COURS 01: INTRODUCTION

AUX COURS D'IMMUNOLOGIE FONDAMENTALE

Dr. Naci D.
Immunologiste
LCB, CHU Khelil Amrane
Department Medecine, Universite A. Mira

OBJECTIVES

- Overview des different notions de base en Immunologie fondamentale

COURS IMMUNOLOGIE FONDAMENTALE

Les Lundi ou Mercredi de 9h00a 12h

THEME DU COURS
Introduction à l'Immunologie Les organes lymphoïdes
Les cellules impliquées dans la réponse immunitaire I : les Lymphocytes B BCR
Les cellules impliquées dans la réponse immunitaire II : les Lymphocytes T TCR
Les cellules impliquées dans la réponse immunitaire III : les CPA, les cellules phagocytaires et les NK
Les Antigènes et le Complexe Majeur d'Histocompatibilité (CMH)
Les Immunoglobulines Les anticorps monoclonaux
Le système du complément
Les cytokines
Les molécules d'adhésion et Chimiokines
Les interactions cellulaires au cours de la réponse immunitaire Exemple des réponses anti-infectieuses

REFERENCES AISEES ATTACHEES AU COURS

Manuel d'immunologie par Charles Janway

Manuel Kuby Immunologie

Roitt's essential Immunology

Il y a bien d'autres references d'immunologie fondamentale simplifiés

Targets of the Immune System

The immune system protects against four classes of pathogens		
Type of pathogen	**Examples**	**Diseases**
Extracellular bacteria, parasites, fungi	*Streptococcus pneumoniae* *Clostridium tetani* *Trypanosoma brucei* *Pneumocystis carinii*	Pneumonia Tetanus Sleeping sickness *Pneumocystis* pneumonia
Intracellular bacteria, parasites	*Mycobacterium leprae* *Leishmania donovani* *Plasmodium falciparum*	Leprosy Leishmaniasis Malaria
Viruses (intracellular)	Variola Influenza Varicella	Smallpox Flu Chickenpox
Parasitic worms (extracellular)	*Ascaris* *Schistosoma*	Ascariasis Schistosomiasis

Figure 1-25 Immunobiology, 7ed. (© Garland Science 2008)

Bacteries

Transformations malignes

Chompignons

Parasites

Virus

Particules physiques et chimiques

HISTORIQUE

1. Transfer de serum
2. Notions de vaccination (variolisation, E.Jenner, Louis Pasteur)
3. Distinction de deux types dimmunité: Immunité humorale versus immunité cellulaire
4. Decouverte de la phagocytose, macrophage, cellules dendritiques
5. Decouverte des Lymphocytes B et BCR (B-Cell Receptor)
6. Decouverte de lymphocytes T, TCR (T-Cell Receptor)
7. Systeme HLA (Human Leucocyte Antigen, Systeme d'histocompatibilité human)
8. …Etudes biochimiques, cellulaires, de biologie moleculaire….

Enfant bulle

Mutation genetique qui a induit l'absence de lymphocytes T)

David

Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

STERILE BUBBLE protected a boy named David, who suffered in the 1970s from severe combined immunodeficiency, or SCID, an inherited disorder in which the immune system is profoundly impaired. SCID patients have better options today and may have more in the future: the first gene therapy approved for clinical trial aims to ease a form of the disorder.

EINSTEIN

FONCTIONS DE L'IMMUNITE

- Defendre l'organisme contre les pathogènes **causant des dommages tissulaires et des maladies**:
    1. Externes(bacteries, virus, fungus, helminthes)
    2. Particules chimiques (pollution)
    3. Endogenes(bactéries/virus internes et cancers)

- Reponses **rapides and specifiques**
- **Memoire immunologique**
- Preserver l'integrité des tissues (**Reparation tissulaire**)

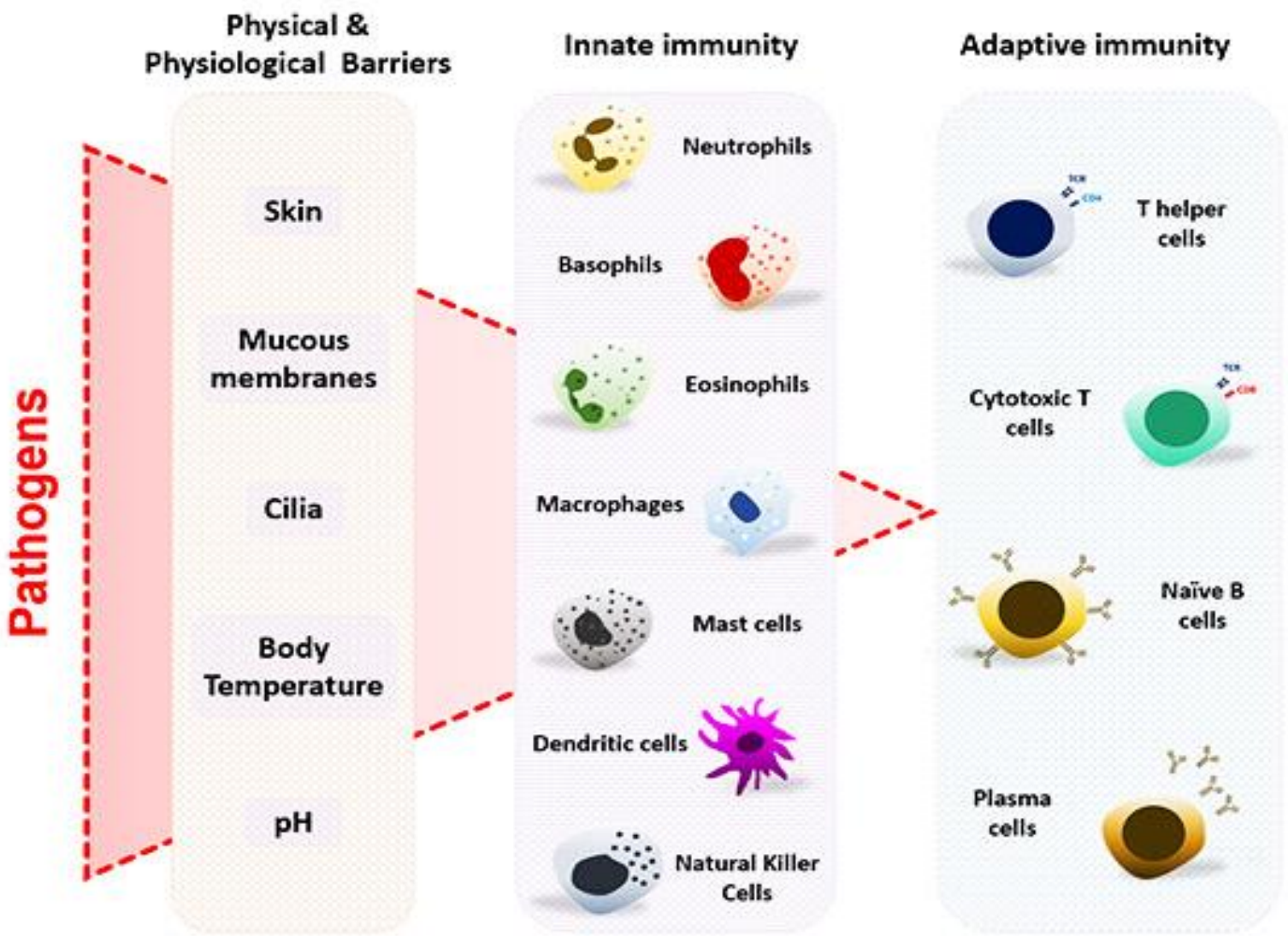
FONCTIONS DE L'IMMUNITE

- **Tolerance Immune soi versus non soi**
- **Tolerance Immune agents inoffensifs versus pathogens** (nutriments, flore microbienne)

FONCTIONS DE L'IMMUNITE

- Majorite des cellules immunitaires se development au niveau de la **moelle osseuse**
- Les cellules immunitaires se diffusent dans toutes les parties de l'organisme
- Influence des facteurs genetiques et de l'environement sur les propores fonctions du systeme immunitaire

LES TROIS BARRIERES IMMUNOLOGIQUES:



IMMUNITE INNEE VERSUS IMMUNITE SPECIFIQUE

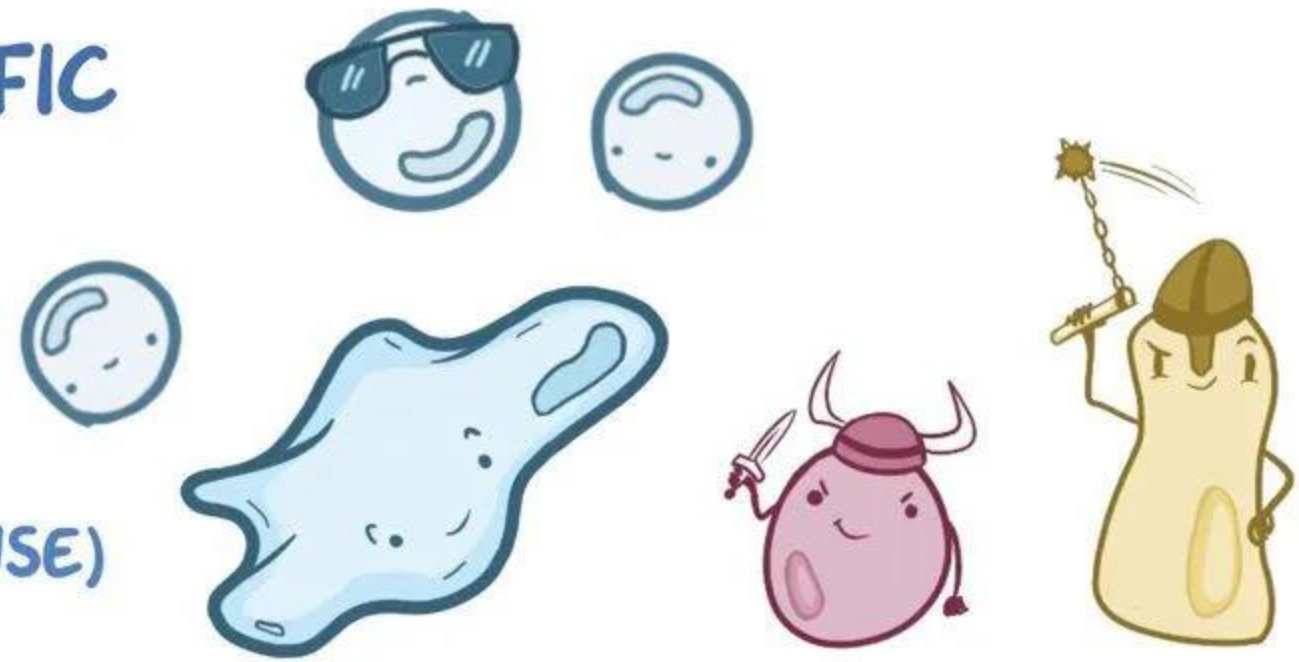
Vertebrate Immunity		
Innate Immune System		Adaptive Immune System
Physical Barriers	Internal Defenses	
• Skin, hair, cilia • Mucus membranes • Mucus and chemical secretions • Digestive enzymes in mouth • Stomach acid	• Inflammatory response • Complement proteins • Phagocytic cells • Natural killer (NK) cells	• Antibodies and the humoral immune response • Cell-mediated immune response • Memory response

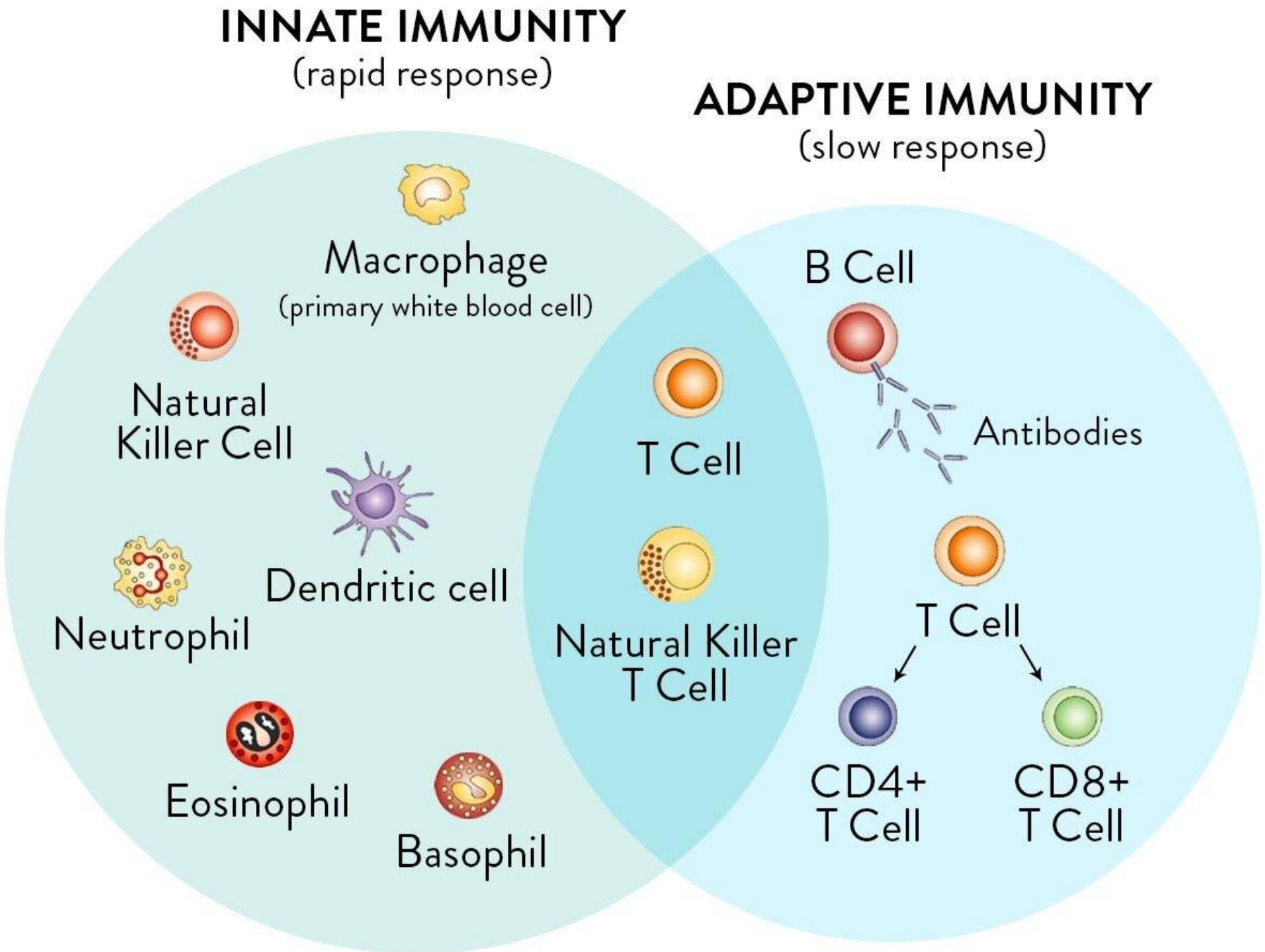
IMMUNE SYSTEM

INNATE IMMUNE RESPONSE

* CELLS ARE NON-SPECIFIC
* RESPONSE = FAST
  (MINUTES - HOURS)
* NO MEMORY
  (ALWAYS THE SAME RESPONSE)

ADAPTIVE IMMUNE RESPONSE




INNATE IMMUNITY
(rapid response)
ADAPTIVE IMMUNITY
(slow response)
Macrophage
(primary white blood cell)
Natural
Killer Cell
Dendritic cell
Neutrophil
Eosinophil
Basophil
T Cell
Natural Killer
T Cell
B Cell
Antibodies
T Cell
CD4+
T Cell
CD8+
T Cell

DIFFERENT TYPES DE CELLULES IMMUNITAIRES

- **Cellules sentinelles** tissulaires: ex. Macrophages, cellules dendritiques, mastocytes…
- **Cellules circulatoires** (Sang, lymphe, migration tissues via les chimiokines): ex. Neutrophiles, monocytes, des eosinophiles, lymphocytes T et B memoires.
- **Cellules tissulaires non migratoires**: Cellules epitheliales (structurales)

03 PHASES DE LA REPONSE IMMUNITAIRE

1. Phase de **l'immunité innée (0-4h):** Reconnaissance et reponse via les médiateurs tissulaires et cellulaires de l'immunité innée qui sont preformés et non spécifiques

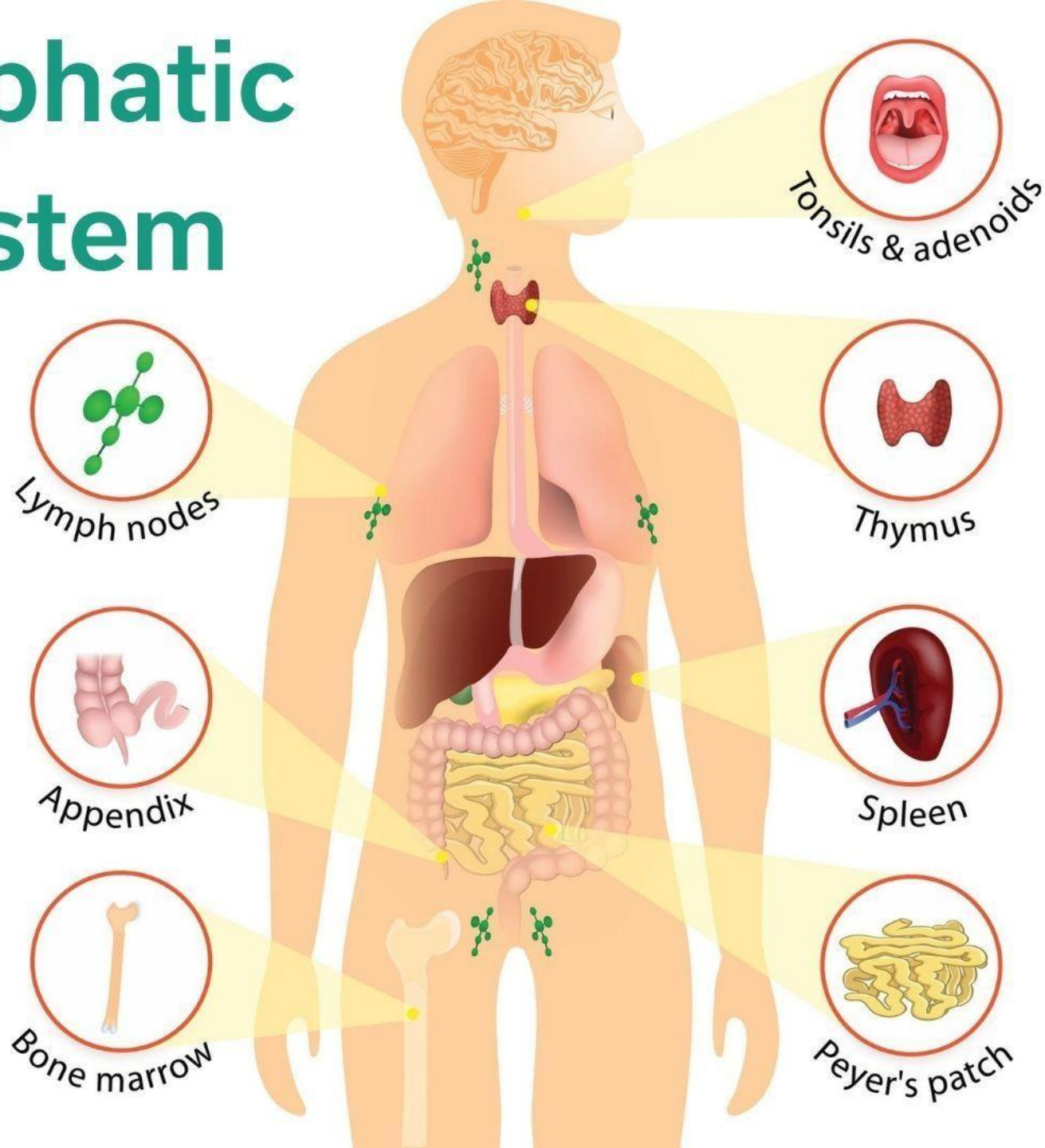
2. Reponse **innée induite précoce (4-96h):** induction de la réaction inflammatoire et chimiotaxie des cellules circulatoires

3. **Reponse adaptative ou acquise (> 96h)**: Transport des antigens vers les organes lymphatiques secondaires, identification et reaction specifique aux antigens via les lymphocytes T et B (anticorps et lymphocytes T effecteurs)

Lymphatic System

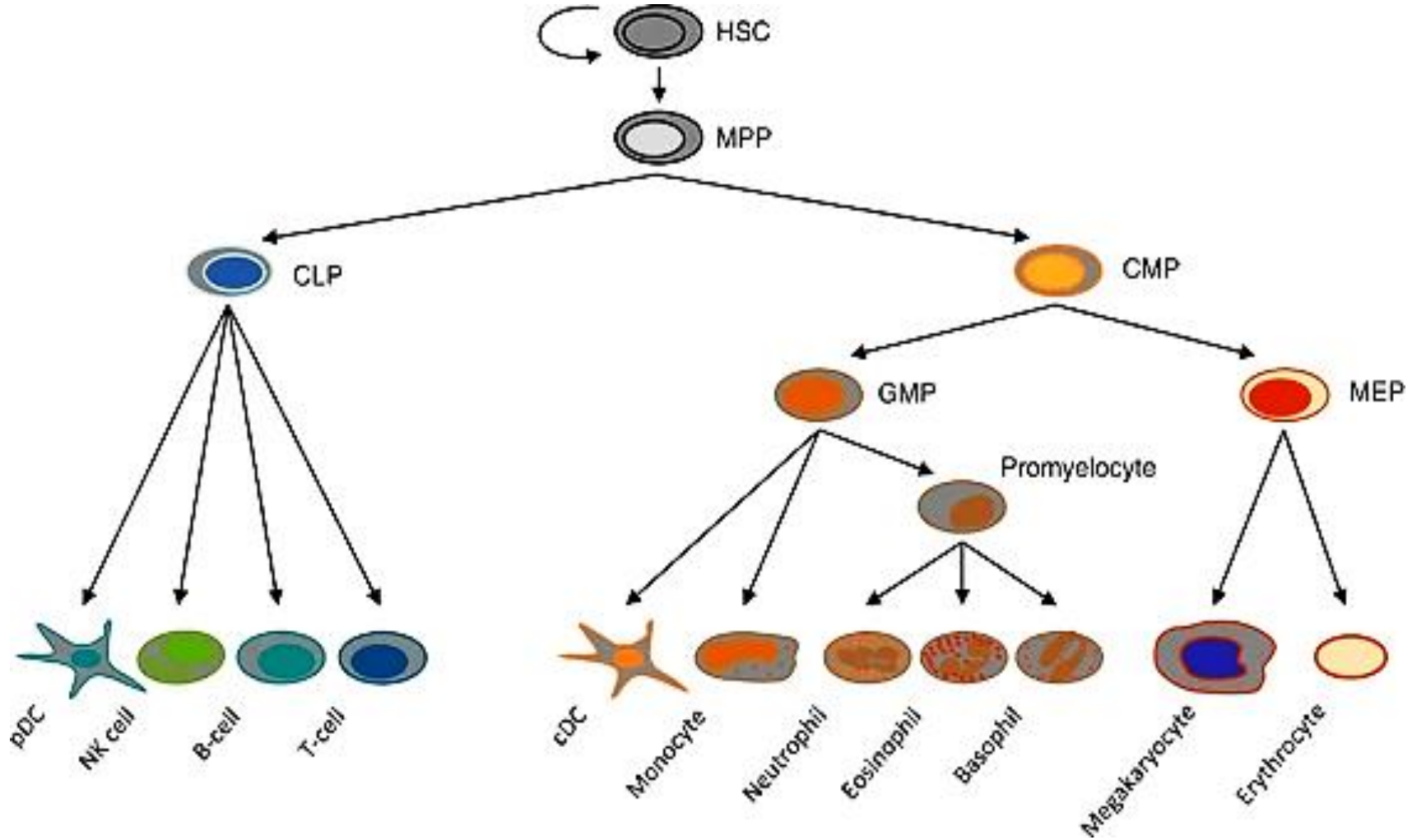
Notion **d'organs lymphoides Primaires** (Moelle osseuse et thymus)

ET **d'organs lymphoides secondaires:** Rate, Gonglions lymphoides et MALT (Tissue lymphoide associé aux muqueuses)



INTEGRIS HEALTH

DEVELOPMENT DES CELLULES IMMUNITAIRES AU NIVEAU DE LA MOELLE OSSEUSE



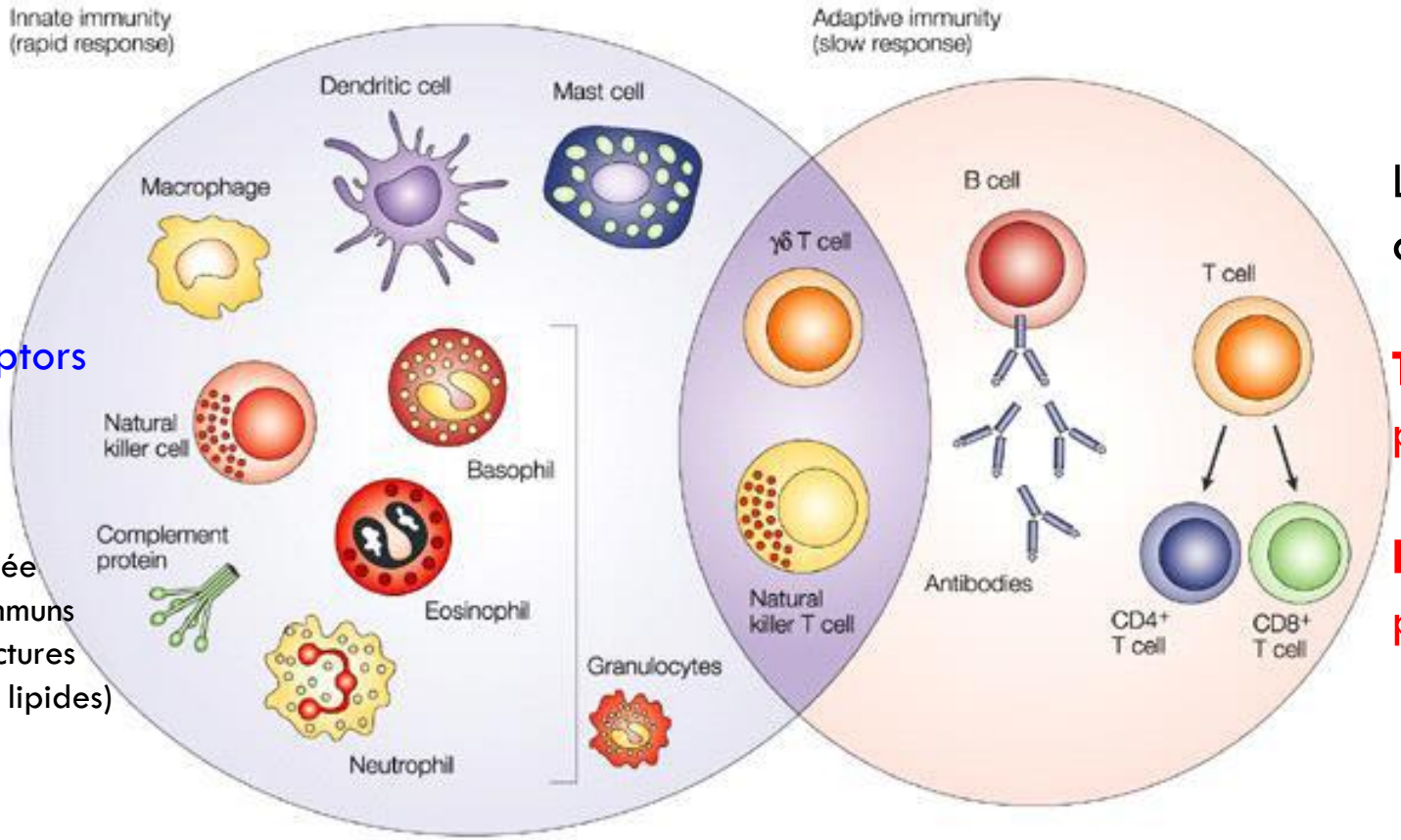
T C Luis et al. *Leukemia* **volume 26,** pages 86–90 (2012)

MECANISMES DE RECONNAISSANCE SPECIFIQUE VERSUS NON SPECIFIQUE

PRR

Pattern recognition receptors

Les cellules de l'immunité innée reconnaissent des motifs communs aux agents *pathogène* (structures peptidiques, carbohydrates, lipides)



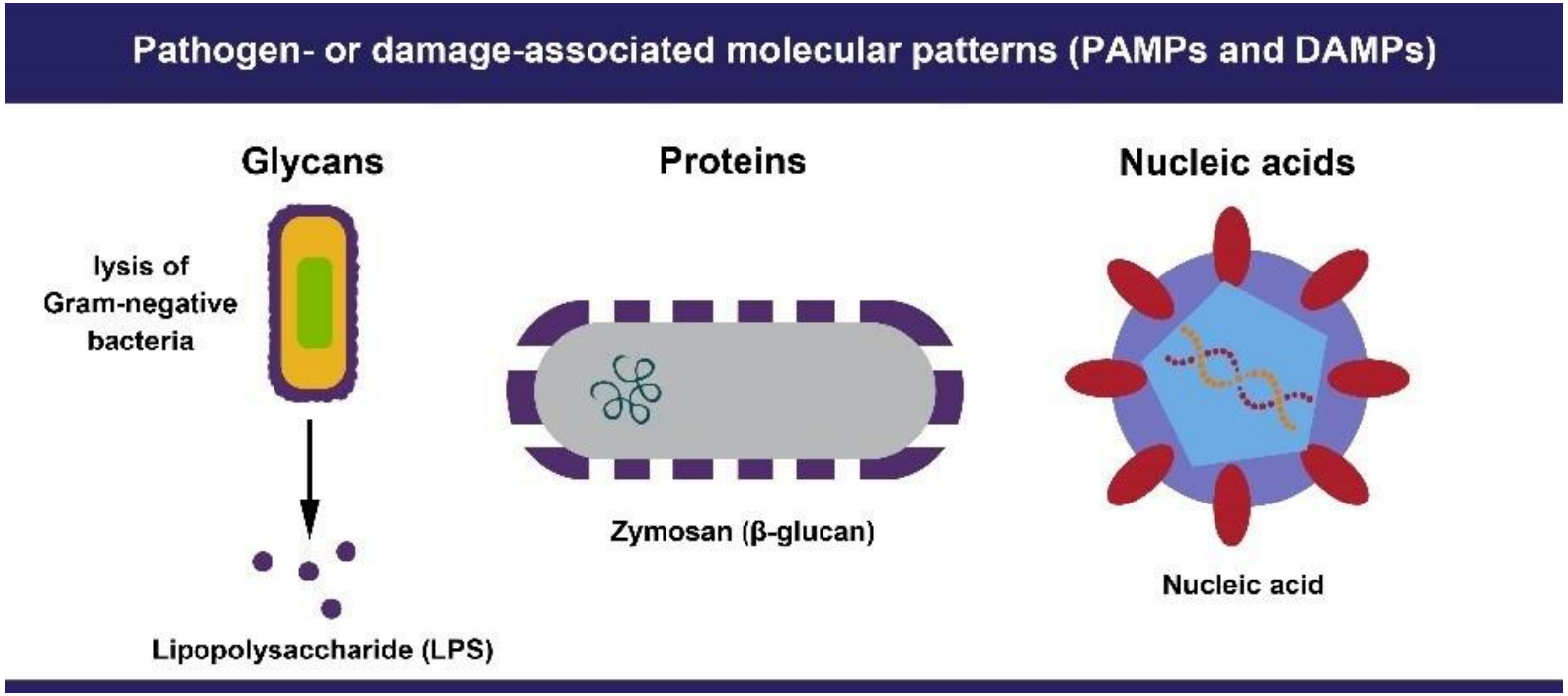
Nature Reviews | Cancer

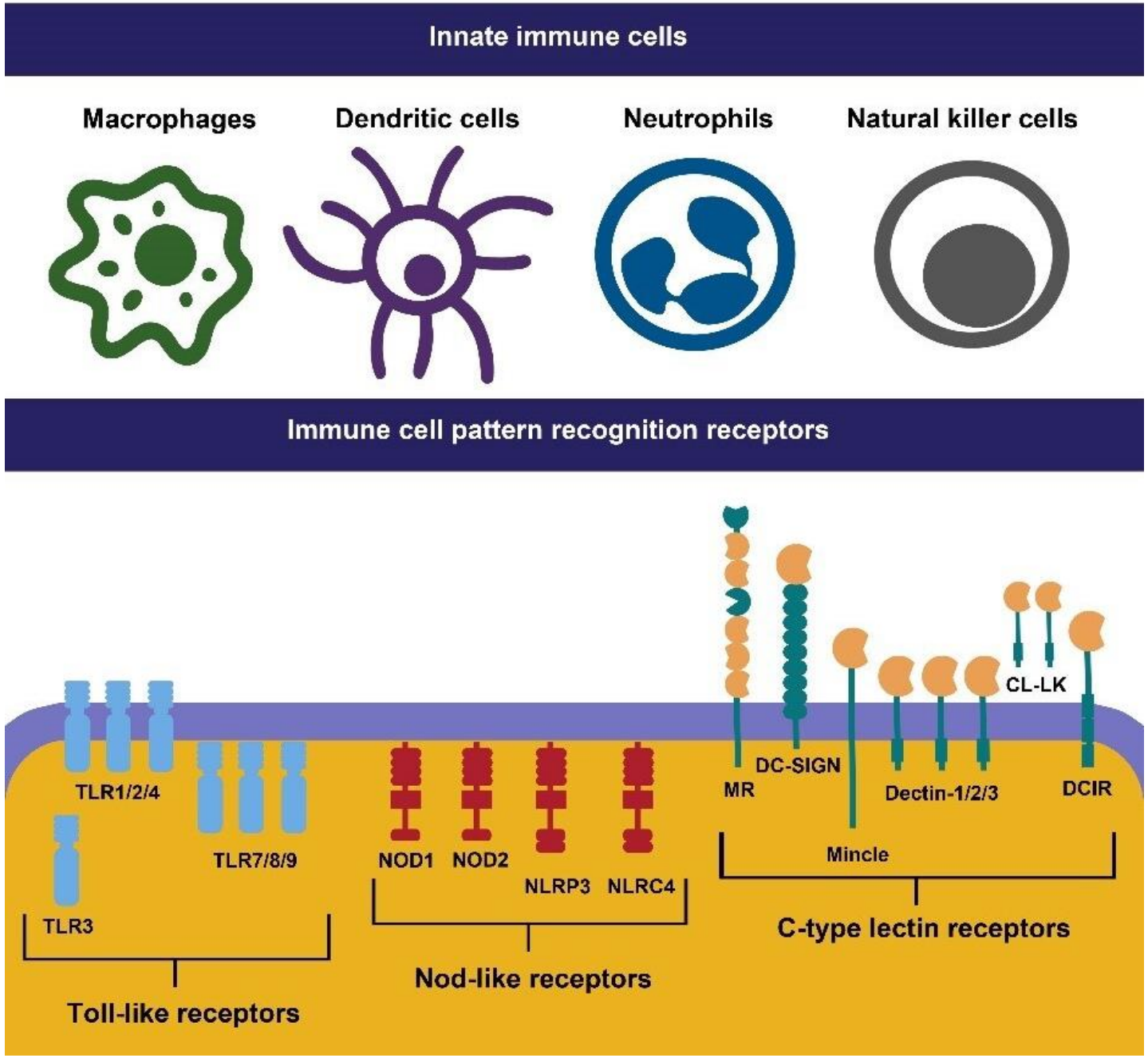
Les recepteurs specifiques aux lymphocytes:

TCR (T-Cell Receptor) pour les Lymphocytes T

BCR (B-Cell Receptor) pour les lymphocytes B

PRR: PATTERN RECOGNITION RECEPTORS



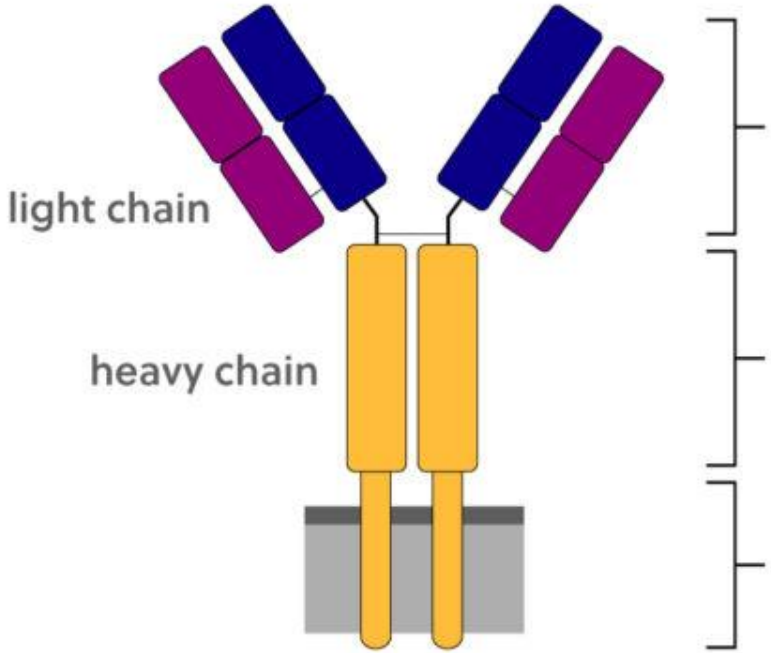

Innate immune cells
Macrophages
Dendritic cells
Neutrophils
Natural killer cells
Immune cell pattern recognition receptors
TLR1/2/4
TLR7/8/9
TLR3
Toll-like receptors
NOD1
NOD2
NLRP3
NLRC4
Nod-like receptors
MR
DC-SIGN
Mincle
Dectin-1/2/3
CL-LK
DCIR
C-type lectin receptors

Structure of T cell and B cell receptors

Peptides lineaires et conformationels

B cell receptor

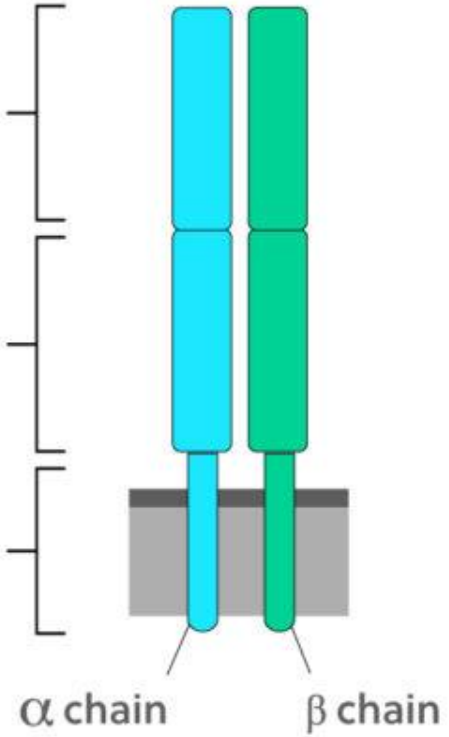
antigen-binding site



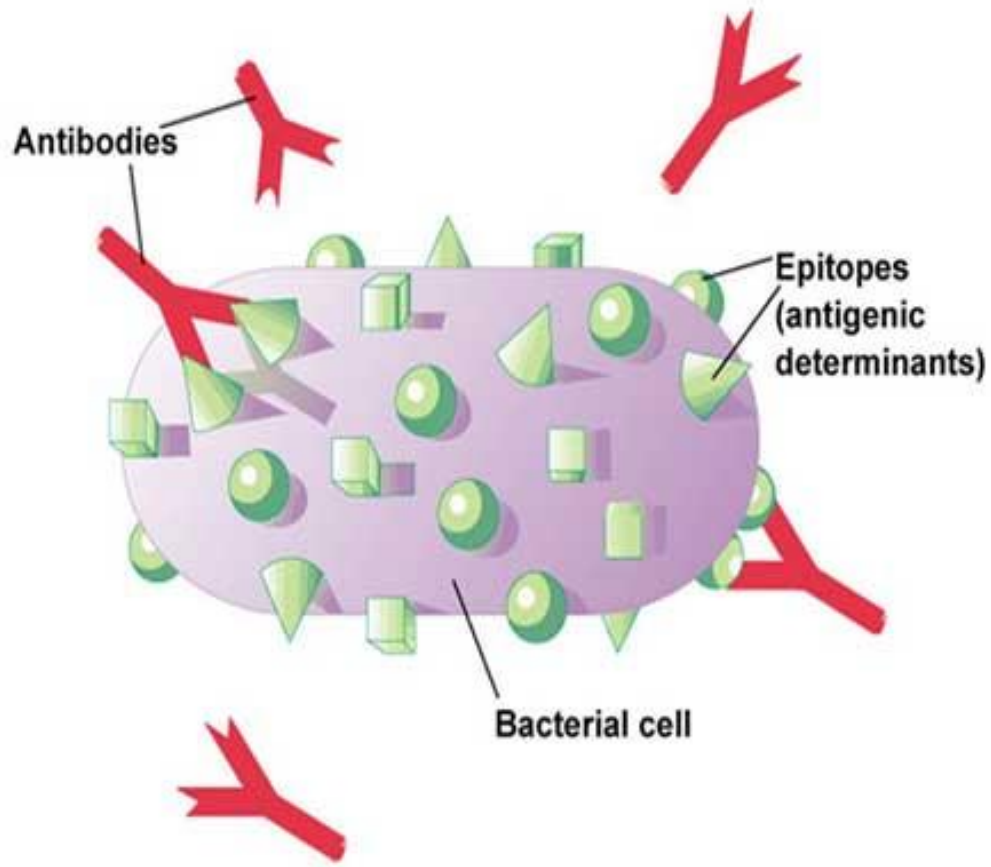
T cell receptor

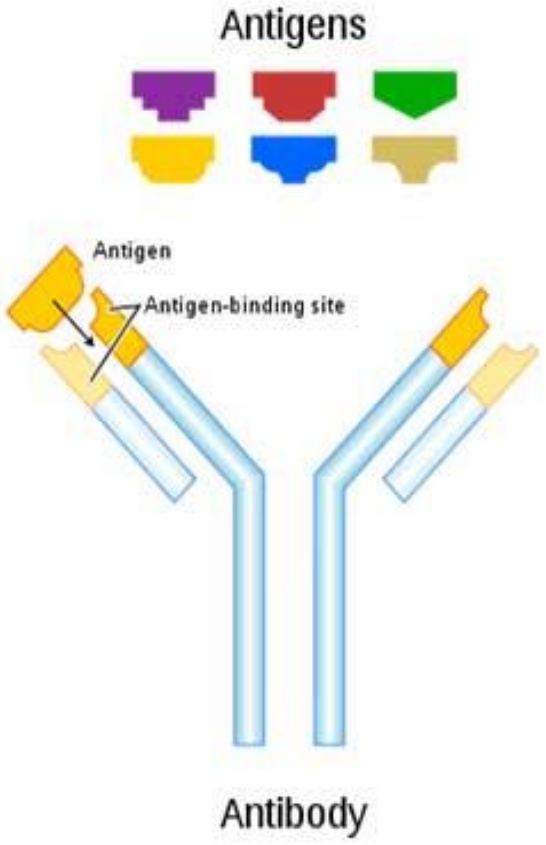
antigen-binding site

Peptides lineaires



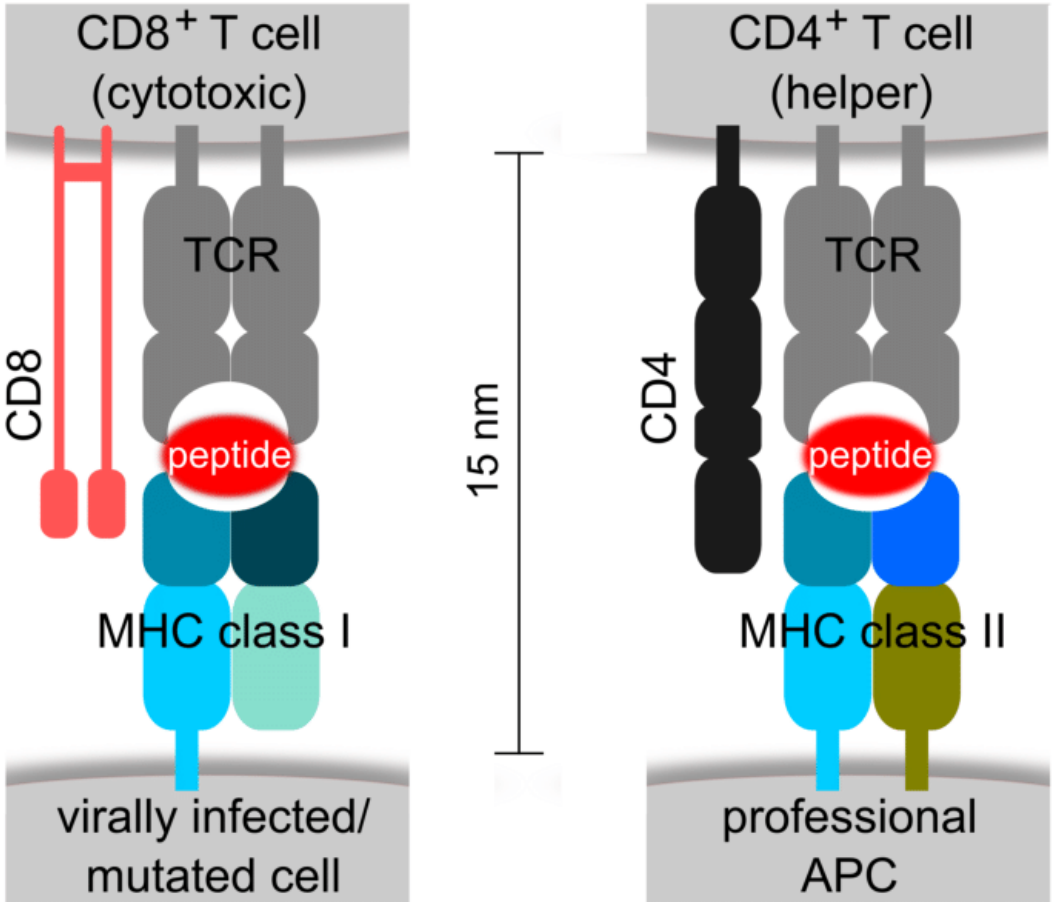
RECONNAISSANCE D'ANTIGENS PAR LES LYMPHOCYTES B ET LES ANTICORPS





RECONNAISSANCE DES ANTIGENS PAR LES LYMPHOCYTES T:

RESTRICTION AU CMH (COMPLEXE MAJEUR D'HISTOCOMPATIBILITE)



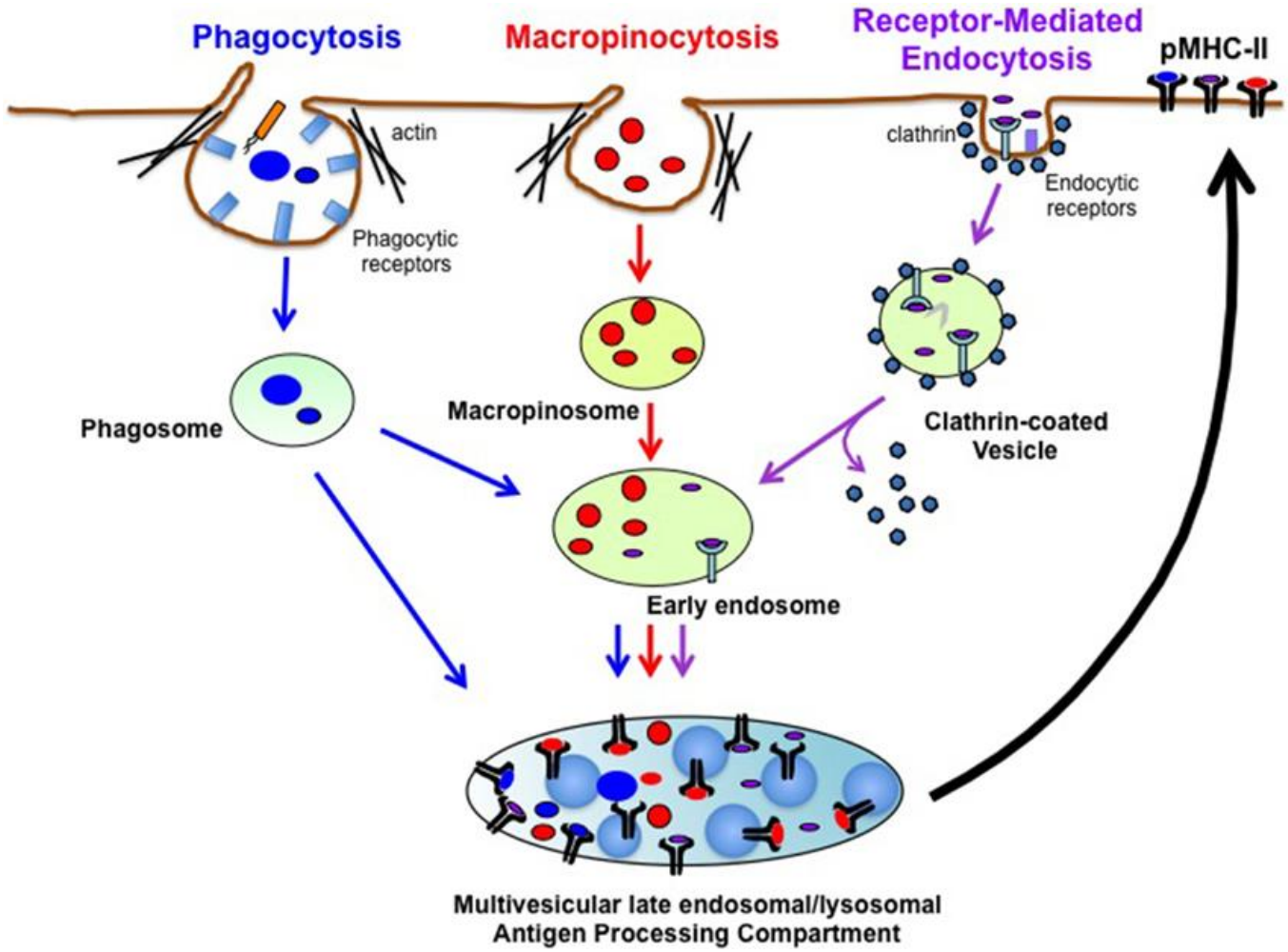
RECONNAISSANCE DES ANTIGENS PAR LES LYMPHOCYTES T (RESTRICTION AU CMH)

1. Capture des antigens par les cellules presentarices d'antigenes (CPA) par phagocytose, endocytose, micro ou macropinocytose.

2. Leur degradation au niveau des endo-lysosomes (fusion des endosomes avec les lysosomes)

3. Presentation des epitopes peptidiques provenent de l'antigene sur la membrane des CPA au sein des molecules CMH.
4. Presentation des complexes peptides-CMH aux lymphocytes T CD4+ et T CD8+.

NB: La reconnaissance d'antigenes par les



REARANGEMENT GENIQUE ALEATROIRE DU TCR ET BCR

permettant de créer une grande diversité de clones T et B pouvant reconnoitre n'importe quel structure antigenique.

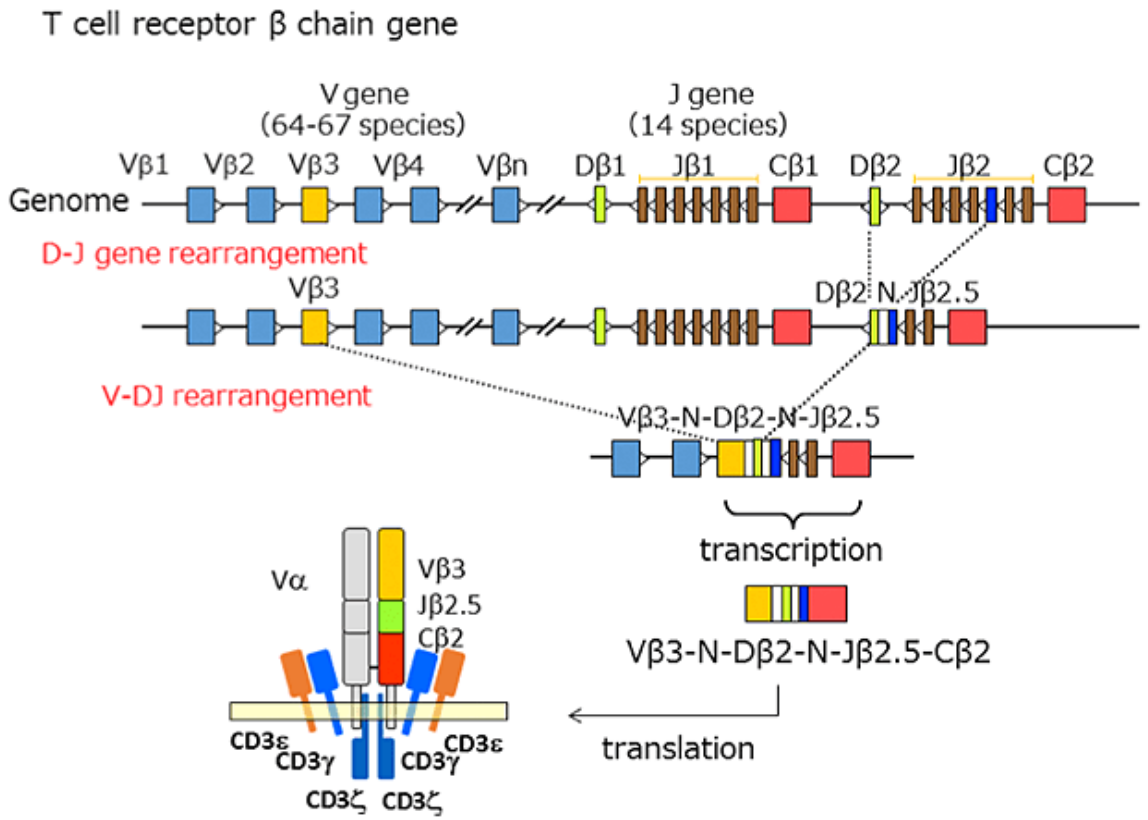
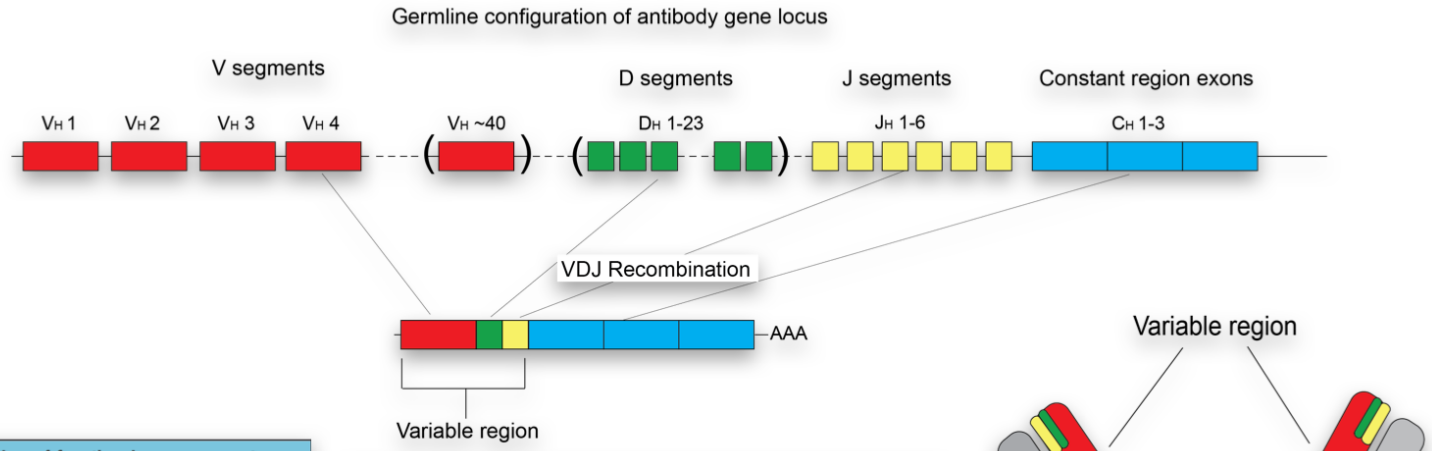


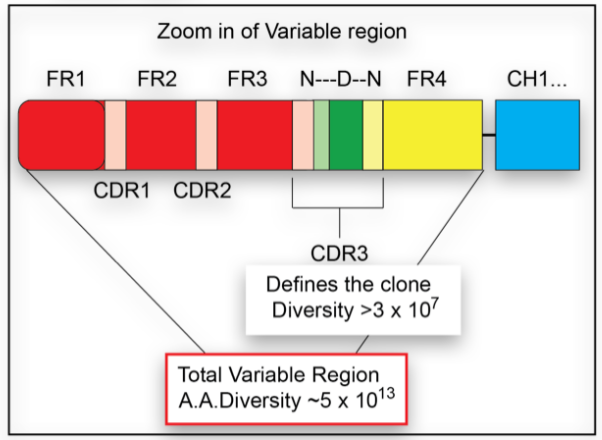
Figure 1. Gene rearrangement in the T cell receptor β chain gene

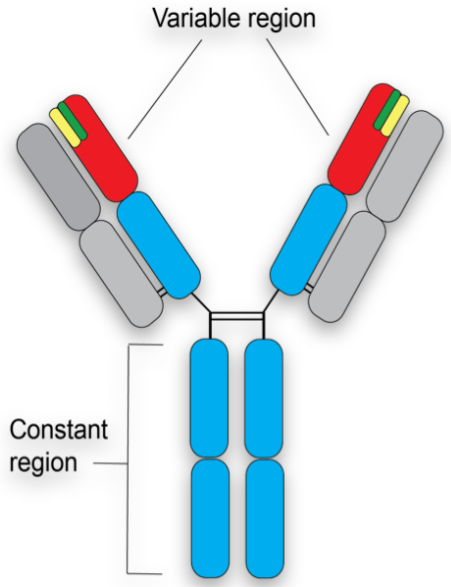
REARANGEMENT GENIQUE ALEATROIRE DU TCR ET BCR

permettant de créer une grande diversité de clones T et B pouvant reconnoitre n'importe quel structure antigenique.

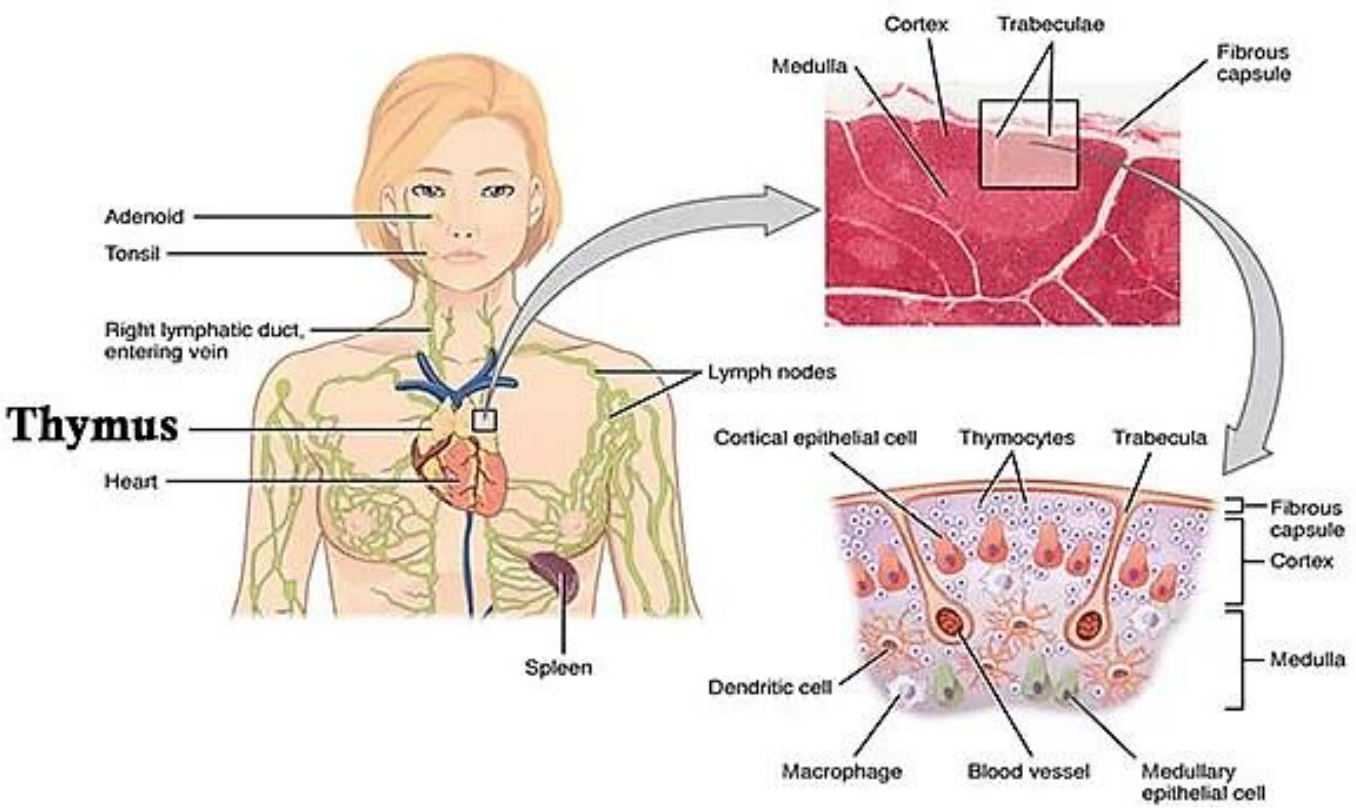


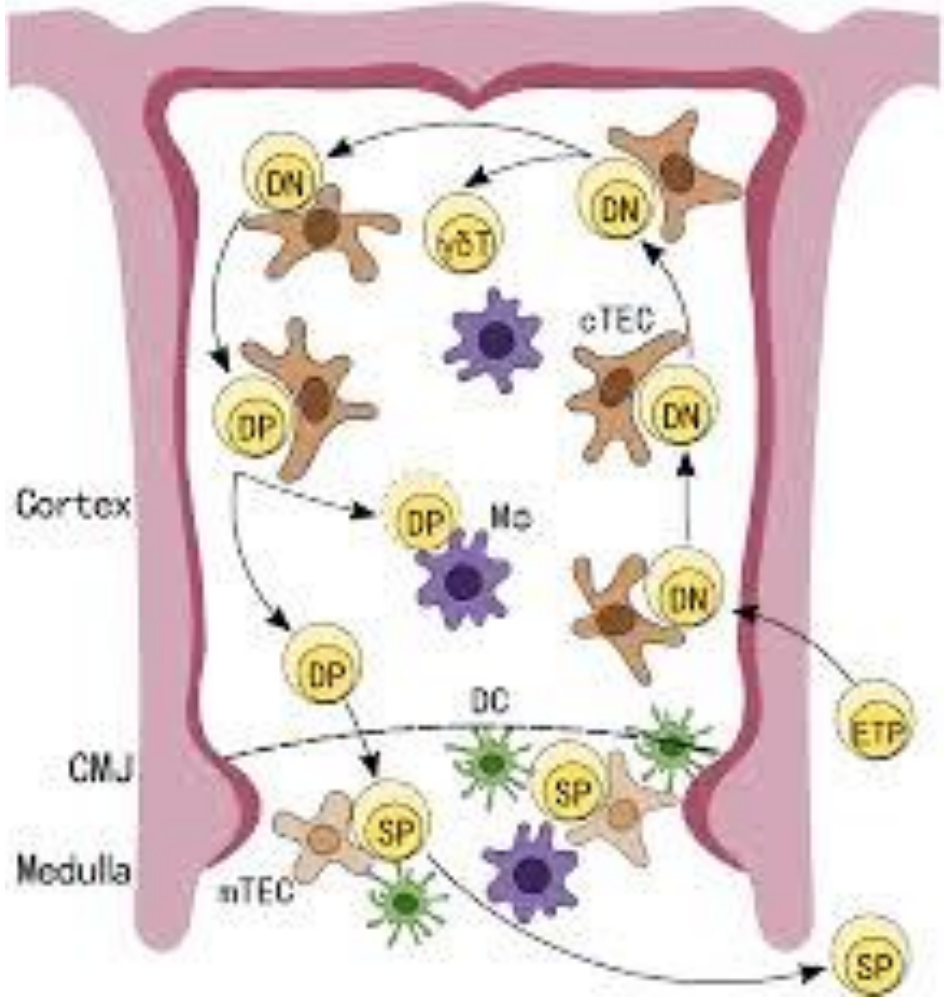
Number of functional gene segments in human immunoglobulin loci			
Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	34–38	29–33	38–46
Diversity (D)	0	0	23
Joining (J)	5	4–5	6
Constant (C)	1	4–5	9



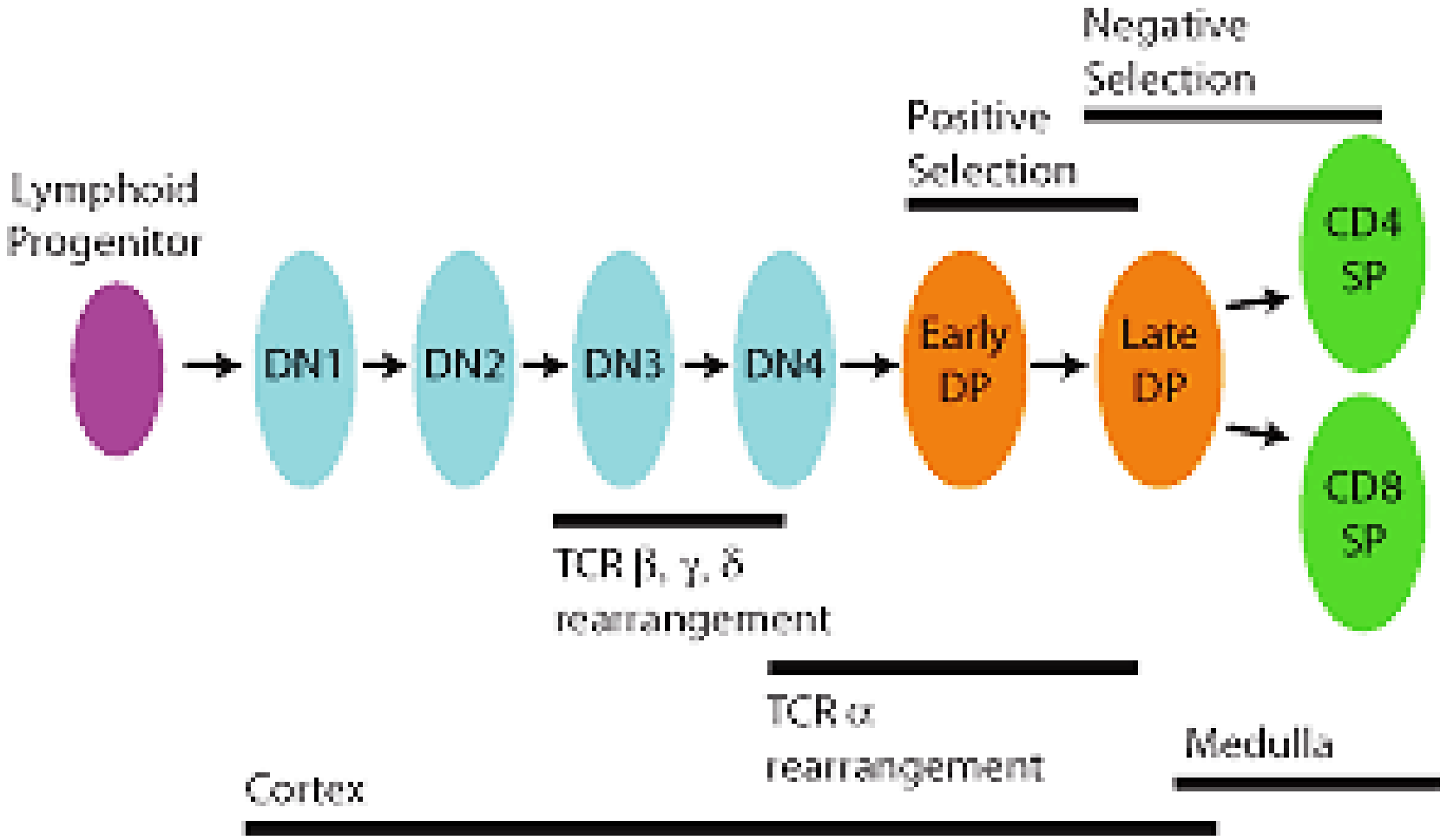


THYMUS: SELECTION ET MATURATION DES THYMOCYTES





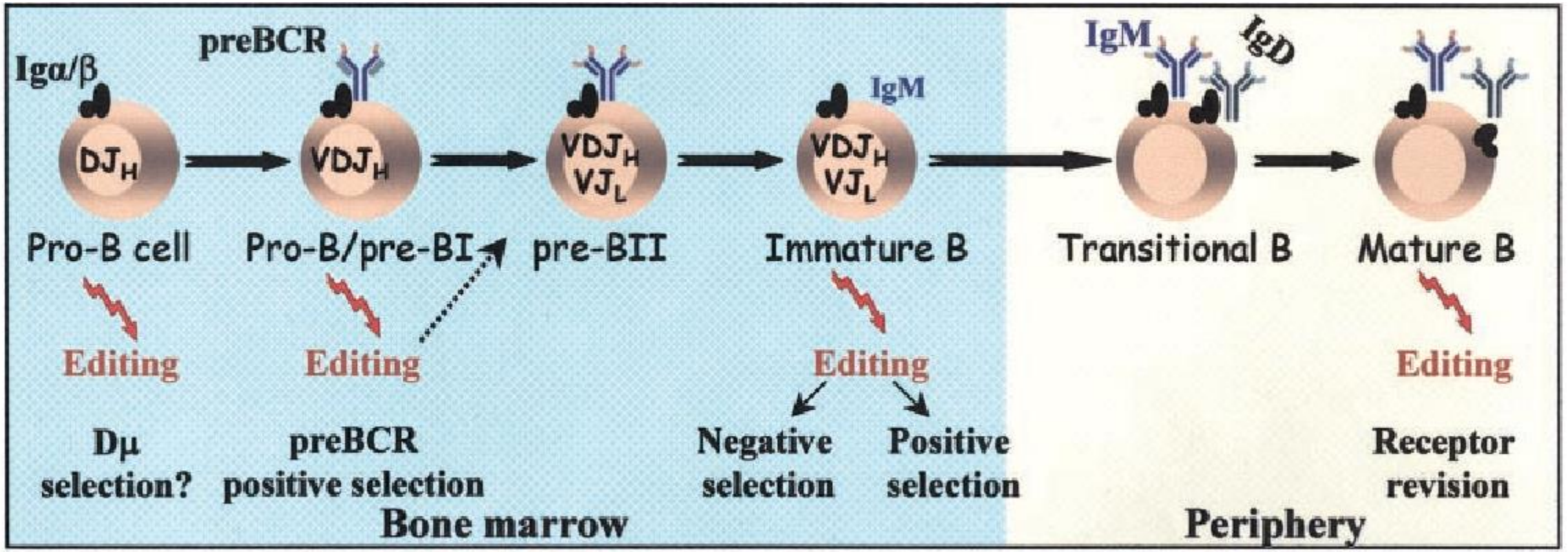
THYMUS: SELECTION ET MATURATION DES THYMOCYTES



Selection positive:
Selection des clones reconnaissant les molecules CMH du soi

Selection negative:
Elimination des clones autoreactifs

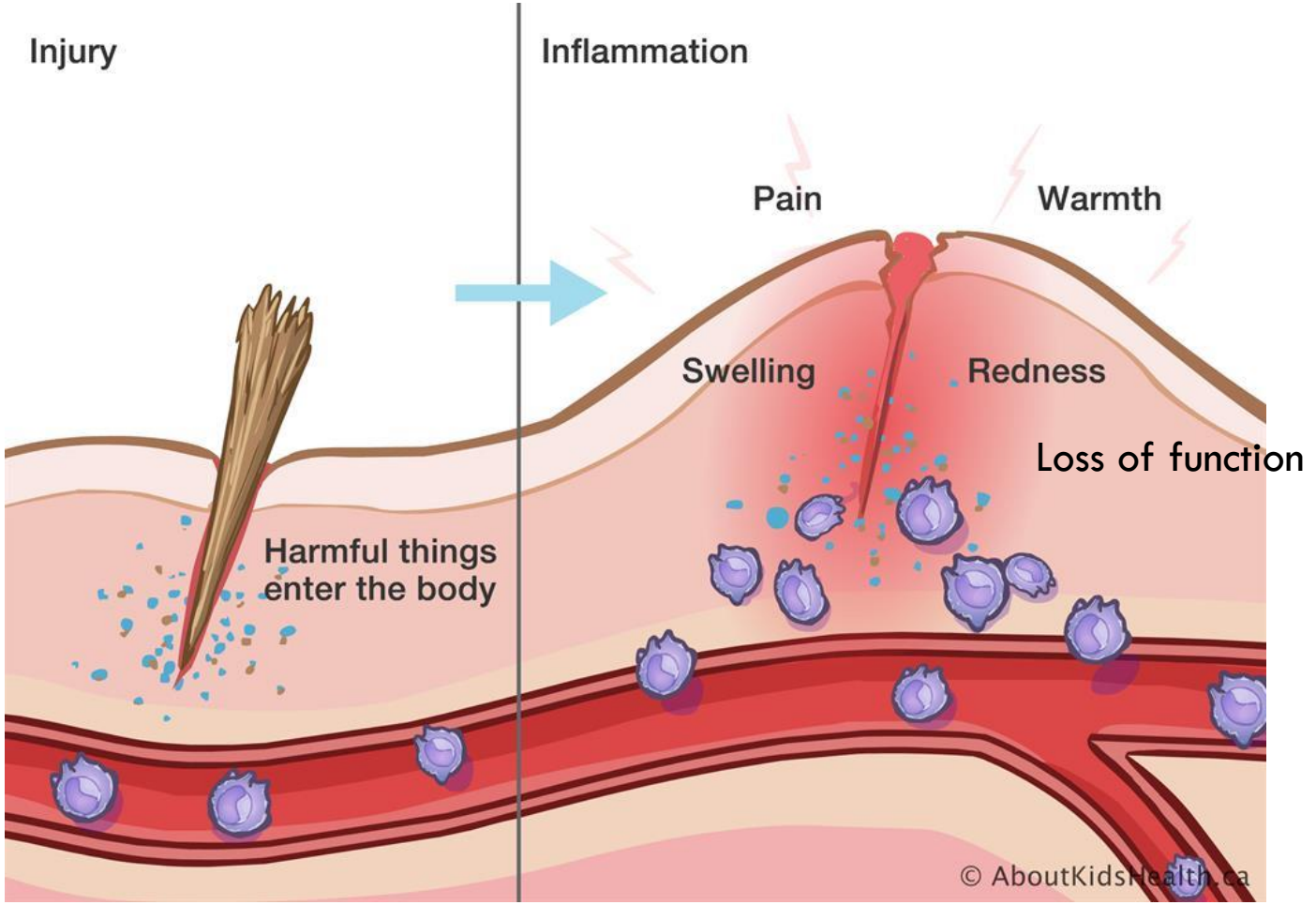
MOELLE OSSEUSE: SELECTION ET MATURATION DES LYMPHOCYTES B: ELIMINATION DES CLONES AUTOREACTIFS



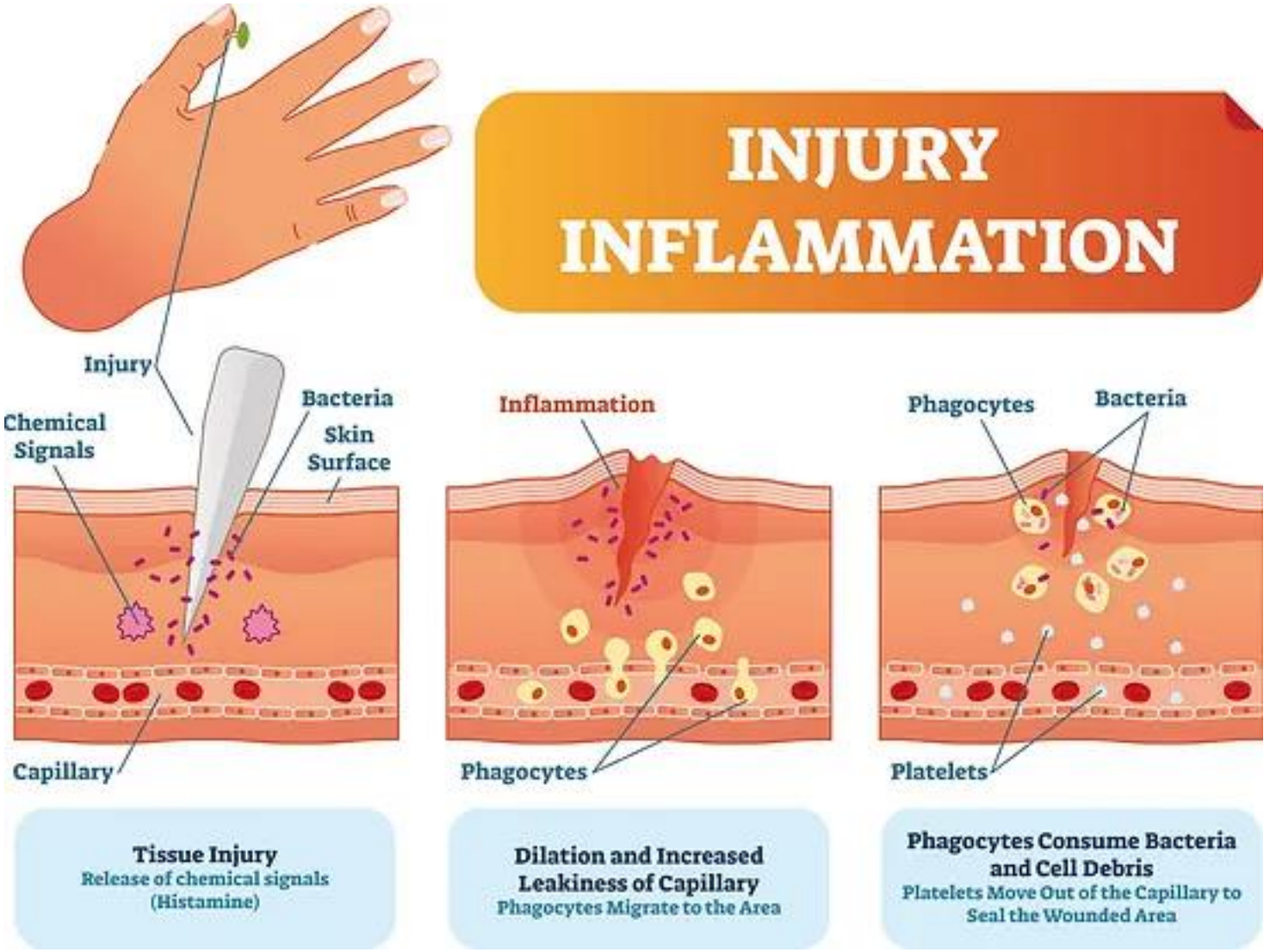
Receptor editing is activated throughout B lymphopoiesis. Selection checkpoints mediated by the pre-BCR or the BCR are specified. B

LA REACTION INFLAMMATOIRE:

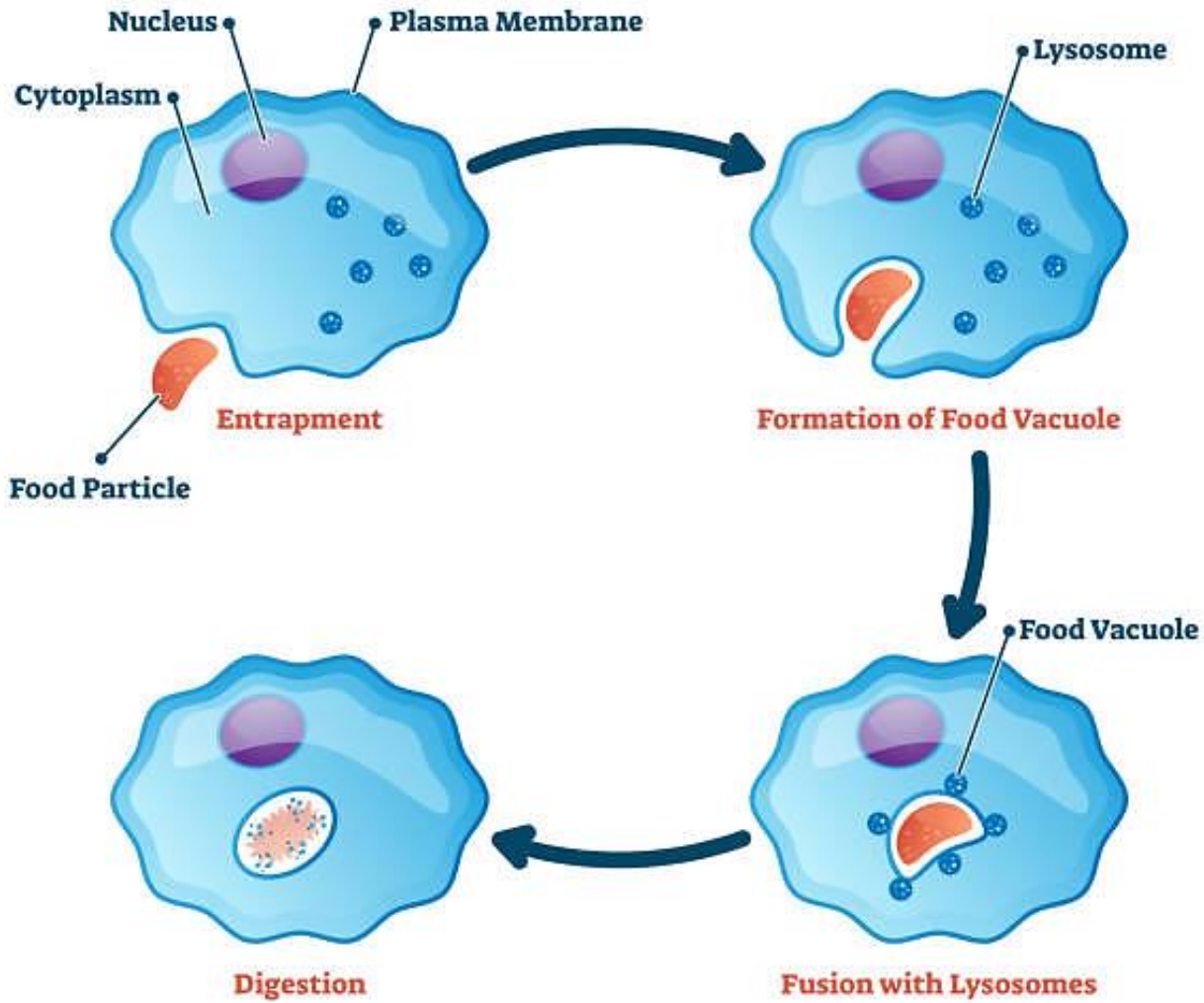
- les 04 (voire 05) **signes cardinaux** d'une reaction inflammatoire



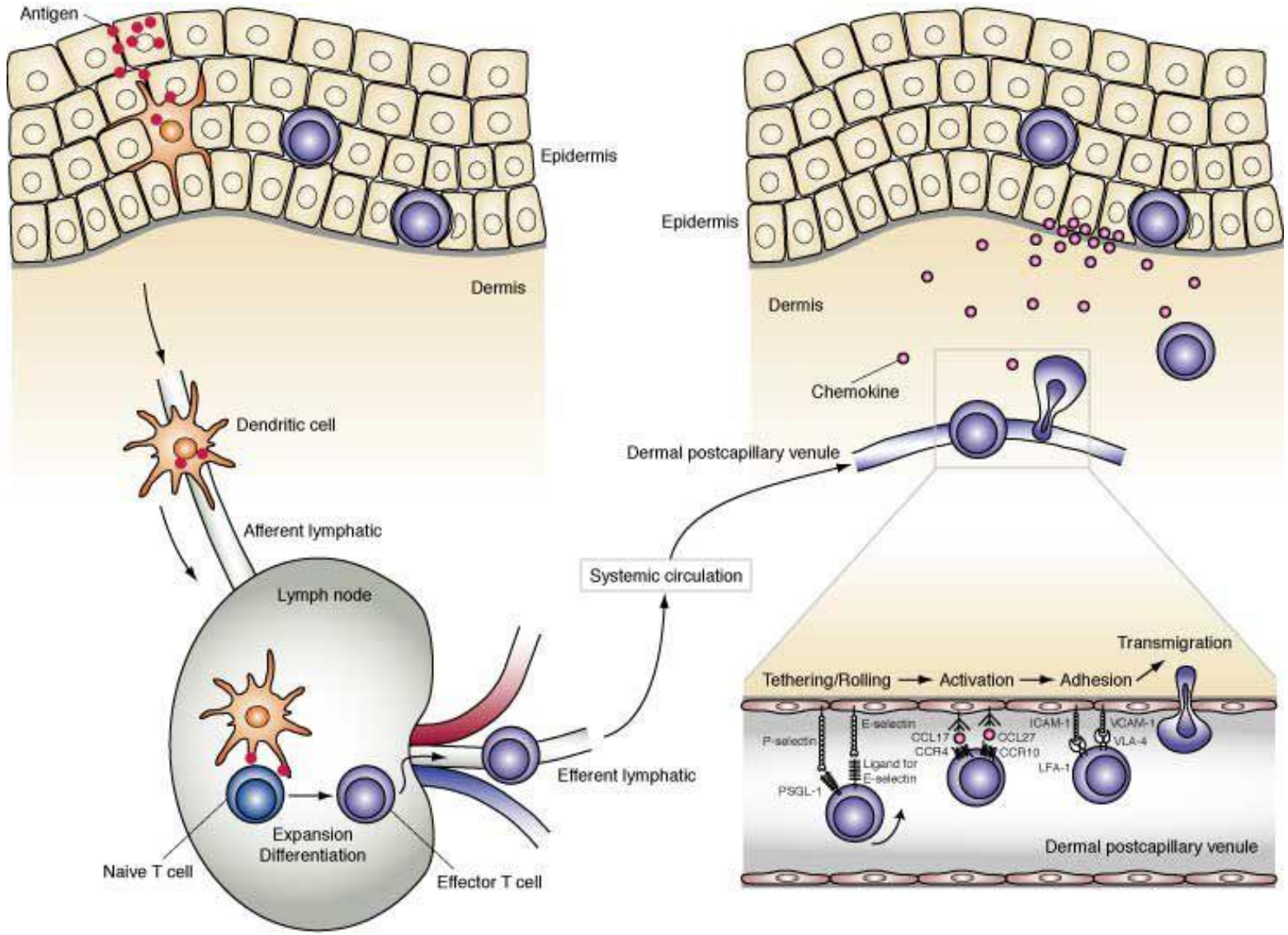
LA REACTION INFLAMMATOIRE



PHAGOCYTOSIS

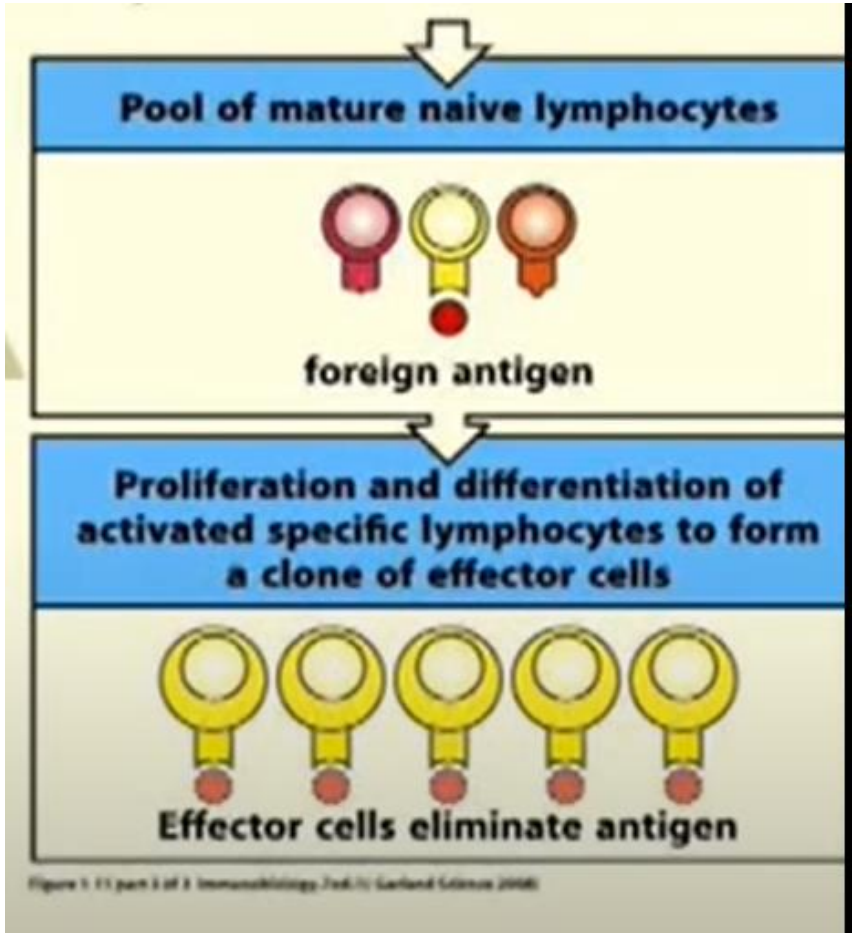


MIGRATION DES CPA AUC ORGANES LYMPHOID SECONDAIRES

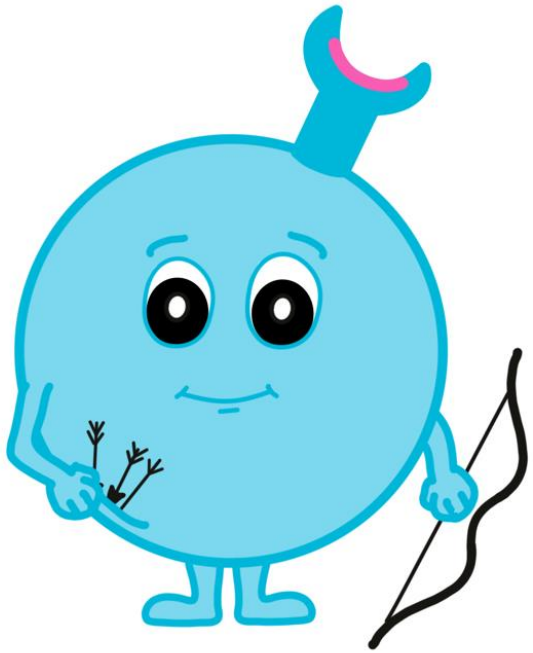


LA SELECTION CLONALE AU NIVEAU D'ORGANES LYMPHOID PERIPHERIQUES

Activation des clones T et B spécifiques a l'antigène.

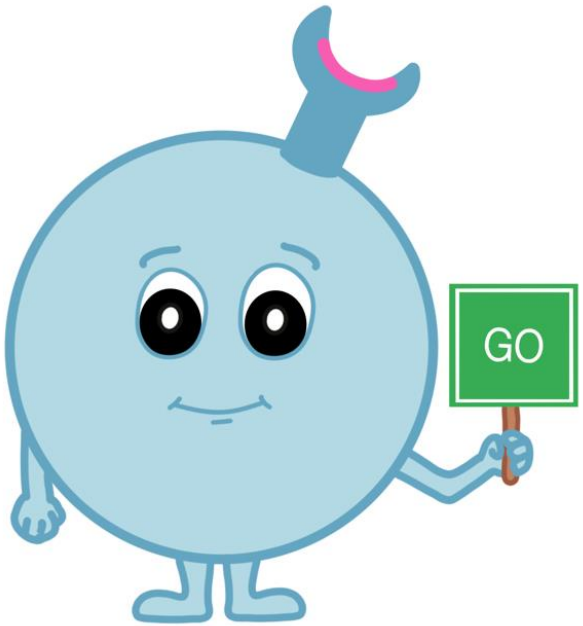


cytotoxic T cells



produce toxic agents to kill their targets

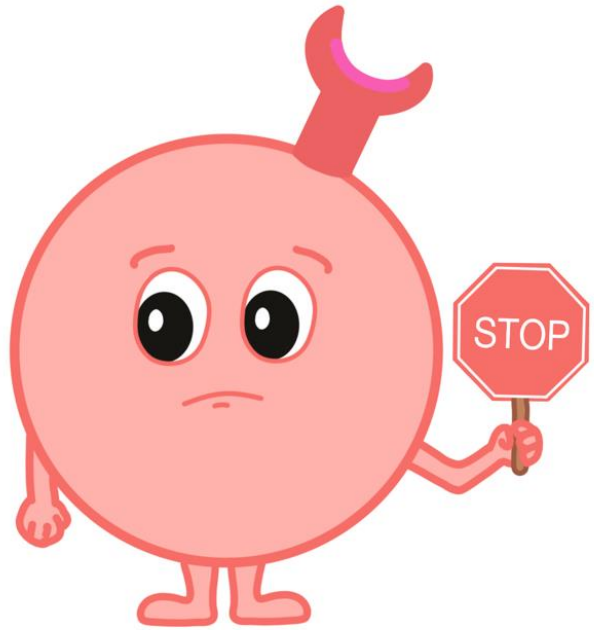
helper T cells



stimulate B cells to make antibodies

stimulate T cells to become active

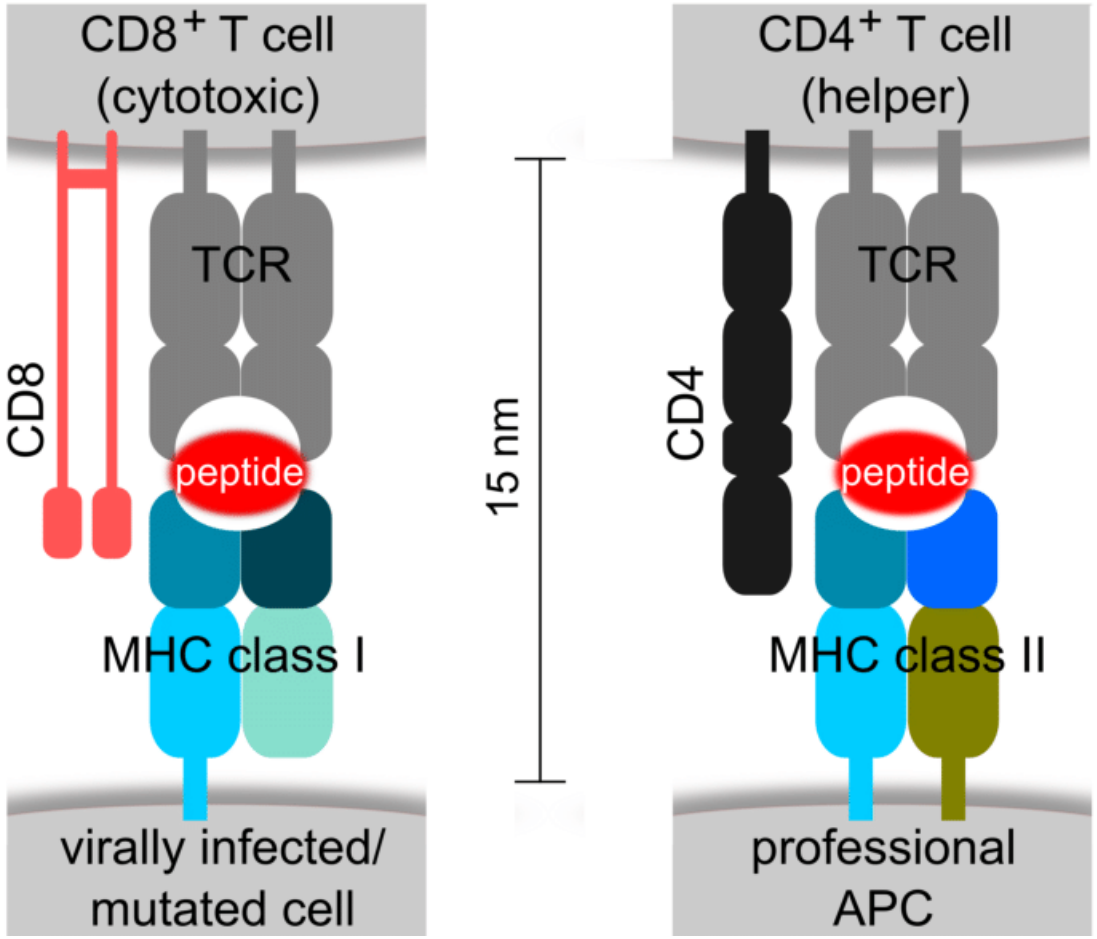
regulatory T cells

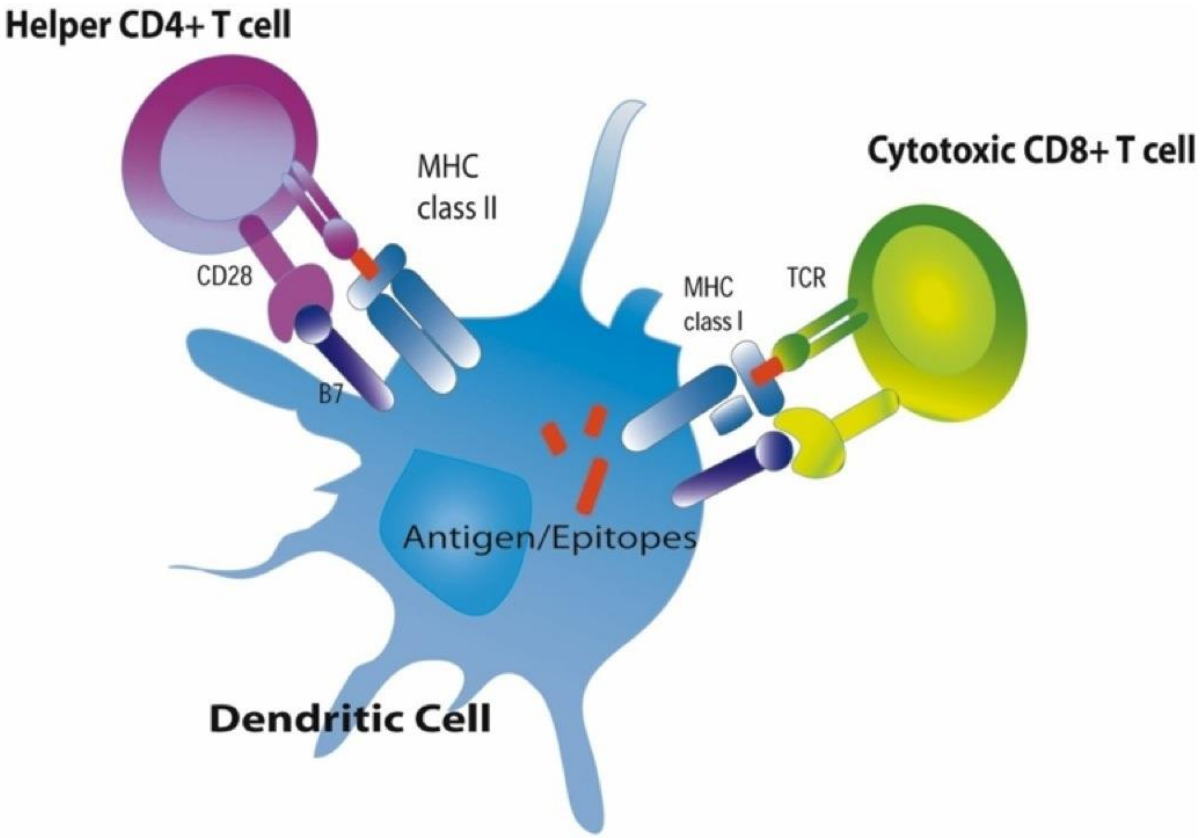


suppress immune responses

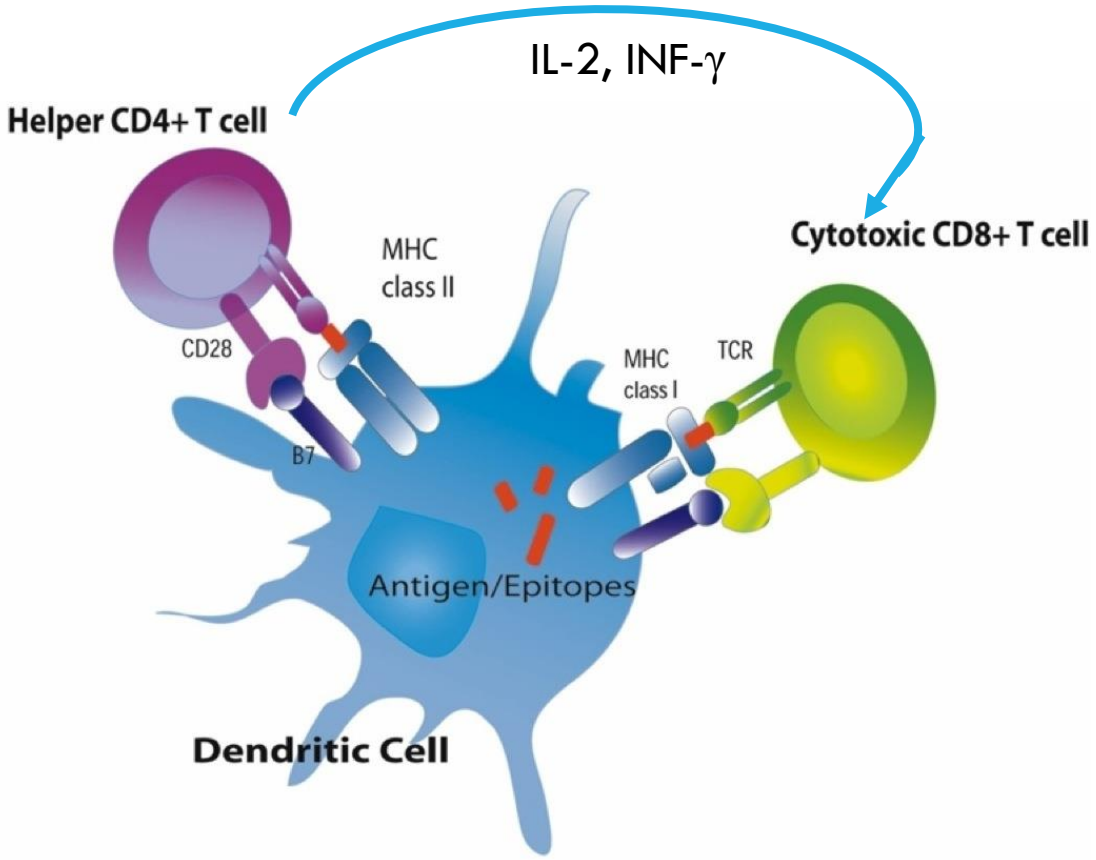
UCIR.org

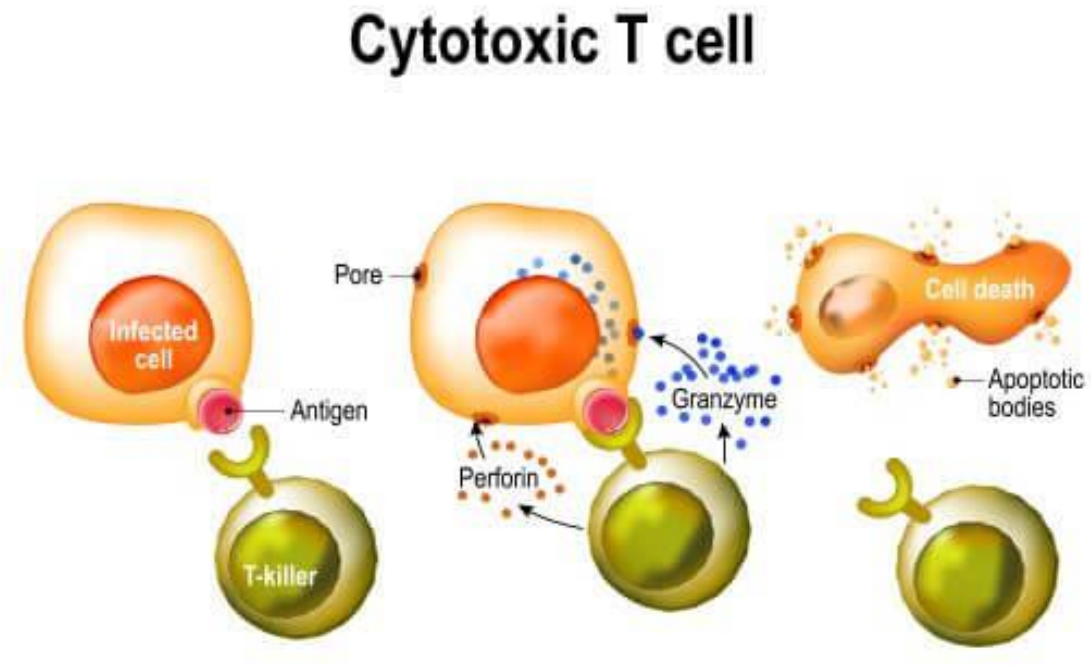
Activation des lymphocytes T CD4+ et T CD8+



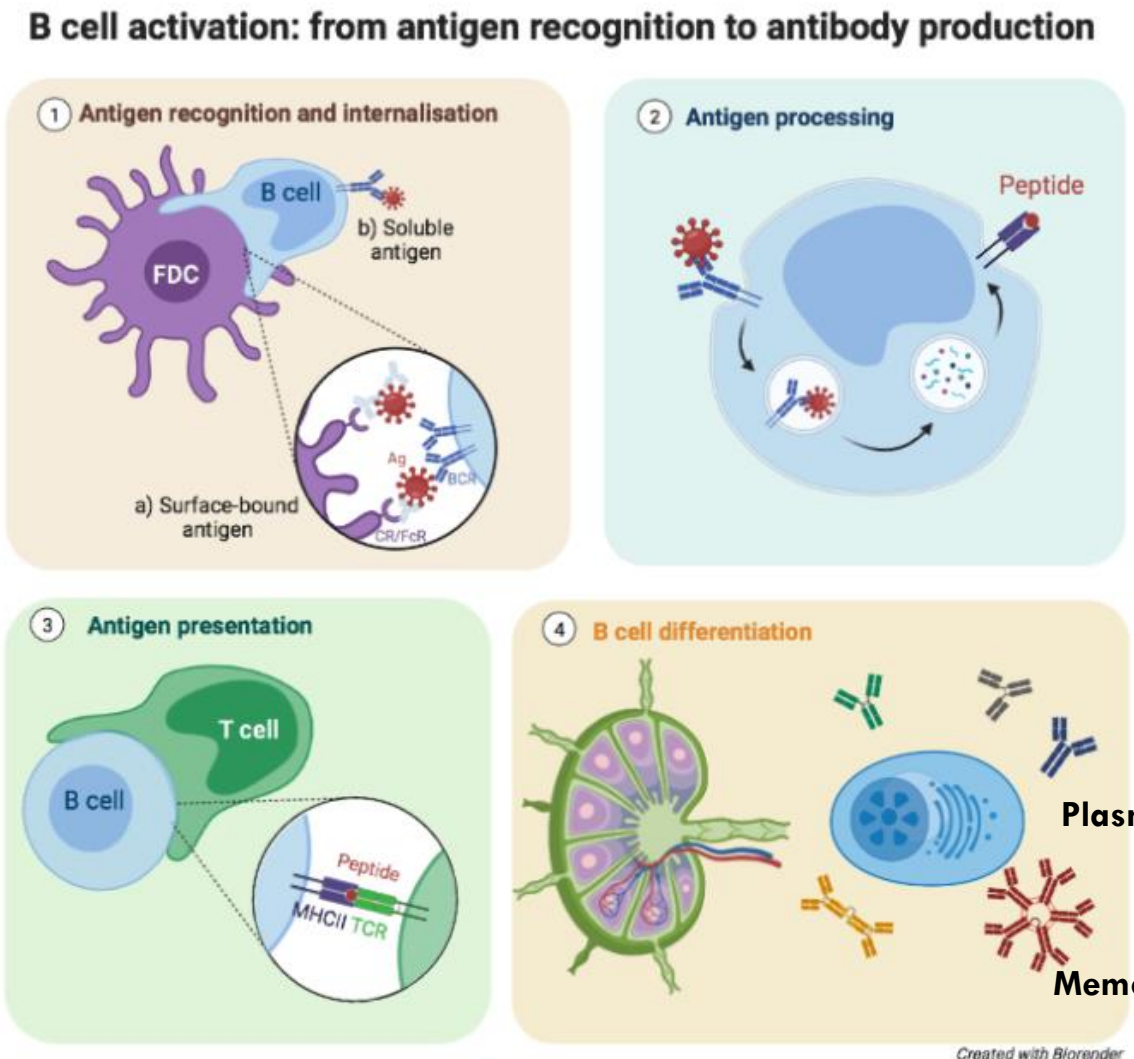


ACTIVATION ET FUNCTION DES LYMPHOCYTES T-CYTOTOXIQUES



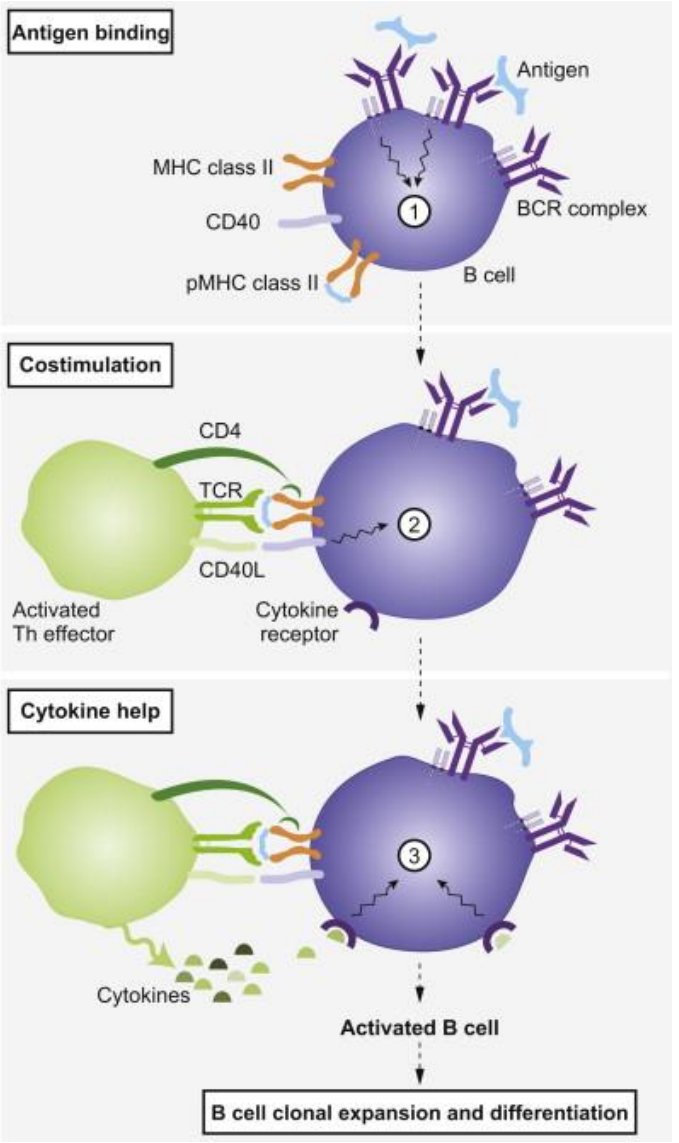


ACTIVATION DES LYMPHOCYTES B

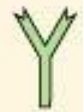
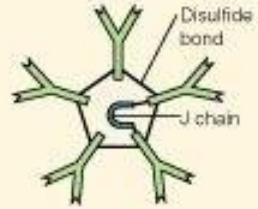
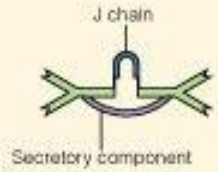
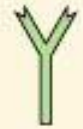


Plasmocytes

Memory B-cells

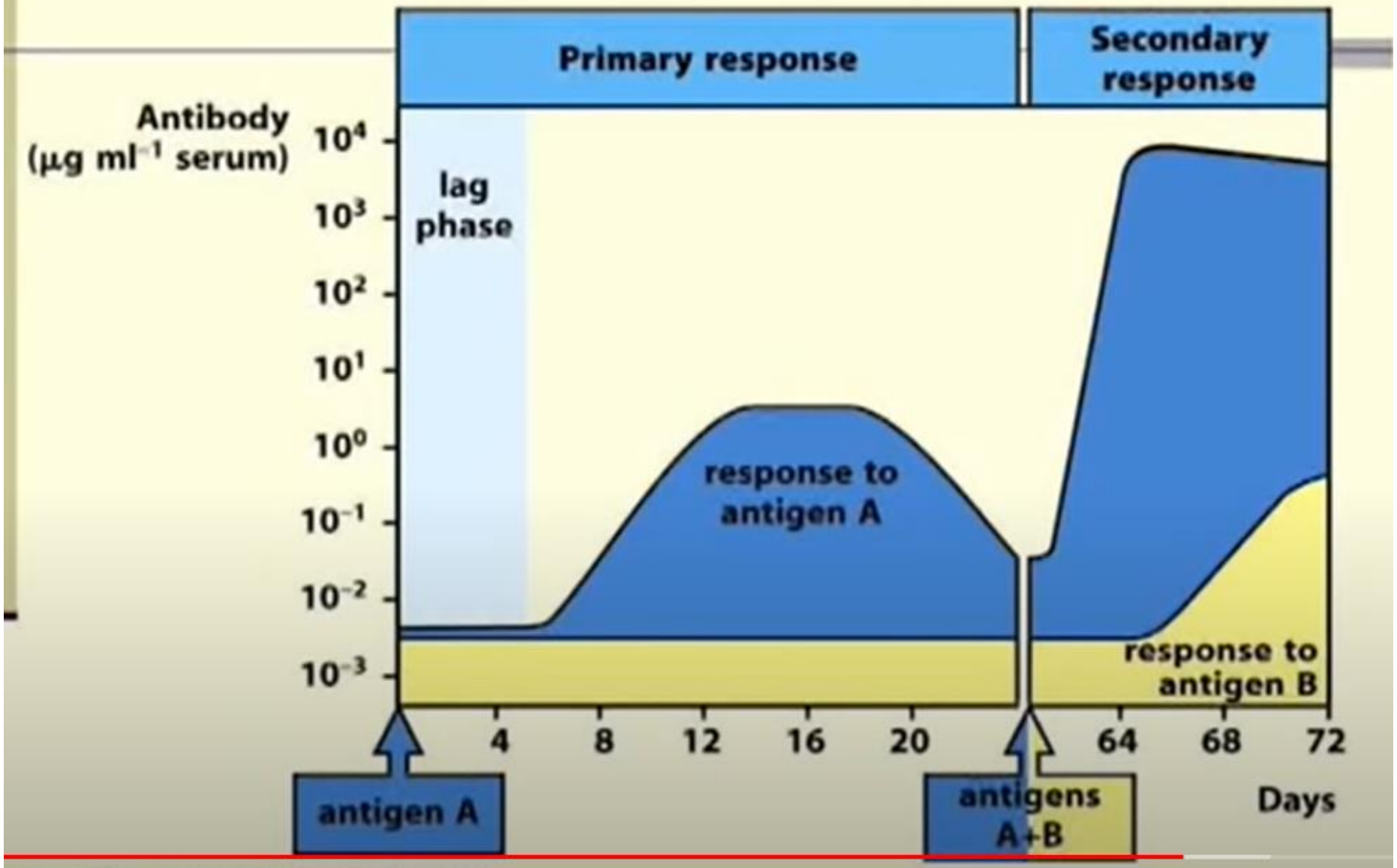


A Summary of Immunoglobulin Classes

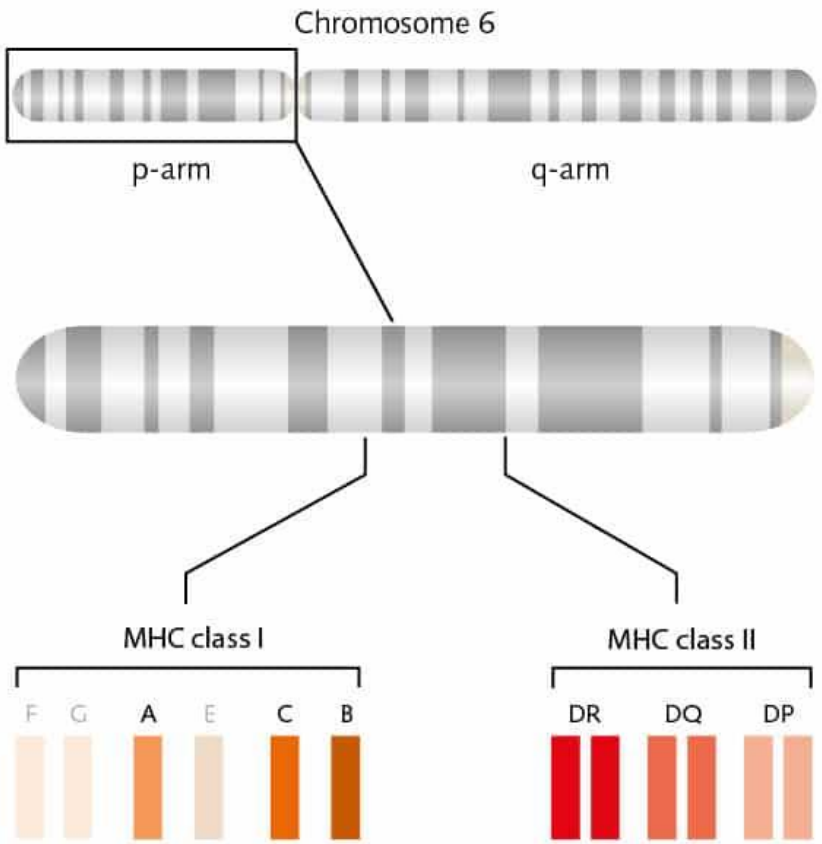
Characteristics	IgG	IgM	IgA	IgD	IgE
					
Structure	Monomer	Pentamer	Dimer (with secretory component)	Monomer	Monomer
Percentage of total serum antibody	80%	5–10%	10–15%*	0.2%	0.002%
Location	Blood, lymph, intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears, saliva, mucus, intestine, milk), blood lymph	B cell surface, blood, lymph	Bound to mast and basophil cells throughout body, blood
Molecular weight	150,000	970,000	405,000	175,000	190,000
Half-life in serum	23 days	5 days	6 days	3 days	2 days
Complement fixation	Yes	Yes	No†	No	No
Placental transfer	Yes	No	No	No	No
Known functions	Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn	Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection	Localized protection on mucosal surfaces	Serum function not known; presence on B cells functions in initiation of immune response	Allergic reactions; possibly lysis of parasitic worms

*Percentage in serum only; if mucous membranes and body secretions are included, percentage is much higher.
†May be yes via alternate pathway.

Development of a Secondary Amplified Respons

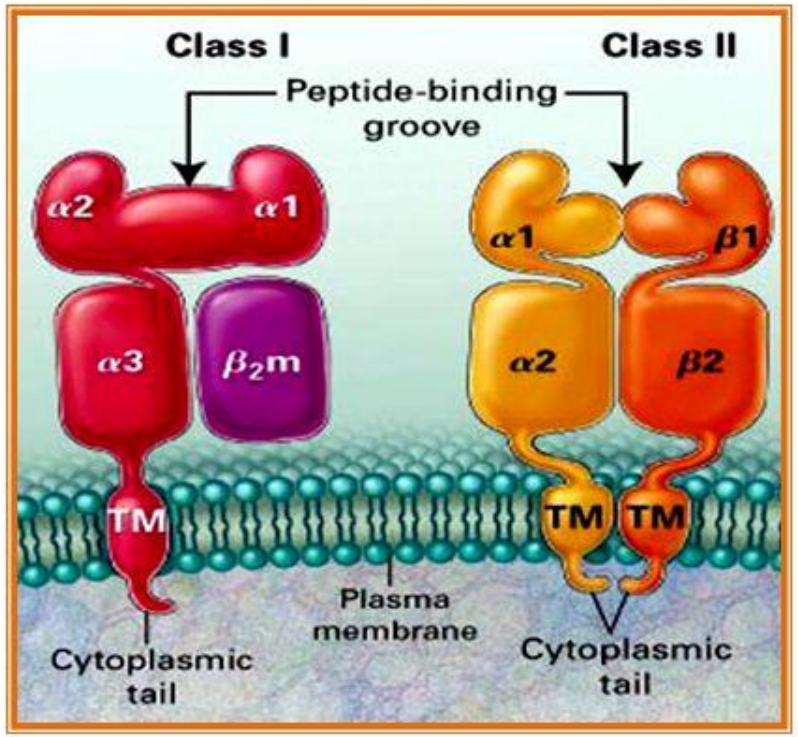


SYSTEME MAJEUR D'HISTOCOMPATIBIE (HLA: HUMAN LEUCOCYTE ANTIGEN)



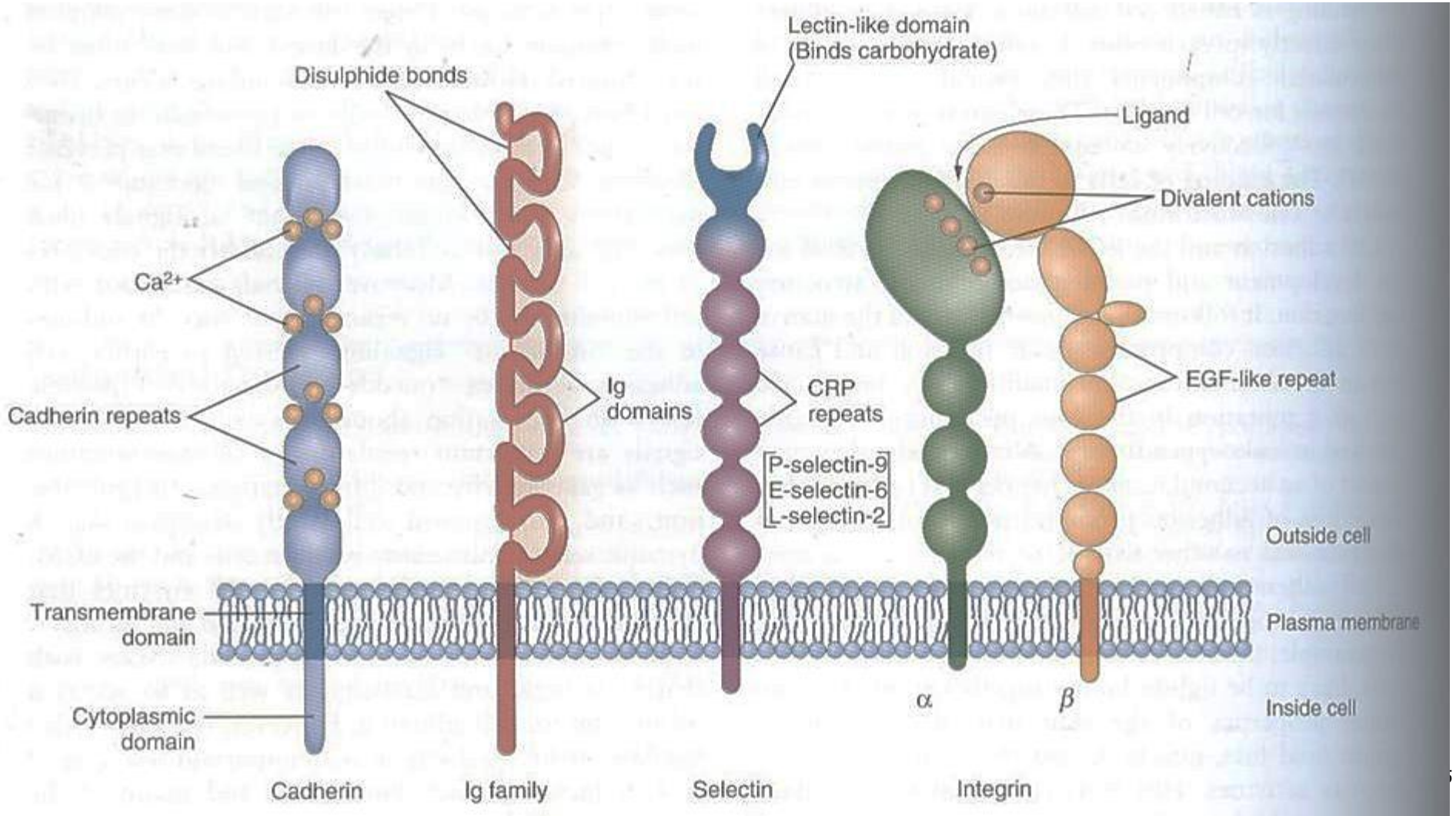
HLA class I and class II antigens

- Monomer with non-covalently associated subunit (β2m)
- Presents antigenic peptides to CD8+ T cells
- Expressed by all nucleated cells

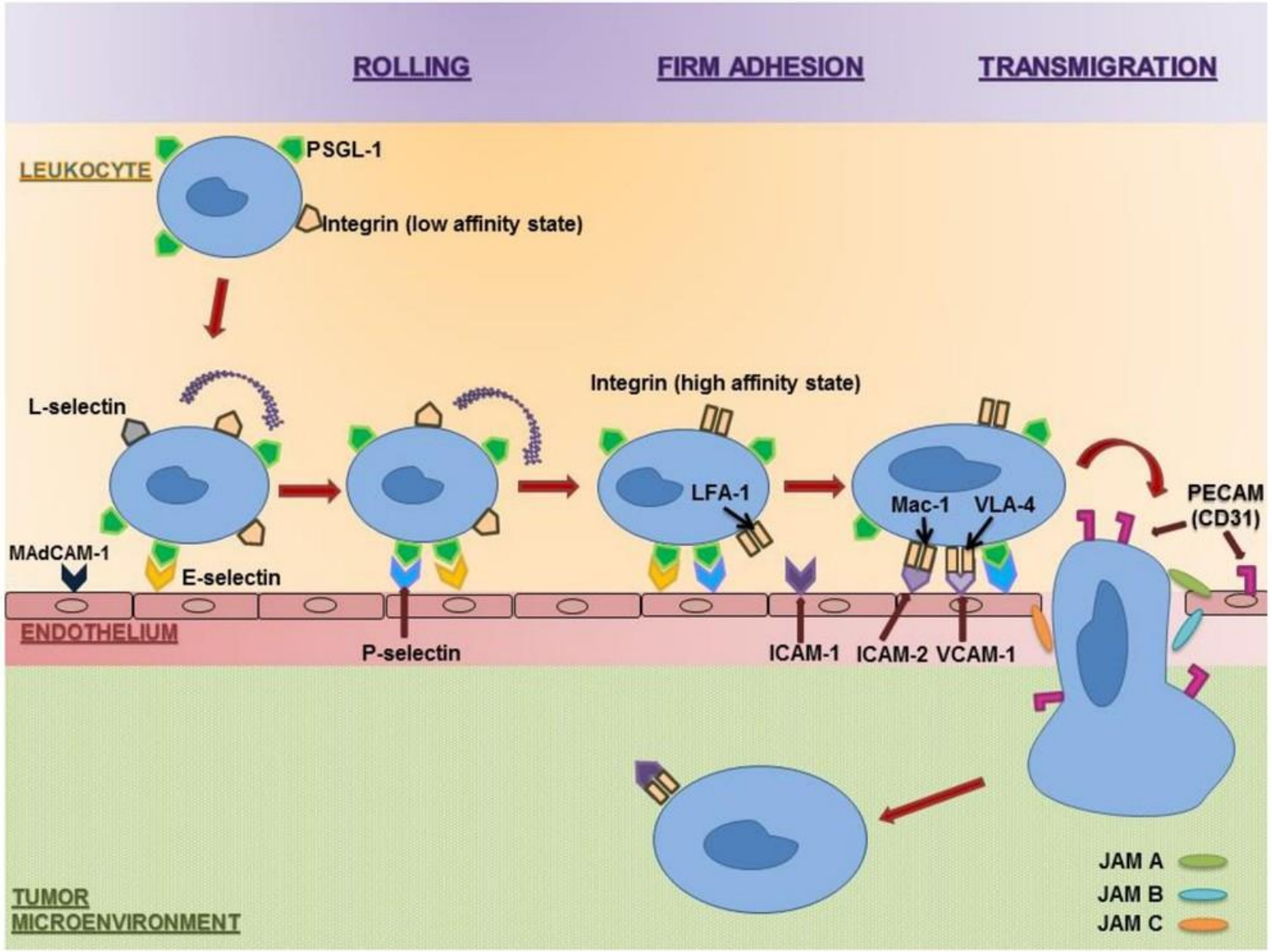


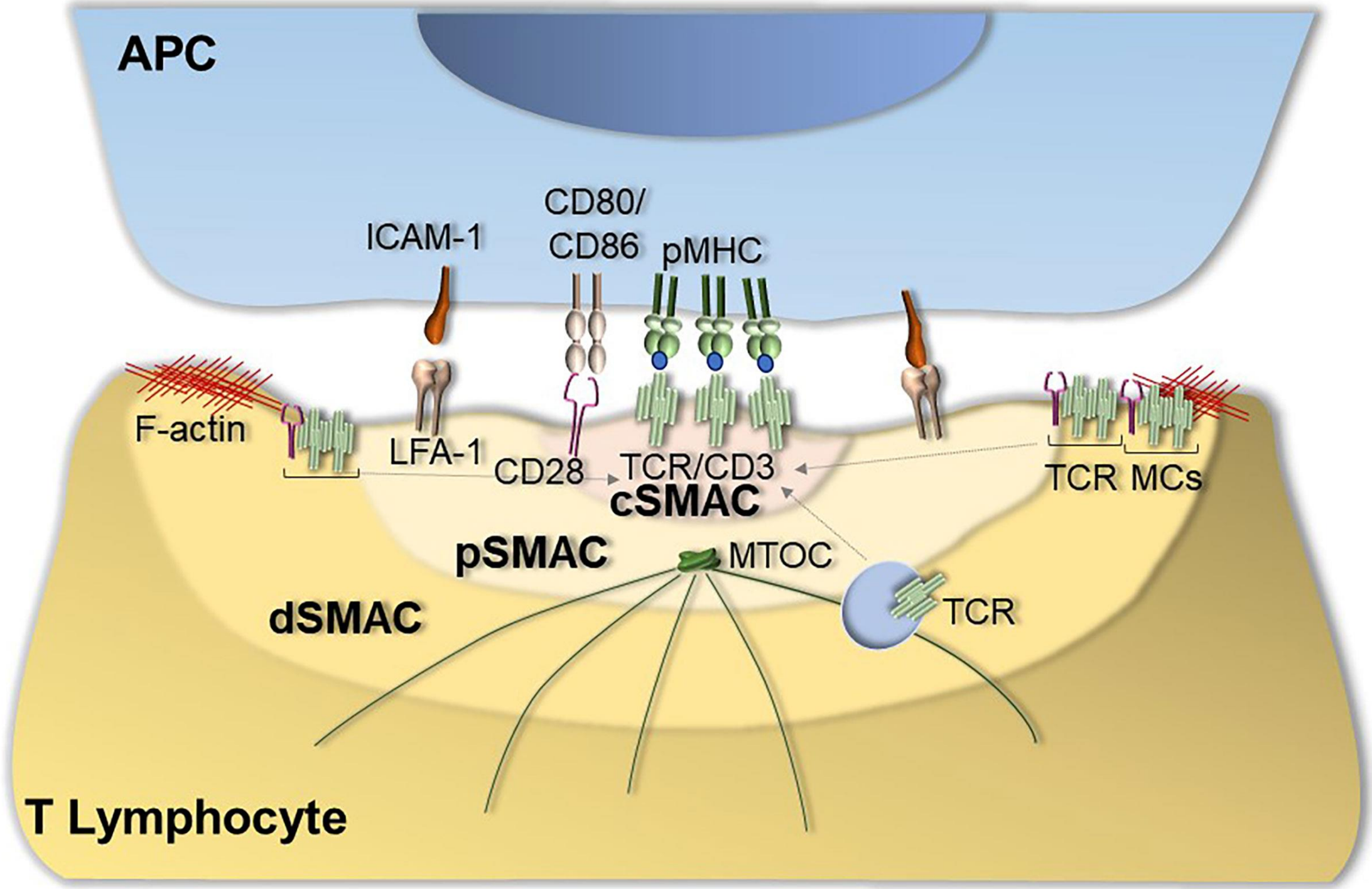
- Heterodimer
- Presents antigenic peptides to CD4+ T cells
- Restricted expression on antigen presenting cells (dendritic cells, B cells, macrophages)
- Inducible on other cells (endothelium and epithelium)

MOLECULES D'ADHESION CELLULAIRES



MOLECULES D'ADHESION CELLULAIRES




APC
ICAM-1
CD80/
CD86
pMHC
F-actin
LFA-1
CD28
TCR/CD3
cSMAC
TCR MCs
pSMAC
MTOC
dSMAC
TCR
T Lymphocyte

CLASSIFICATIONS OF CYTOKINES

ACCORDING TO DIVISION OF LABOR

T- helper 1 type of cytokines
e.g IL-2, IL-12, TNF-α ,IFN-γ

T- helper 2 type of cytokines
e.g IL-3, IL-4, IL-5, IL-13

T- helper 3 type of cytokines
e.g IL-10, TGF-β

STRUCTURAL CLASSIFICATION OF CYTOKINES

IL-2/IL-4 family
e.g IL-2, IL-4, IL-5, granulocyte-macrophage colony stimulating factor

TNF family
TNF-α, lymphotoxin-α, LT-β, FasL, CD40L, TRAIL, LIGHT

IL-1 family
IL-1α, IL-1β, IL-1, IL-18

STRUCTURAL CLASSIFICATION BASED ON RECEPTORS

Heamatopoitin family receptors
(class I receptors)
Growth hormone
Prolactin
Erythropoitin
Interleukin
(2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 15, 16, 17, 25)
Granulocyte macrophage colony stimulating factor
Granulocyte colony stimulating factor

Interferon/ IL-10family receptors
(class II receptors)
Type I interferons
(IFNC, β, δ, κ, ω, I, IL–28A, IL-28)
Interferons γ
Interleukin (10, 19, 20, 22, 24)

RECEPTOR CLASSIFICATION BASED ON POSITION OF CYSTEINE RESIDUES NEAR THE N-TERMINUS

CC

CXC

C

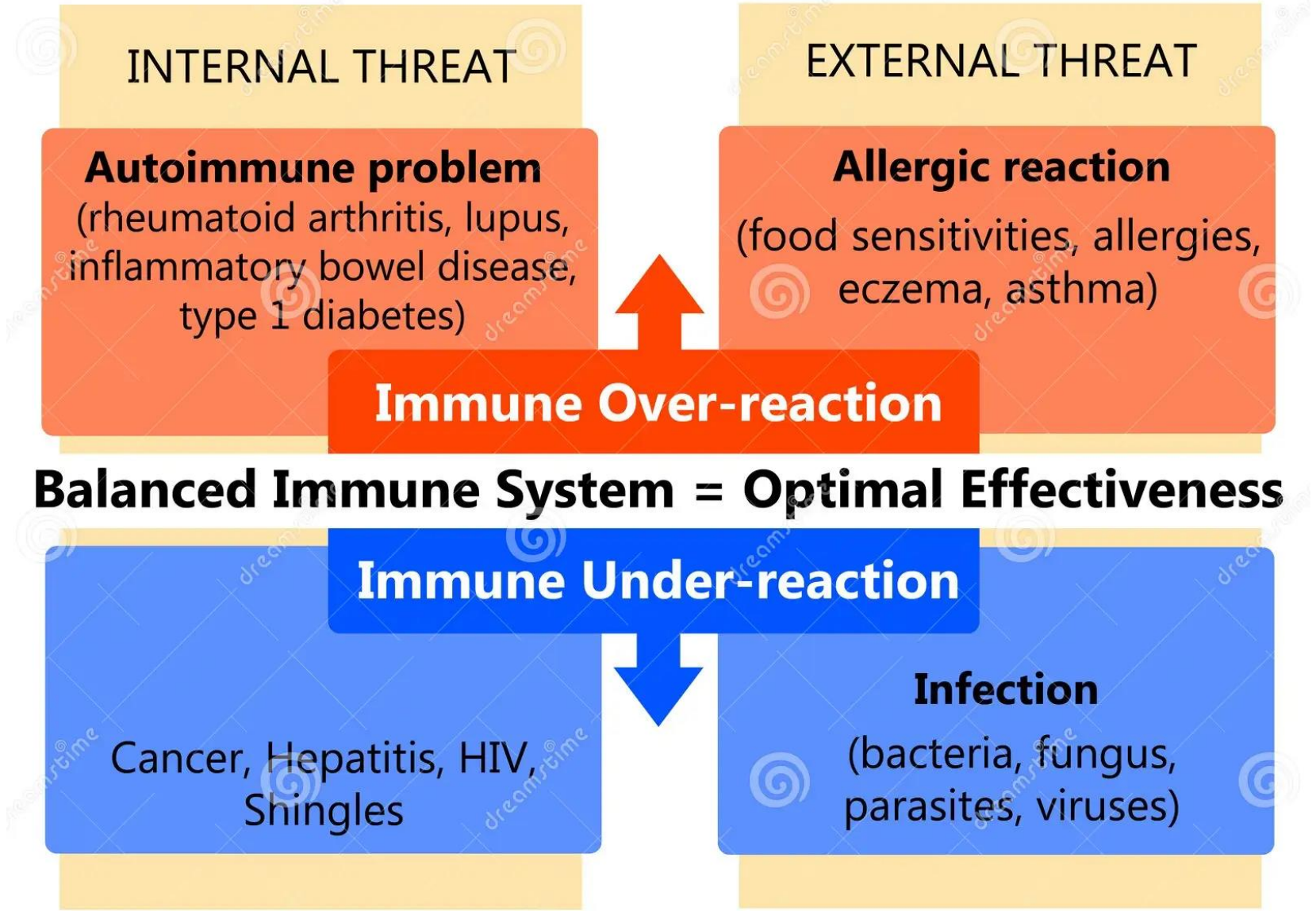
CX3C

FUNCTIONAL CLASSIFICATION

Those produced after inflammatory stimuli
(inflammatory chemokines)

Those produced consecutively in tissues
(homing chemokines)

A Balanced Immune System



CONCLUSION

- Role de l'immunité dans le maintain de l'intégrité de l'organisme.
- Distinction du soi du non soi pathogène
- Tolerance du soi et du non soi non pathogène
- Immunité innée versus immunité spécifique
- Reconnaissance via PPR versus TCR/BCR
- Restriction de la reconnaissance du TCR au CMH du soi.
- Immunité spécifique humorale versus immunité a mediation cellulaire.
- Dysregulation immunitaire: Hypersensibilité versus Deficit immunitaire.