Overview of immune system

The immune system consist of two interconnected arms

Innate immunity

- Detect molecular components shared with all pathogens

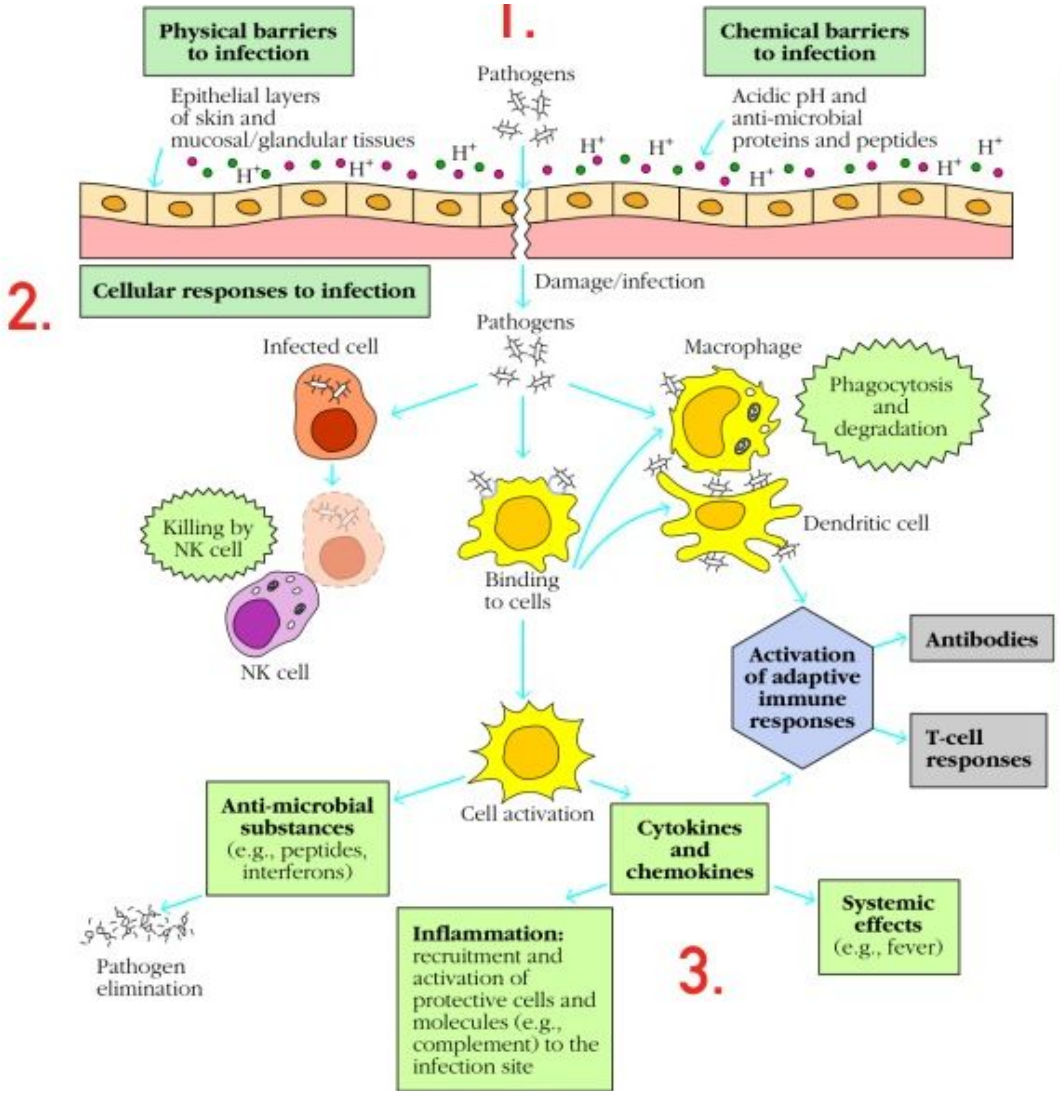
Adaptive immunity

- Molecular components (“antigenes”) specific to individual pathogen

Innate immunity

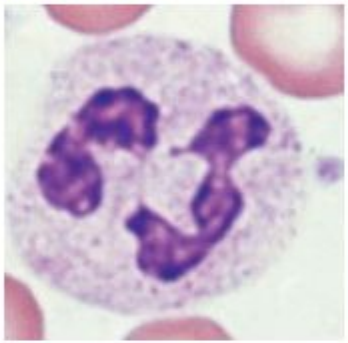
- First line of defense against microbes
- Exist before exposure to microbes
- Found in Plants, Insects, Vertebrates
- *3 Essential function*
  1.) Initial response to microbes
  2.) Eliminate damaged cells and initiate the process of tissue repair
  3.) Stimulates adaptive immune response
- *2 Major type of responses*
  1.) Inflammation
  2.) Antiviral defense

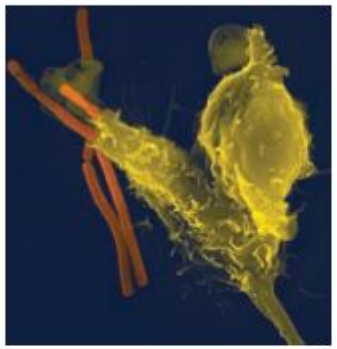
Components of innate immunity

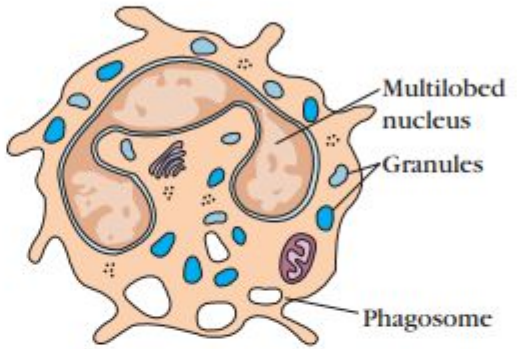


1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines
   - Anti-microbial substances

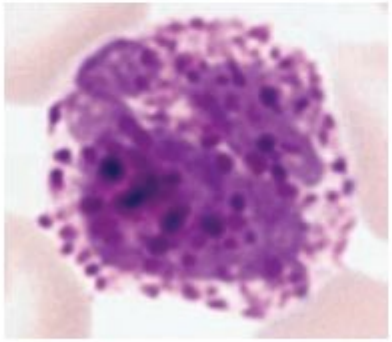
(a) Neutrophil

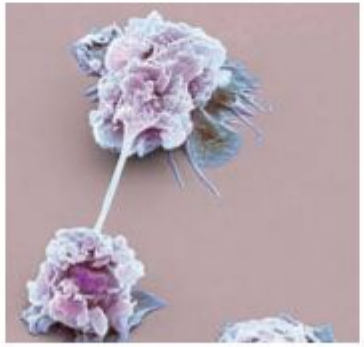


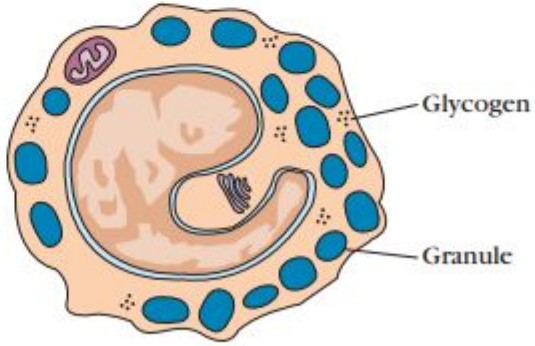




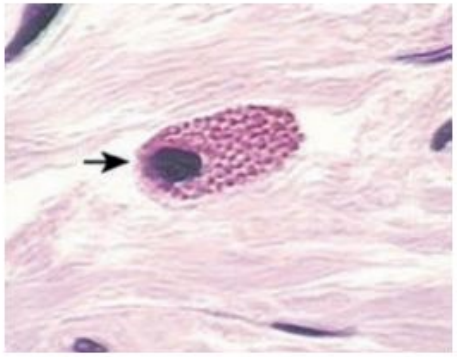
(b) Basophil

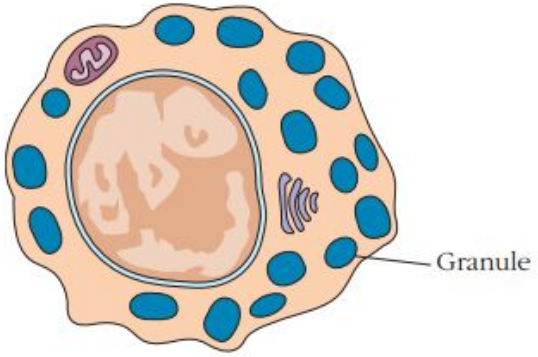




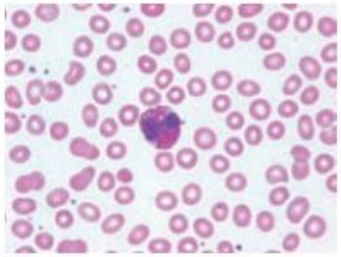


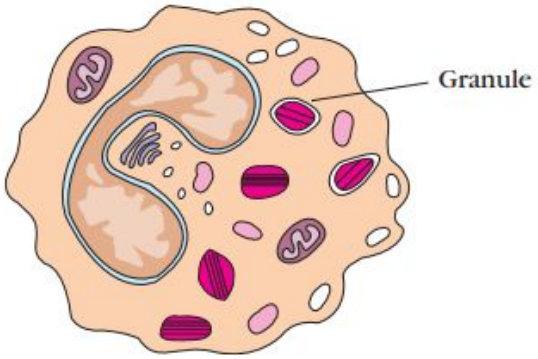
(c) Mast cell



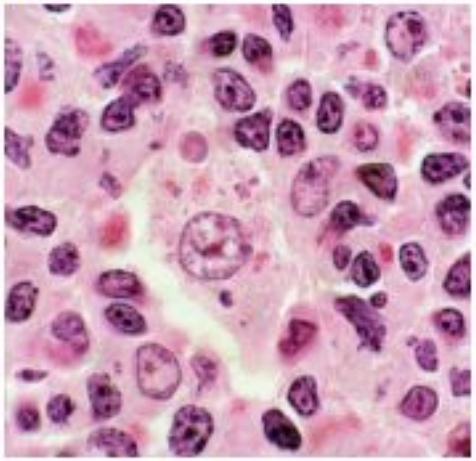


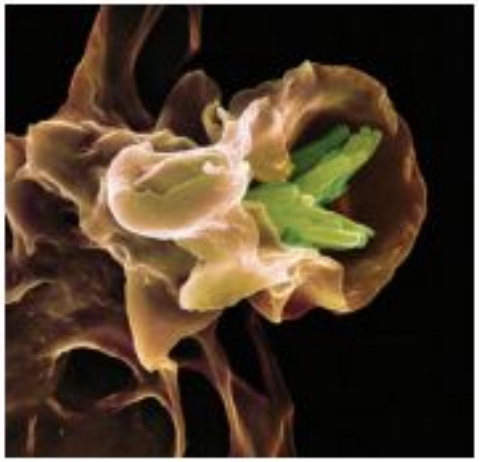
(d) Eosinophil

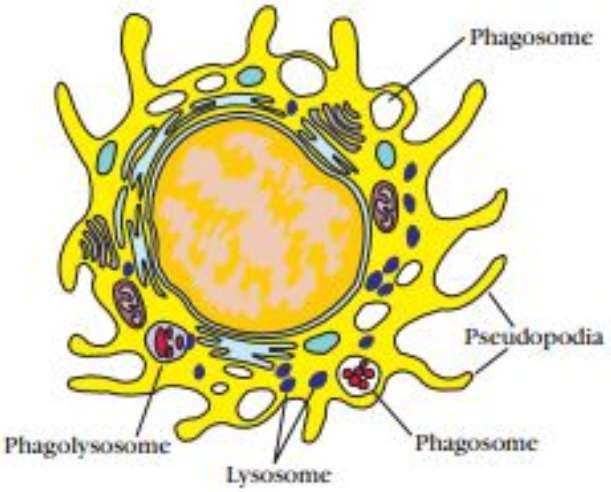




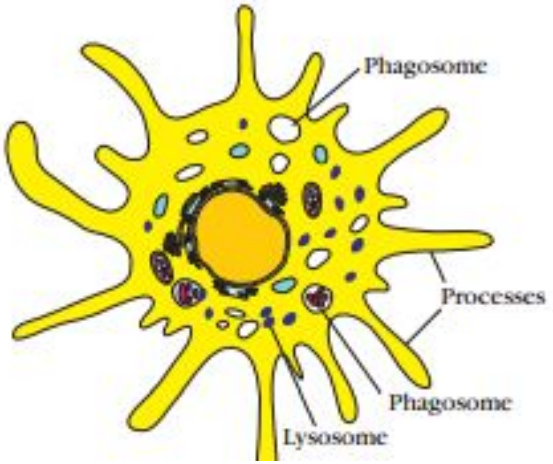
(b) Macrophage







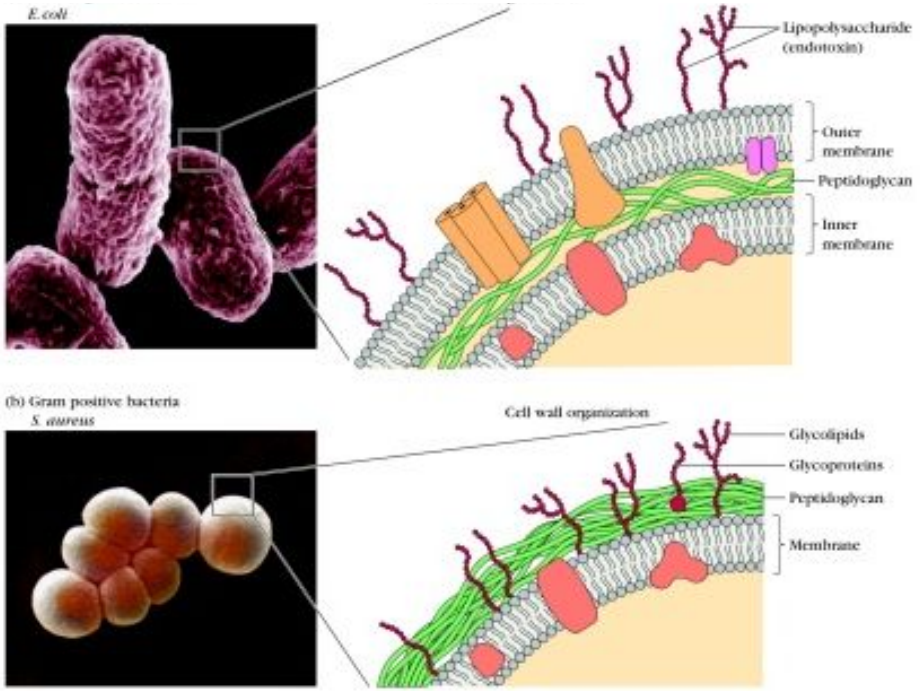
(c) Dendritic cell



Pathogen recognition

The receptors of the innate immune system recognize conserved pathogen-associated molecular patterns (PAMPs).

Receptors are called pattern-recognition receptors (PRRs)

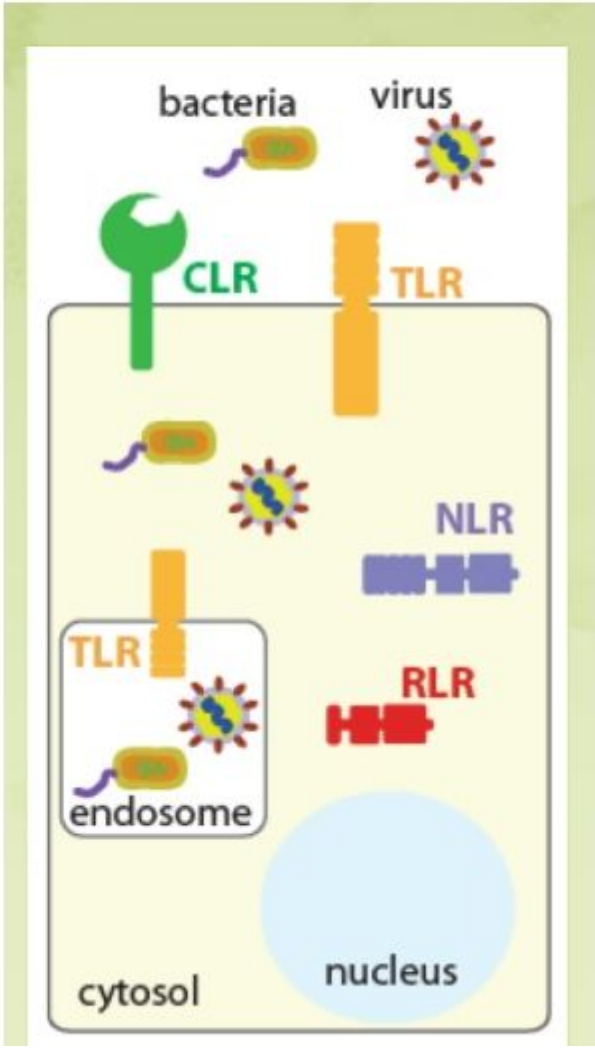


Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

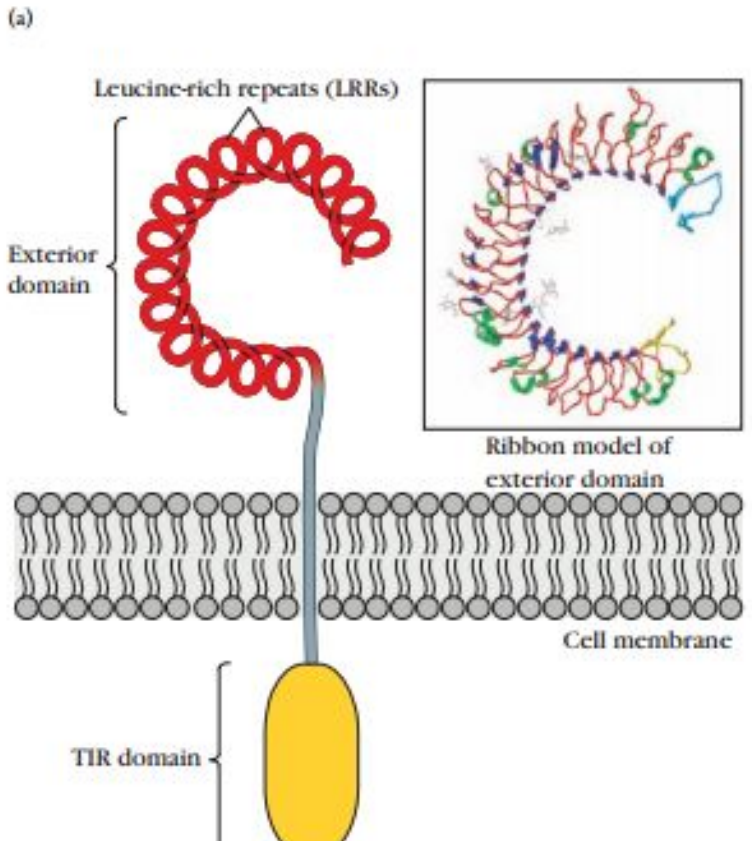
Protein recognition receptors:

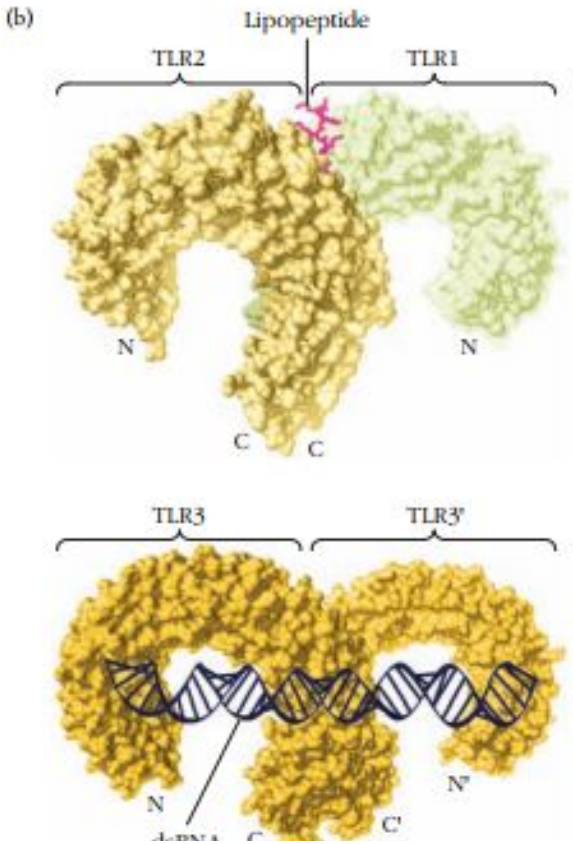
4 Major classes of Signaling PRRs

1.) Toll-like receptors (TLRs) : Transmembrane PRRs
2.) C-Type Lectin Receptors (CLRs): Transmembrane PRRs
3.) NOD-like receptors (NLRs) : Cytosolic PRRs
4.) Retinoid acid–inducible gene (RIG)-like receptors (RLRs) : Cytosolic PRRs



Protein recognition receptors: Toll-like receptors





ABLE 5-4 TLRs and their microbial ligands

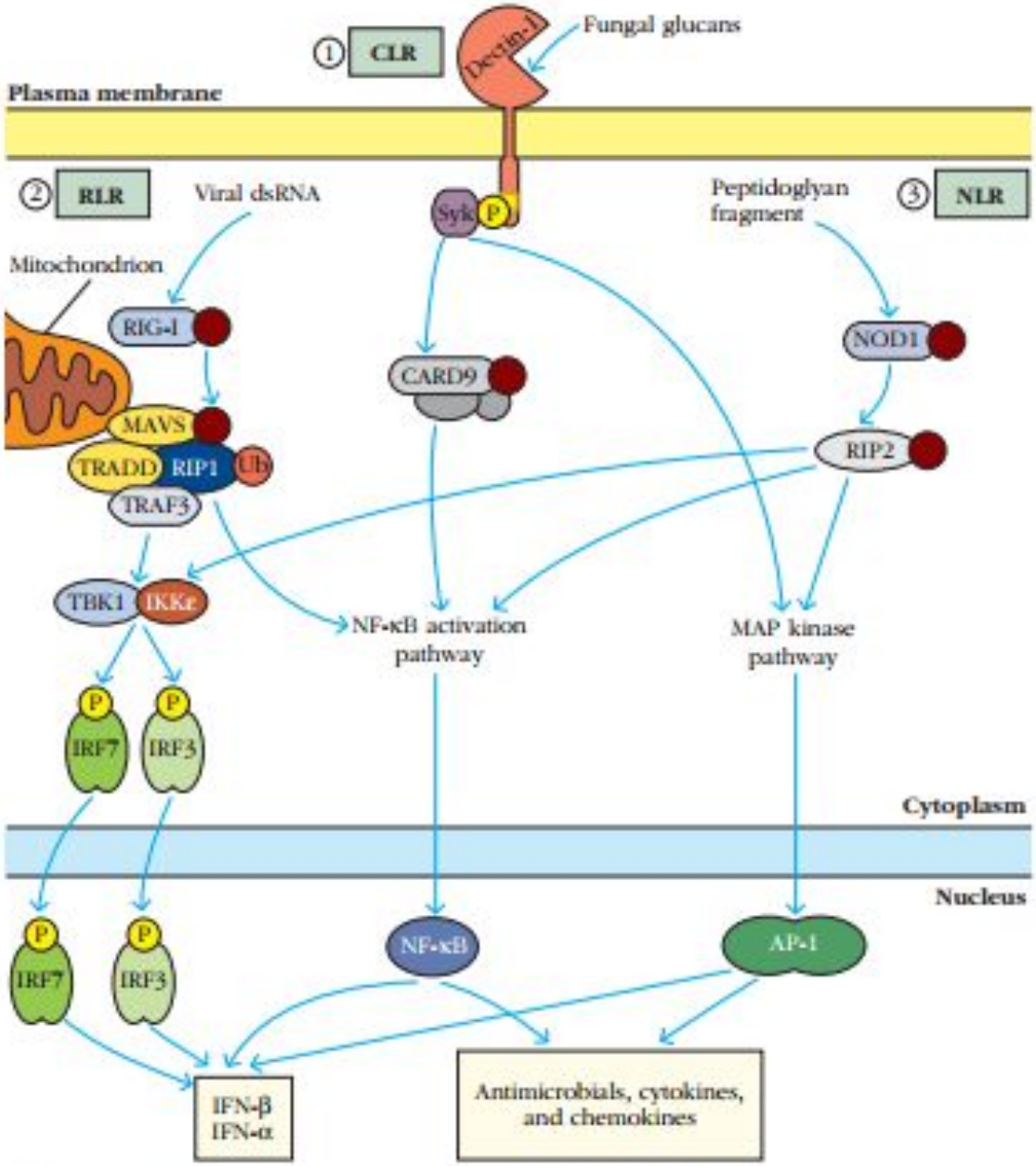
TLRs*	Ligands	Microbes
TLR1	Triacyl lipopeptides	Mycobacteria and Gram-negative bacteria
TLR2	Peptidoglycans	Gram-positive bacteria
	GPI-linked proteins	Trypanosomes
	Lipoproteins	Mycobacteria and other bacteria
	Zymosan	Yeasts and other fungi
	Phosphatidlyserine	Schistosomes
TLR3	Double-stranded RNA (dsRNA)	Viruses
TLR4	LPS	Gram-negative bacteria
	F-protein	Respiratory syncytial virus (RSV)
	Mannans	Fungi
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopolypeptides	Mycobacteria and Gram-positive bacteria
	Zymosan	Yeasts and other fungi
TLR7	Single-stranded RNA (ssRNA)	Viruses
TLR8	Single-stranded RNA (ssRNA)	Viruses
TLR9	CpG unmethylated dinucleotides	Bacterial DNA
	Dinucleotides	
	Herpes virus components	Some herpesviruses
	Hemozoin	Malaria parasite heme byproduct
TLR10	Unknown	Unknown
TLR11	Unknown	Uropathogenic bacteria
	Profilin	Toxoplasma
TLR12	Unknown	Unknown
TLR13	Unknown	Vesicular stomatitis virus

Protein recognition receptors: C-type lectin receptors

- Plasma membrane receptors
  - monocytes, macrophages, dendritic cells, neutrophils, B cells, and T-cell subsets

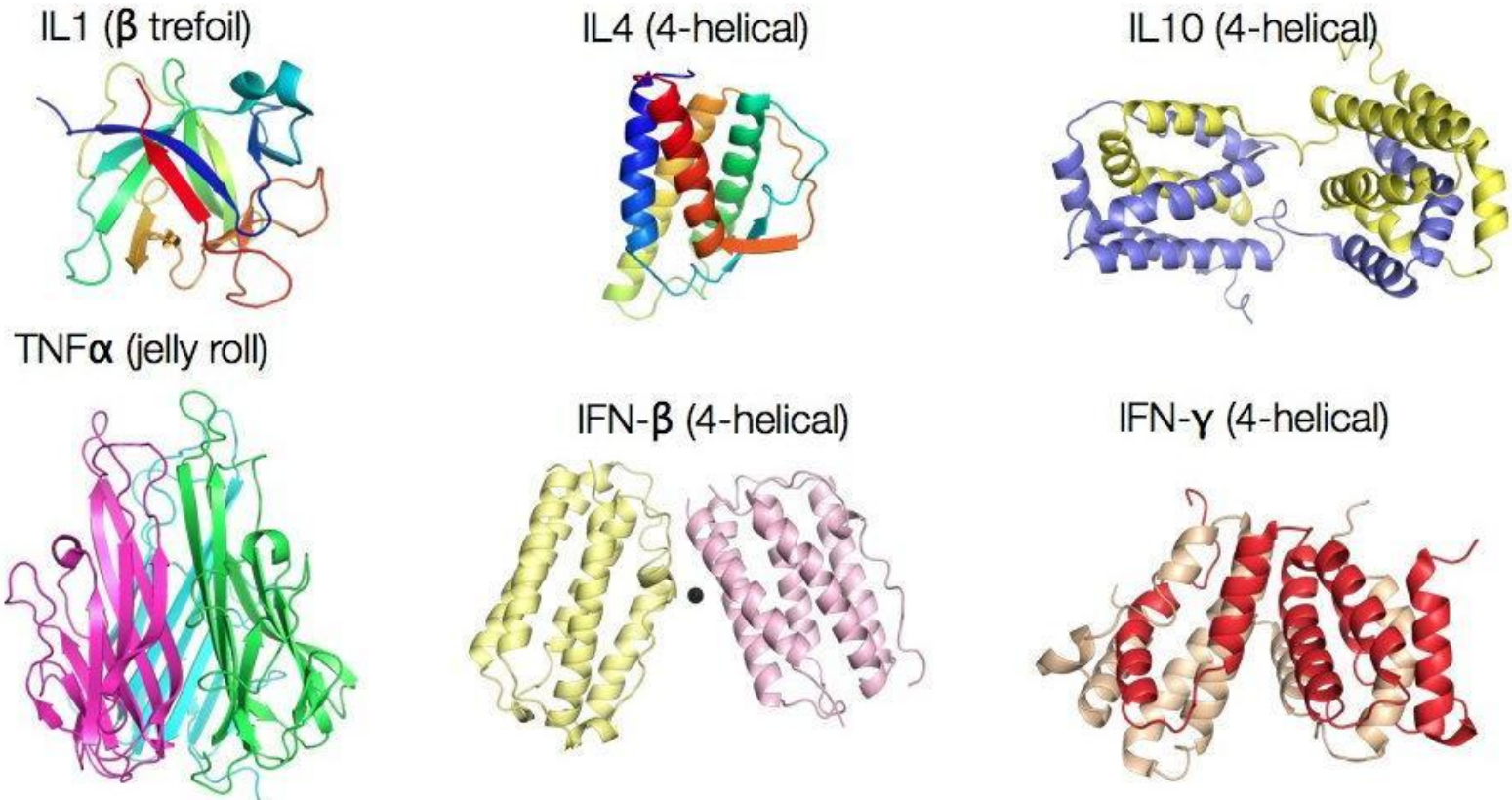
- Recognize carbohydrate components of fungi, mycobacteria, viruses, parasites, and some allergens (peanut and dust mite proteins)

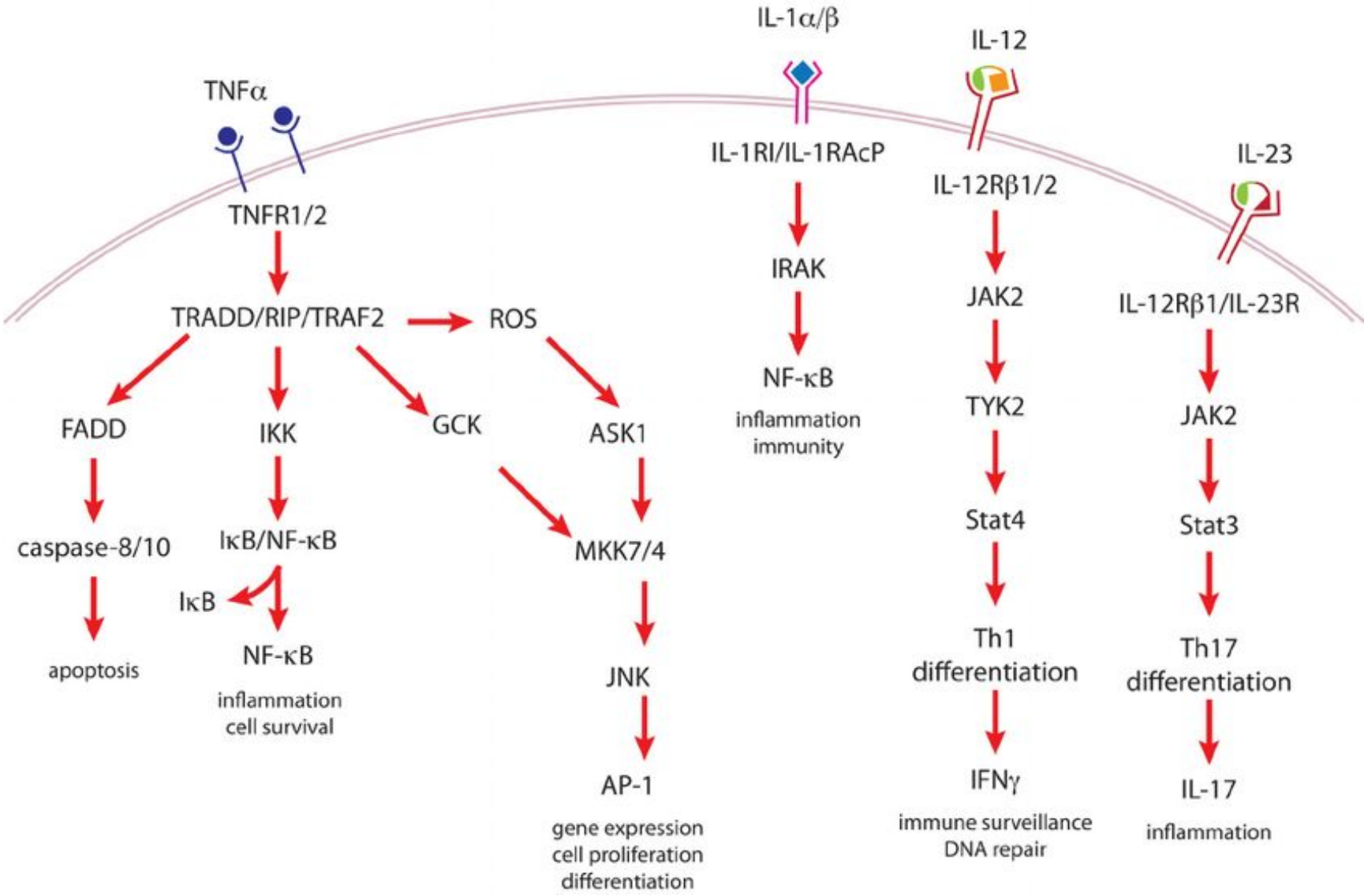
- Human : 15 CLRs that function as PRRs
  - Most recognize sugar moieties
    - mannose --> mannose receptor, DC-SIGN
    - fucose --> Dectin-2, DC-SIGN
    - glucans --> Dectin-1


1
CLR
Dectin-1
Fungal glucans
Plasma membrane
2
RLR
Viral dsRNA
Syk
P
Peptidoglyan fragment
3
NLR
Mitochondrion
RIG-I
NOD1
CARD9
MAVS
TRADD
RIP1
Ub
TRAF3
RIP2
TBK1
IKKε
NF-κB activation pathway
MAP kinase pathway
P
IRF7
IRF3
Cytoplasm
Nucleus
NF-κB
AP-1
IFN-β
IFN-α
Antimicrobials, cytokines, and chemokines

Cytokine

Cytokine are broad family of small proteins (5-20 kDa) that are important in cell signaling.

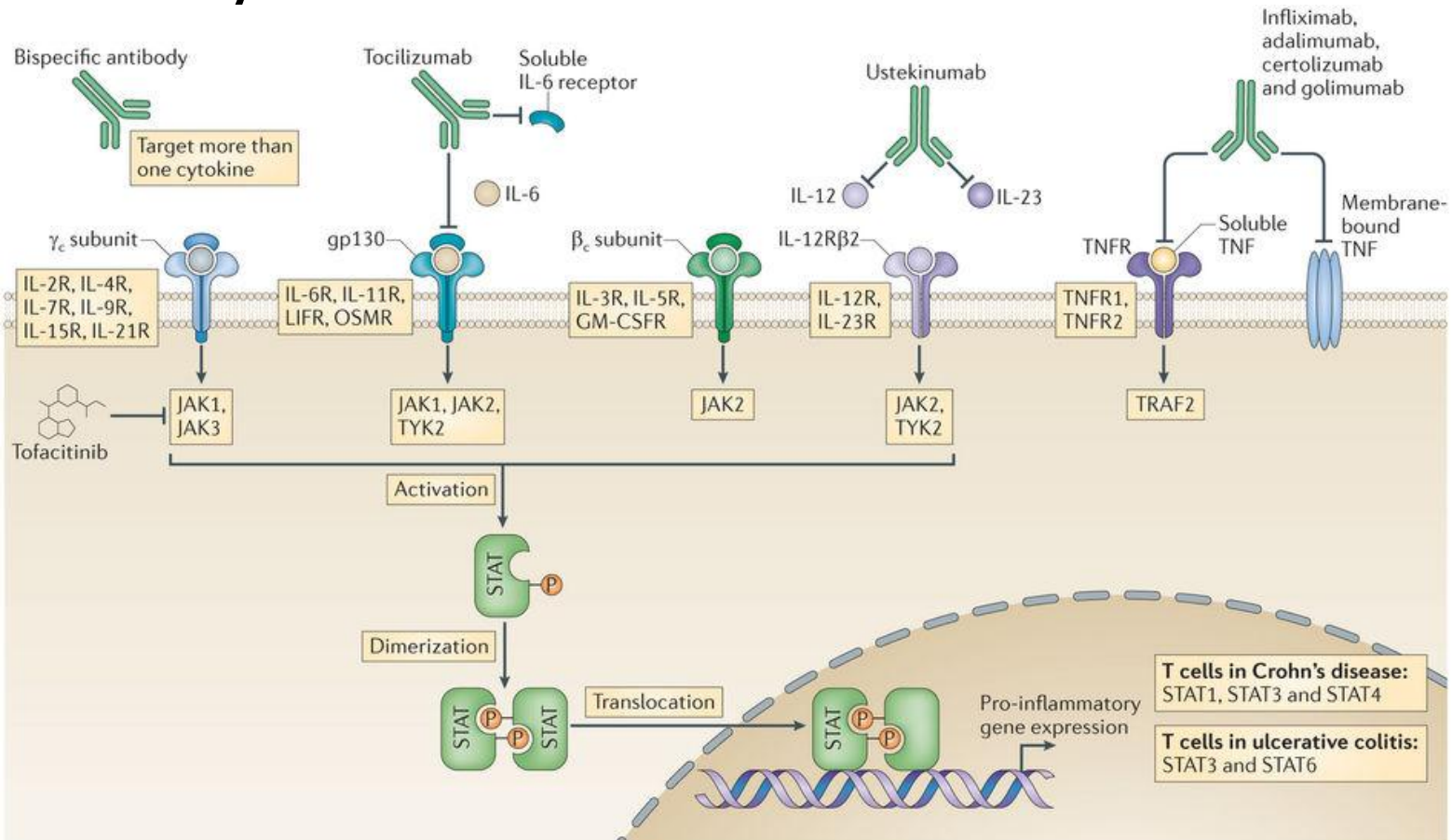



IL-1α/β
IL-12
TNFα
IL-1RI/IL-1RAcP
IL-12Rβ1/2
IL-23
TNFR1/2
IRAK
JAK2
IL-12Rβ1/IL-23R
TRADD/RIP/TRAF2
ROS
NF-κB
TYK2
JAK2
FADD
IKK
GCK
ASK1
inflammation
immunity
Stat4
Stat3
caspase-8/10
IκB/NF-κB
MKK7/4
Th1
differentiation
Th17
differentiation
IκB
NF-κB
JNK
IFNγ
IL-17
apoptosis
inflammation
cell survival
AP-1
immune surveillance
DNA repair
inflammation
gene expression
cell proliferation
differentiation

Cytokine	Secreted by†	Targets and effects
	SOME CYTOKINES OF INNATE IMMUNITY	
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor-α (TNF-α)	Macrophages, monocytes, neutrophils, activated T cells and NK cells	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells, and T_H2 cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B-cell lineage)
Interferon-α (IFN-α) (this is a family of molecules)	Macrophages dendritic cells, virus-infected cells	Induces an antiviral state in most nucleated cells; increases MHC Class I expression; activates NK cells
Interferon β (IFN-β)	Macrophages, dendritic cells, virus-infected cells	Induces an antiviral state in most nucleated cells; increases MHC Class I expression; activates NK cells
	SOME CYTOKINES OF ADAPTIVE IMMUNITY	
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells, mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN-γ)	T_H1 cells, $CD8^+$ cells, NK cells	Activates macrophages; increases expression MHC Class I and Class II molecules; increases antigen presentation

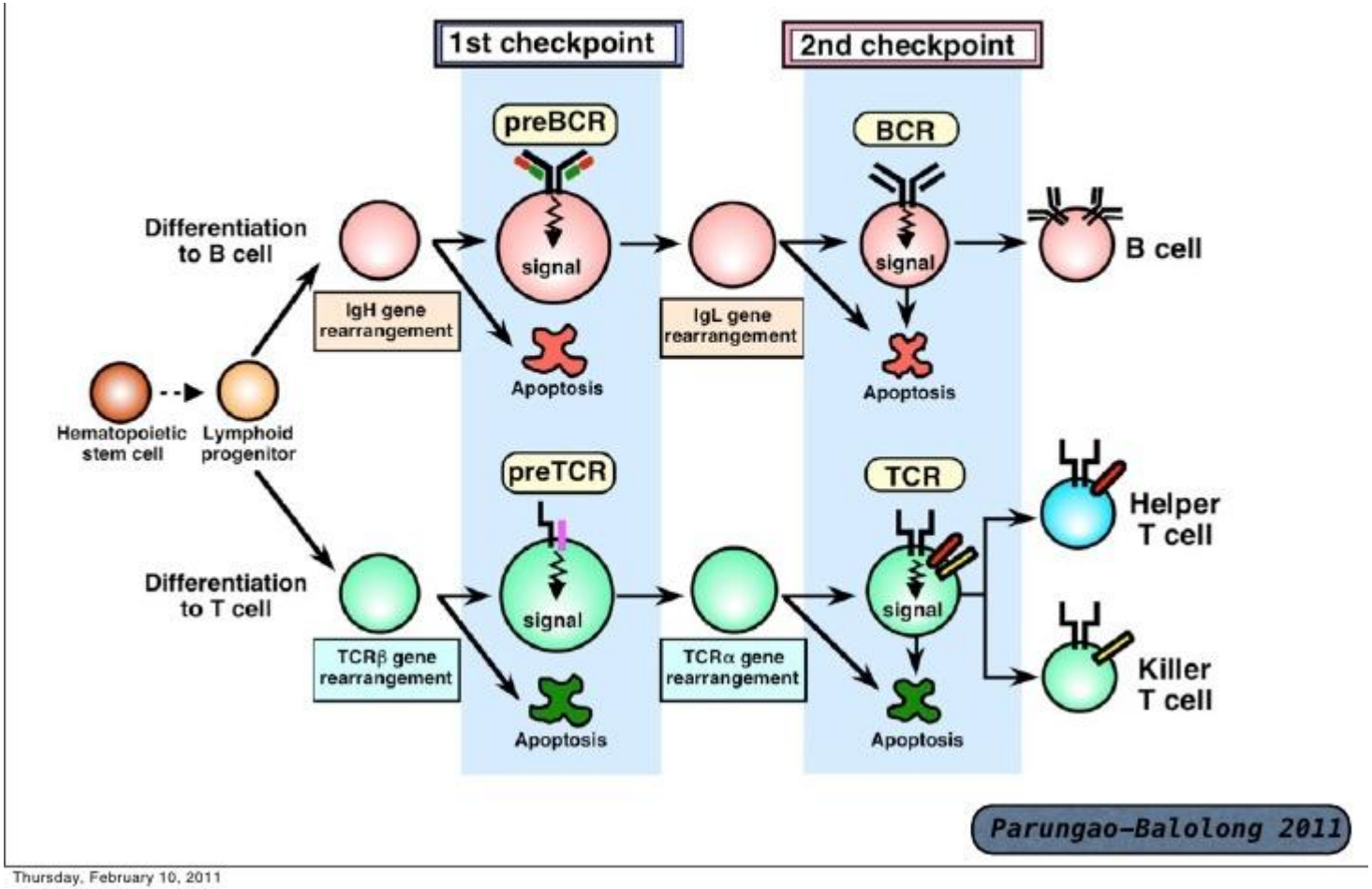
Cytokine/anticytokine therapy

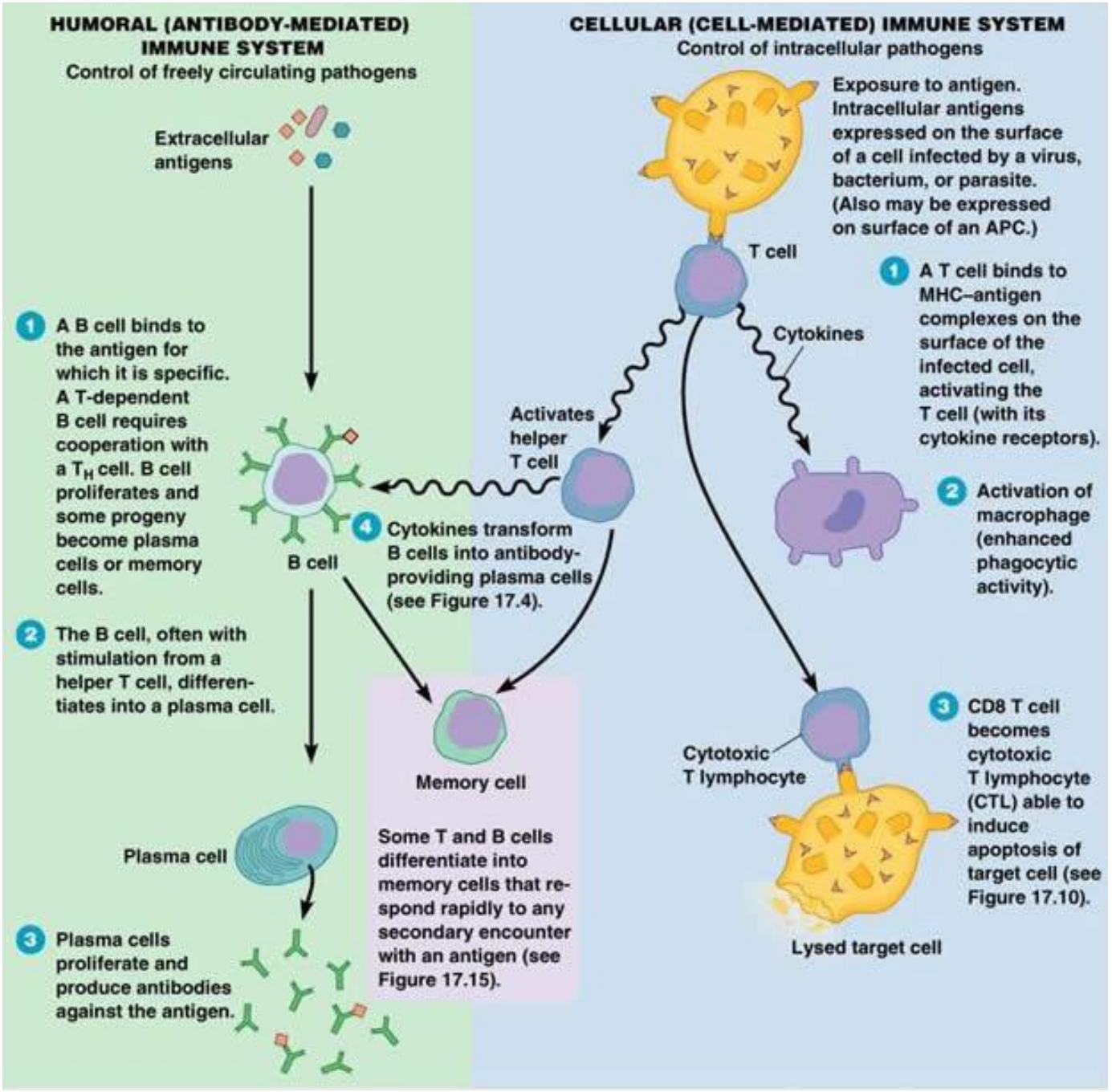
Therapies have been developed with the express aim to block/inhibitor restore the activity of specific cytokines.

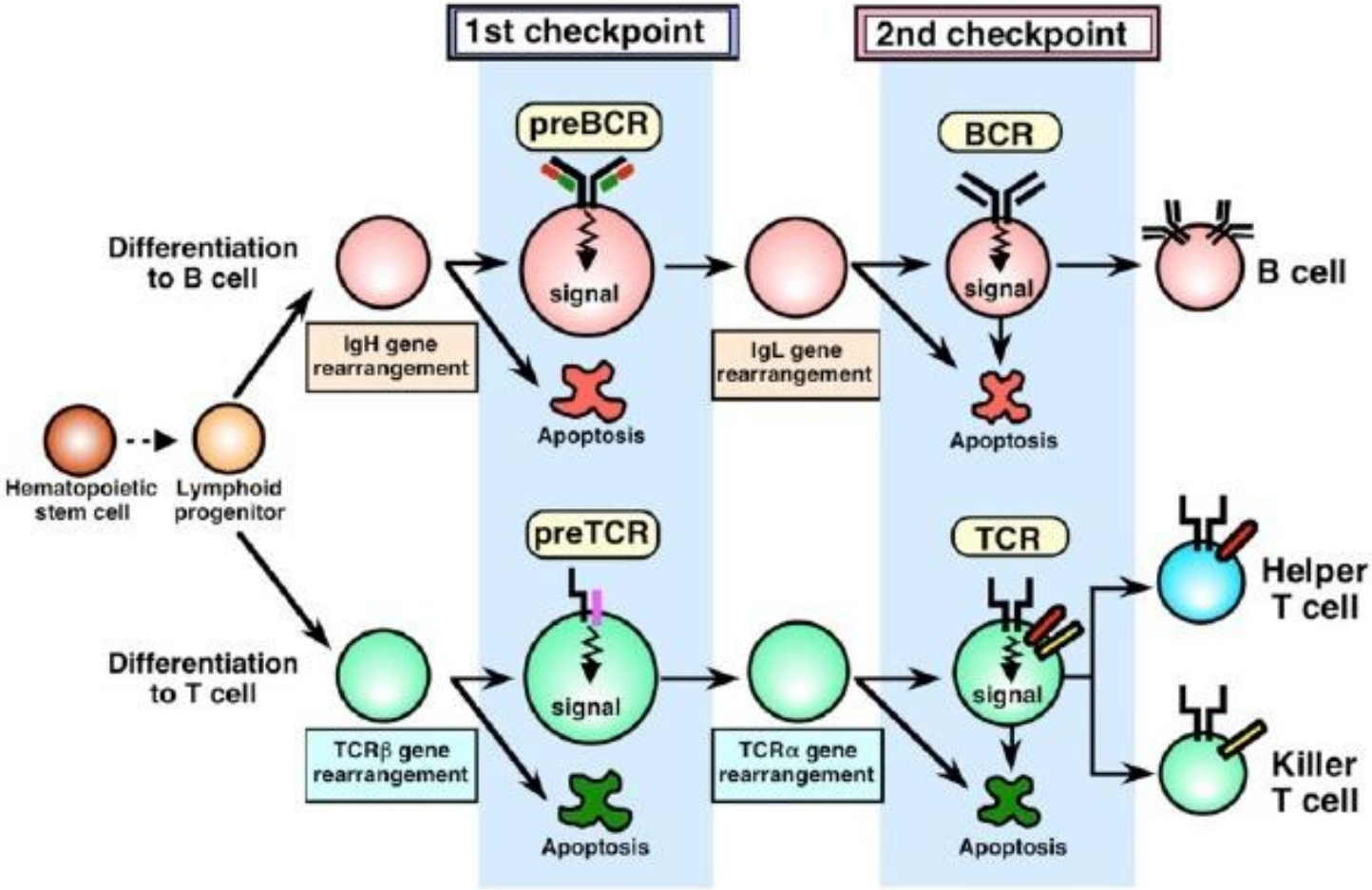


Adaptive immune system

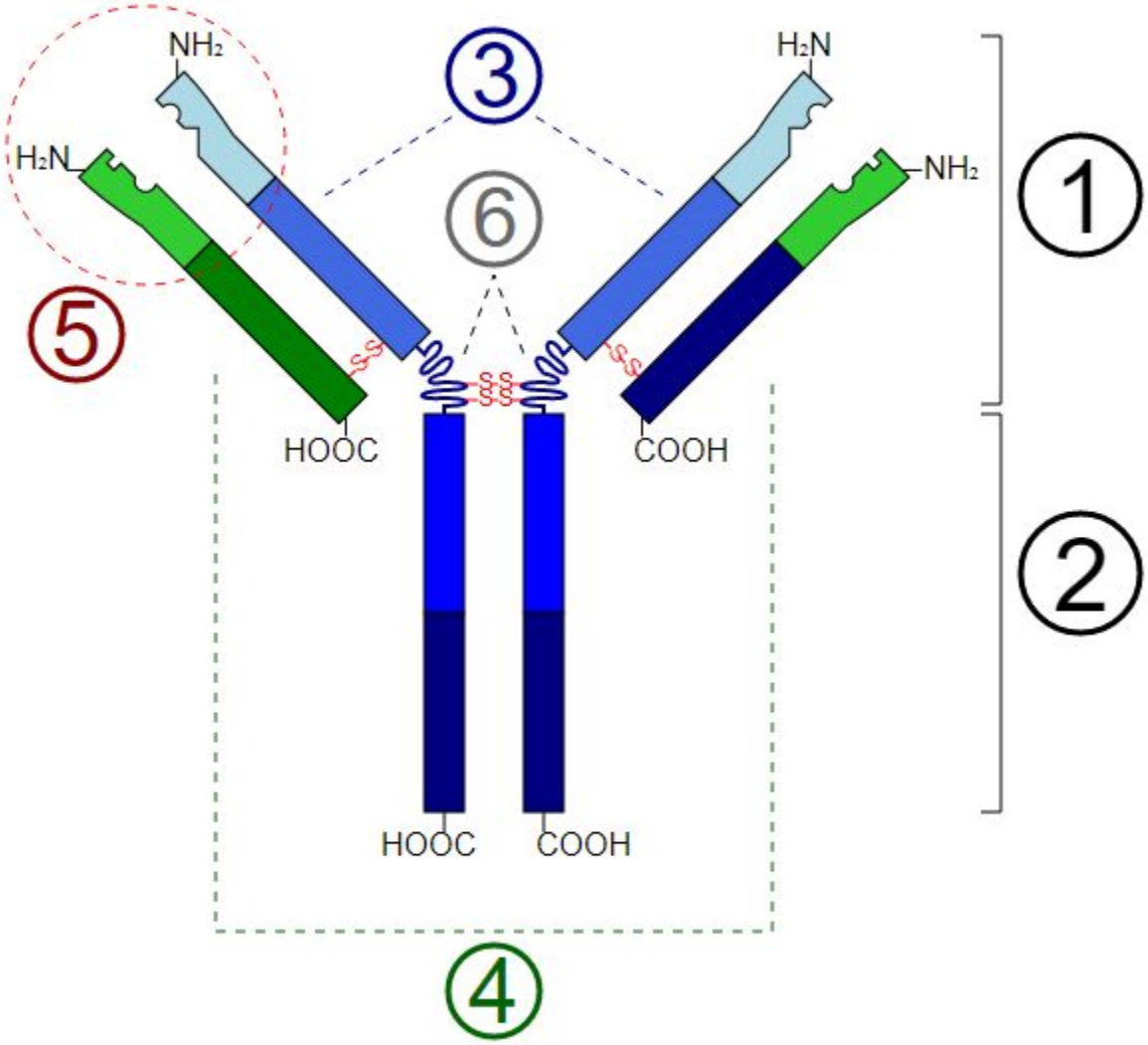
Major players
T and B lymphocytes




HUMORAL (ANTIBODY-MEDIATED) IMMUNE SYSTEM
Control of freely circulating pathogens
Extracellular antigens
1 A B cell binds to the antigen for which it is specific. A T-dependent B cell requires cooperation with a T_H cell. B cell proliferates and some progeny become plasma cells or memory cells.
B cell
2 The B cell, often with stimulation from a helper T cell, differentiates into a plasma cell.
Plasma cell
3 Plasma cells proliferate and produce antibodies against the antigen.
Activates helper T cell
4 Cytokines transform B cells into antibody-providing plasma cells (see Figure 17.4).
Memory cell
Some T and B cells differentiate into memory cells that respond rapidly to any secondary encounter with an antigen (see Figure 17.15).
CELLULAR (CELL-MEDIATED) IMMUNE SYSTEM
Control of intracellular pathogens
Exposure to antigen. Intracellular antigens expressed on the surface of a cell infected by a virus, bacterium, or parasite. (Also may be expressed on surface of an APC.)
T cell
1 A T cell binds to MHC–antigen complexes on the surface of the infected cell, activating the T cell (with its cytokine receptors).
Cytokines
2 Activation of macrophage (enhanced phagocytic activity).
Cytotoxic T lymphocyte
3 CD8 T cell becomes cytotoxic T lymphocyte (CTL) able to induce apoptosis of target cell (see Figure 17.10).
Lysed target cell

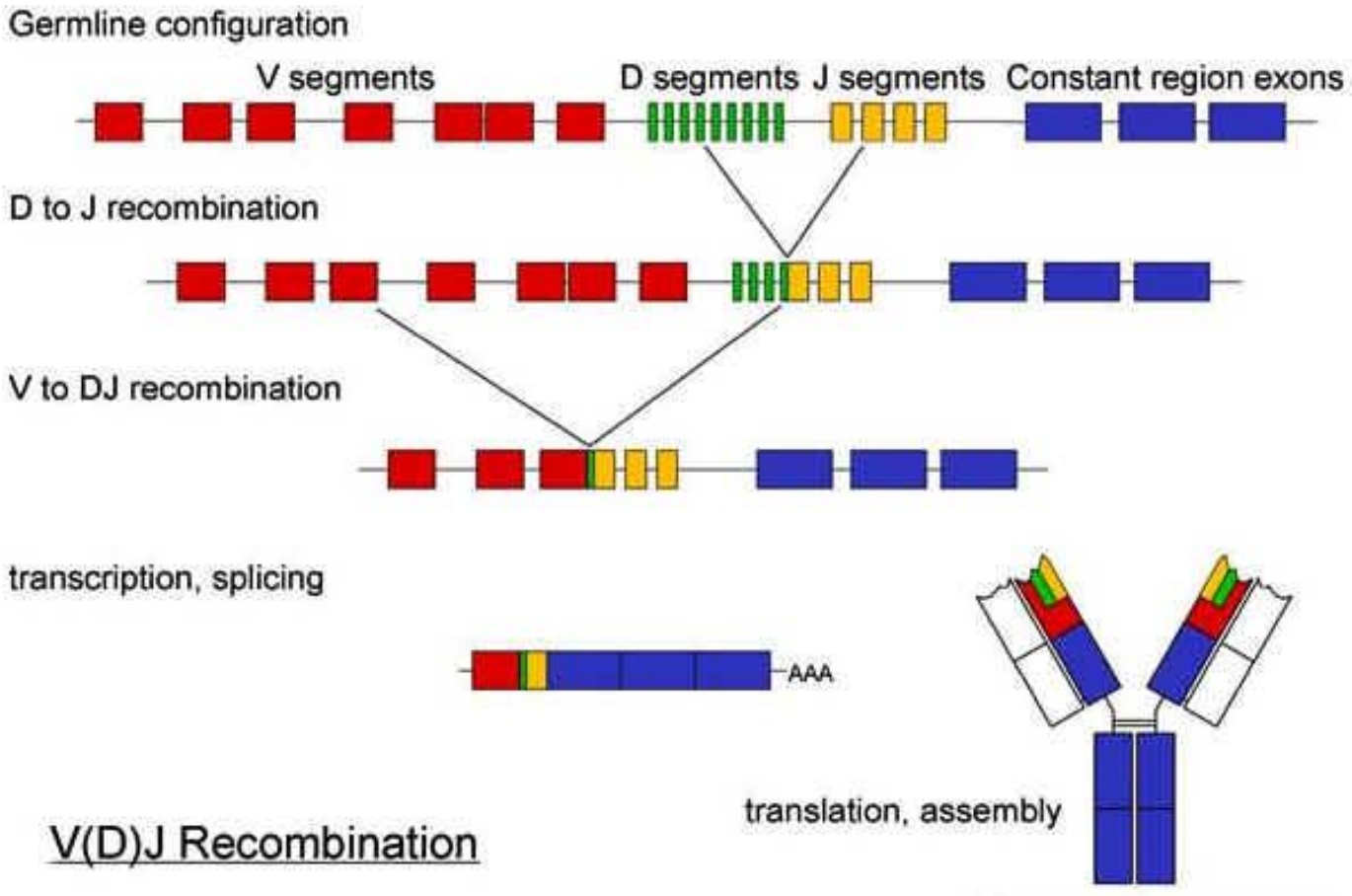

1st checkpoint
2nd checkpoint
preBCR
BCR
Differentiation to B cell
signal
signal
B cell
IgH gene rearrangement
IgL gene rearrangement
Apoptosis
Apoptosis
Hematopoietic stem cell
Lymphoid progenitor
preTCR
TCR
Helper T cell
Differentiation to T cell
signal
signal
TCRβ gene rearrangement
TCRα gene rearrangement
Killer T cell
Apoptosis
Apoptosis
Parungao-Balolong 2011

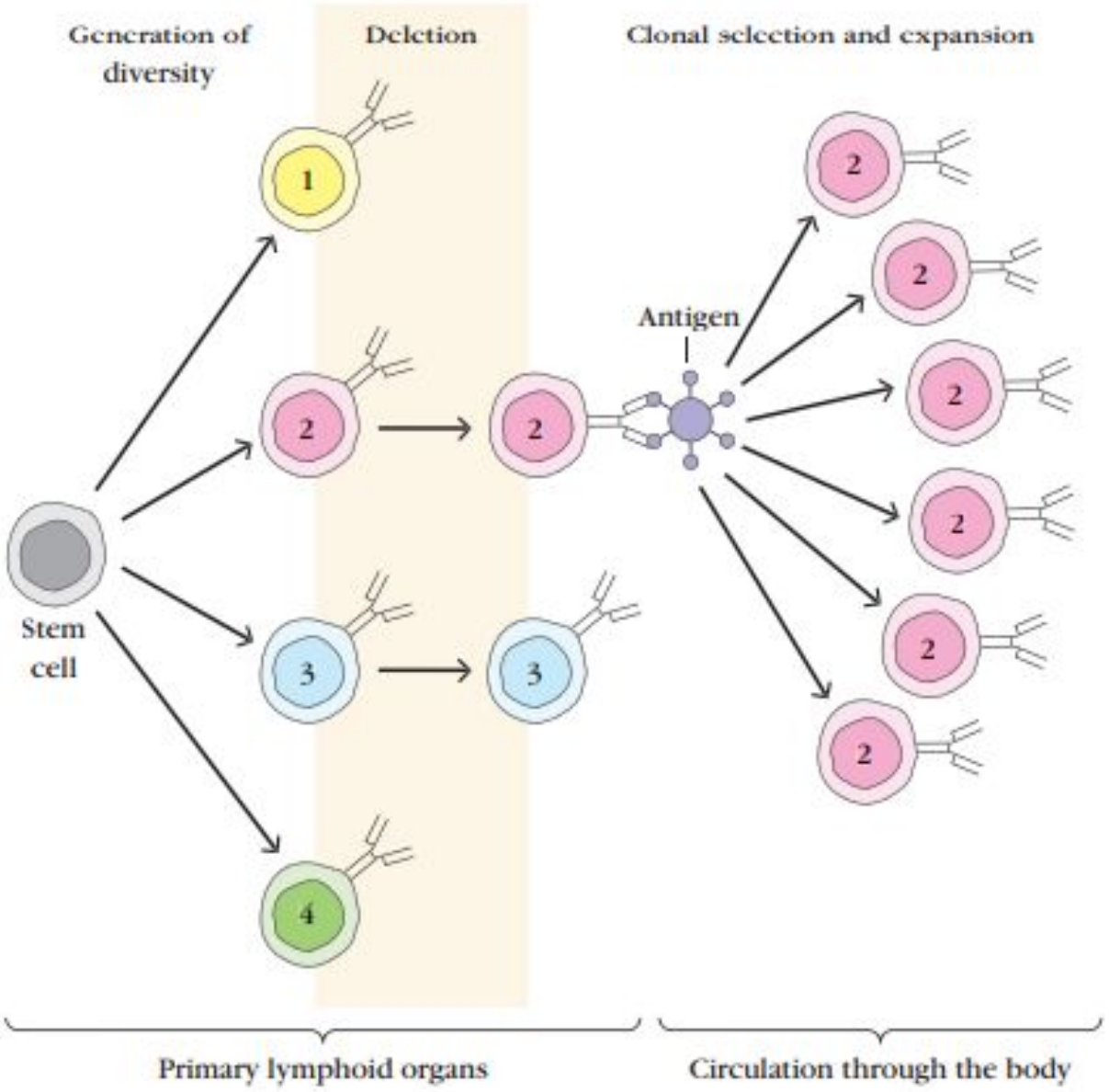
Humoral immunity
B cells



1)Fab region
2)Fc region
3)Heavy chain (blue) with one variable (VH) domain followed by a constant domain (CH1), a hinge region, and two more constant (CH2 and CH3) domains
4)Light chain (green) with one variable (VL) and one constant (CL) domain
5)
Antigen binding site (paratope)
Hinge regions

Origen of diversity – alternative splicing



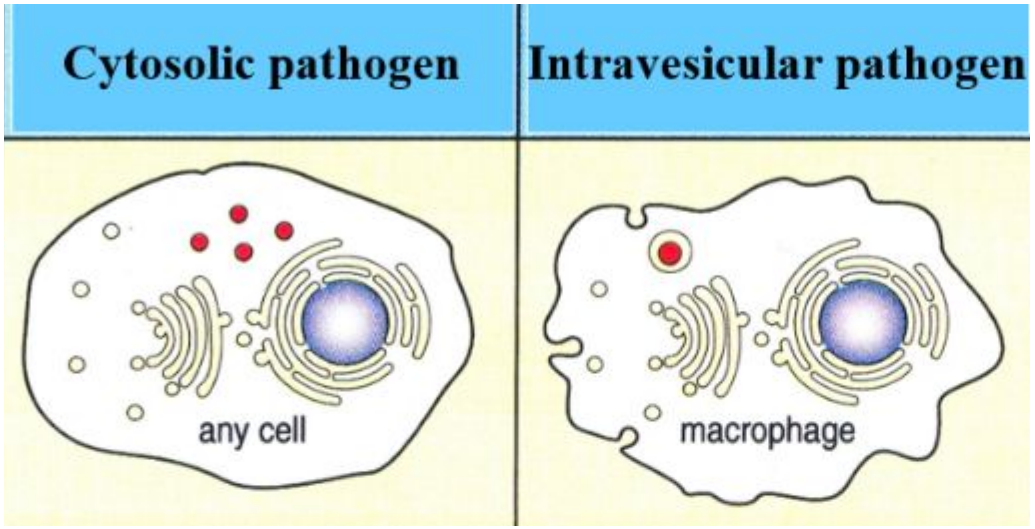

Generation of diversity
Deletion
Clonal selection and expansion
Antigen
Stem cell
1
2
2
2
2
2
2
2
2
2
3
3
4
Primary lymphoid organs
Circulation through the body

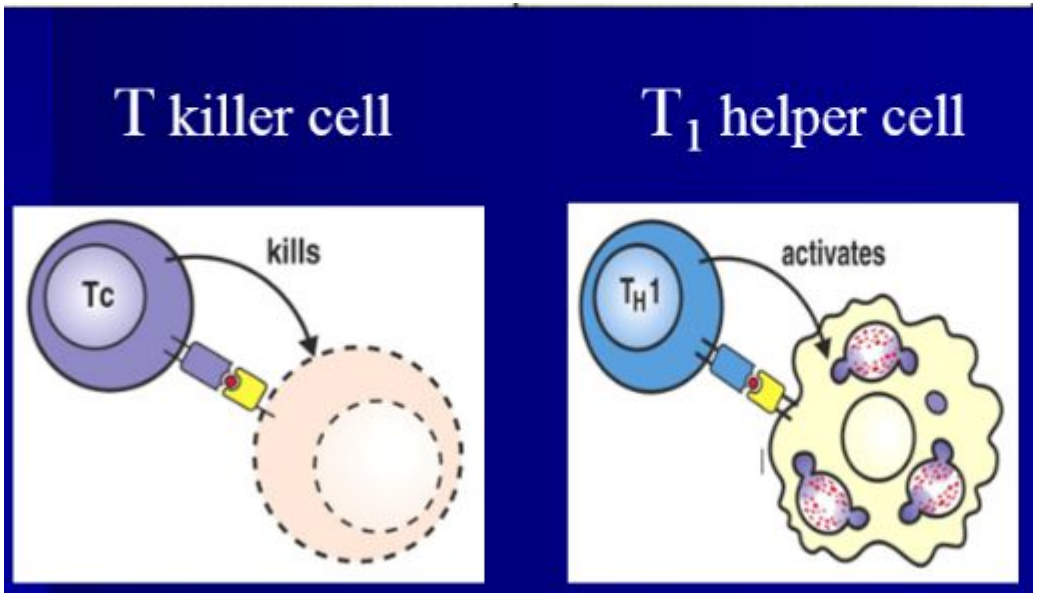
Function of antibodies

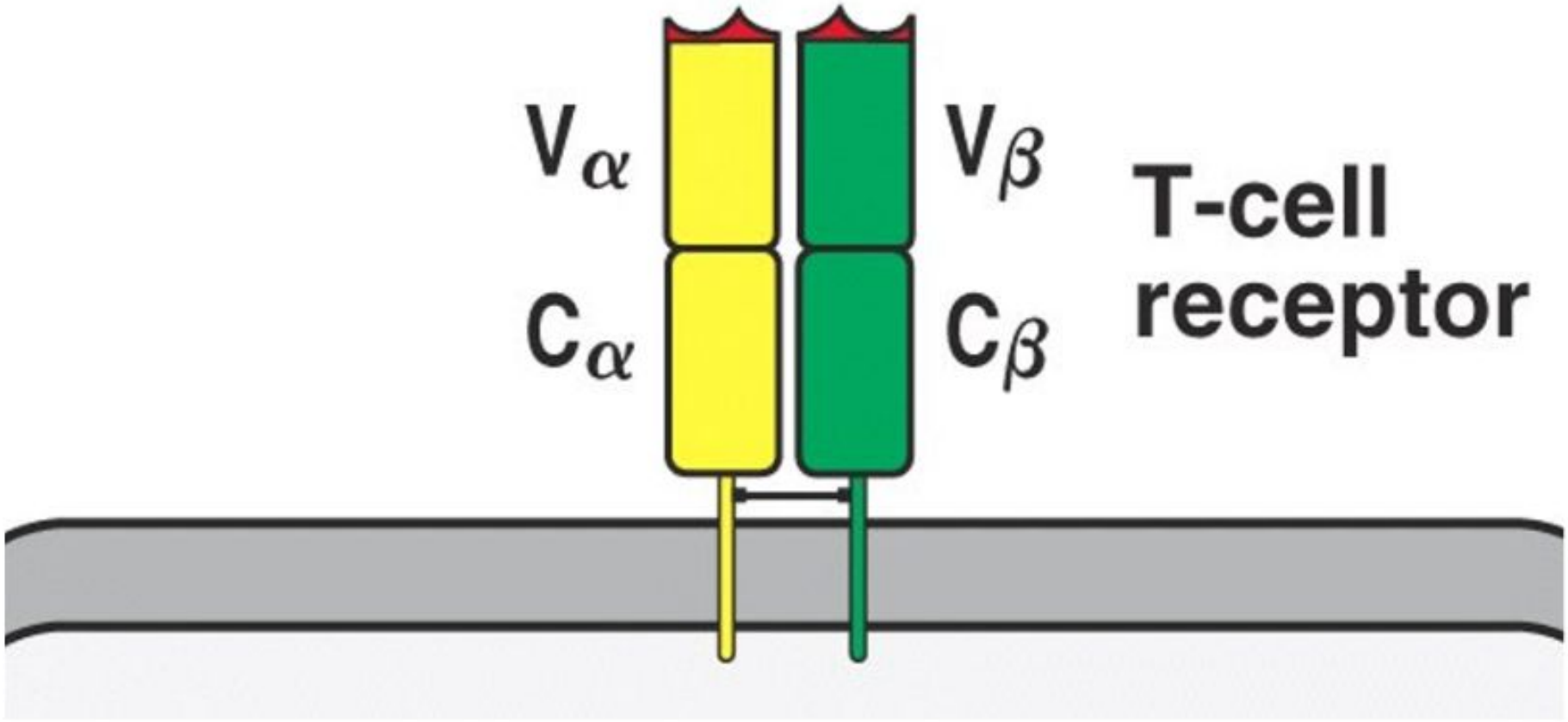
- Prevent adhesion of pathogens (bacteria and viruses)
- Neutralize toxins
- Opsonization of bacteria
- Complement activation

Adaptive immune system
Cellular immunity

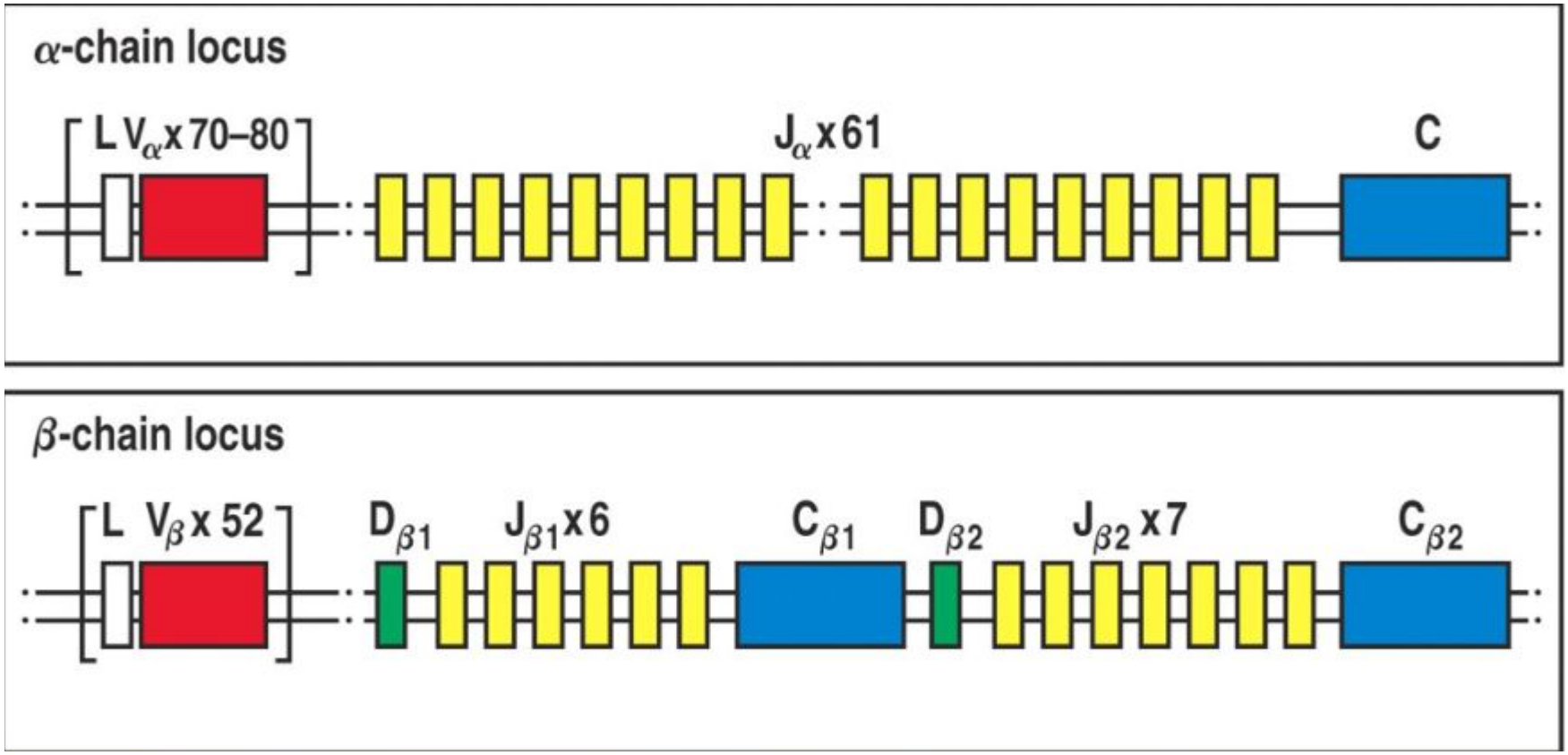
Cellular immunity



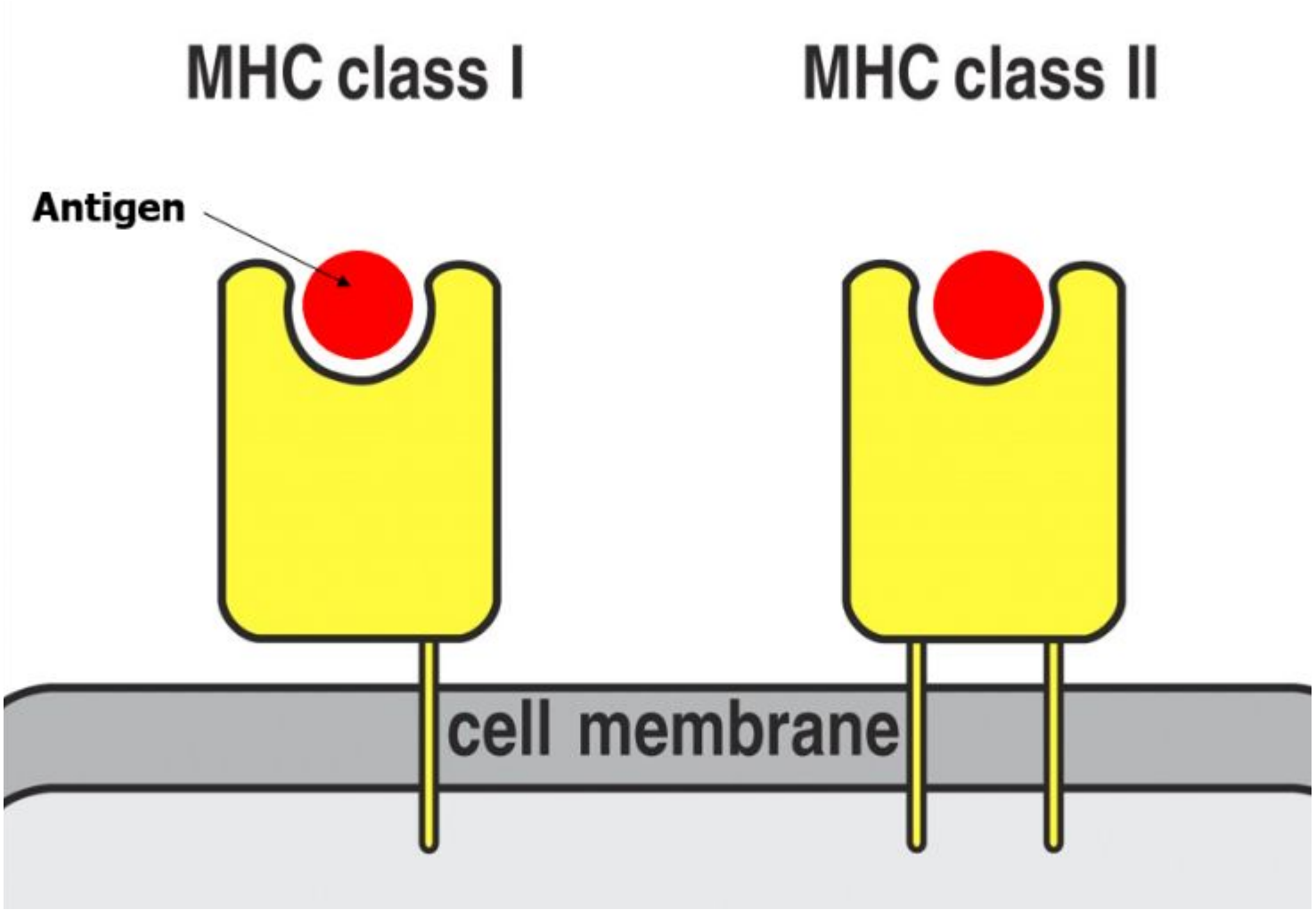



Vα
Vβ
Cα
Cβ
T-cell
receptor

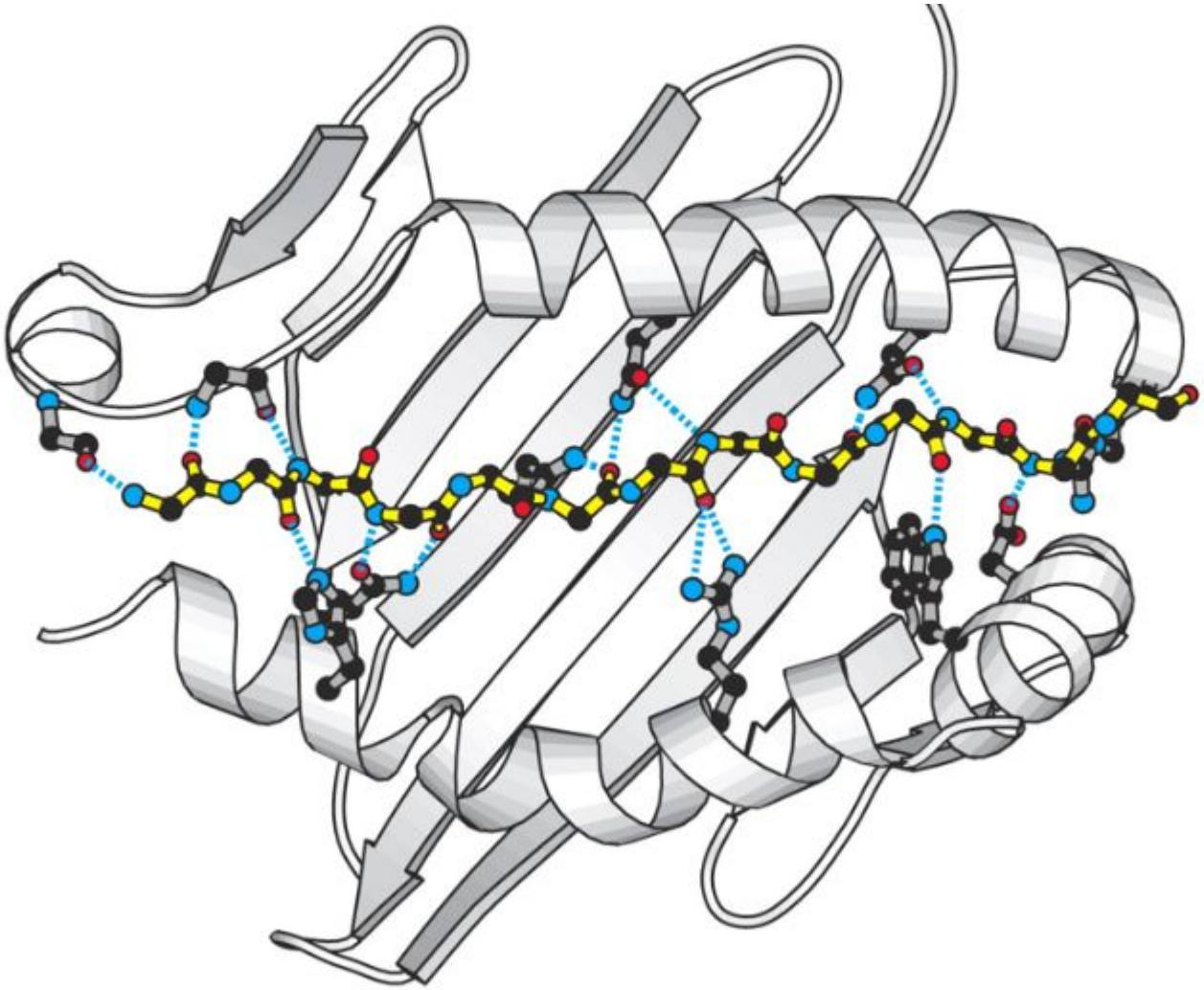
Origen of variation in TCR



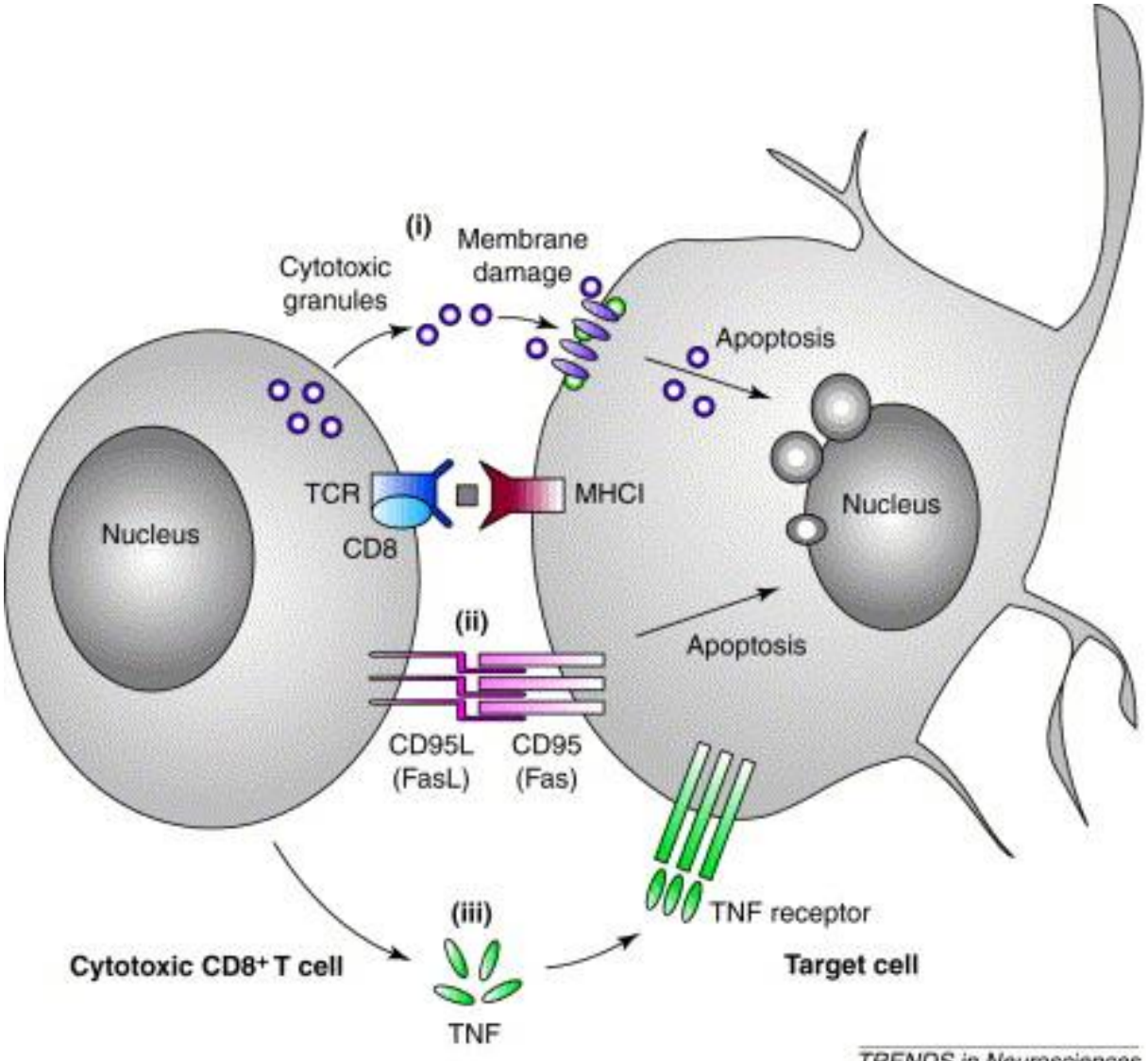
How to know what happening in the cell?



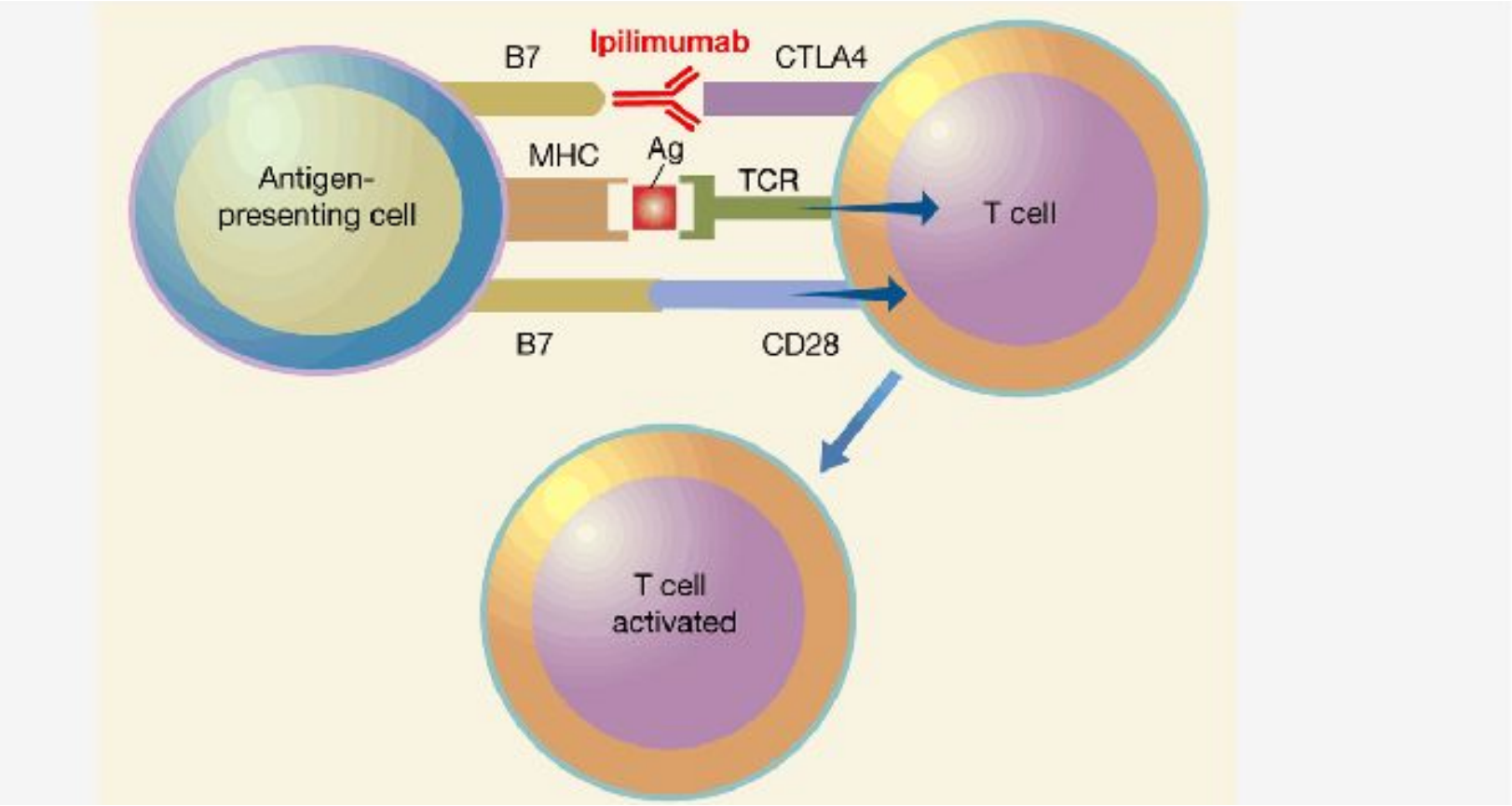
MHC with peptide



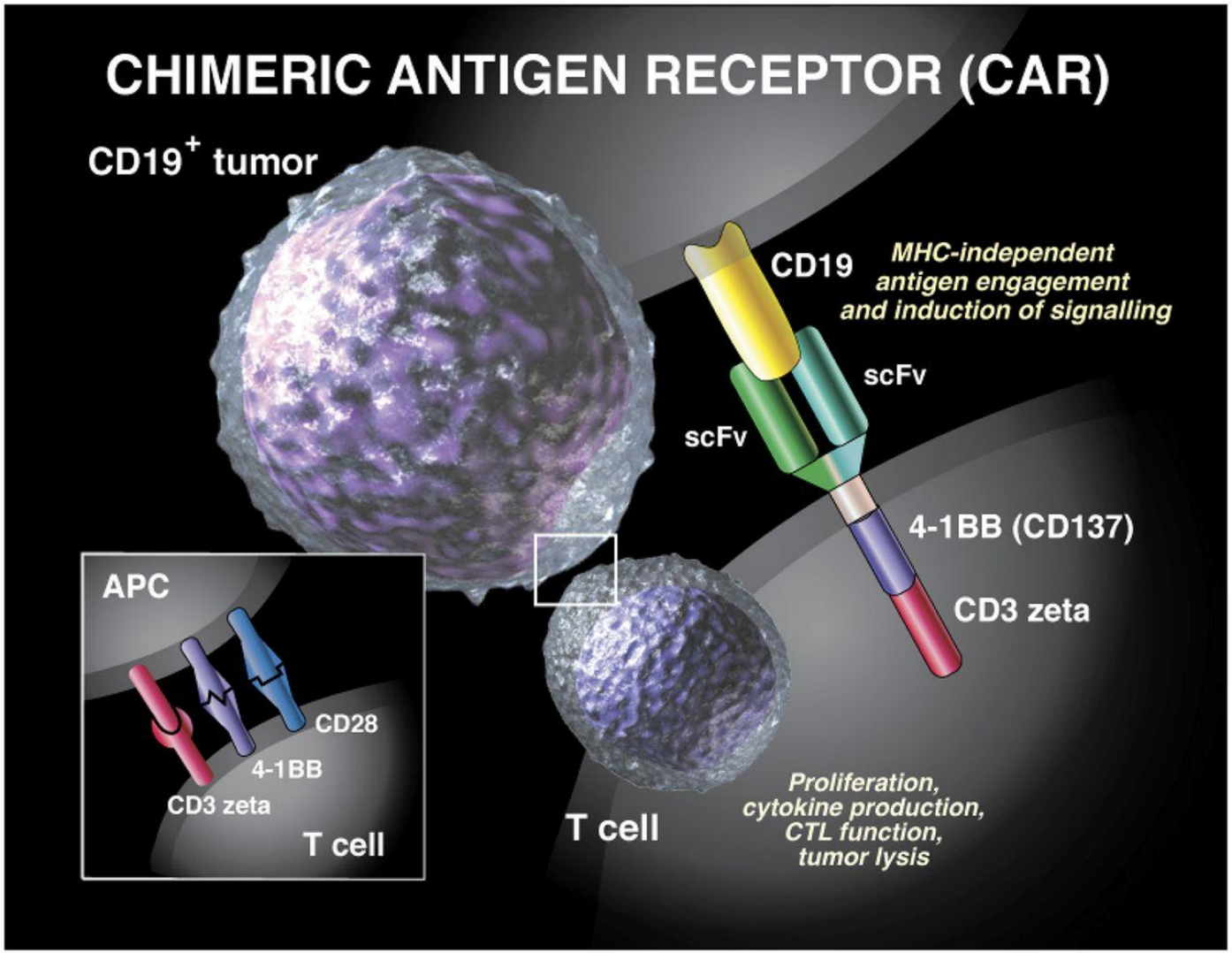
Killer kiss

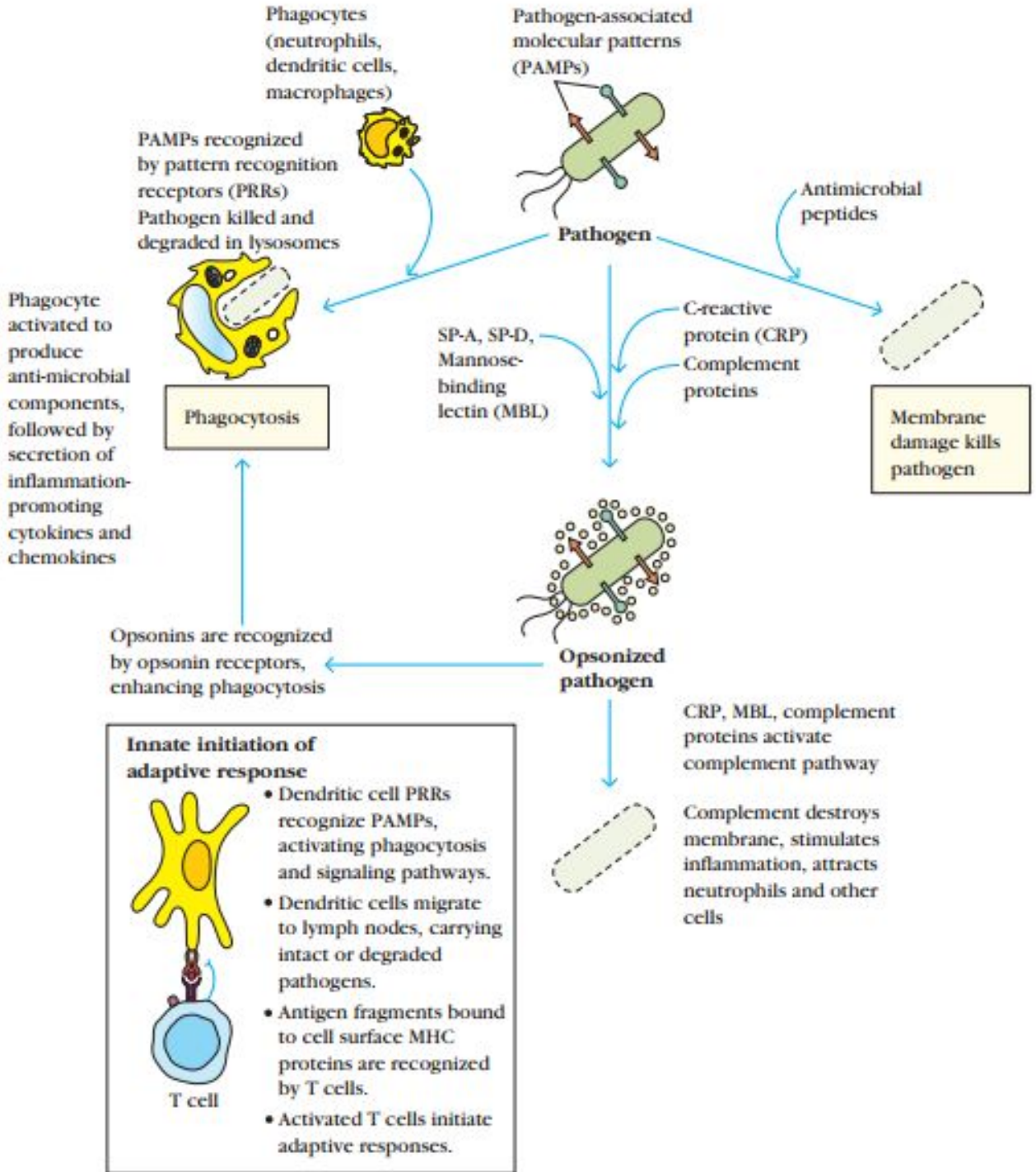

(i)
Membrane damage
Cytotoxic granules
Apoptosis
Nucleus
TCR
CD8
MHCI
Nucleus
(ii)
Apoptosis
CD95L (FasL)
CD95 (Fas)
TNF receptor
(iii)
Cytotoxic CD8+ T cell
Target cell
TNF

Cancer cells can inhibit T-cells



T-CAR


CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent antigen engagement and induction of signalling
scFv
scFv
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation, cytokine production, CTL function, tumor lysis


Phagocytes (neutrophils, dendritic cells, macrophages)
Pathogen-associated molecular patterns (PAMPs)
PAMPs recognized by pattern recognition receptors (PRRs)
Pathogen killed and degraded in lysosomes
Pathogen
Antimicrobial peptides
Phagocyte activated to produce anti-microbial components, followed by secretion of inflammation-promoting cytokines and chemokines
Phagocytosis
SP-A, SP-D, Mannose-binding lectin (MBL)
C-reactive protein (CRP)
Complement proteins
Membrane damage kills pathogen
Opsonized pathogen
Opsonins are recognized by opsonin receptors, enhancing phagocytosis
CRP, MBL, complement proteins activate complement pathway
Complement destroys membrane, stimulates inflammation, attracts neutrophils and other cells
Innate initiation of adaptive response
• Dendritic cell PRRs recognize PAMPs, activating phagocytosis and signaling pathways.
• Dendritic cells migrate to lymph nodes, carrying intact or degraded pathogens.
• Antigen fragments bound to cell surface MHC proteins are recognized by T cells.
• Activated T cells initiate adaptive responses.
T cell