Immune system - introduction

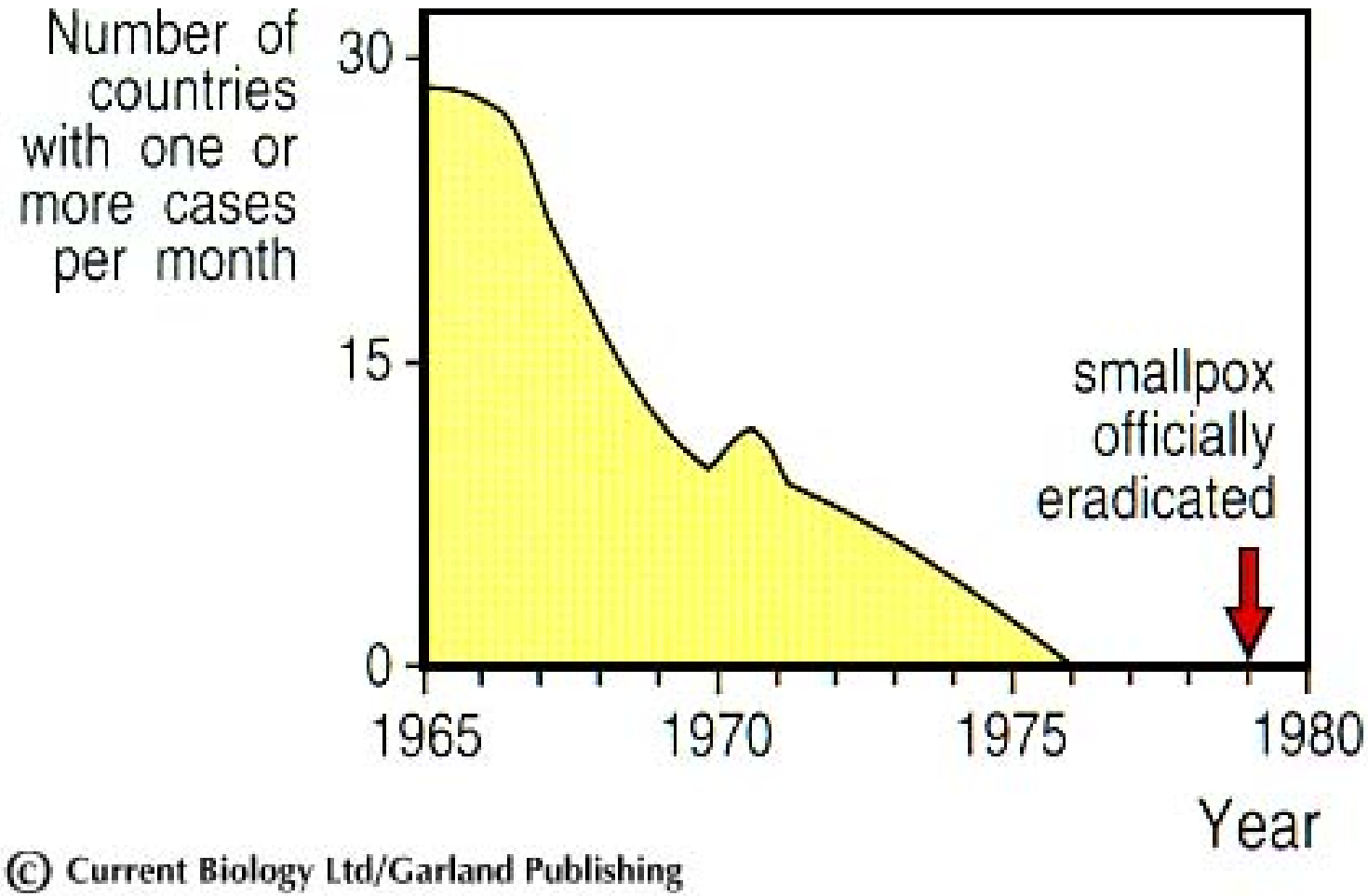
Radek Spisek

Institute of Immunology, 2nd Medical School, Charles University

Edward JENNER

1749-1823

Eradication of variola (smallpox)



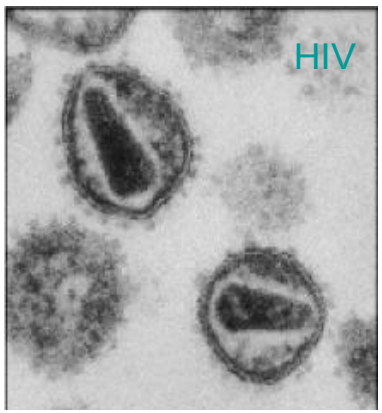
‘Know The Enemy’

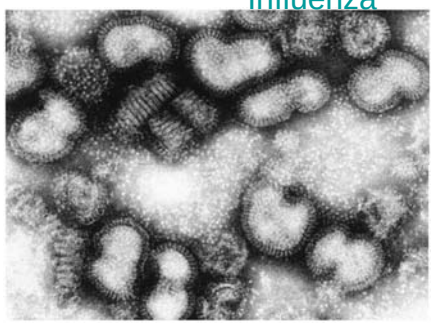
- The immune system exists to prevent and combat infection

- Everything else is secondary to this primary objective
  - Autoimmunity
  - Allergy
  - Tumour immunology
  - Transplantation

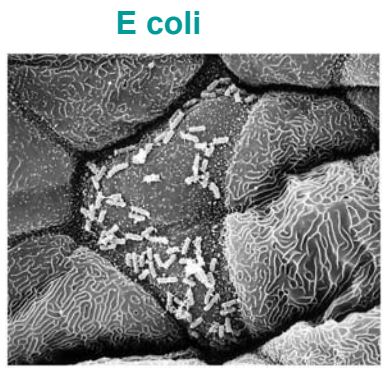
The Enemy

Viruses



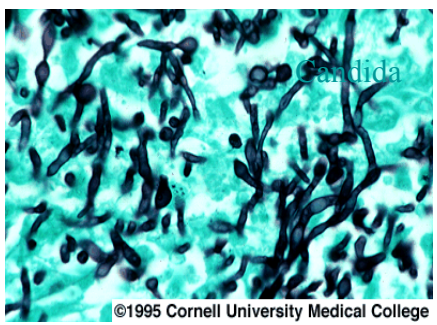


Bacteria

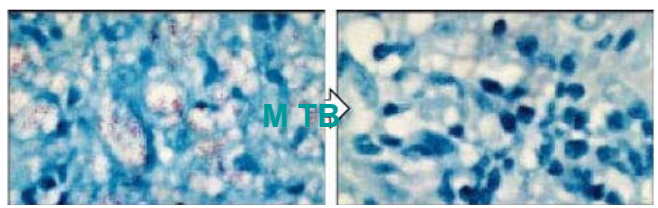


Parasites

Fungi



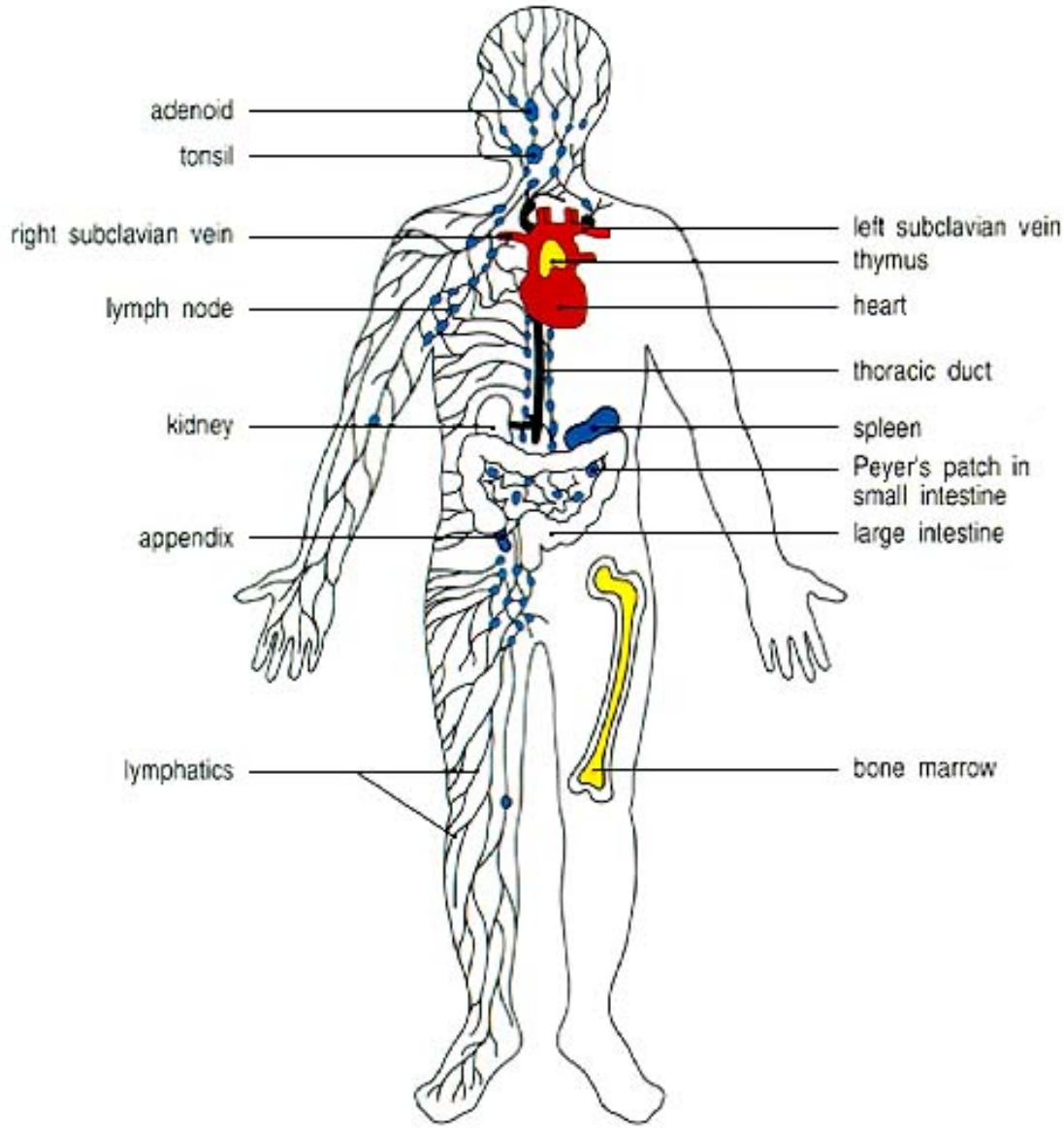
Mycobacteria



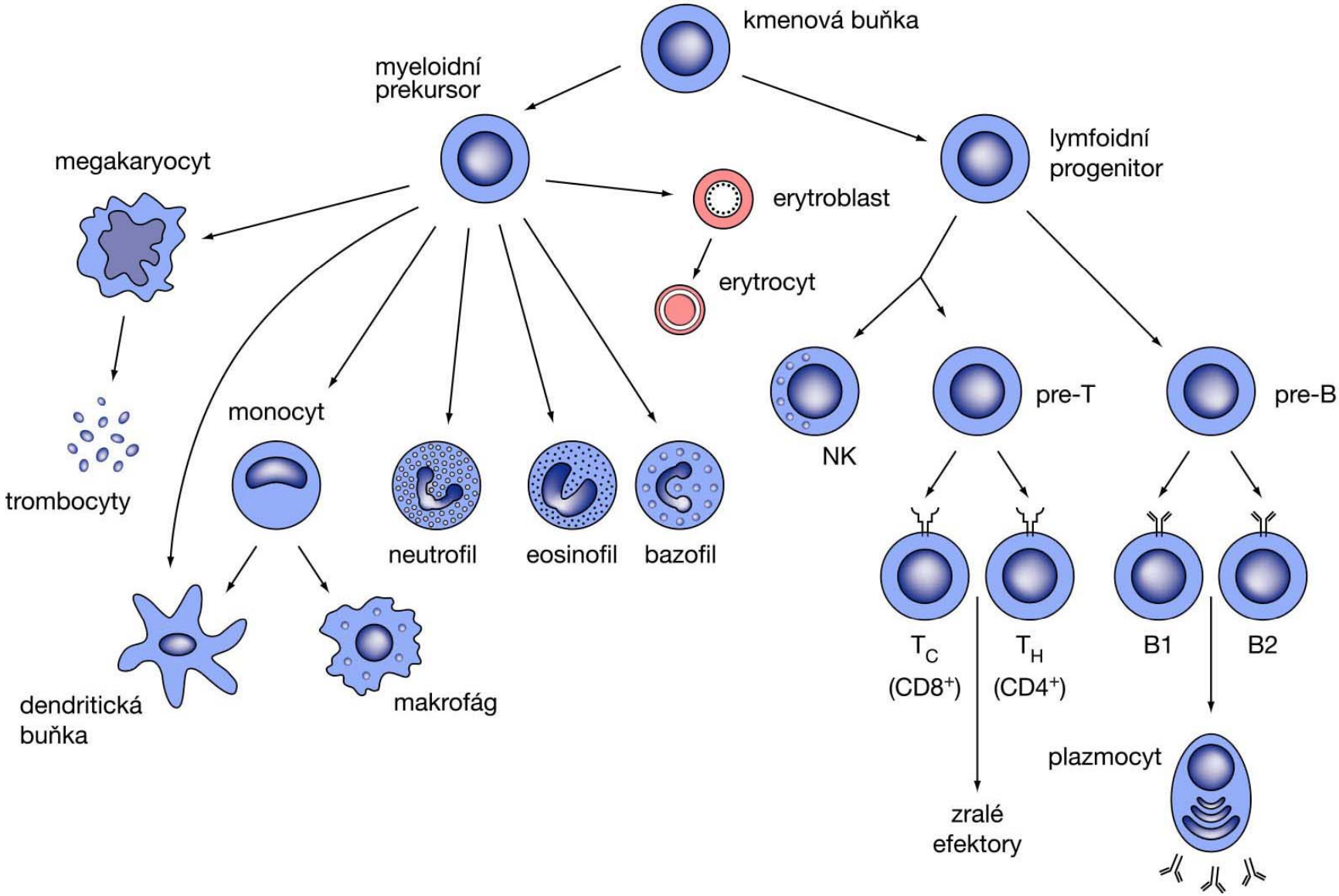
Antigens

- exo - antigens: microbes, foreign substances (alo, xeno-grafts, vaccines, sera, drugs – haptens
- auto-antigens: self tissue
- Chemical structure: proteins, glykoproteins, mucoproteins, polysacharides, lipids, glykolipids, fosfolipids
- Membrane receptors, enzymes, nuclear structures, secerned products (bacterial toxines)

Components of the immune system

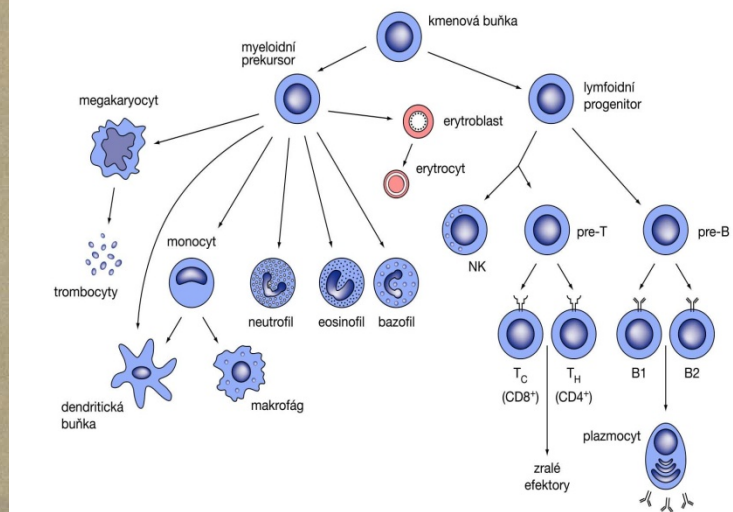


Hematopoetic system



Hematopoetic stem cell- CD34

SCT- stem cell transplantation



The Defence

Innate Defence

- Non Specific barriers
  - Anatomical/Physiological
- Acute phase reactants and Inflammation
  - Complement/Interferons/CRP
- Innate cells
  - PMN/Macrophages/NK cells

Adaptive Defence

- Adaptive immunity
  - B cells – Antibody
  - T cells – Orchestration, Cytokines, Lytic granules

Why Differentiate between the Innate and Acquired Immunity ?

Innate Immunity

- Characteristics:
  - Universal
  - Rapid
  - Lacks memory
  - Non specific but ...

Acquired Immunity

- Characteristics:
  - Not universal
  - ‘Slow’ to develop
  - Possesses memory
  - Specific but….
  - ‘Plays to the tune of the Innate immune system’

Innate Immunity

- Mechanical barriers
  - Inhibit attachment and penetration of microorganisms
    - Intact skin
    - Mucus
    - Cilia
    - Saliva,tears, urine for expelling microbes
    - Coughing, sneezing and shedding!
- Chemical barriers
  - HCL
  - Lysozyme
  - pH

Innate Immunity

- Inflammation
- Proteolytic cascades
- Phagocytosis
- Cytokines
- Natural Killer cells

Cell type	Relative representation (%)
Neutrophil granulocytes	60 - 70
Eosinophil granulocytes	1 - 3
Basophil granulocytes	< 2
Monocytes	5 - 10
Lymphocytes	20 - 40

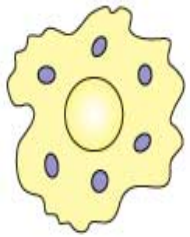
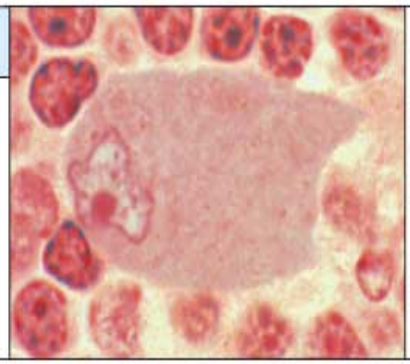
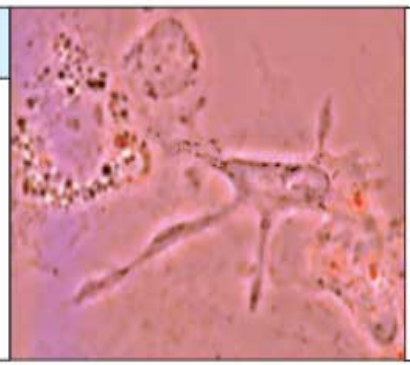
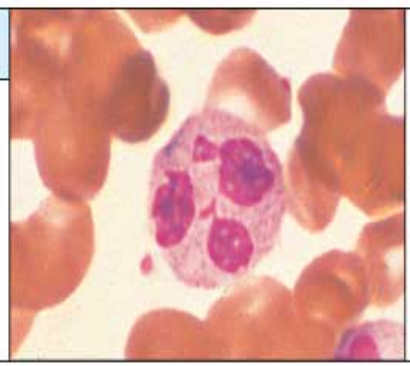
Cell		Activated function
Macrophage 		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell 		Antigen uptake in peripheral sites Antigen presentation in lymph nodes
Neutrophil 		Phagocytosis and of activation bactericidal mechanisms

Fig 1.4 part 1 of 2 © 2001 Garland Science

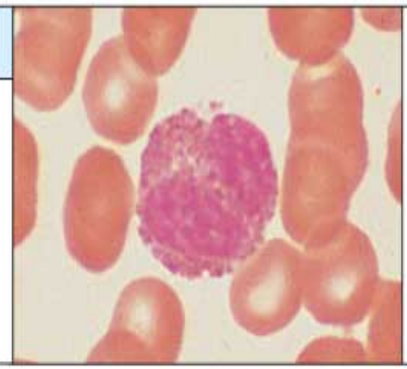
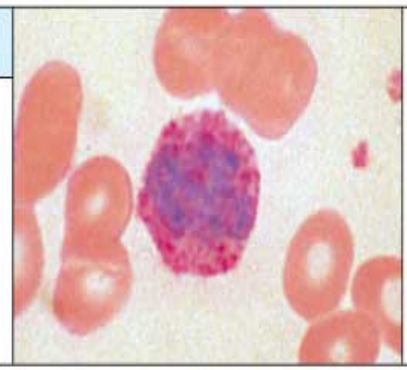
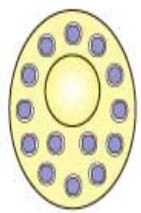
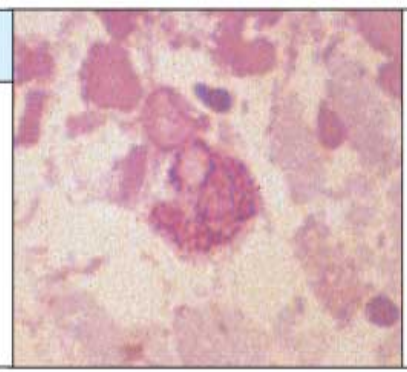
Cell		Activated function
Eosinophil 		Killing of antibody-coated parasites
Basophil 		Unknown
Mast cell 		Release of granules containing histamine and other active agents

Fig 1.4 part 2 of 2 © 2001 Garland Science

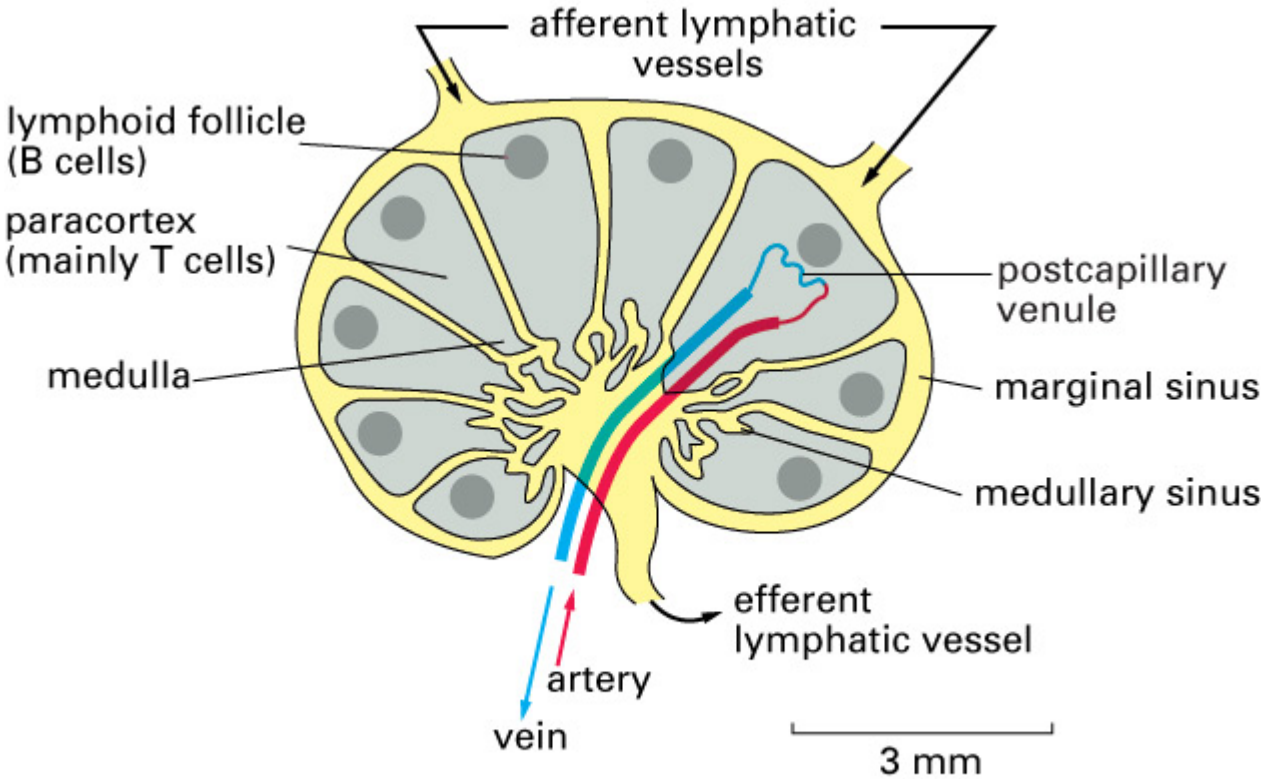


Figure 24–16. Molecular Biology of the Cell, 4th Edition.

2. ANTIGEN NONSPECIFIC MECHANISMS; PHAGOCYTES, GRANULOCYTES

PHAGOCYTOSIS

- **NEUTROPHIL GRANULOCYTES REMOVAL OF BACTERIA; PUS**
- **MACROPHAGES – MAINLY REMOVAL OF DAMAGED AND DYING CELLS**

MECHANISMS:

  - **RECEPTORS OF "FOREIGN" STRUCTURES (TLR, LECTINS)**
  - **OPSONIZATION (Ig, COMPLEMENT) – BINDING TO Fc-RECEPTORS, COMPLEMENT RECEPTORS**
  - **ENGULFMENT**
  - **"KILLING"**
    - **FUSION WITH LYSOSOMES (LOW pH, ENZYMES, DEFENSINS)**
    - **OXIDATIVE BURST**

OXIDATIVE (RESPIRATORY) BURST

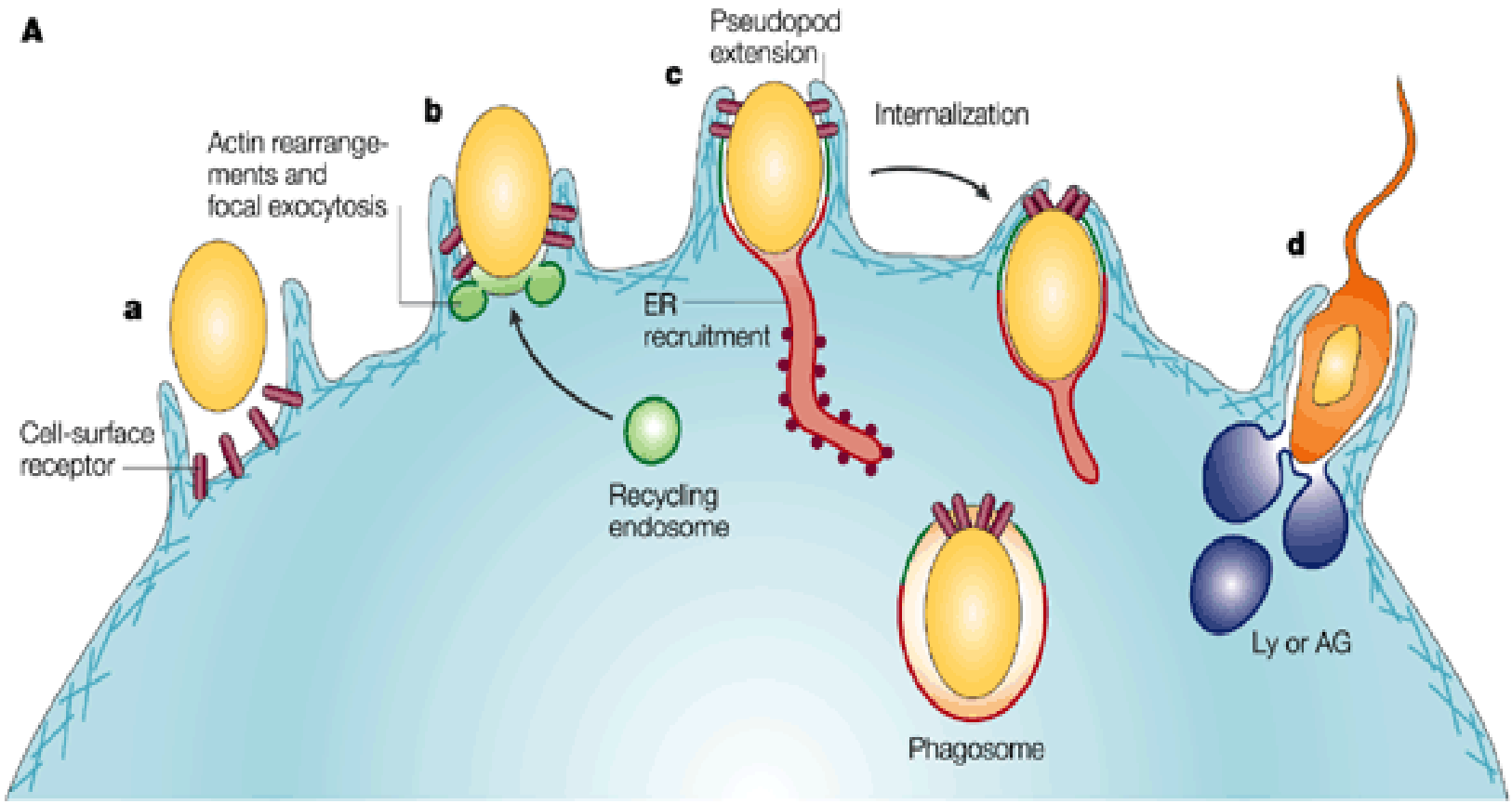
- **Prodution of reactive oxygen compounds by the enzyme NADPH-oxidase**
- **Localized in the phagosome membrane and catalyses the reactions:**

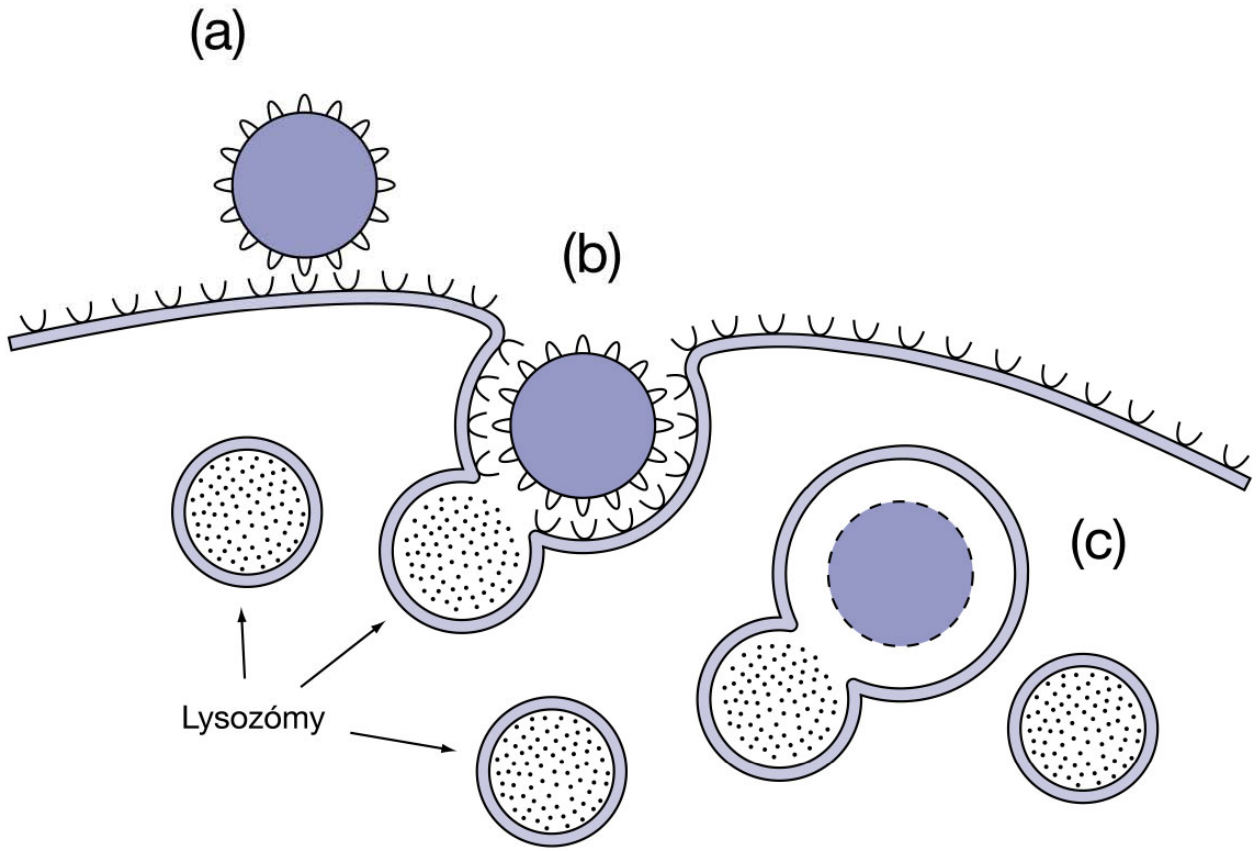
  (surface) $O_2 \rightarrow O_2^-$ **(superoxide anion-radical)**

  (cytoplasm) $NADPH \rightarrow NADP^+ + H^+$

- **Superoxide reacts further to produce toxic compounds ("singlet oxygen", H_2O_2, ClO^-)**

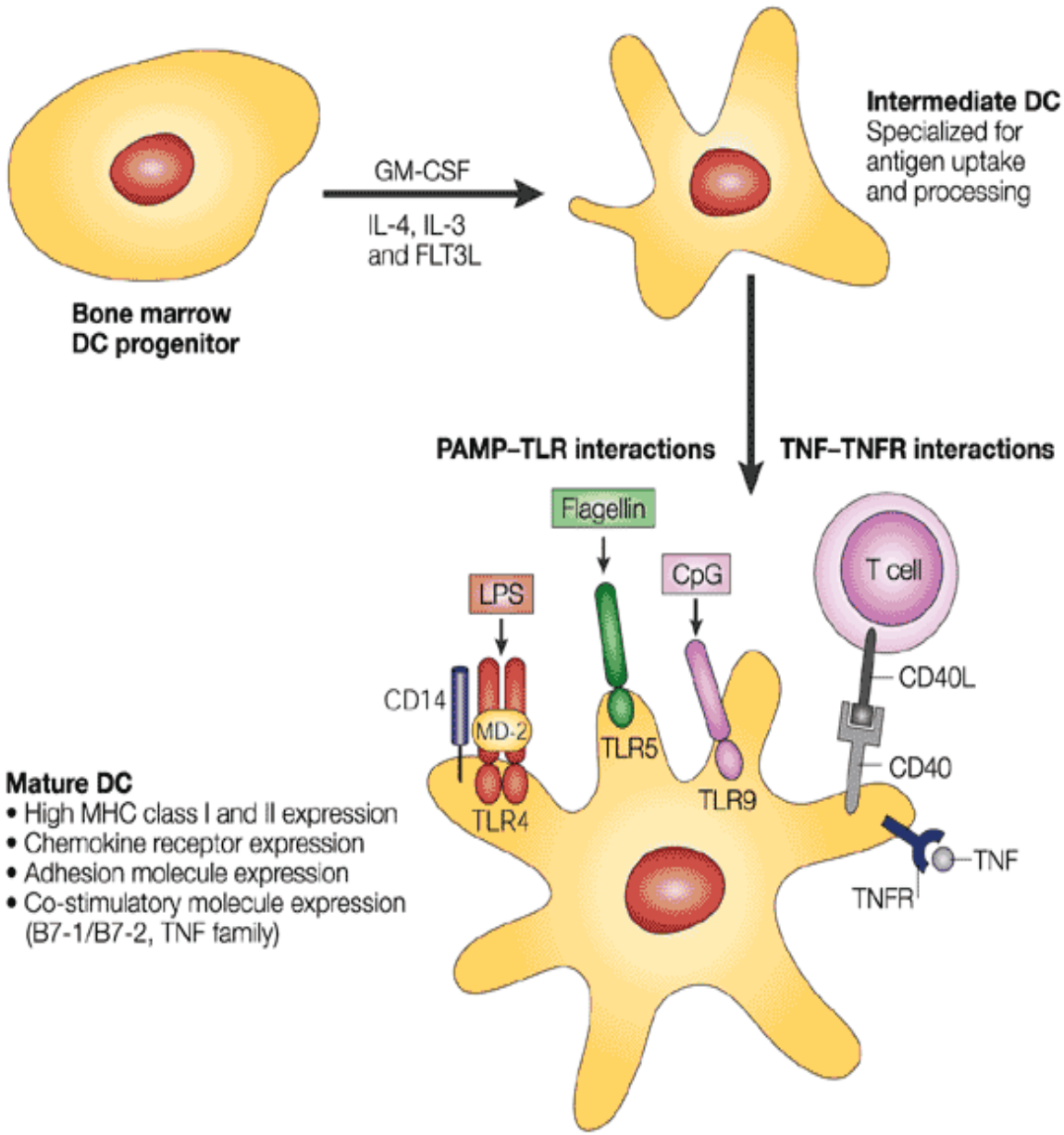
PHAGOCYTOSIS




(a)
(b)
(c)
Lysozómy

ESSENTIAL LINK BETWEEN THE INNATE AND ADAPTIVE SYSTEMS:

DENDRITIC CELLS


Bone marrow
DC progenitor
GM-CSF
IL-4, IL-3
and FLT3L
Intermediate DC
Specialized for
antigen uptake
and processing
PAMP–TLR interactions
TNF–TNFR interactions
Flagellin
LPS
CpG
T cell
CD14
MD-2
TLR5
TLR9
CD40L
CD40
TLR4
TNF
TNFR
Mature DC
• High MHC class I and II expression
• Chemokine receptor expression
• Adhesion molecule expression
• Co-stimulatory molecule expression
(B7-1/B7-2, TNF family)
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DENDRITIC CELLS MUST BE PRE-STIMULATED BY

DANGER SIGNALS

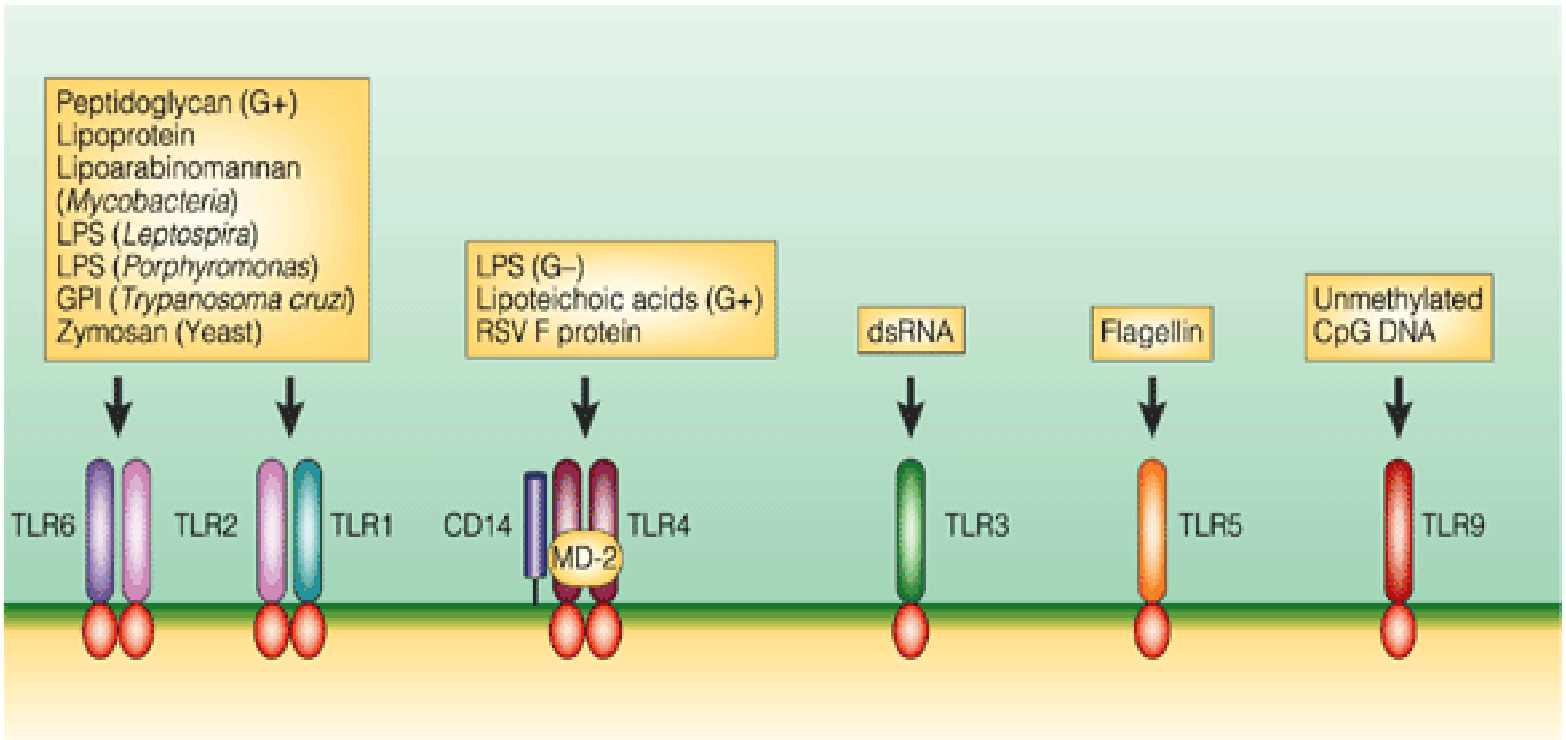
TO BE ABLE TO ACTIVATE T LYMPHOCYTES

DANGER SIGNALS:

- EXOGENOUS (PAMPs)

- ENDOGENOUS (e.g. STRESS PROTEINS RELEASED FROM NECROTIC CELLS)

TOLL-LIKE RECEPTORS



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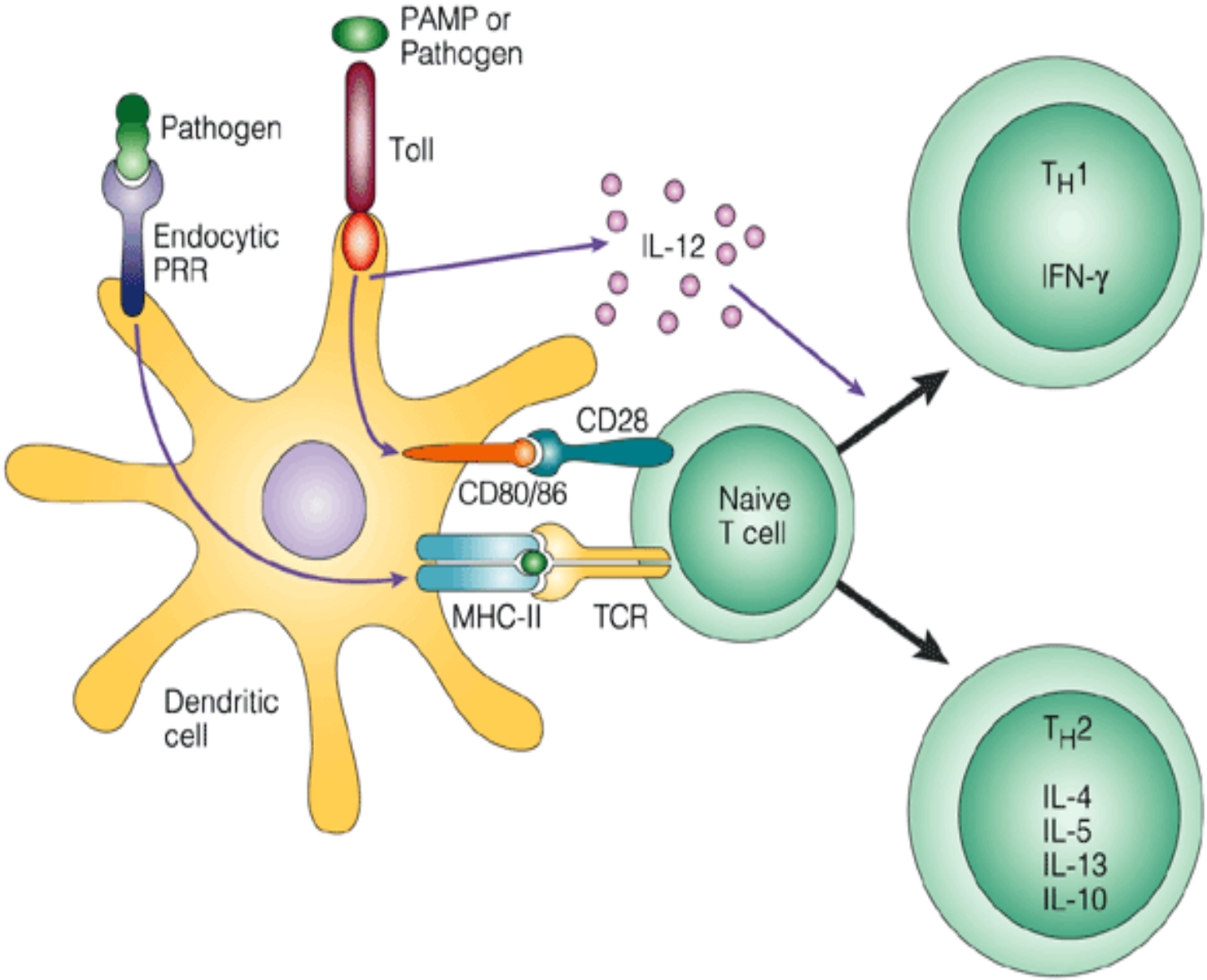

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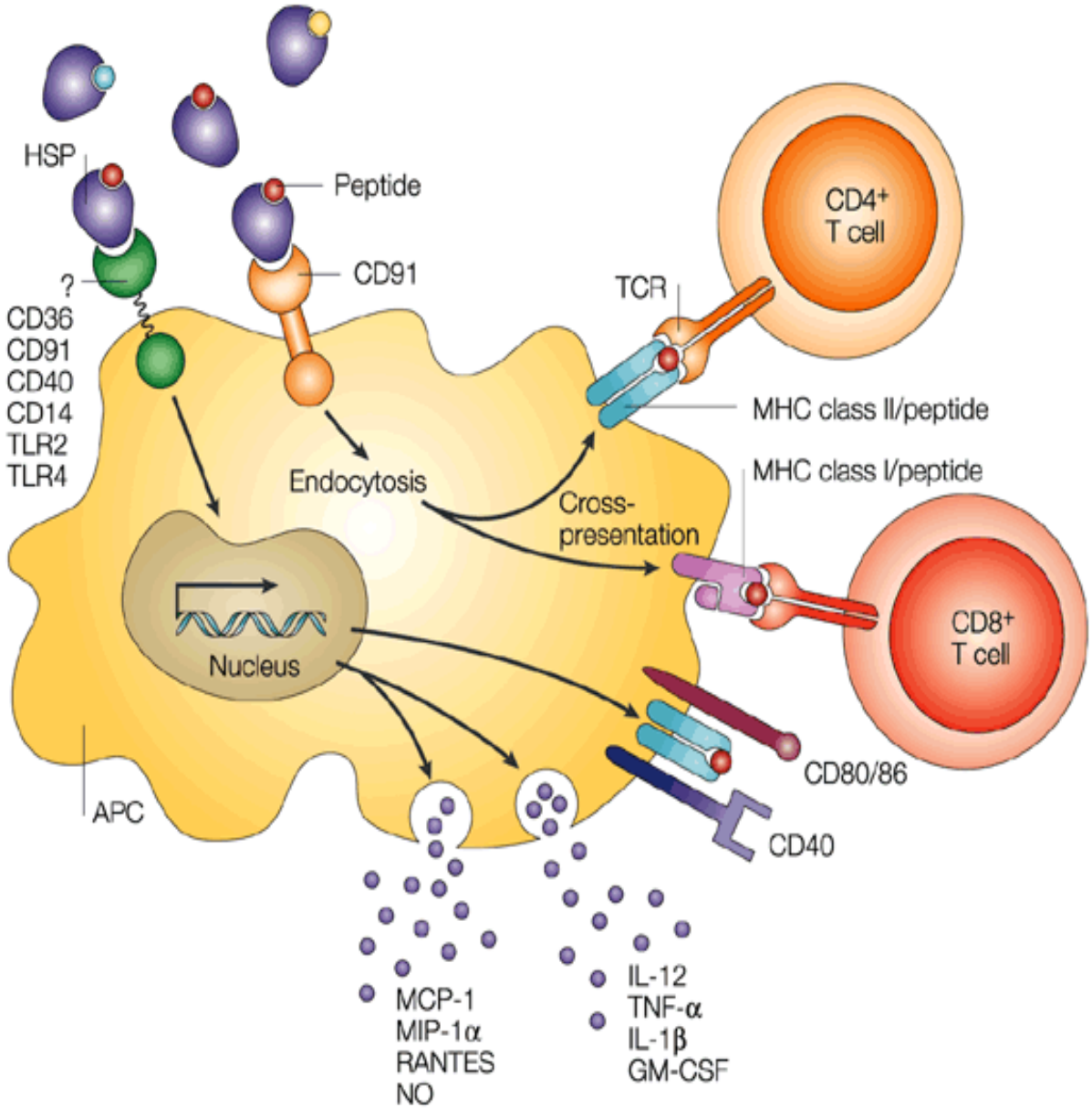
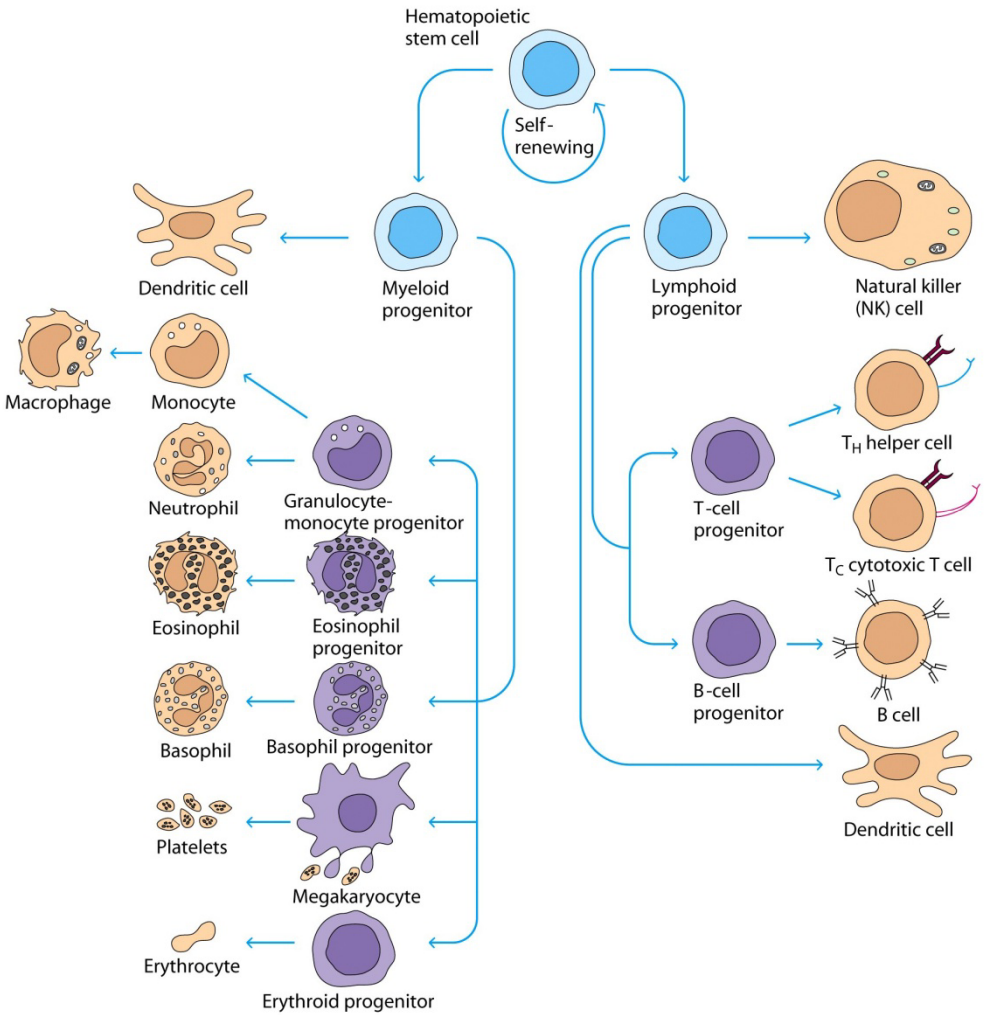
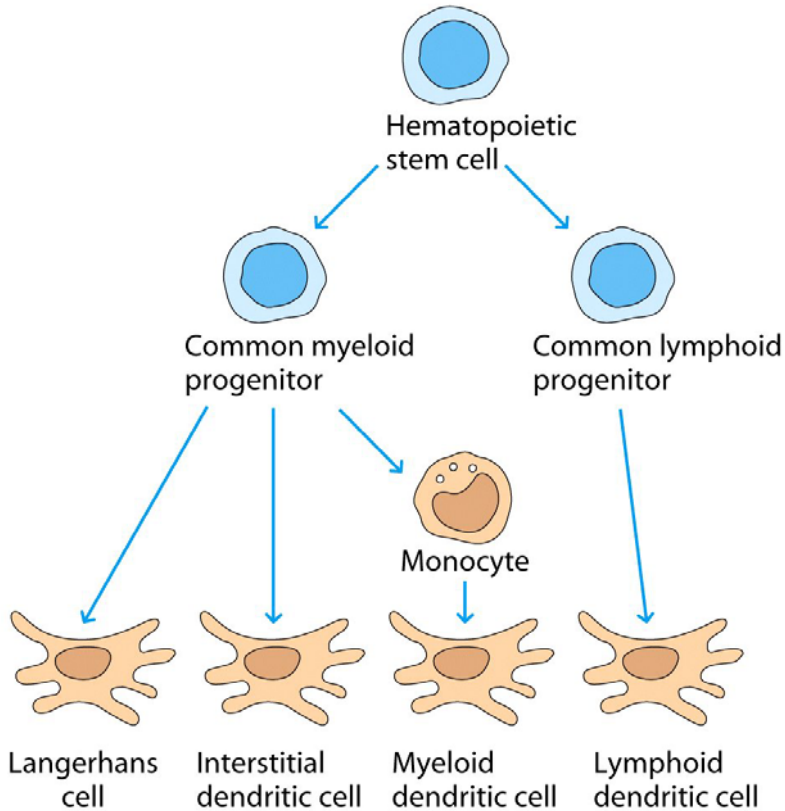

HSP
Peptide
?
CD91
CD36
CD91
CD40
CD14
TLR2
TLR4
CD4+
T cell
TCR
MHC class II/peptide
MHC class I/peptide
Endocytosis
Cross-
presentation
Nucleus
CD8+
T cell
CD80/86
CD40
APC
MCP-1
MIP-1α
RANTES
NO
IL-12
TNF-α
IL-1β
GM-CSF

Adaptive Immunity

Effector cells



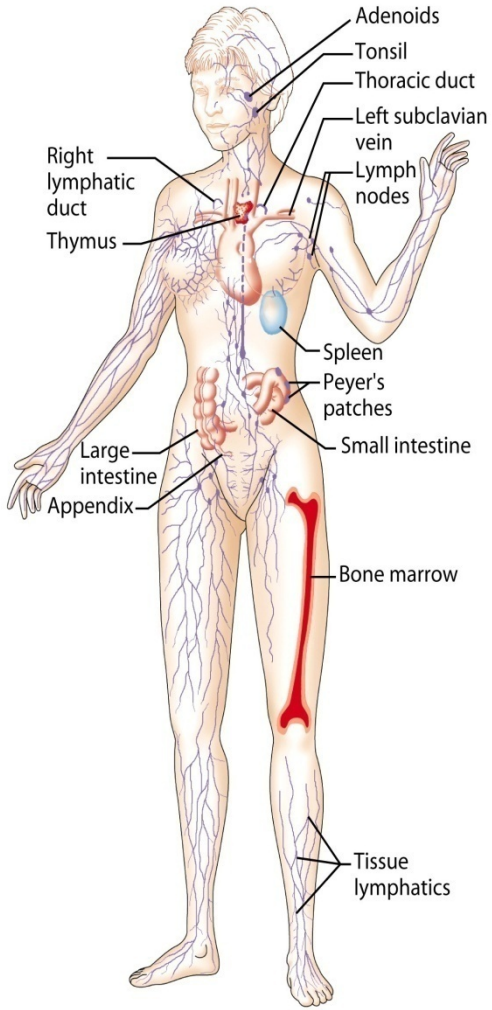
APCs



Lymphoid Tissues

Primary (Central) Lymphoid organs

Thymus
Bone Marrow



Secondary (Peripheral) Lymphoid organs

Spleen
Lymph nodes
MALT
GALT

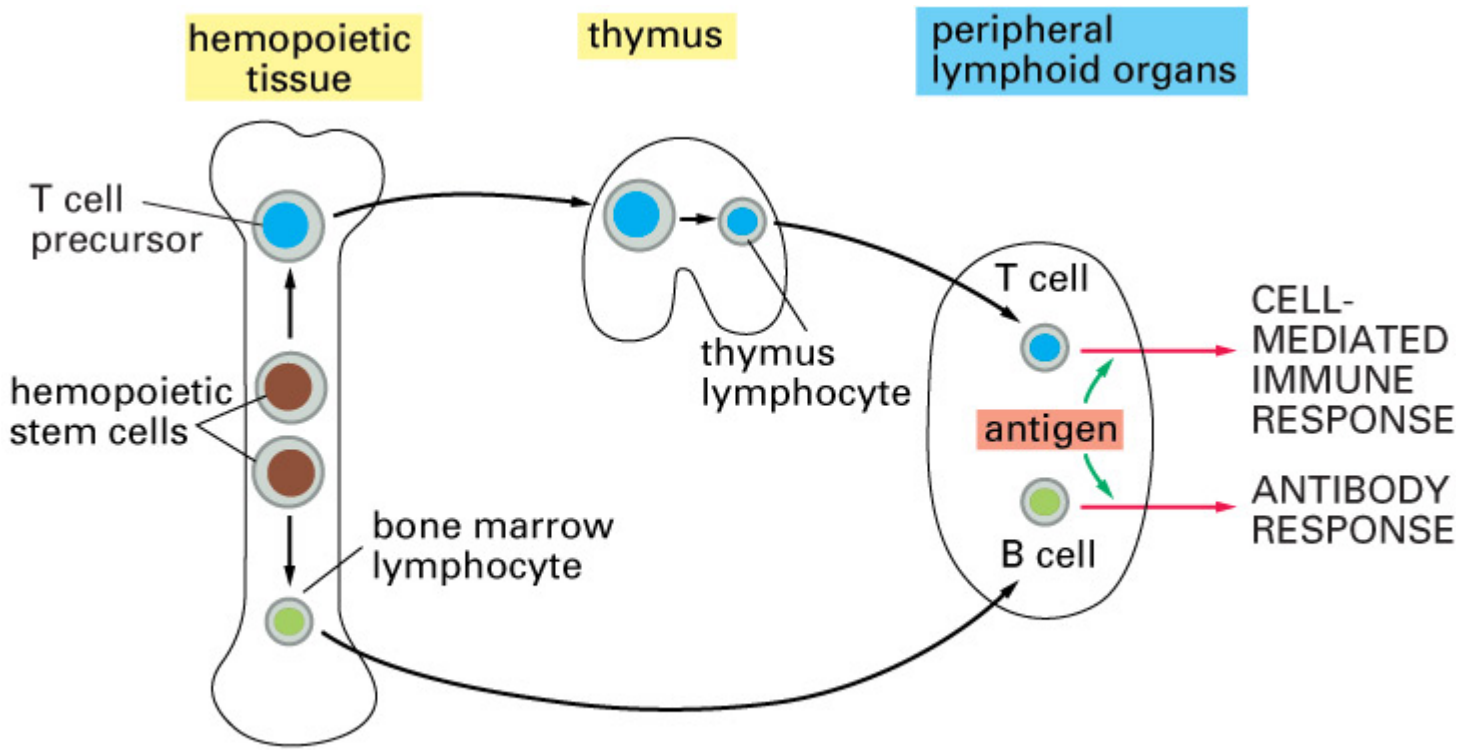
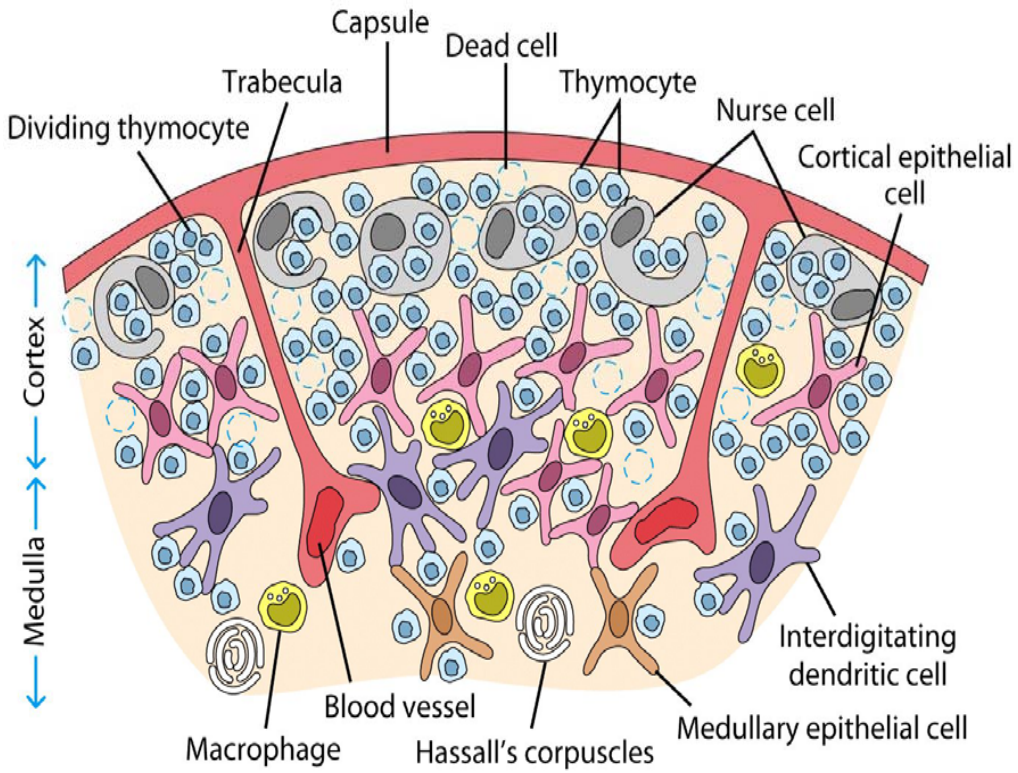


Figure 24–6. Molecular Biology of the Cell, 4th Edition.

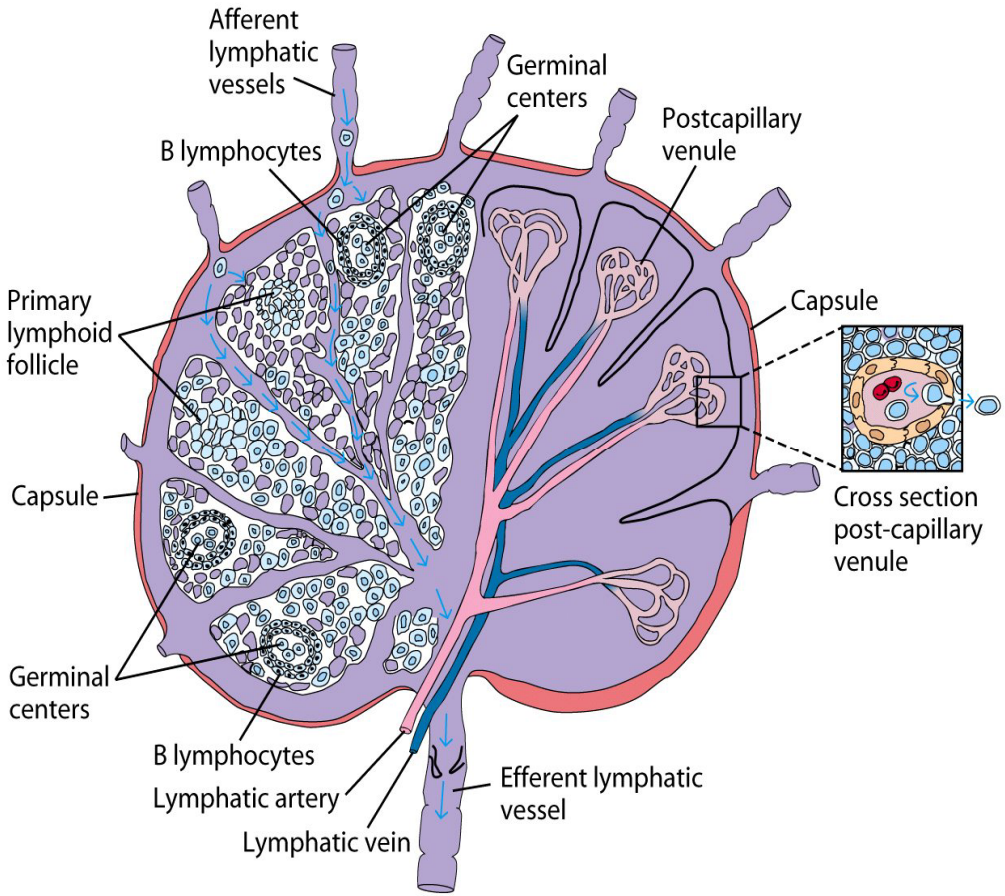
THYMUS

- T cell selection takes place in the thymus
- Requirement for antigen presentation to T cells
- Positive/negative selection
- Emergence of self tolerant CD4 T cells and CD8 T cells



Lymph Node

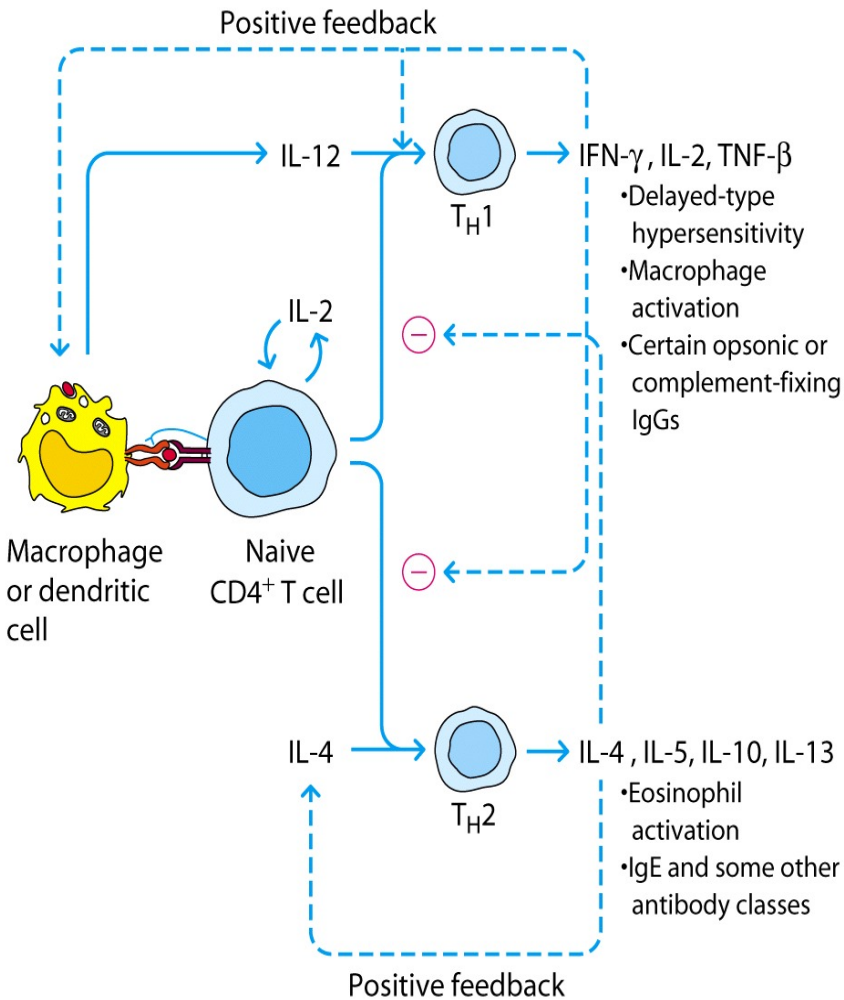
- The lymph node is the meeting point of recirculating T cells B cells and APC with foreign antigen
- B cell development continues in the LN through the process of CLONAL SELECTION
- SHM and CSR are important changes that occur here
- Plasma cells (Ig producing factories) return to the BM



The soldiers and artillery of the Adaptive defense

CD4 T cells

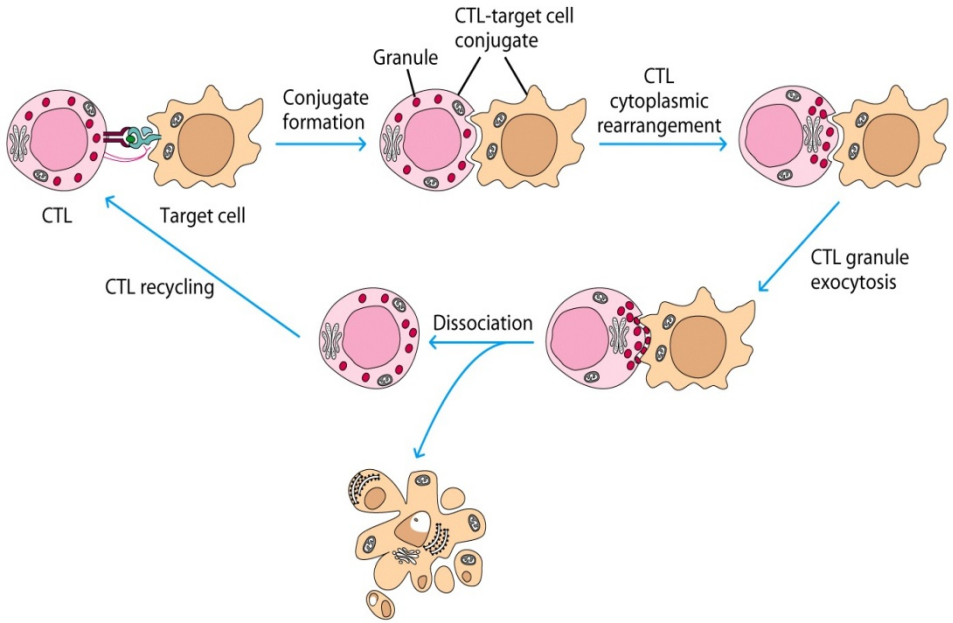
Cytokine/function	T_H1	T_H2
CYTOKINE SECRETION		
IL-2	+	–
IFN-γ	++	–
TNF-β	++	–
GM-CSF	++	+
IL-3	++	++
IL-4	–	++
IL-5	–	++
IL-10	–	++
IL-13	–	++
FUNCTIONS		
Help for total antibody production	+	++
Help for IgE production	–	++
Help for IgG2a production	++	+
Eosinophil and mast-cell production	–	++
Macrophage activation	++	–
Delayed-type hypersensitivity	++	–
T_C-cell activation	++	–

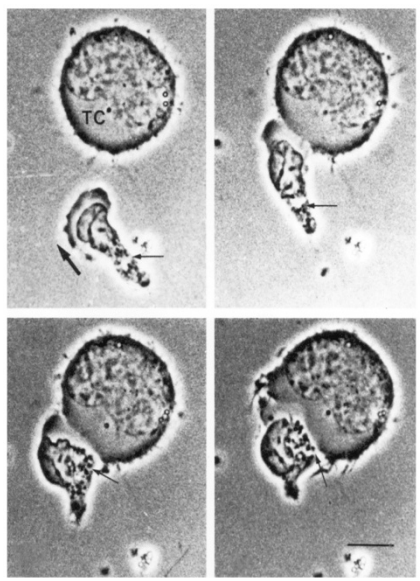


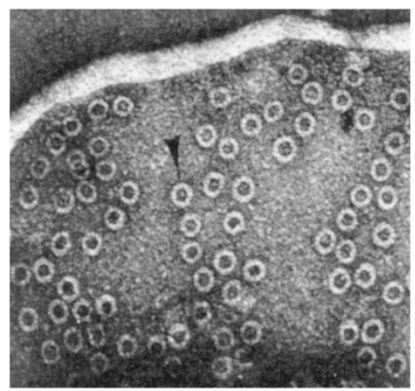
The soldiers and artillery of the Adaptive defense

CD8

- CD8 T cells are the CTLs
- Exocytosis of granules or a FAS/FASL sytem operates to mediate apoptotic cell death in the target cell
- Targeted to MHC class I presented viral peptides



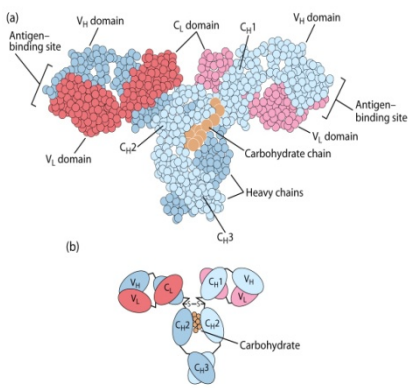


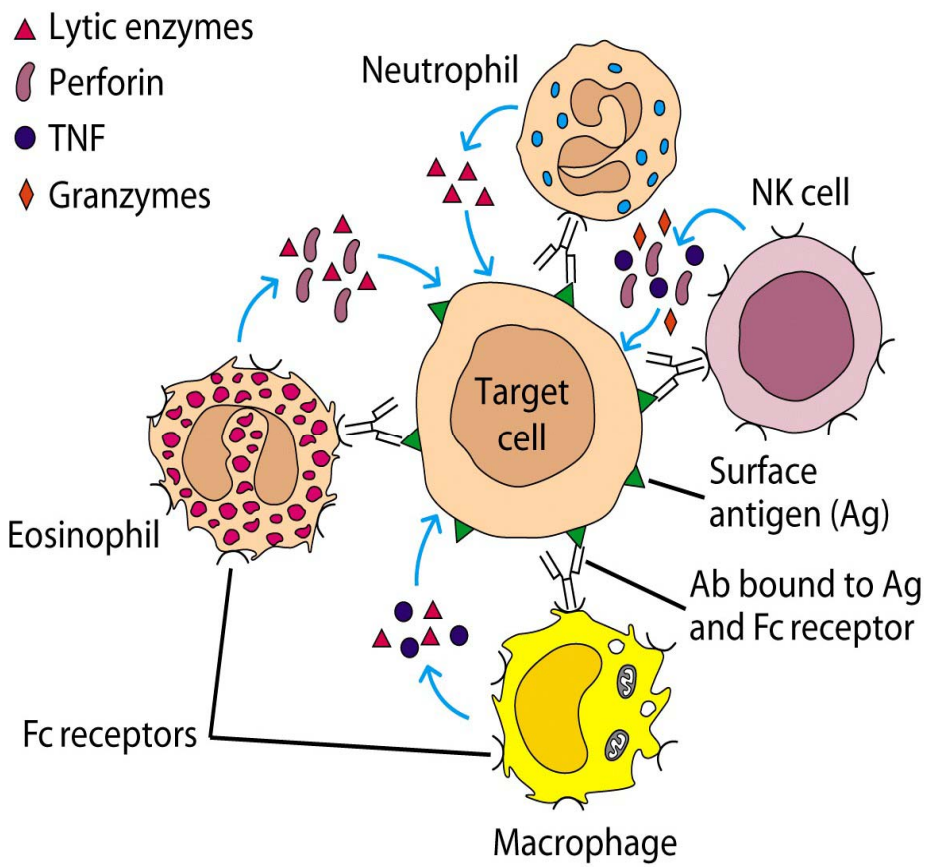


The soldiers and artillery of the Adaptive defense

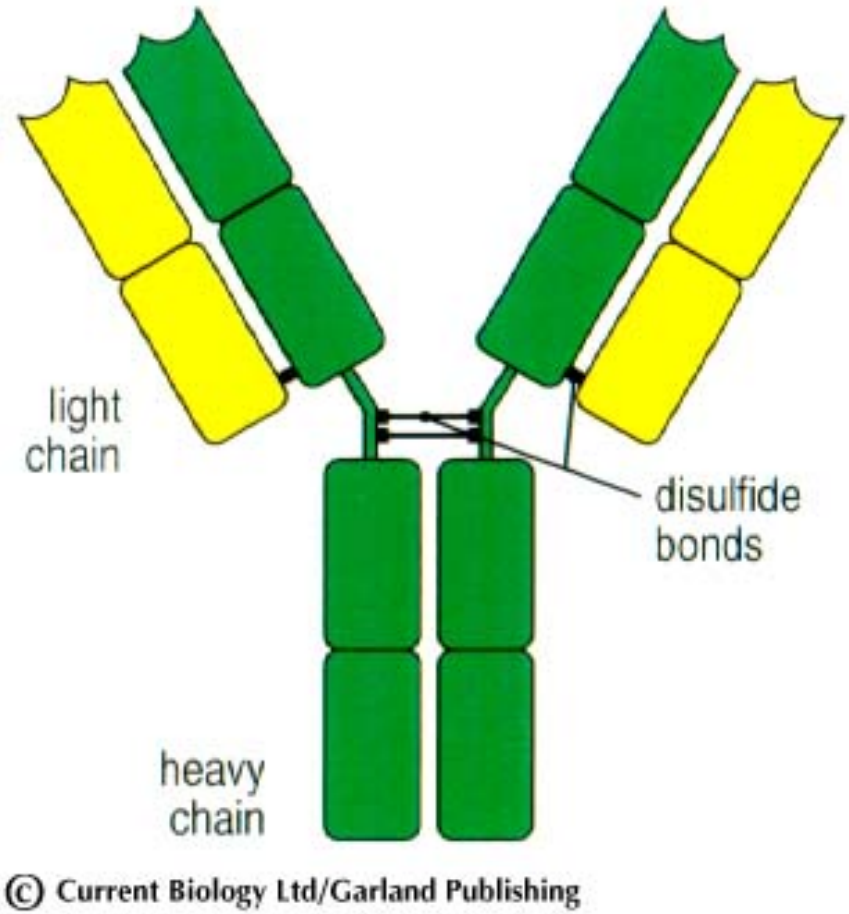
B cells

- Antibodies specific for a pathogen can engage multiple effector responses
- The Fc region determines the effector response that is used
- The Fab region provides the specificity

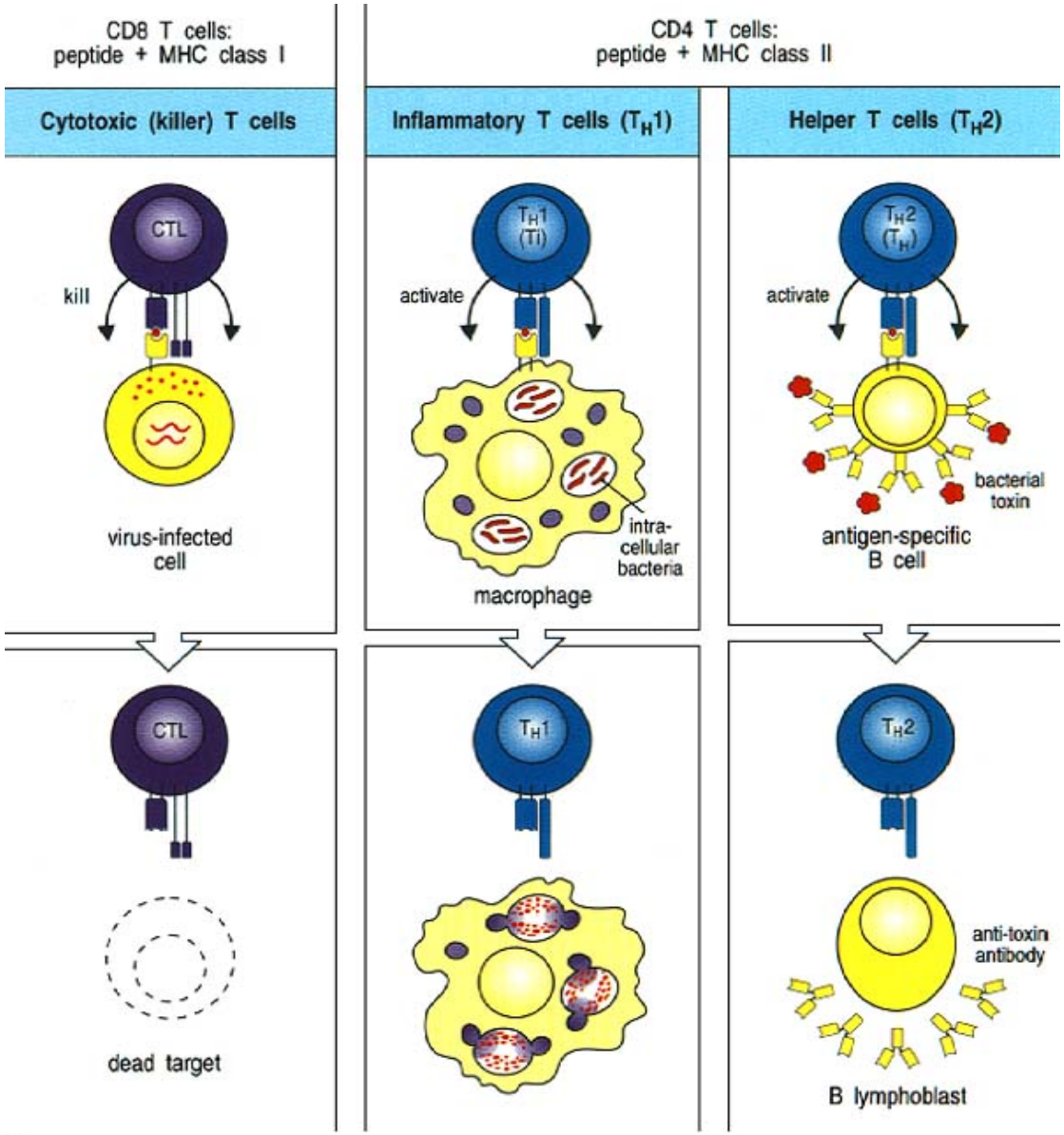




Immunoglobulin structure



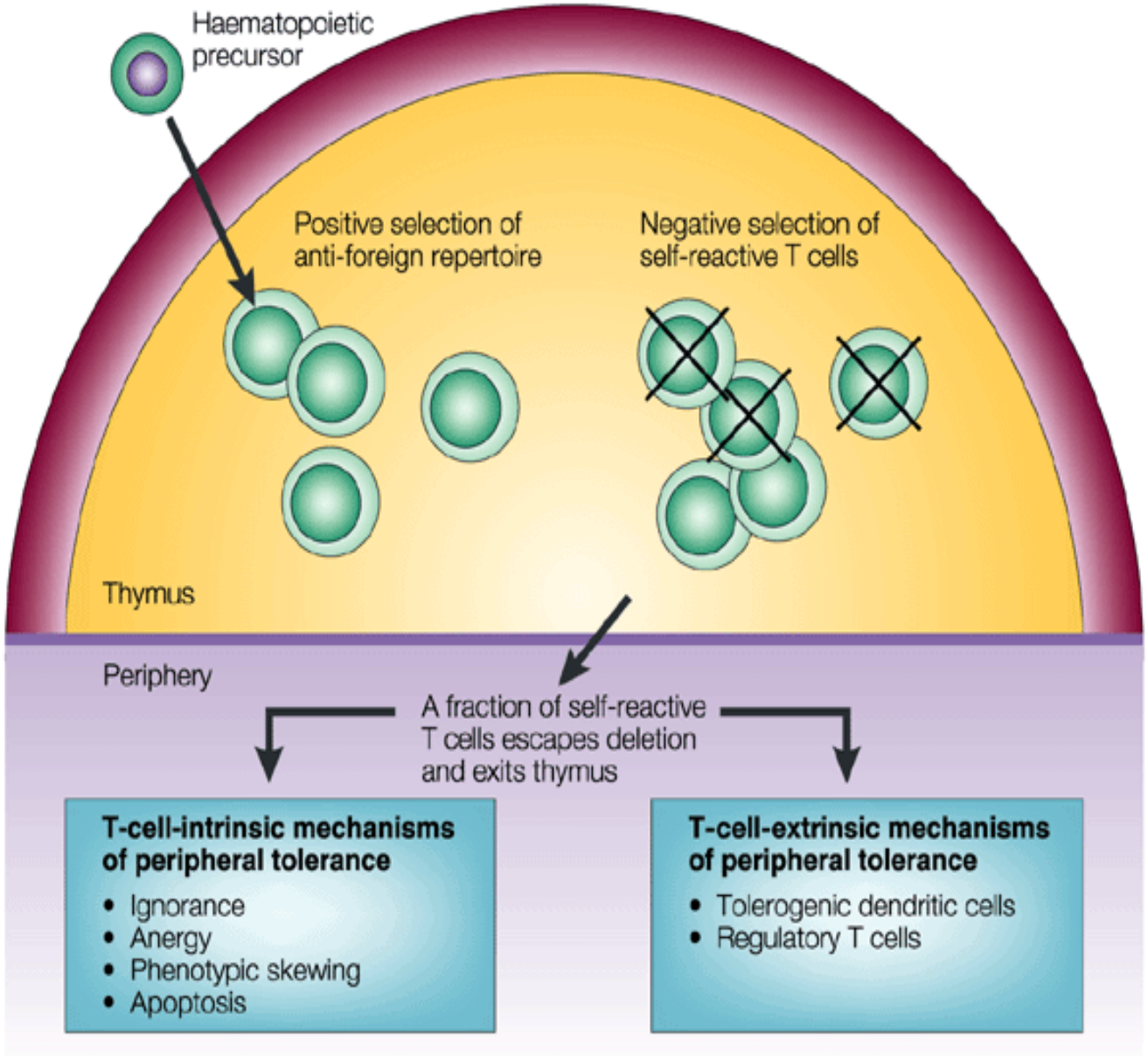
Cytotoxic T cells Helper Th1 Helper Th2



SELF-TOLERANCE

BIG PROBLEM:

HOW TO MAINTAIN SELF-TOLERANCE AND PREVENT AUTOIMMUNITY?



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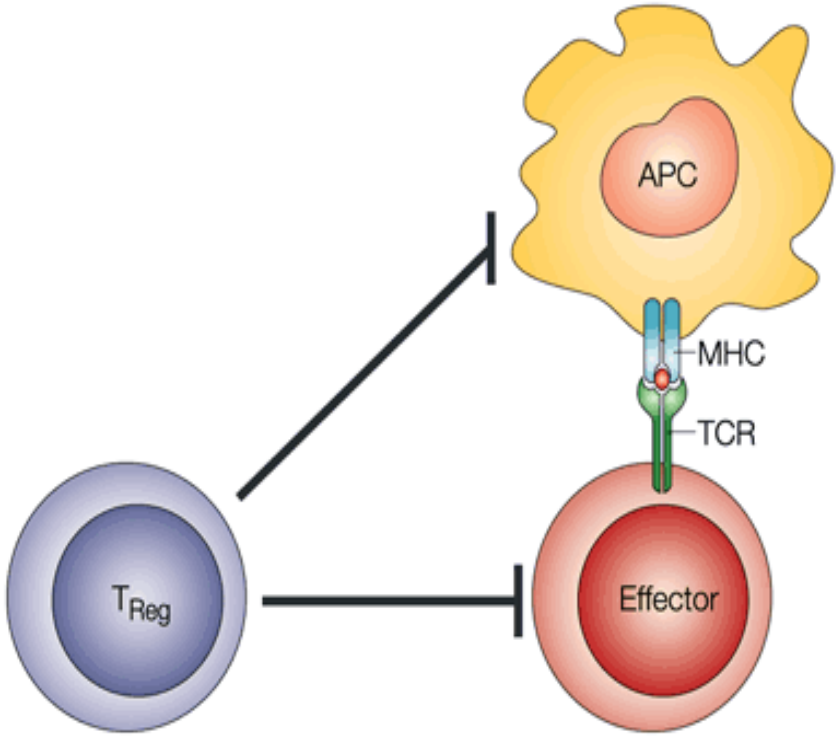
IMMUNOLOGICAL HIT
(WITH EMBARRASSING HISTORY…)

REGULATORY (= SUPPRESSOR) T LYMPHOCYTES

(Treg, Ts, Th3, Tr1…)



Benefits:
- T-cell homeostasis
- prevents autoimmune disease
- tolerance after transplantation
- prevents GVHD
- prevents allergy
- prevents hypersensitivity

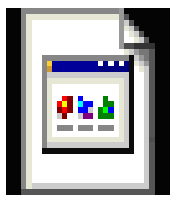
Detrimental effects:
- down-regulation of tumour immunity
- down-regulation of immunity to infection

REGULATORY T LYMPHOCYTES ARISE IN:

- THYMUS (SUPPRESS AUTOIMMUNITY)

- PERIPHERY (THESE DOWN-REGULATE EXCESSIVE IMMUNE RESPONSES

Immune reaction

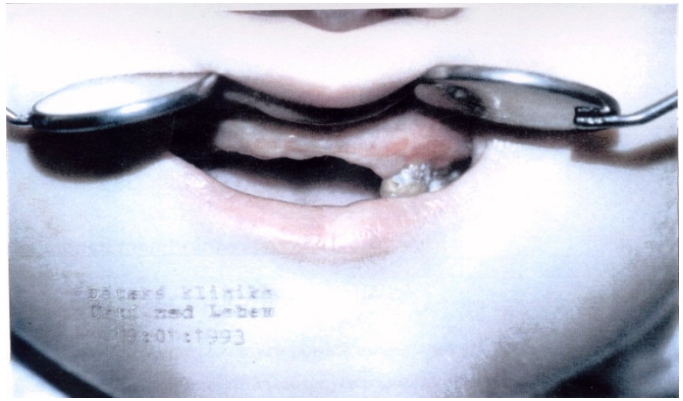


Imunitní reakce.exe

Disorders of immunity

- immune deficiencies
- allergy
- autoimmunity
- tumors

Imunodeficiencies



- Decreased resistance to infections
- Primary (inherited)- genetic disorders
- aquired – malnutrition
- - infection (HIV, mumps..)
  - metabolic diseases
  - drugs, iatrogenic
  - stress

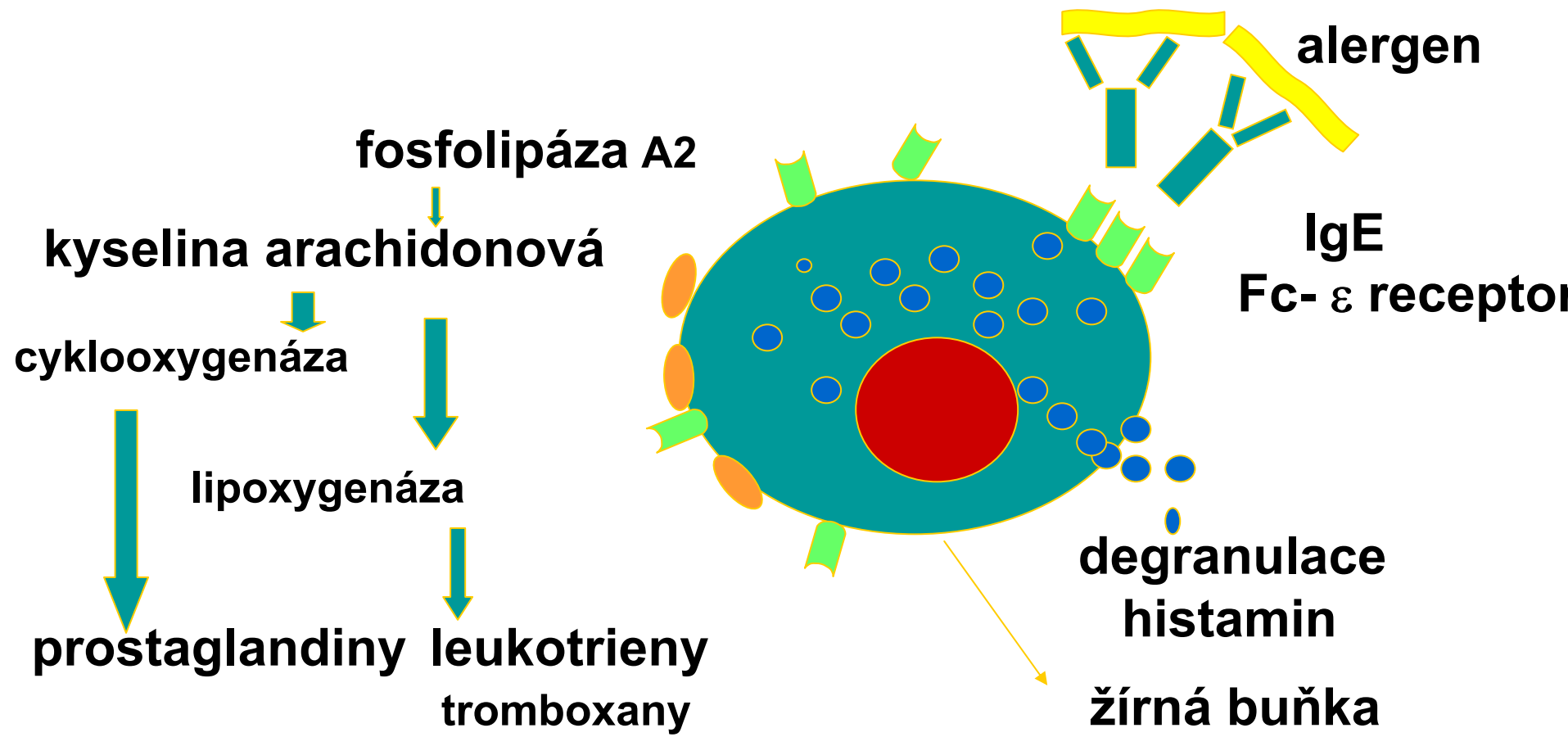
Allergy

Inhalation allergy – hay fever, asthma atopic ekzema

food allergy

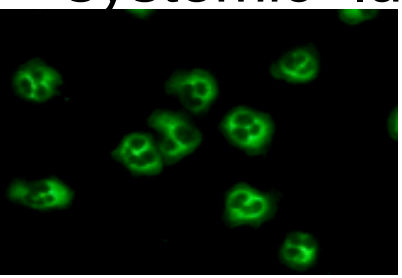
drug allergy

Imunopatologická reakce I.typu - časná přecitlivělost



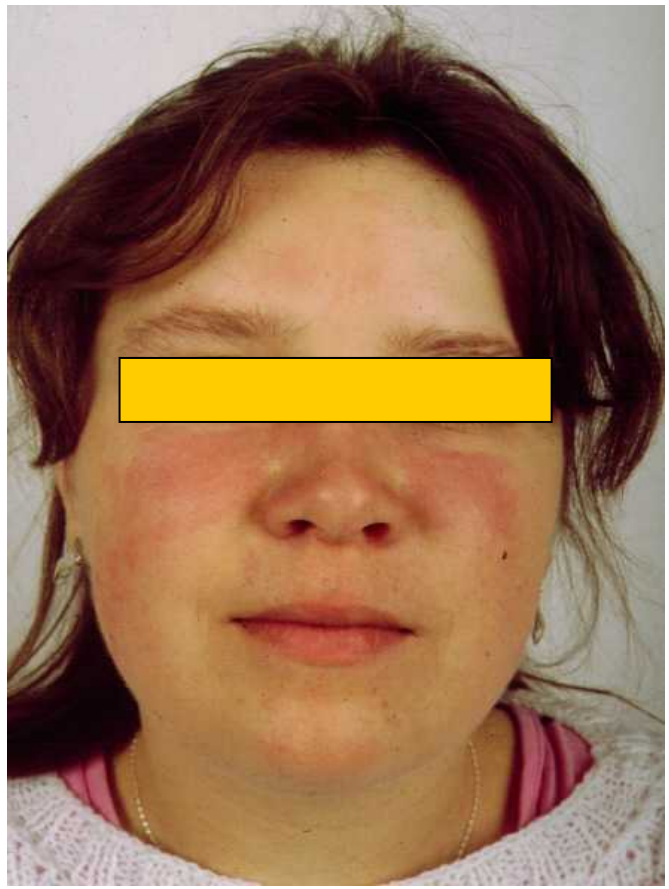
Autoimmune diseases

systemic- lupus erytematodes



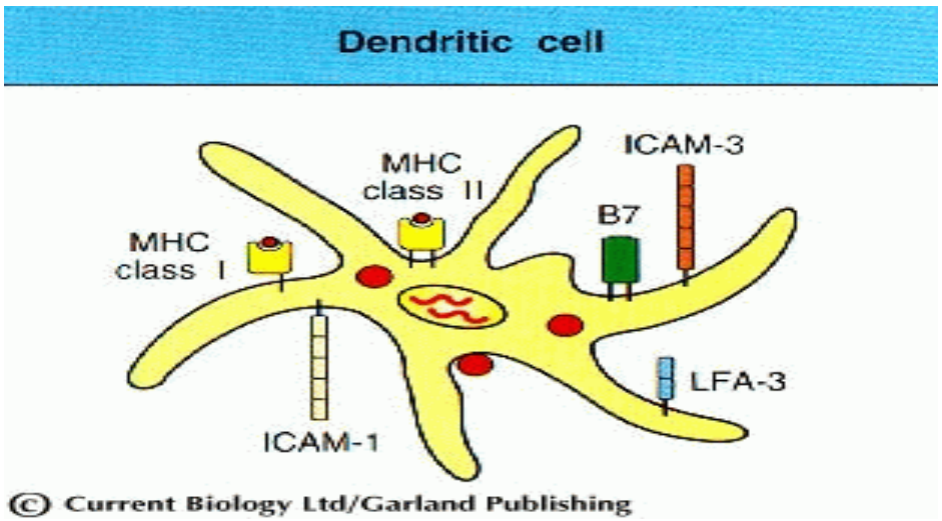
revmatoid artritis
Sjogren syndrom
vasculitis

Organ specific - endocrinopathies
(thyreoiditis,
type I. diabetes,
multiple sclerosis)

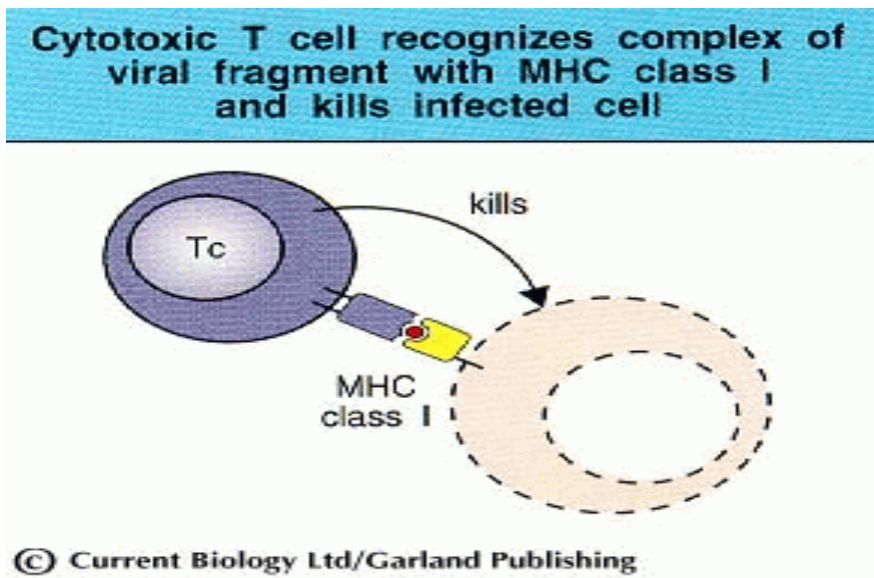


Antitumor immunity

1. Tumor recognition by DC

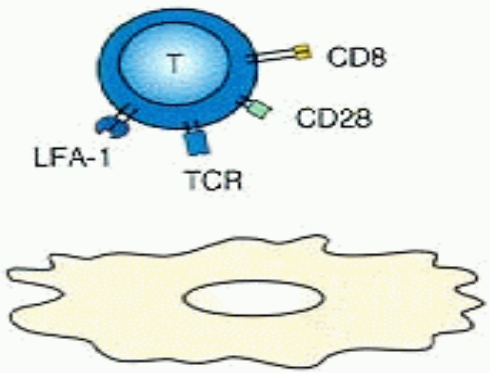


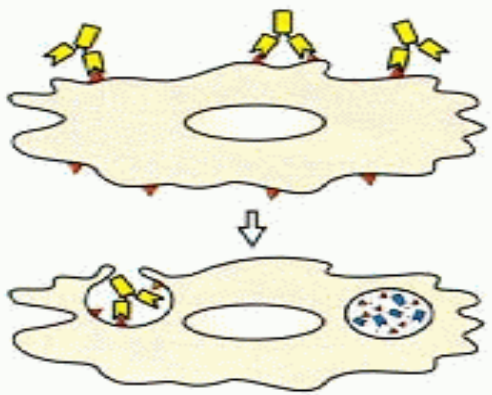
2. Effector mechanisms (T_H1 a T_C cells, macrofages, NK cells)

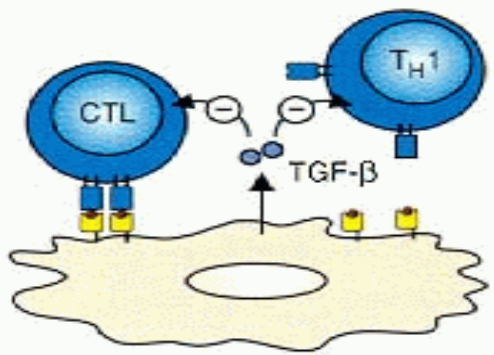


Mechanisms whereby tumors escape immune recognition

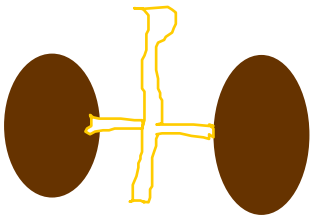
Low immunogenicity	Antigenic modulation	Tumor-induced immune suppression
No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules	Antibody to tumor cell-surface antigens may induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants	Factors (eg TGF-β) secreted by tumor cells inhibit T cells directly

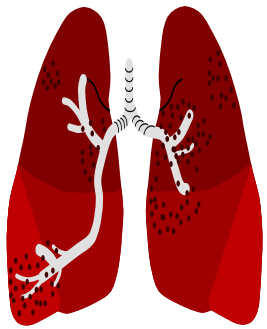


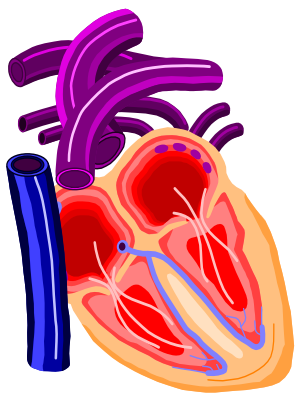


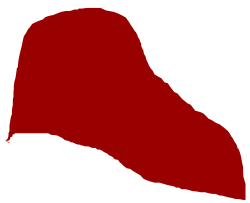


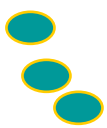
Transplantation immunity











alo-transplantace
xeno-transplantace

donor ⇄ recipient

rejection
Graft versus host