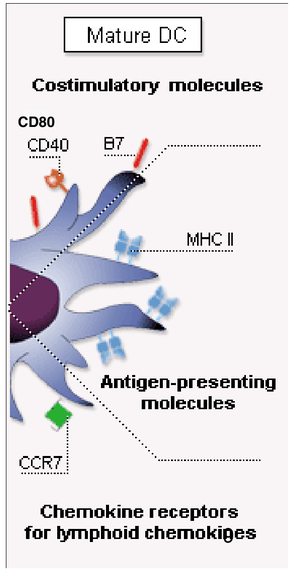
Immature DCs occur in all tissues where antigen may enter into the body

high capacity for antigen uptake but a limited capacity for antigen presentation

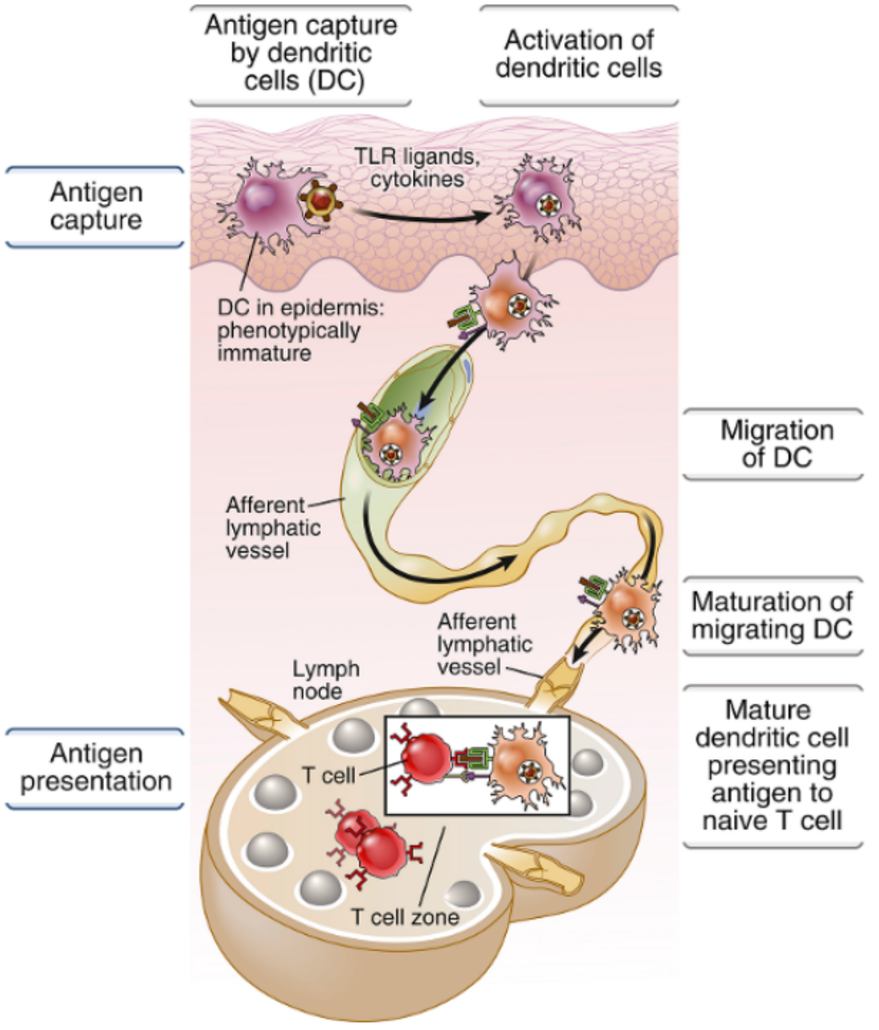


Mature DCs are exclusively found in the T cell areas of secondary lymphoid organs

They are characterized by a high propensity for antigen presentation and T cell activation but a reduced ability to capture antigens.



Dendritic cells (3)

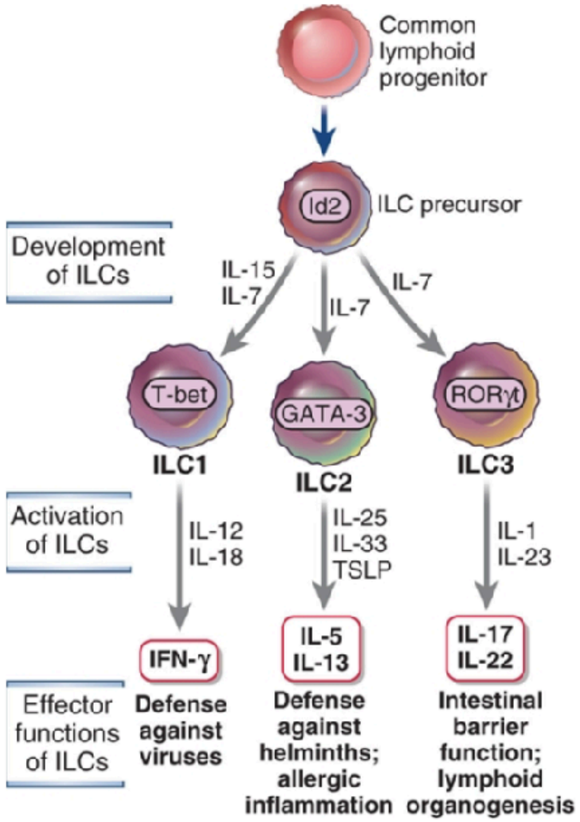


Natural killer cells and innate lymphoid cells

- Subsets of bone marrow–derived cells with lymphoid morphology and effector functions similar to those of T cells but lacking T cell antigen receptors
- Provide early defense against infectious pathogens, recognize damaged/stressed cells, instruct adaptive immune responses

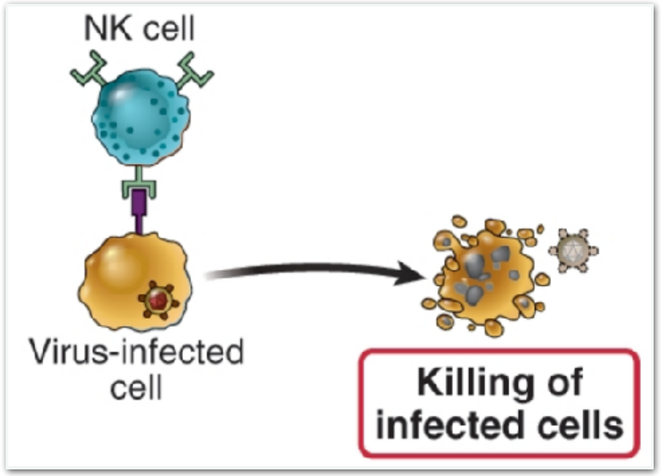
Innate lymphoid cells:

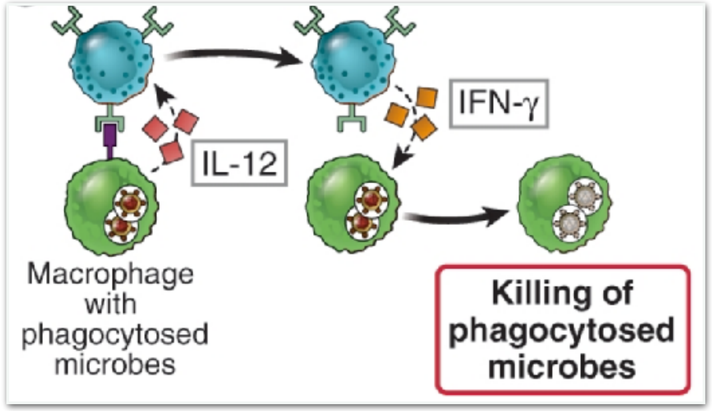
- Function still under intensive research investigation
- It is possible that ILCs are early responders to microbes that colonize tissues, and over time this role is assumed by differentiated effector T cells, which are more specific and produce larger amounts of cytokines



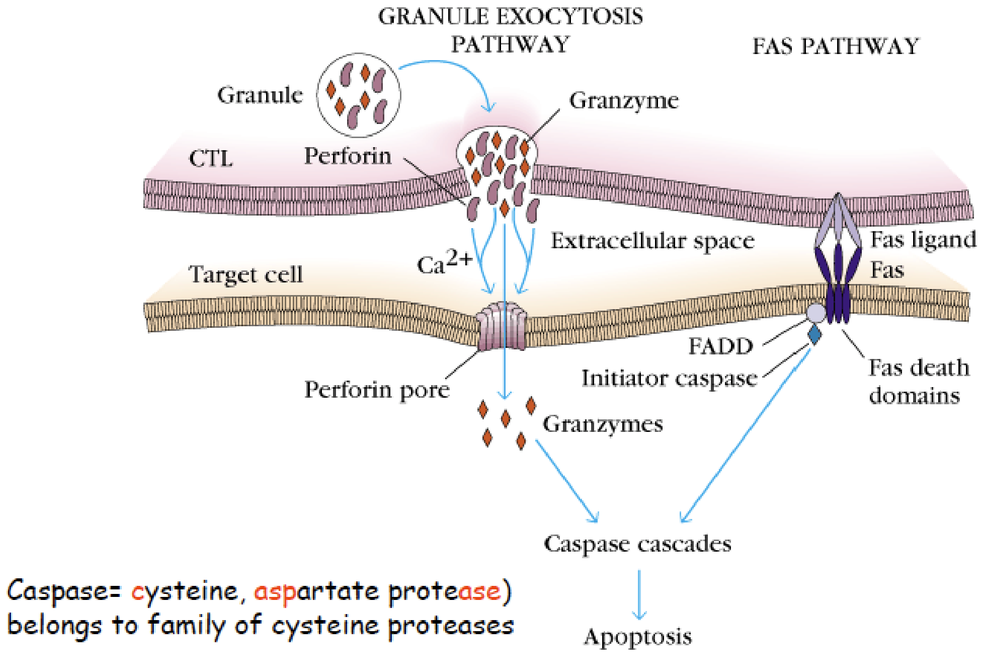
Natural killer cells (NK cells) (1)

- **NK cells are cytotoxic cells that play important roles in innate immune responses, mainly against viruses and intracellular bacteria.**
- Mostly found in the blood and spleen.
- Develop in the BM from same precursor as T cells and B cells
- Distinctive cytoplasmic granules (containing cytotoxic proteins including granzyme and perforin)
- Function to contain infection until the AG-specific T cell response is established (!)
- Activation of killing via NK cells is accomplished by type I IFNs or other cytokines (IL-12)





Natural killer cells (NK cells) (2)



Caspase= cysteine, aspartate protease)
belongs to family of cysteine proteases

Natural killer cells (NK cells) (3)

NK cell function is enhanced by IL-12, type I IFNs, IL-18 and, IL-15.

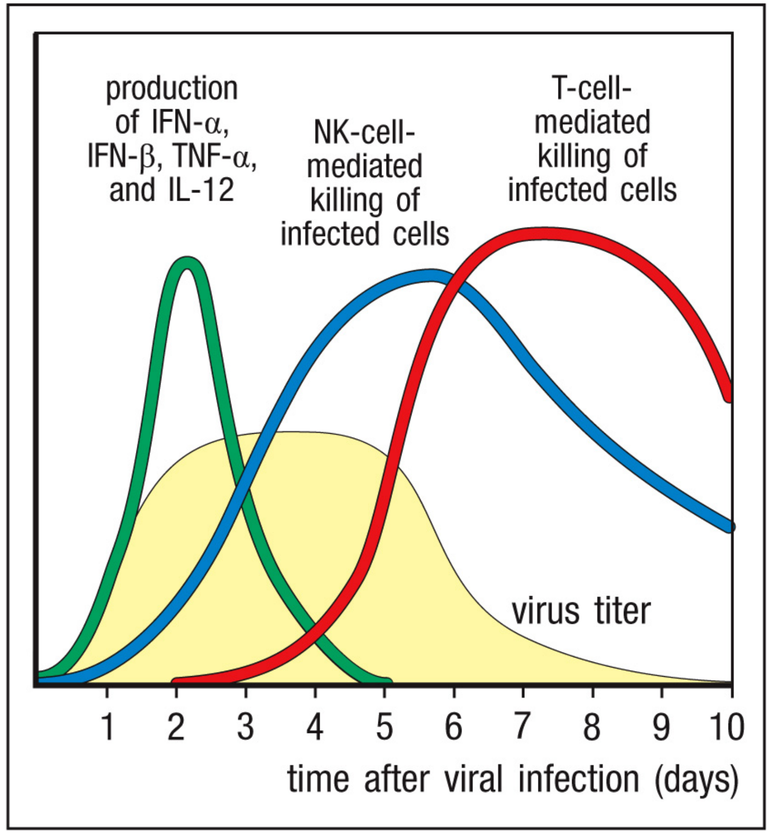
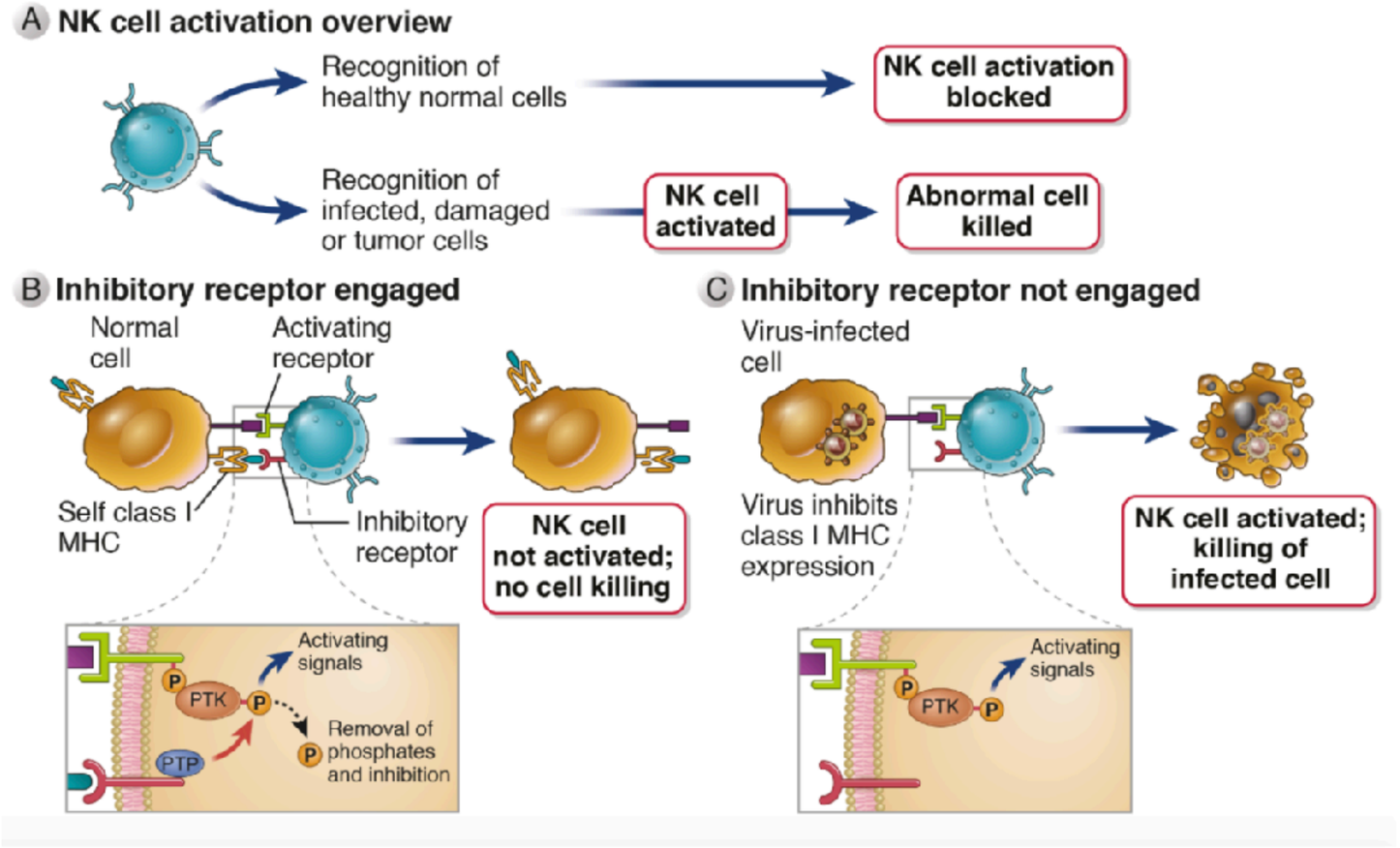


Figure 3.38 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

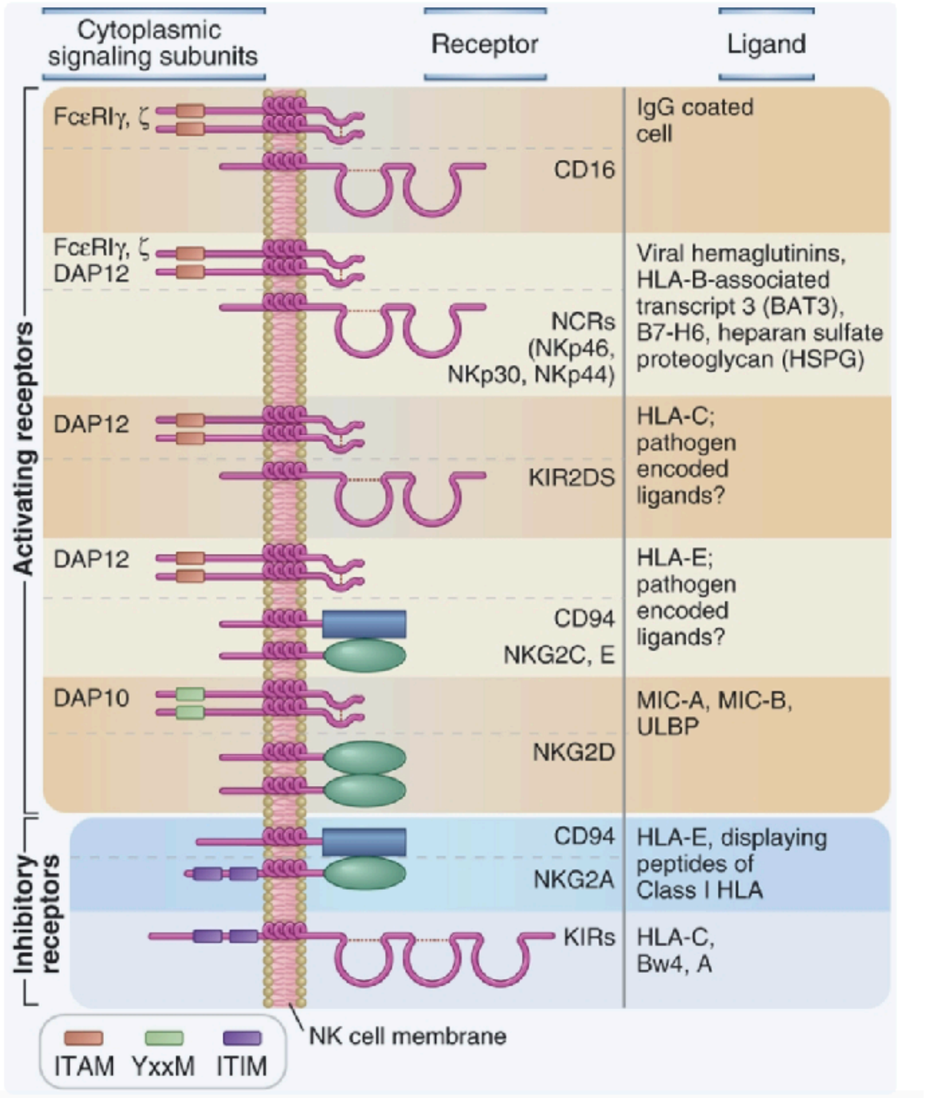
Natural killer cells (NK cells) (4)

- NK cells distinguish infected and stressed cells from healthy cells, and NK cell function is regulated by a balance between signals that are generated from activating receptors and inhibitory receptors.



Structure and ligands of NK cell receptors

- NK cell receptors belong to either the KIR (=killer cell immunoglobulin-like receptors) or the C-type lectins
- KIR genes are polymorphic, meaning that several allelic variants exist in the human population



Mast cells

- Mast cells are bone marrow–derived cells present in the skin and mucosal epithelia
- Contain granules, which are filled with preformed inflammatory mediators, such as histamine
- Express high-affinity plasma membrane receptors for a type of antibody called IgE
- Express PRRs
- Upon activation, they release many potent inflammatory mediators that defend against parasite infections, or cause symptoms of allergic diseases.