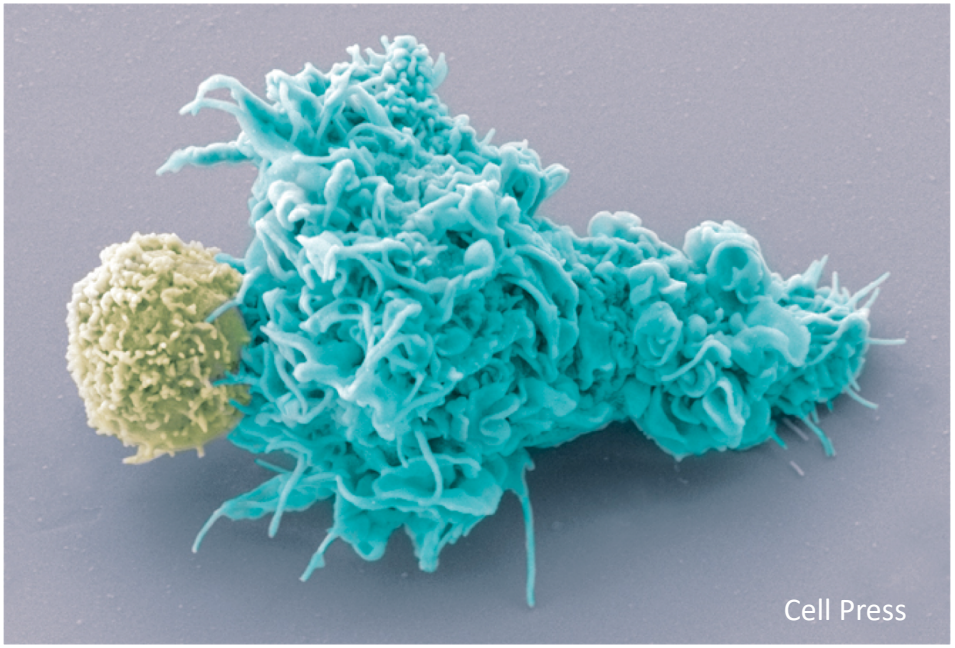
The Immune System



Immune synapse between a T cell and a Dendritic cell

Image: Olivier Schwartz and Electron Microscopy Core Facility, Institut Pasteur

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

HSeT
Health Sciences
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I. Introduction to the Immune System

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Introduction to Immunology

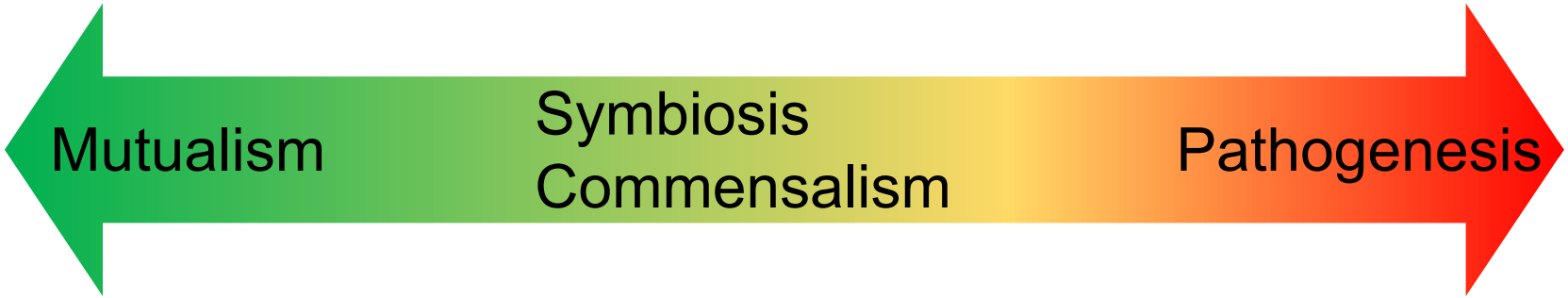
Objectives of the immunology module:

- ❑ Understand the structure and function of the immune system (from molecules to tissues to organisms)
- ❑ Gain insight into the innate and adaptive defences against microbes
- ❑ Discover some applied aspects of immunology: transplantation, vaccination, allergy, auto-immune diseases

Recommended reading:

- Immunology, by Eric Espinosa and Pascal Chillet, published by Ellipses
- Basic Immunology, by Abul K. Abbas and Andrew Lichtman, published by Elsevier-Masson

Host-pathogen interactions are **diverse**

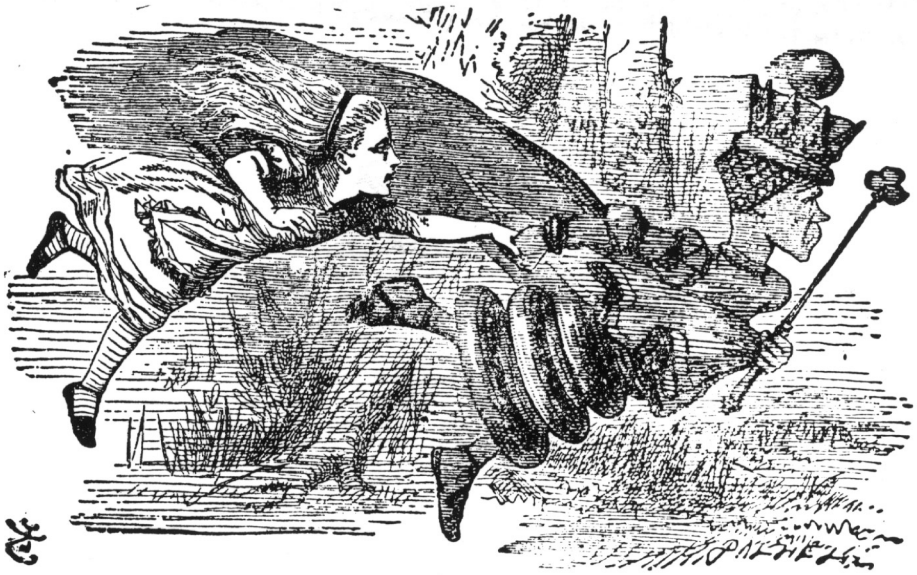


Different **types of pathogens**:

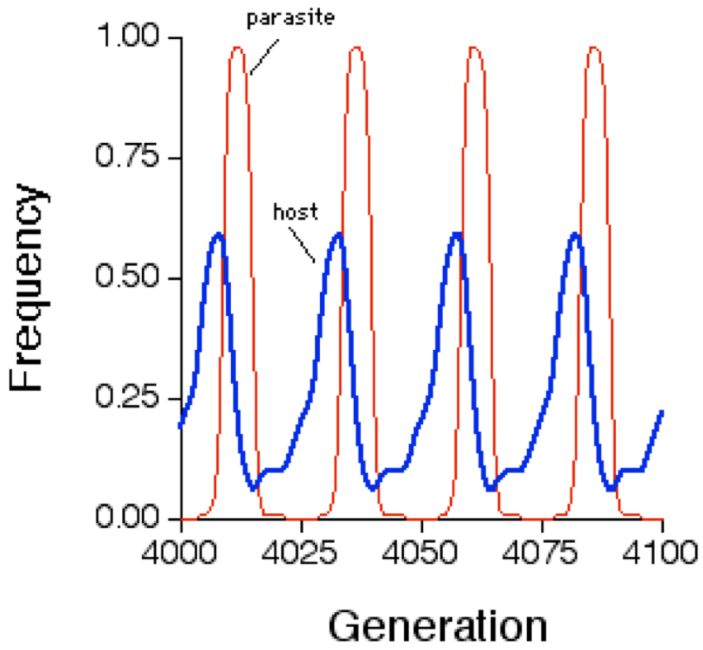
- Co-evolved (ex. Tuberculosis, HIV, Helminths) or opportunistic (ex. *Aspergillus, Pseudomonas*)
- Host-specific, multi-niche, free-living
- Long-term or short-term interactions with their hosts

Microbiota: an "ecological community of commensal, symbiotic and pathogenic microorganisms" associated with a Metazoan.

Host-pathogen interactions are dynamic

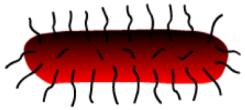


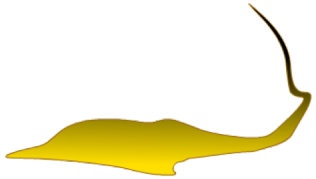
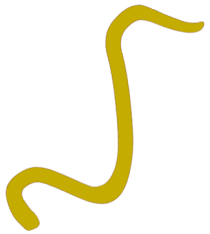
The Red Queen hypothesis



The immune system is costly in terms of resource allocation. There is a trade-off between immunity and other physiological functions.

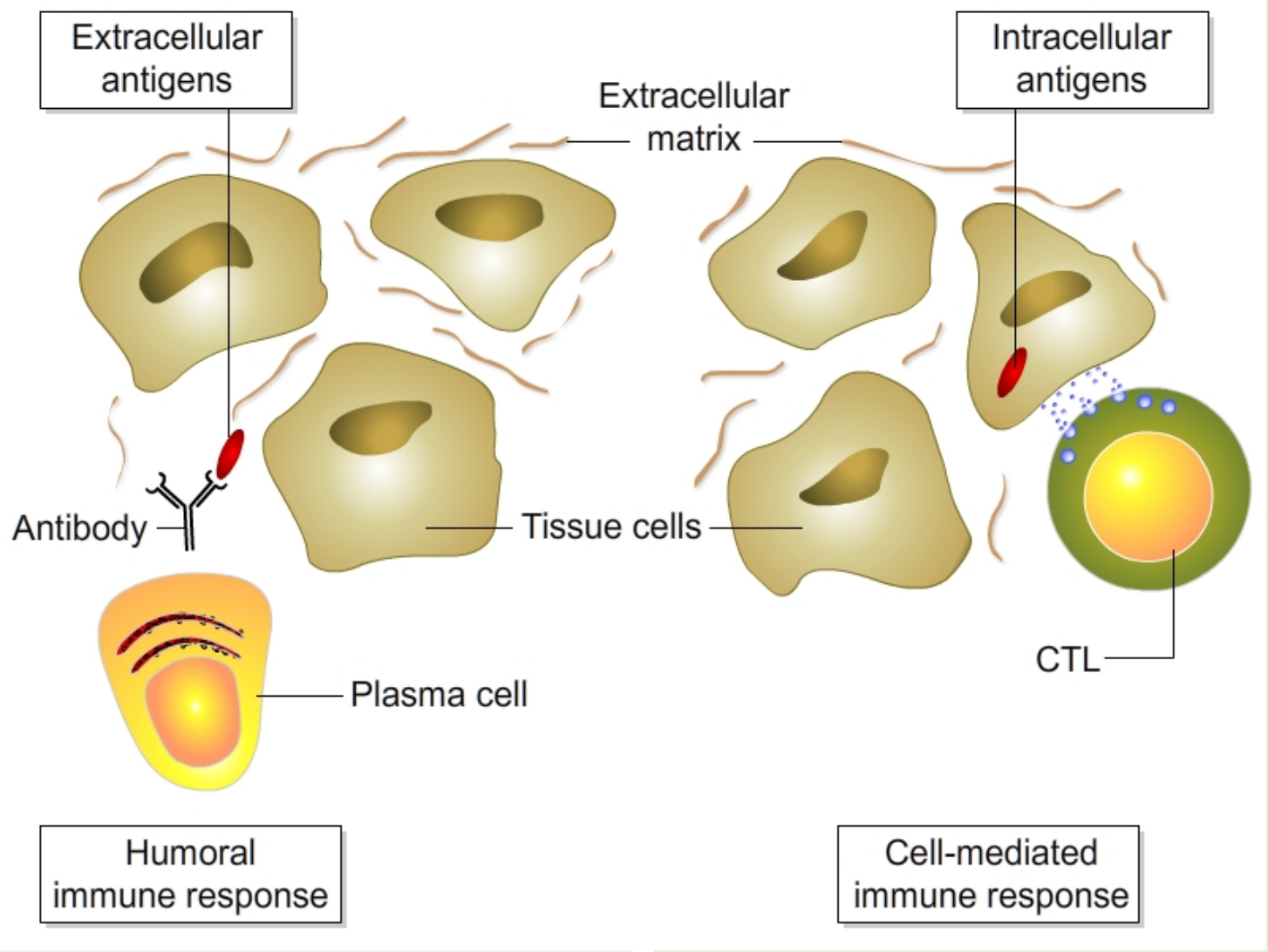
Classes of disease-causing agents




Bacteria	Viruses	Protozoans	Worms	Fungi
Salmonella	HIV (AIDS)	*Plasmodium* (Malaria)	*Schistosoma* (dermatitis, hepato-, splenomegaly)	Dermatophytes (cutaneous mycosis)
Shigella (dysentery)	*Influenza* (Flu)	*Leishmania* (cutaneous lesions)	*Tenia* (asymptomatic)	Saprophytes (subcutaneous mycosis)
Staphylococcus aureus	HAV, HBV (Hepatitis)	*Trypanosoma* (sleeping sickness, Chagas disease)		
Pneumococcus (otitis, pneumonia)	*Rotavirus* (diarrhea)	*Toxoplasma gondii* (fetal abnormalities)		
		Entamoeba histolytica (dysentery)		
		Cryptosporidium parvum (diarrhea)		

Different pathogen lifestyles require different immune responses



Three ways to resist microbial infection

- **Avoidance** (behavioural): to avoid interaction with microbes

- **Resilience** (or **disease tolerance**): to better endure the consequences of the infection (e.g. repair, detoxification)

- **Immunity**: to recognize and eliminate invading microbes

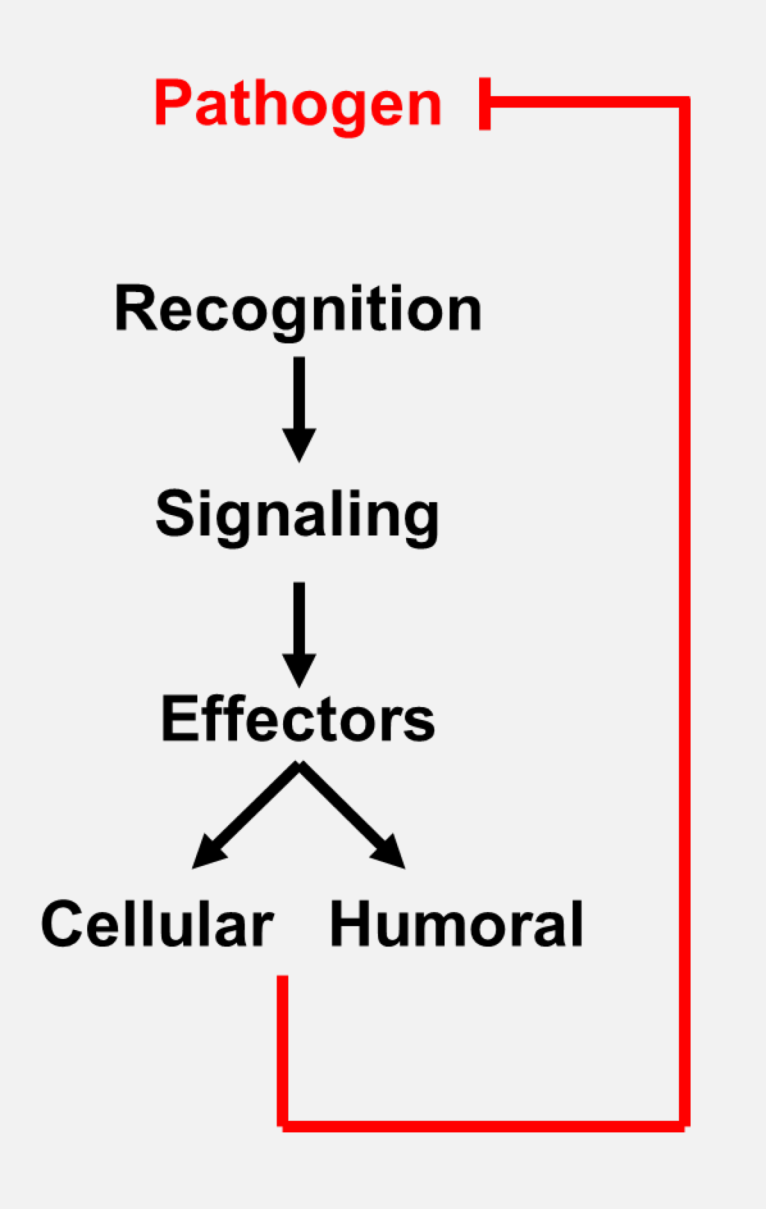
Introduction to the Immune System

Immunity is defined as resistance to disease, specifically infectious disease. The collection of **cells, tissues, and molecules** that mediate resistance to infections is called the **immune system**.

Immune function	**Consequences**
Defence against infections	• Immunocompromised individuals are at higher risk of infections (e.g. AIDS) • Vaccination creates protective immunity
Recognition of foreign tissues (grafts) and proteins	Interferes with transplantation and gene therapy
Defence against tumours	Immunotherapy against cancer
Tolerance of (intestinal) microbiota	Microbiota confinement rupture causes chronic inflammation

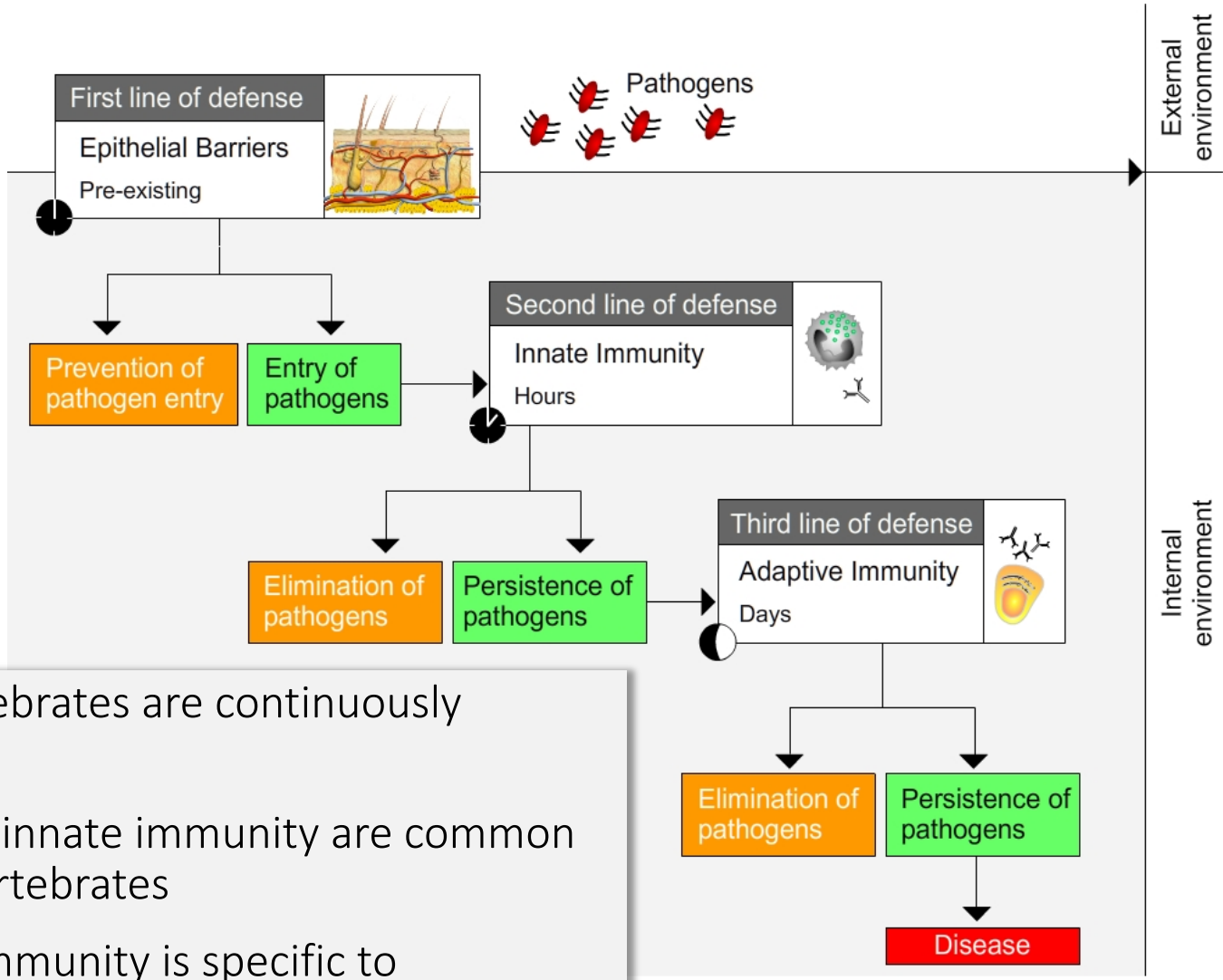
Introduction to the Immune System

- An immune system requires
  - efficient recognition mechanisms (infectious non-self)
  - targeted effector mechanisms
- Immune disorders include
  - immune deficiencies
  - auto-immune diseases/allergies



Three lines of defence against infection

1. Epithelial barriers
2. Innate Immunity
3. Adaptive Immunity

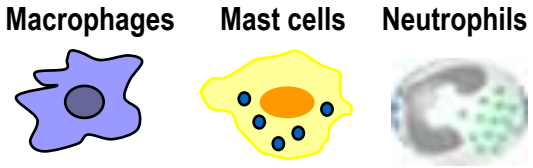


- Invertebrates and vertebrates are continuously exposed to microbes
- Epithelial barriers and innate immunity are common to invertebrates and vertebrates
- B and T cell adaptive immunity is specific to vertebrates

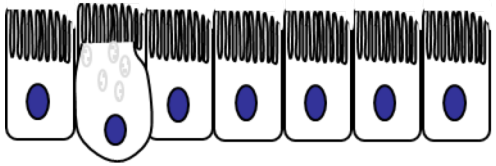
Innate Immunity

The innate immune system consists of:

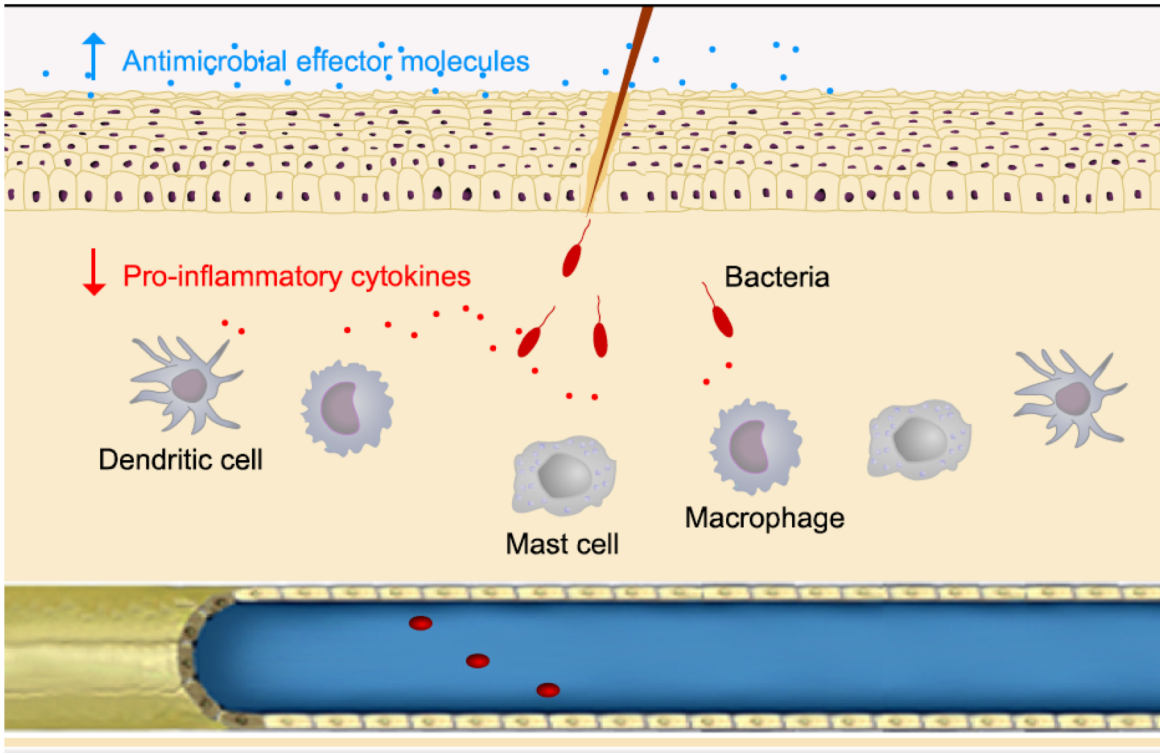
- a wide variety of **cells**
  - circulating in the blood and scattered in organs



  - forming tissues that separate the outside from the inside world

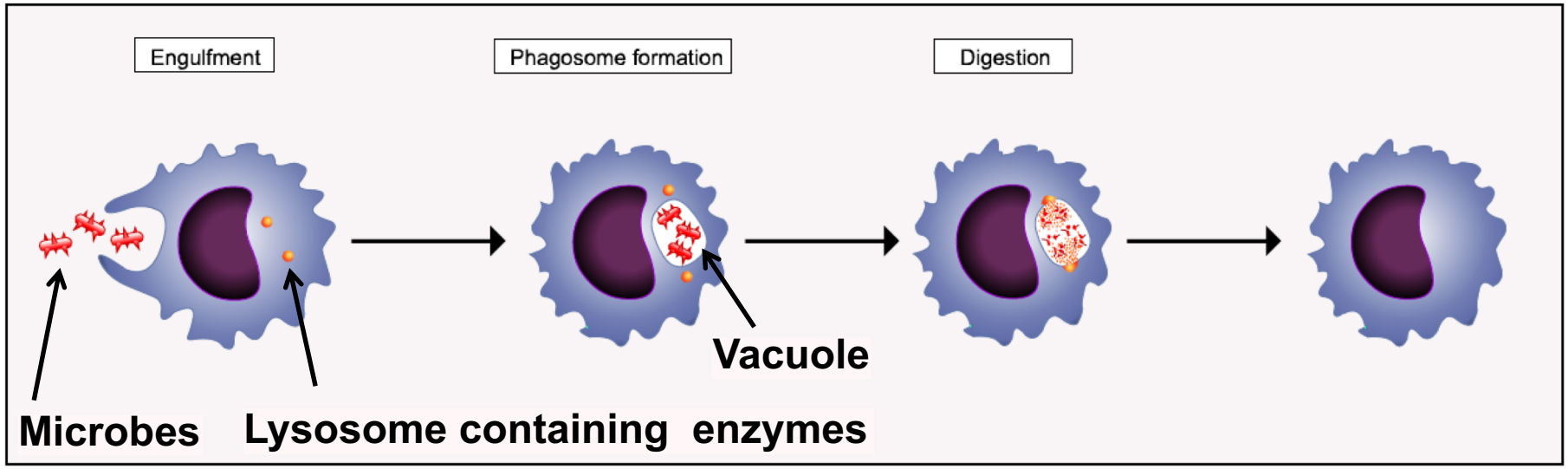


- **molecules** produced by innate immune cells or the liver
  - antimicrobial peptides
  - acute phase proteins
  - complement
  - cytokines & chemokines



Phagocytosis: a universal mechanism of defence

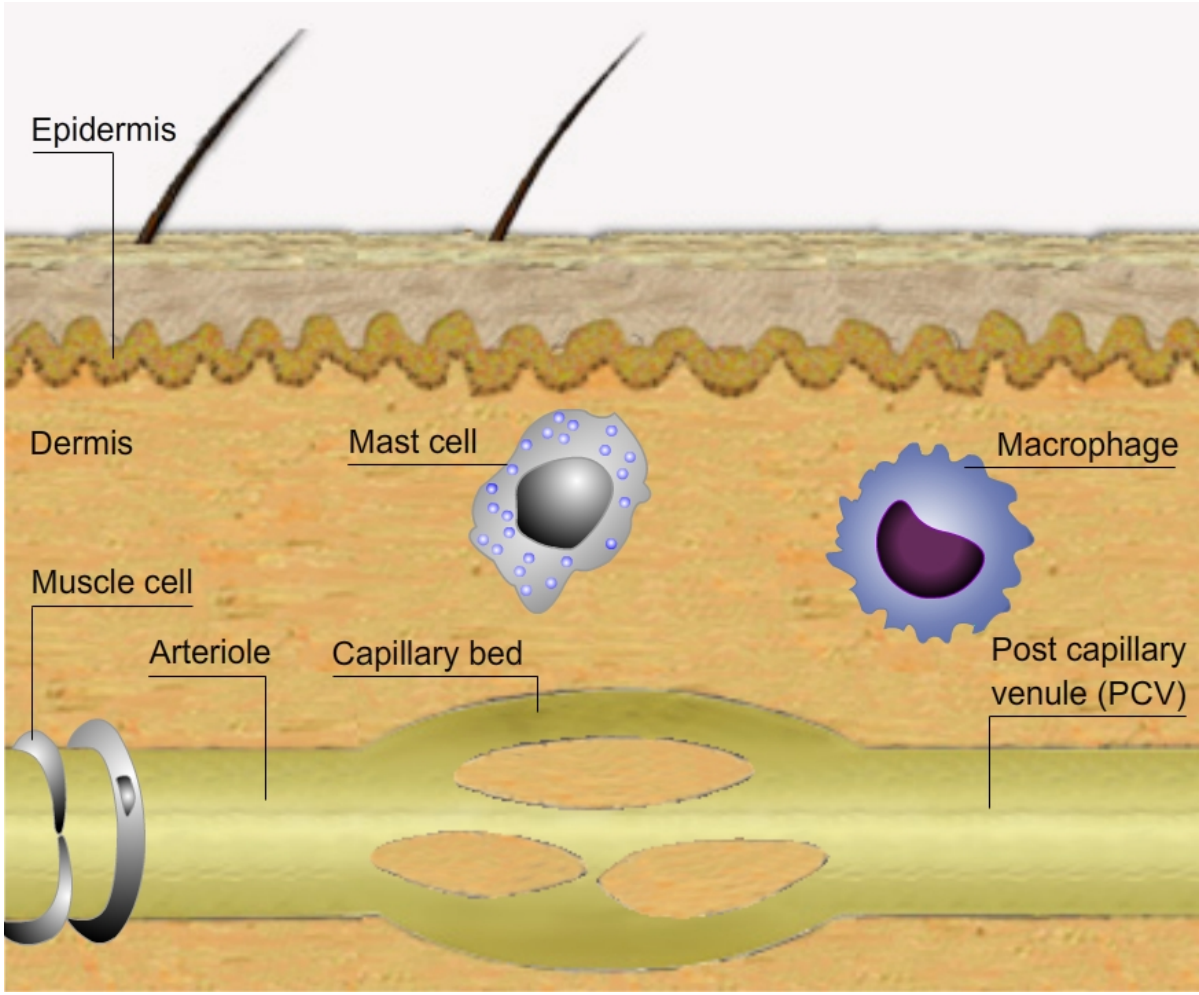
Phagocytic cells include neutrophils, macrophages, and dendritic cells.



The inflammatory response

After tissue injury, **mast cells** degranulate. The **histamines** they release affect local blood vessels: blood flow increases and more macrophages and antimicrobial proteins exit the vessel towards the wounded tissue.

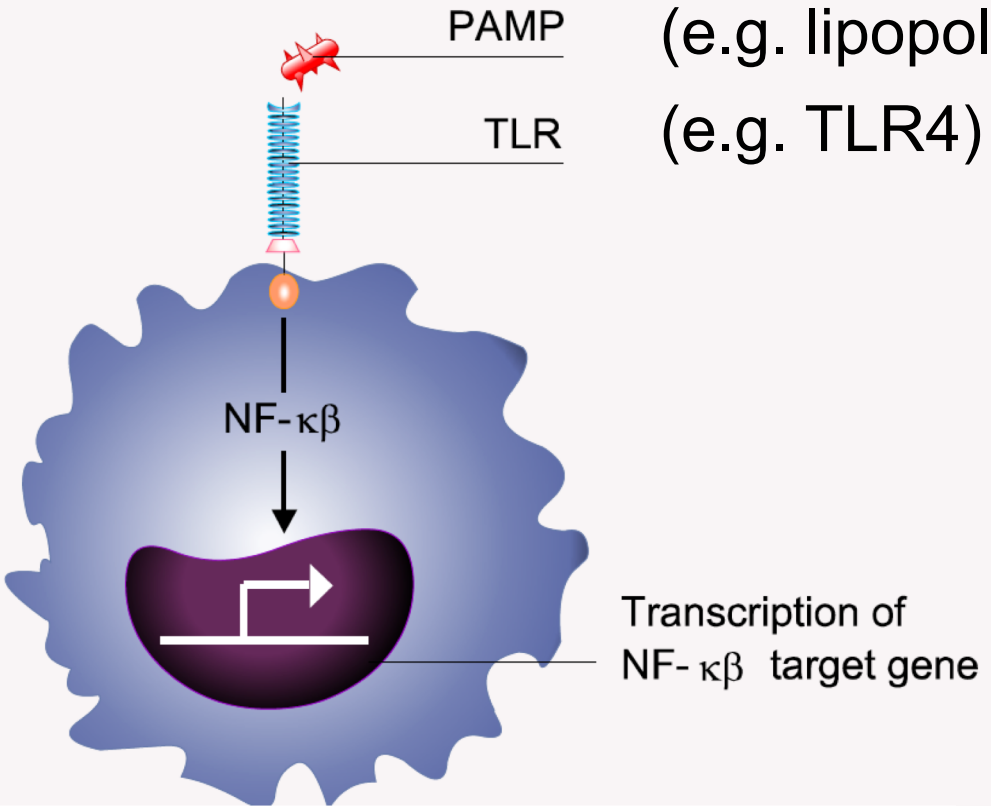
These changes are called the **inflammatory response**.



Chemokines are chemoattractants.

Cytokines are secreted molecules signaling between different elements of the immune system.

Innate immunity is triggered by receptors that detect molecular structures unique to microbes or molecules that signal damage



(e.g. lipopolysaccharide, LPS)

(e.g. TLR4)

Conclusion 1A

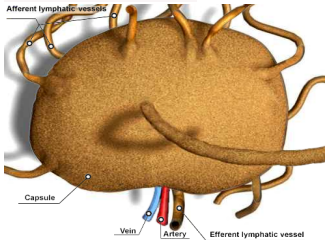
- The physiological function of the immune system is to protect individuals against infections.
- Innate immunity is the earliest line of defence, mediated by cells and molecules that are always present and ready to eliminate infectious microbes.
- Innate immunity consists of barrier tissues (epithelia) and a wide variety of molecules produced by innate immune cells or the liver.
- Innate immune mechanisms are diverse: phagocytosis, degranulation, interferons, complement, antimicrobial peptides
- Inflammation is a rapid reaction that recruits blood cells and immune molecules to the site of infection

Third line of defence: adaptive immunity

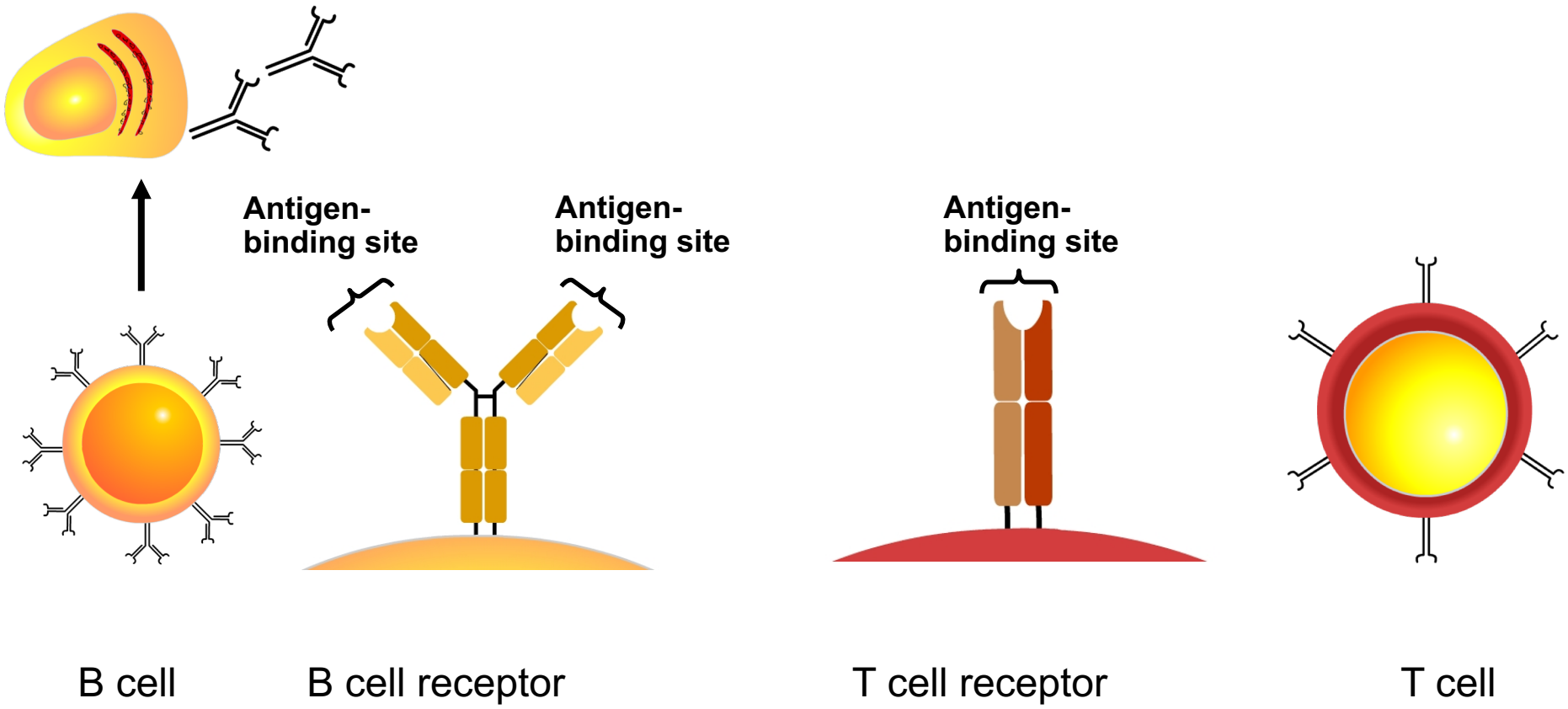
- A host defence unique to vertebrates
- Mobilizes defences that are adapted to each specific disease-causing agent
- Retains a “memory” of previous encounters

The adaptive immune system consists of:

- Cells called **lymphocytes**
- **Molecules** produced by lymphocytes, including antibodies
- Organs called **lymphoid organs** where lymphocytes divide and reproduce, mature, and perform some of their functions. Lymphocytes migrate in and out of lymphoid organs.



Antigen receptors on B and T lymphocytes



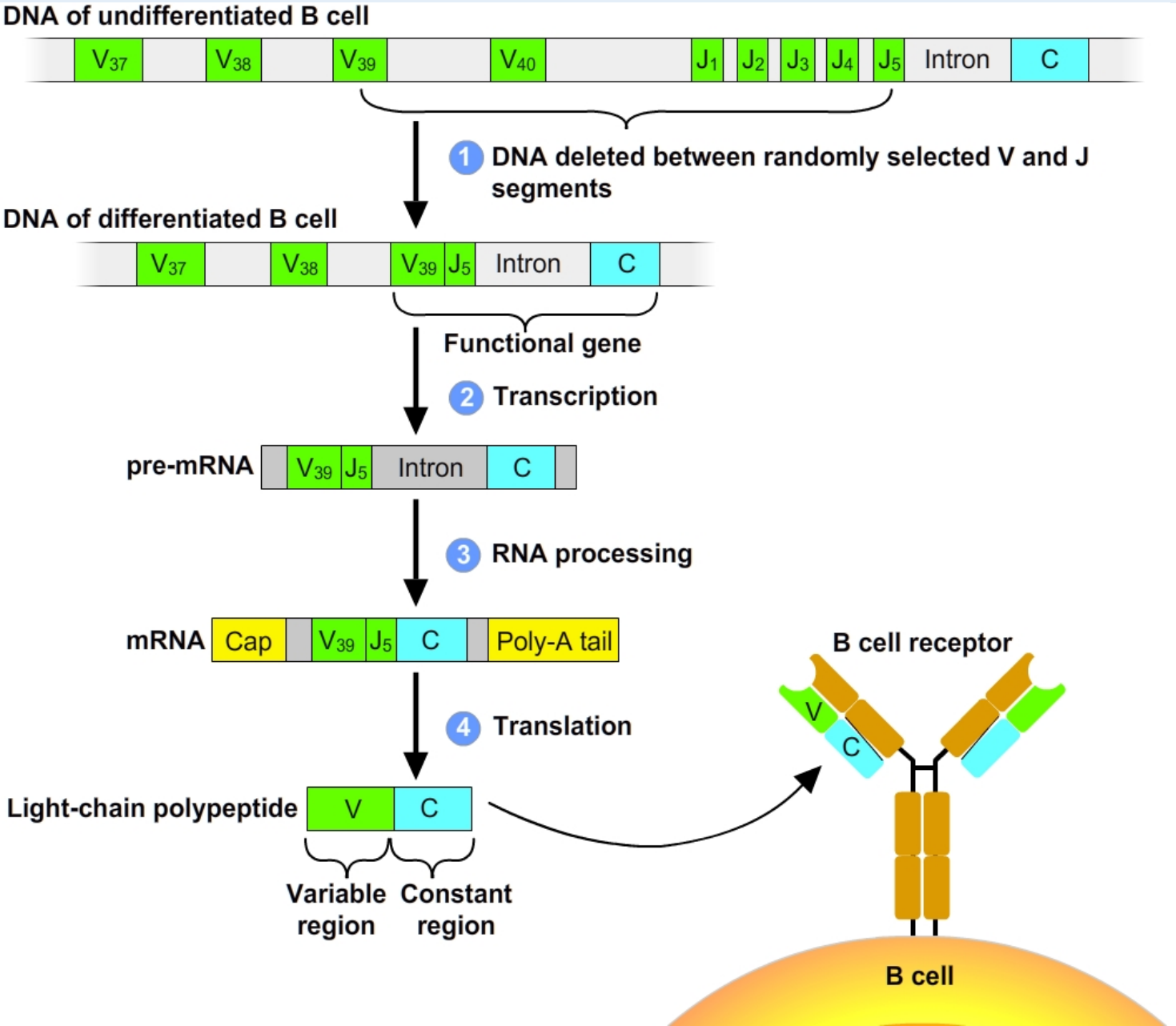
The human body contains an extensive repertoire of B and T cells with specific antigen binding specificity.

Generation of the B and T cell repertoires

What are the mechanisms that define receptor specificity?

What are the mechanisms that prevent activation of an immune response against self-antigens?

Immunoglobulin gene rearrangement



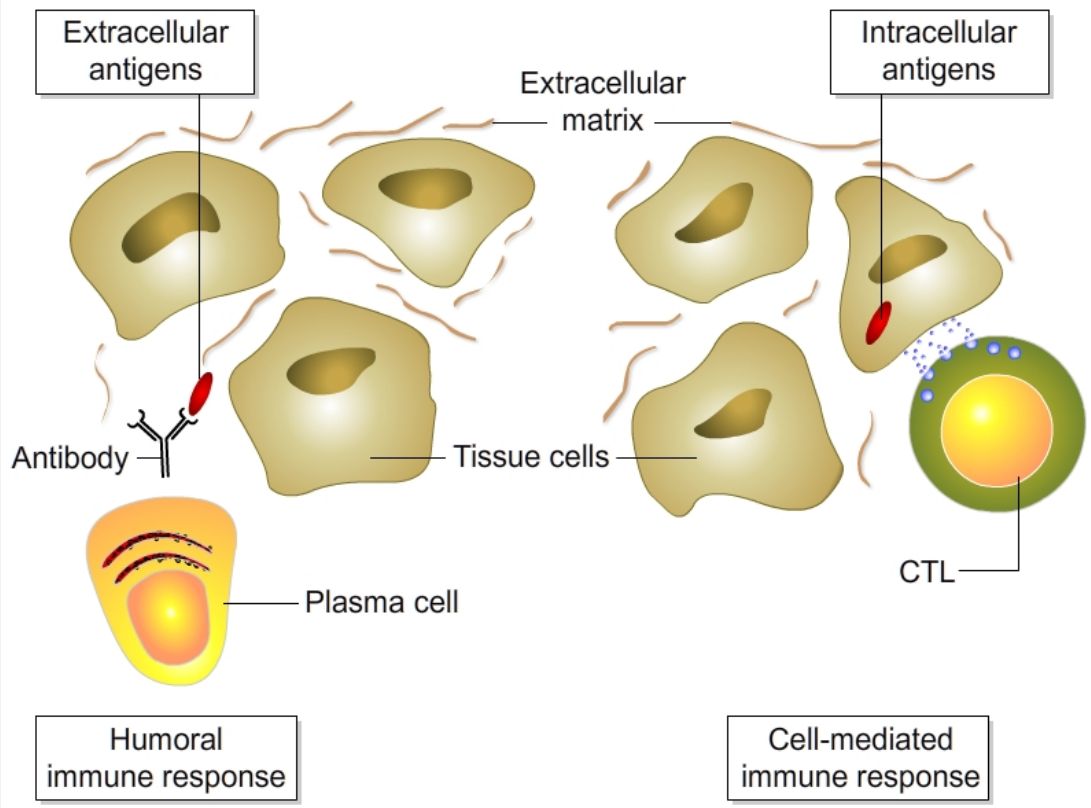
Origin of Self-Tolerance

- Antigen receptors are generated by random rearrangement of DNA.
- As lymphocytes mature in the bone marrow or the thymus, they are tested for self-reactivity.
- Lymphocytes with receptors specific for the body's own molecules are destroyed by apoptosis, or rendered nonfunctional.

Abbas, Basic Immunology

Two types of adaptive immunity: humoral and cellular

- **Humoral immunity** is mediated by antibodies, which are produced by B lymphocytes.
- **Cell-mediated immunity** is mediated by T lymphocytes:
- **2 classes of T cells:**
  - CD4 or helper T cells (T_H)
  - CD8 or Cytotoxic T Cells (CTL)

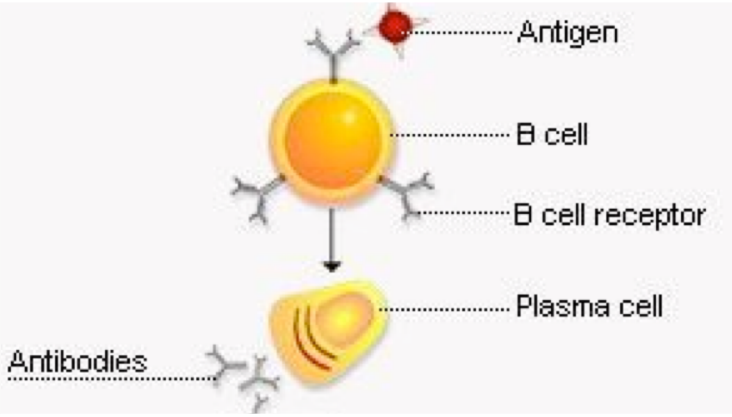


Humoral immunity: Antibodies

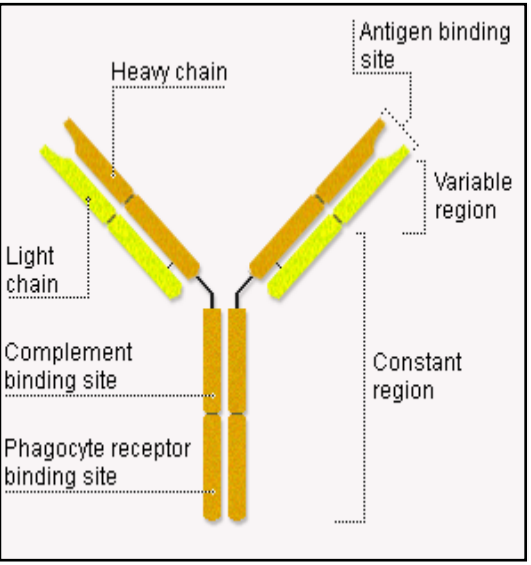
Antibodies are produced by B lymphocytes

2 forms: - **membrane bound: receptor**

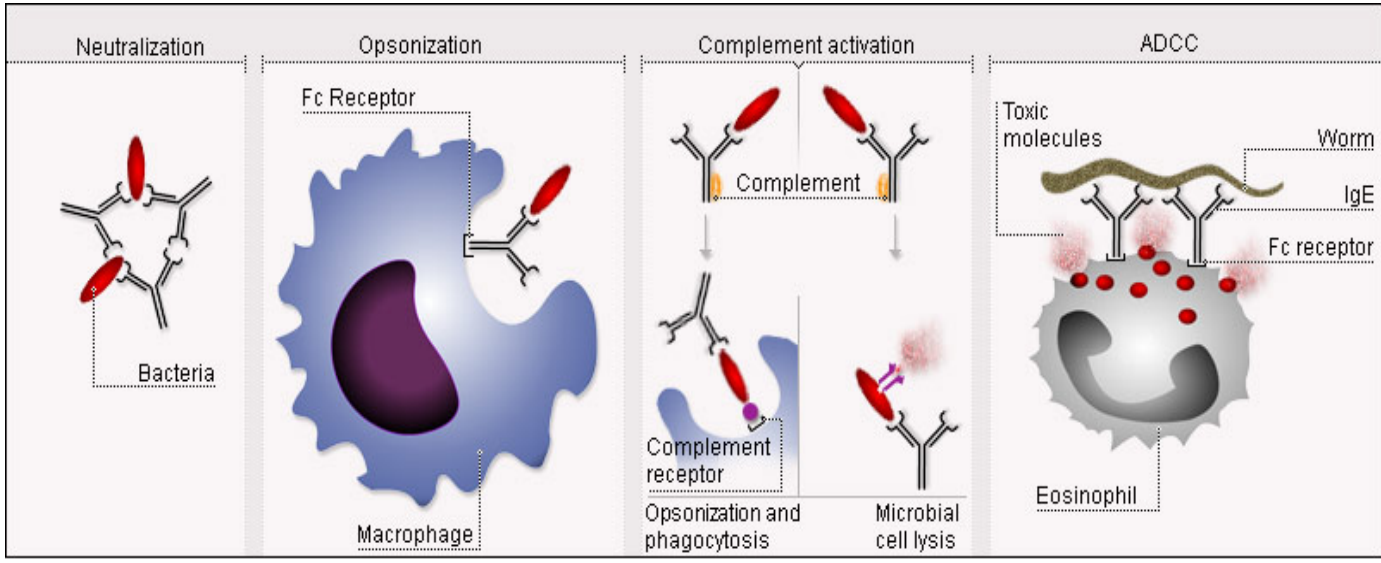
- **secreted: antibody**



Structure



Function



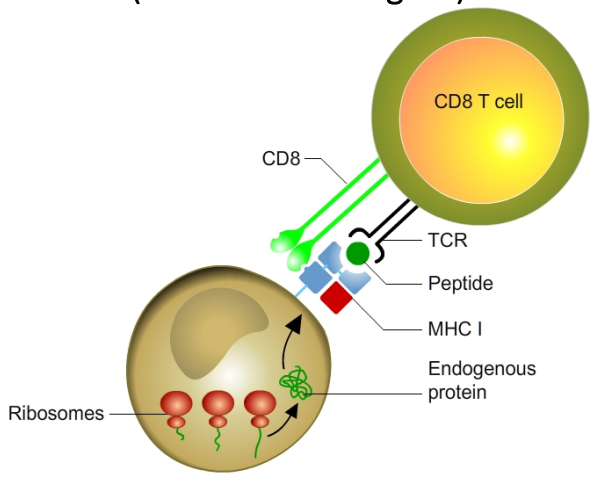
Cellular response: CD4 and CD8 T cells

CD4 T cells activate phagocytes to destroy ingested microbes.

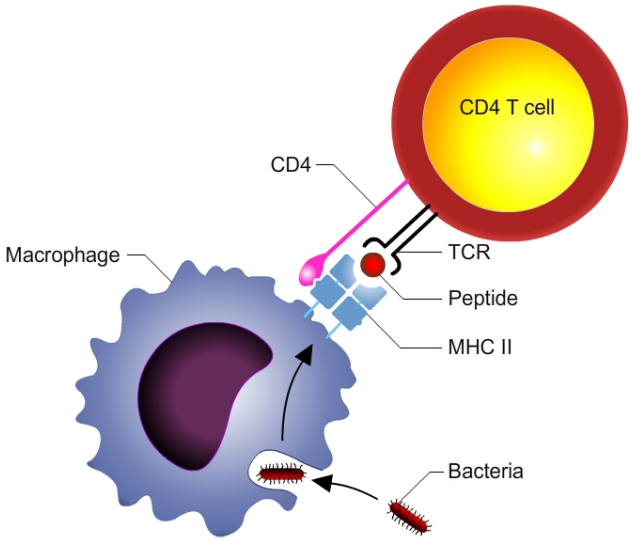
CD8 T cells kill host cells harboring infectious microbes.

- Antigens are presented on **Major Histocompatibility Complex (MHC)** molecules.
- MHC genes are **highly polymorphic** and were initially discovered for their implication in graft rejection
- 2 types:
  - MHC class I: on all cells
  - MHC class II: on Antigen Presenting Cells (APCs) (Dendritic cells, B cells, Macrophages)

MHC class I (intracellular antigens)

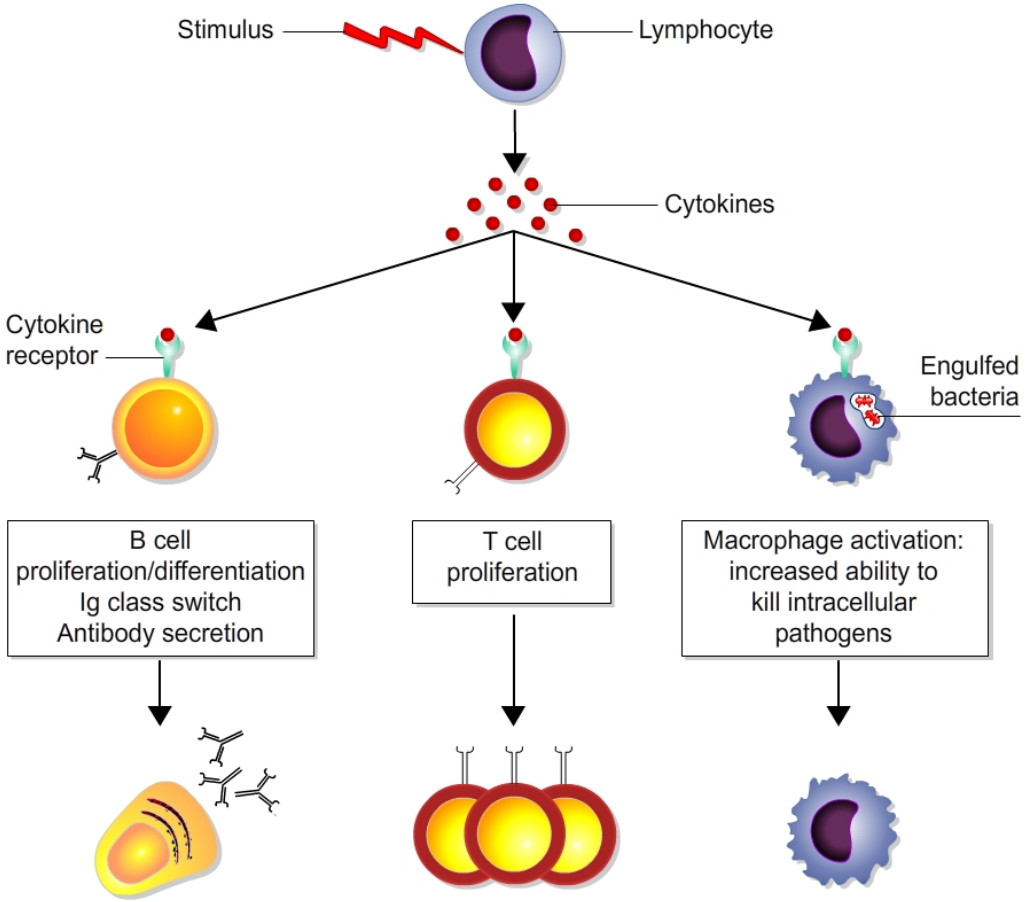


MHC class II (mostly extracellular antigens)

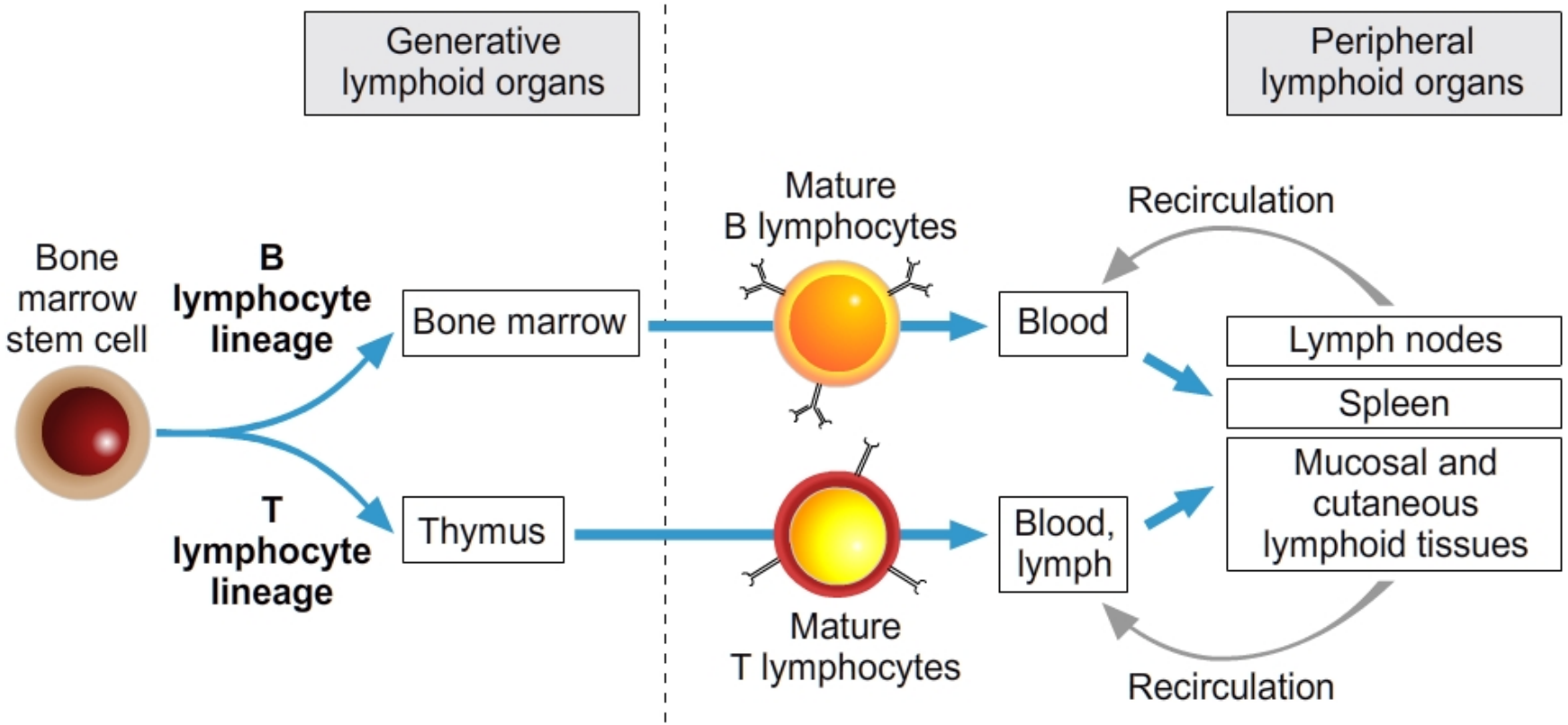


Cytokines: mediators of adaptive immunity

- Cytokines are produced by B and T lymphocytes and other immune cells. They include:
  - Interleukins
  - Interferons
  - Chemokines
- Promote T cell growth
- Promote antibody production
- Activate lymphocytes and macrophages



Maturation and circulation of lymphocytes



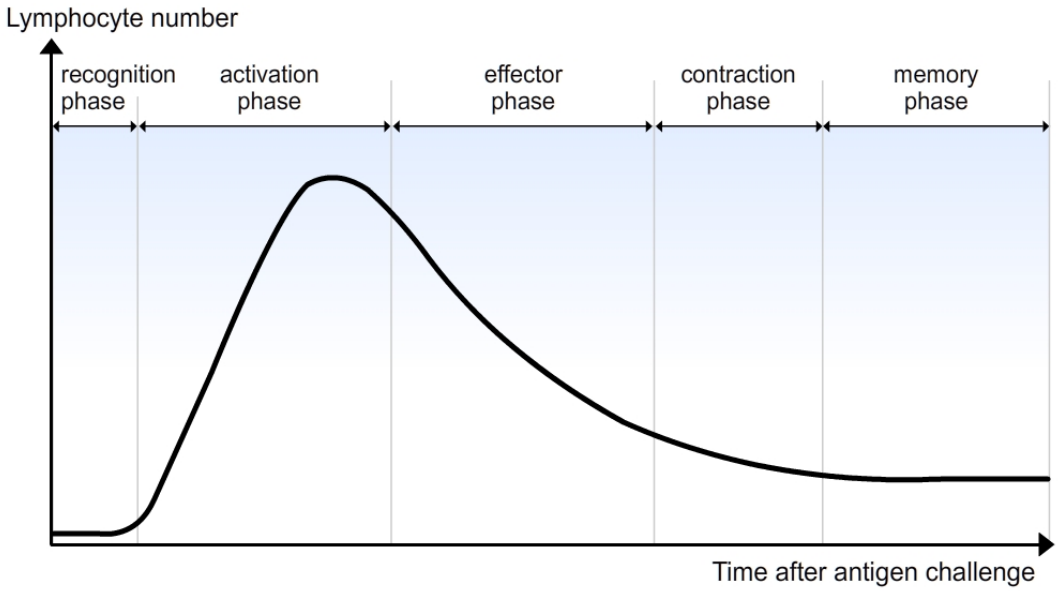
Lymphocytes develop from precursors in the **generative lymphoid organs** (the bone marrow and thymus).

Mature lymphocytes enter the **peripheral lymphoid organs**, where they respond to foreign antigens. From here they recirculate to the **blood and lymph**.

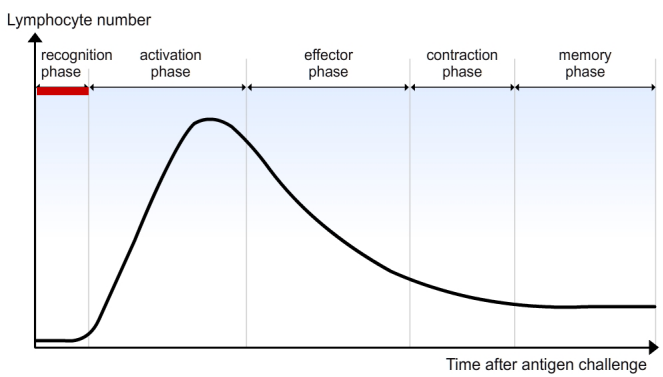
The adaptive response occurs in several steps

Mounting an adaptive immune response requires:

1. **A recognition phase**: recognition of the pathogen or other foreign material by lymphocytes
2. **An activation phase**, whereby antigen-specific lymphocytes receive a co-stimulatory signal to proliferate and differentiate into effector cells.
3. **Clonal expansion** of the antigen-specific lymphocytes.
4. **An effector phase**, during which effector lymphocytes are dispatched to the sites of antigen entry.
5. **A contraction phase** which occurs following clearance of the antigen.
6. **A memory phase**, during which surviving cells specific for the priming antigen may persist over long periods of time.



Step 1: Presentation of antigens by dendritic cells



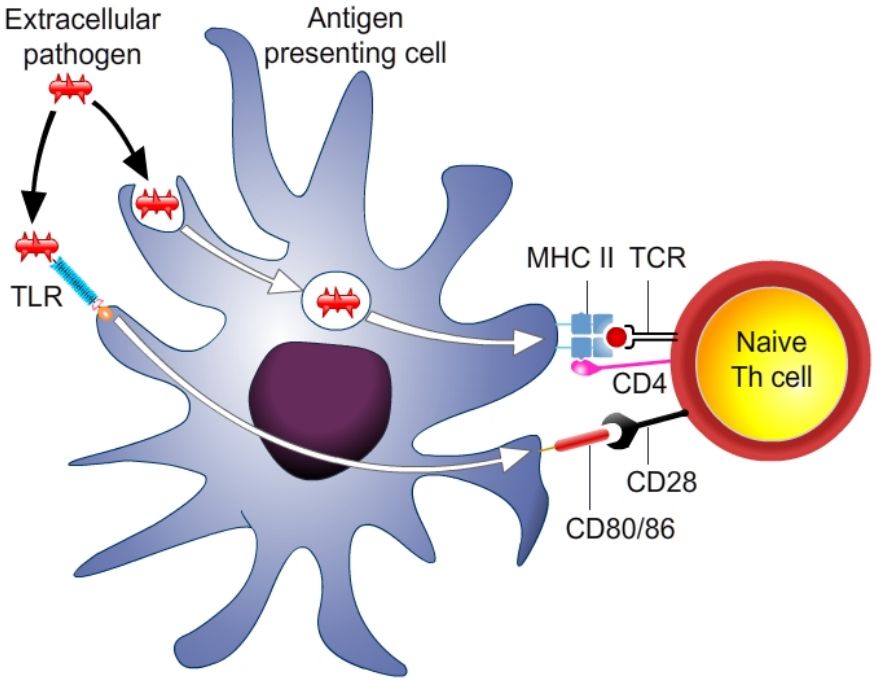
Full activation of antigen-specific lymphocytes requires two signals:

"signal 1" : the antigen itself

"signal 2" : innate immune responses

This requirement for microbe-dependent second signals ensures that lymphocytes respond to infectious agents and not to harmless, noninfectious substances.

Dendritic cells integrate the two signals and present antigens to T cells.



Consequence:

For vaccines that contain antigens rather than whole microbes, substances called **adjuvants** have to be added to trigger innate immune reactions.

Two signals

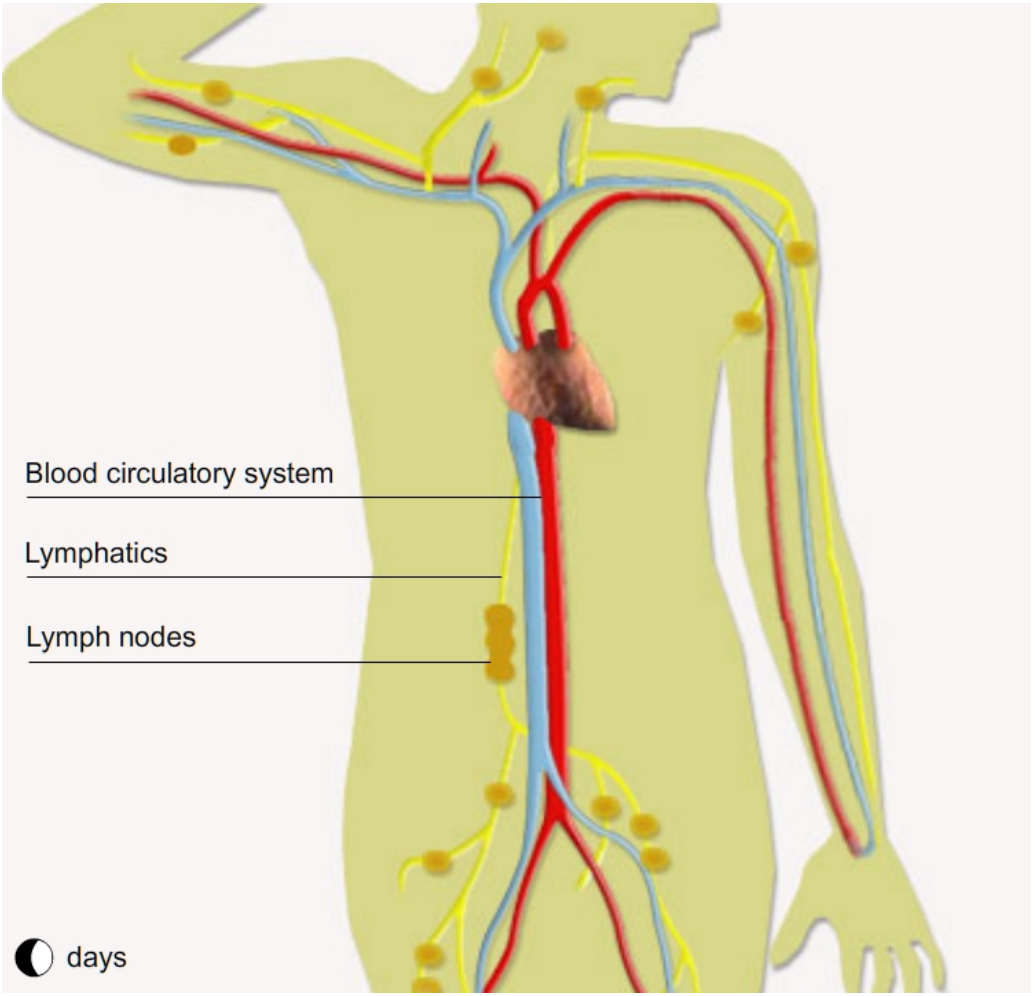
1. Antigens (peptides) → TCR
2. PAMPs/DAMPs → Co-stimulation

Antigen presentation: role of dendritic cells

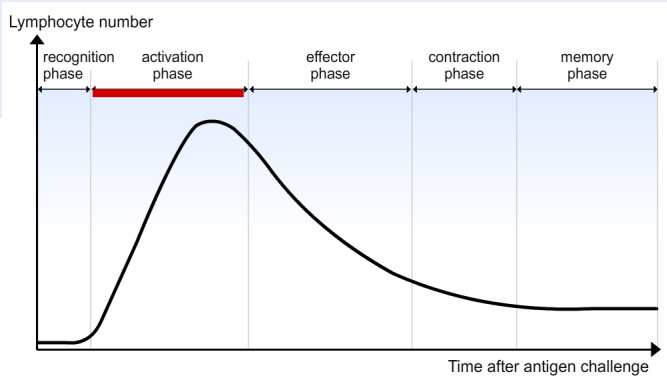
Antigen sampling by dendritic cells (DCs) that migrate from infected tissues to lymph nodes and spleen

Antigen recognition and activation: interaction between DCs and T cells

Antigen clearance: Migration of activated T cells to site of infection

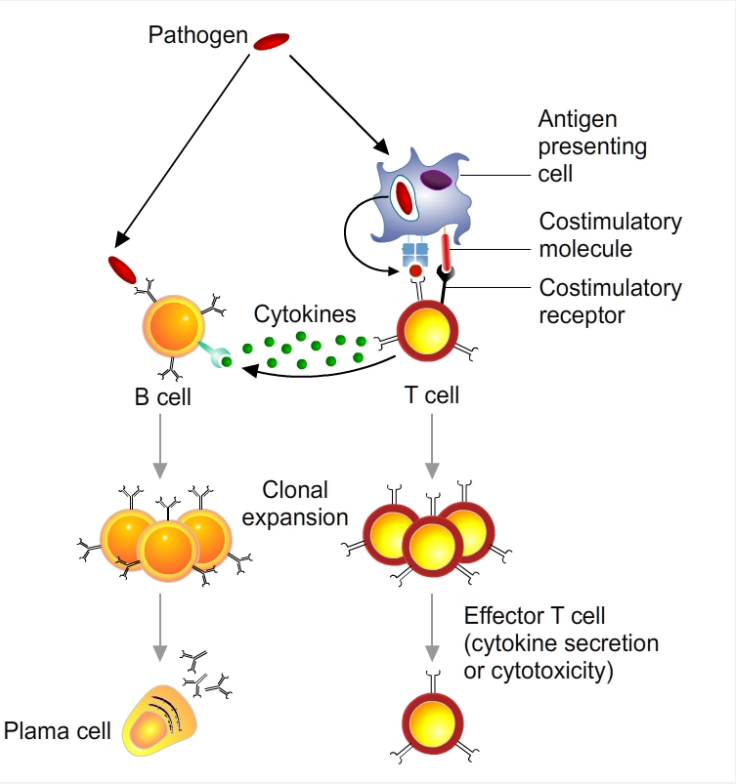


Step 2: Activation phase

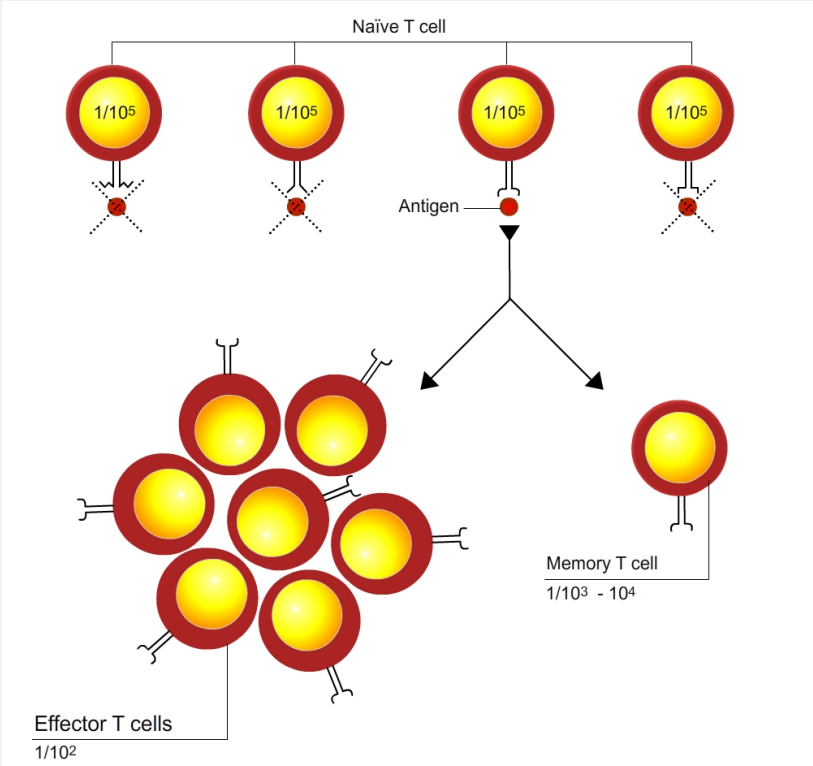


Mounting an adaptive immune response requires an **activation phase**, during which antigen-specific lymphocytes receive a co-stimulatory signal to proliferate and differentiate into effector cells.

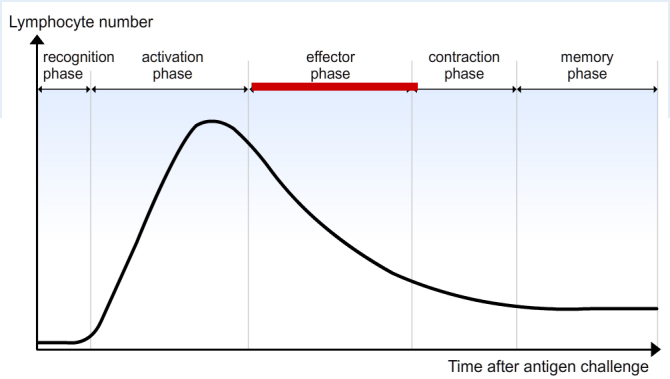
Activation



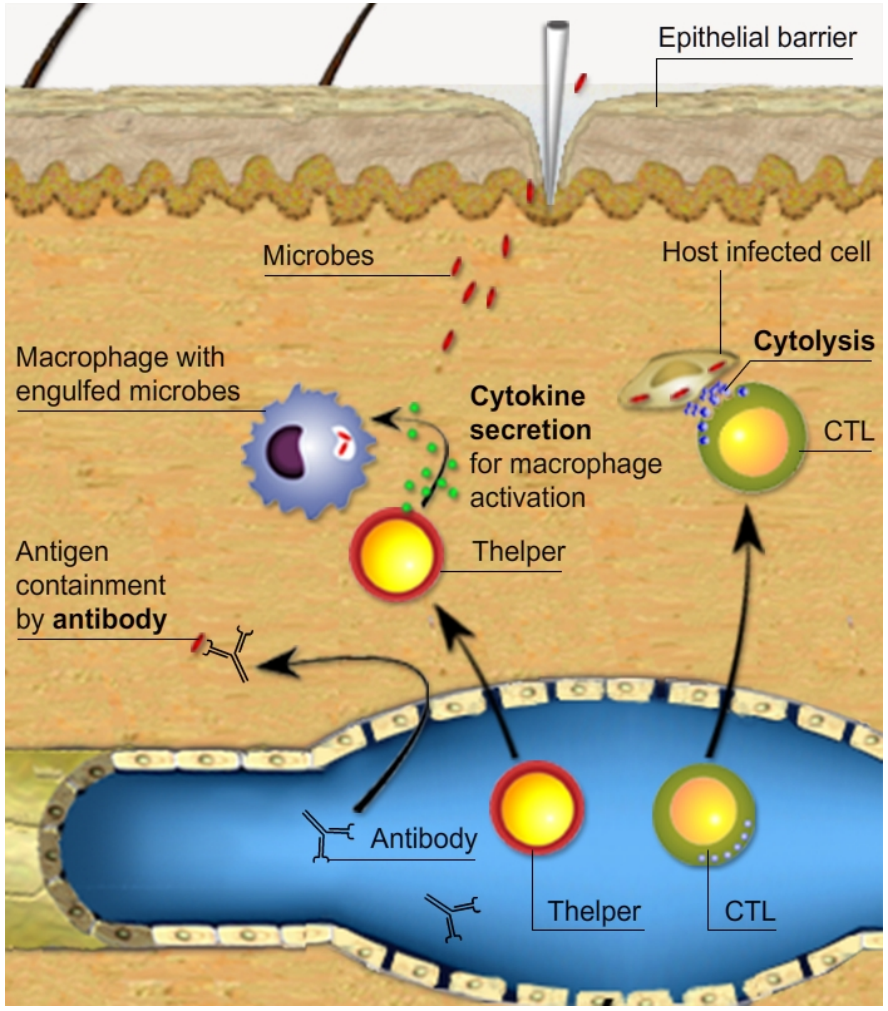
Proliferation: clonal expansion of the antigen-specific lymphocytes

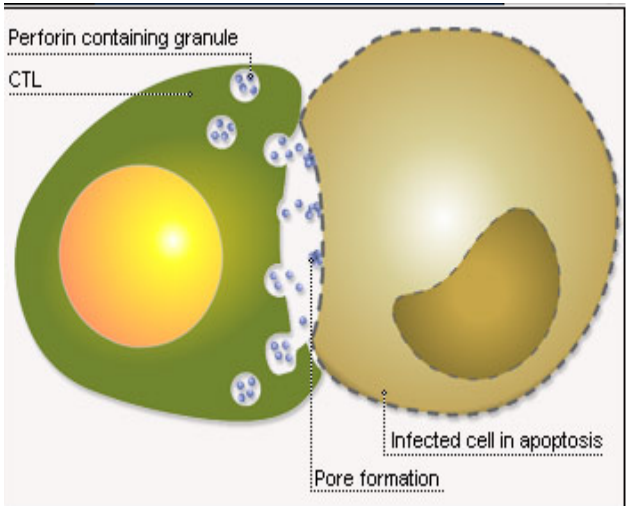


Step 3: Effector phase



Mounting an adaptive immune response requires an **effector phase**, during which effector lymphocytes are dispatched to the sites of antigen entry.

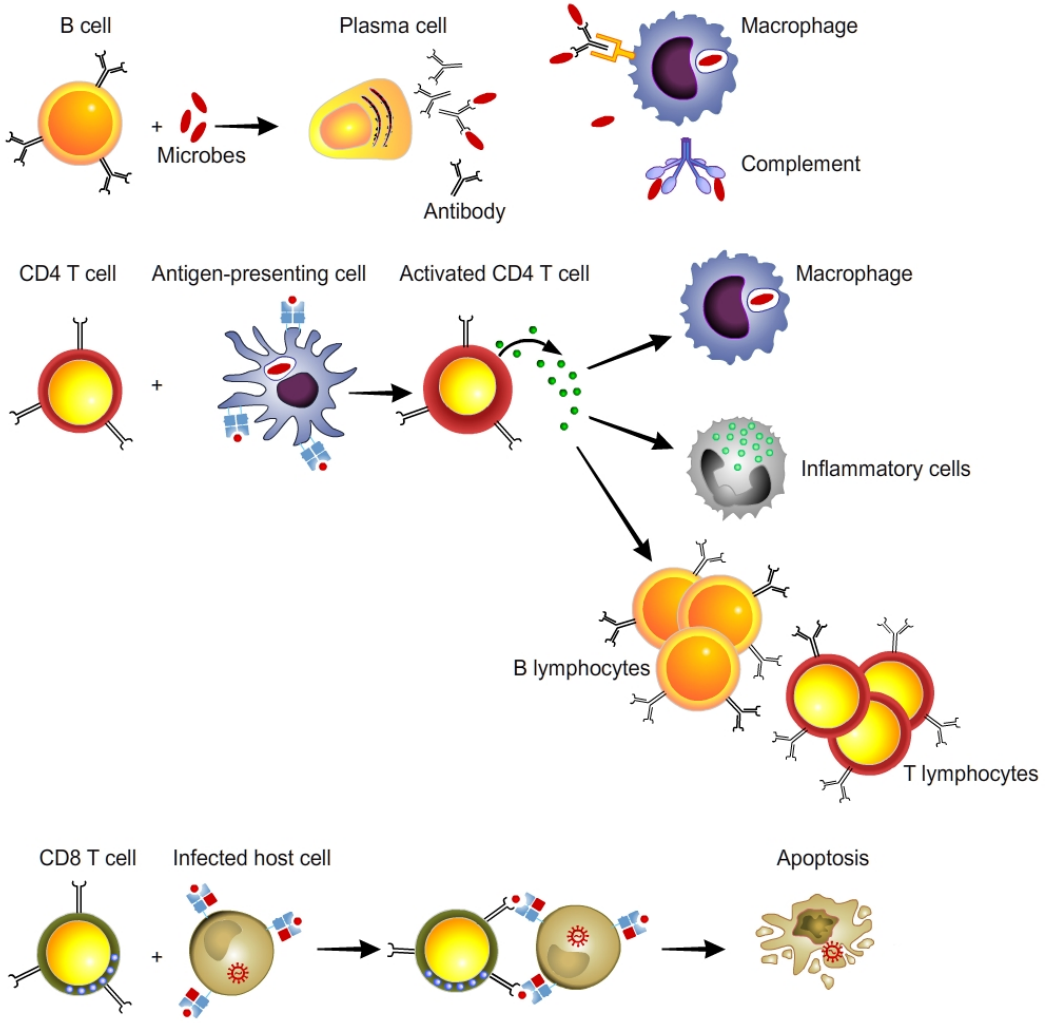




Conclusion 1B: Different Classes of lymphocytes

Different classes of lymphocytes recognize distinct types of antigens and differentiate into effector cells whose function is to eliminate the antigens.

- **B lymphocytes** recognize soluble or cell surface antigens and differentiate into antibody-secreting cells.
- **Helper T lymphocytes** recognize antigens on the surface of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation.
- **Cytotoxic (cytolytic) T lymphocytes** recognize antigens on infected cells and kill these cells.

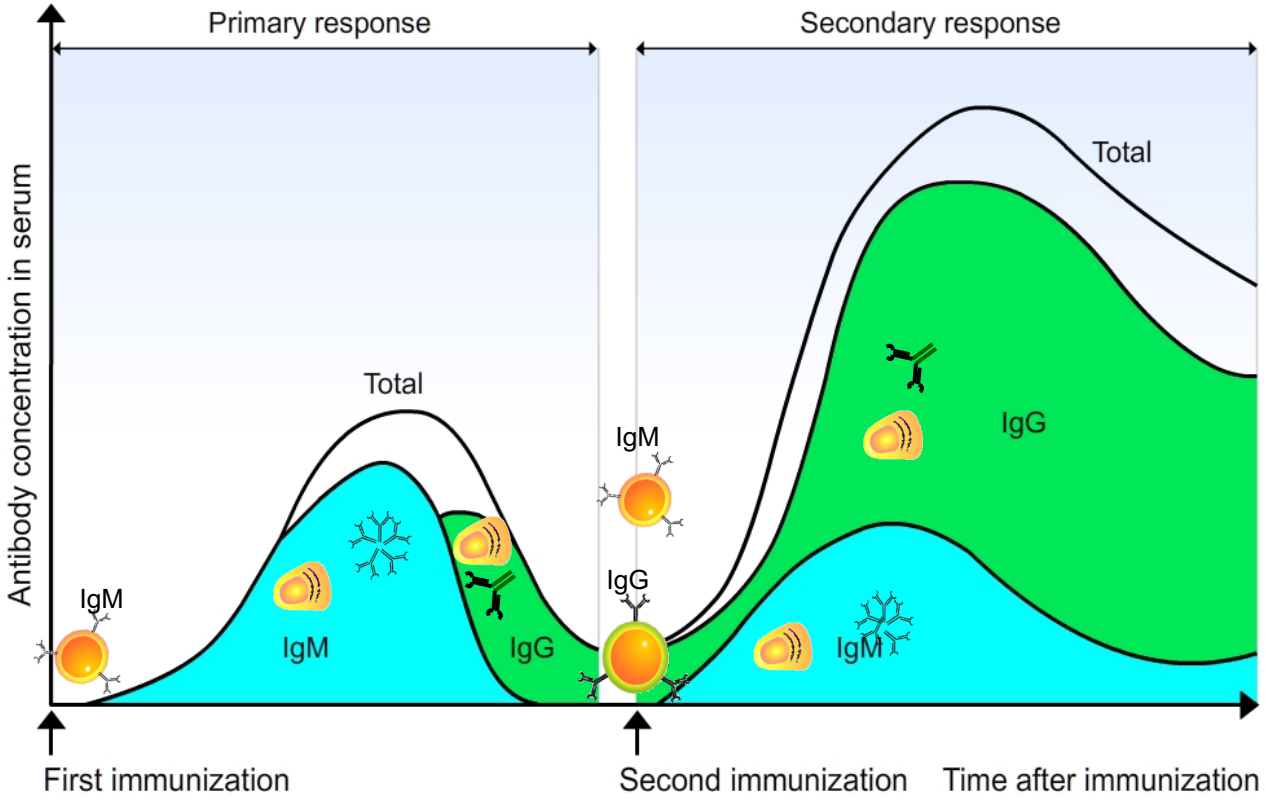


Primary versus secondary B cell response

Primary antibody response

First contact with an antigen activates naïve B cells.

- long lag period (5-10 days)
- low magnitude
- IgM > IgG (low affinity)

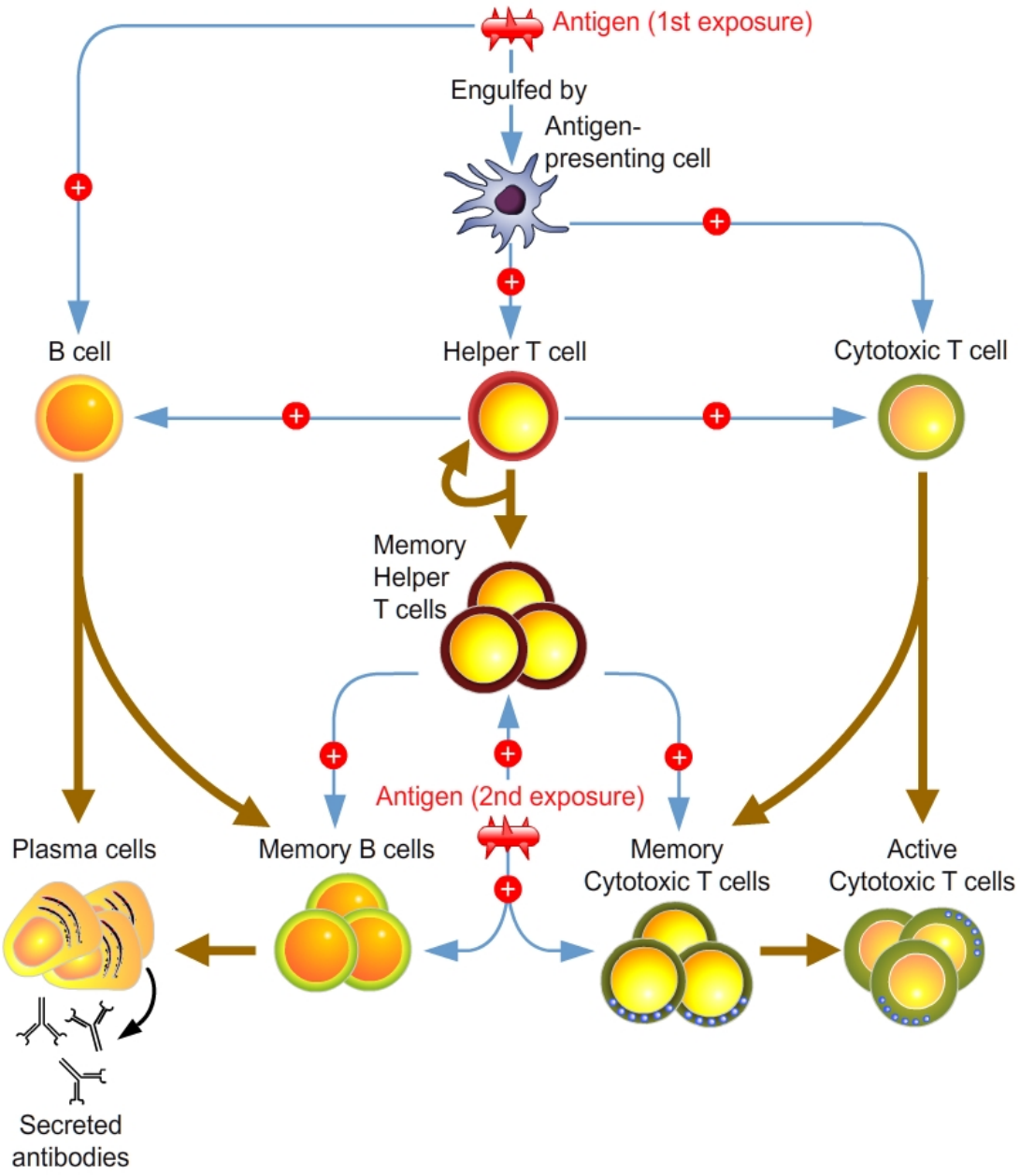


Secondary antibody response

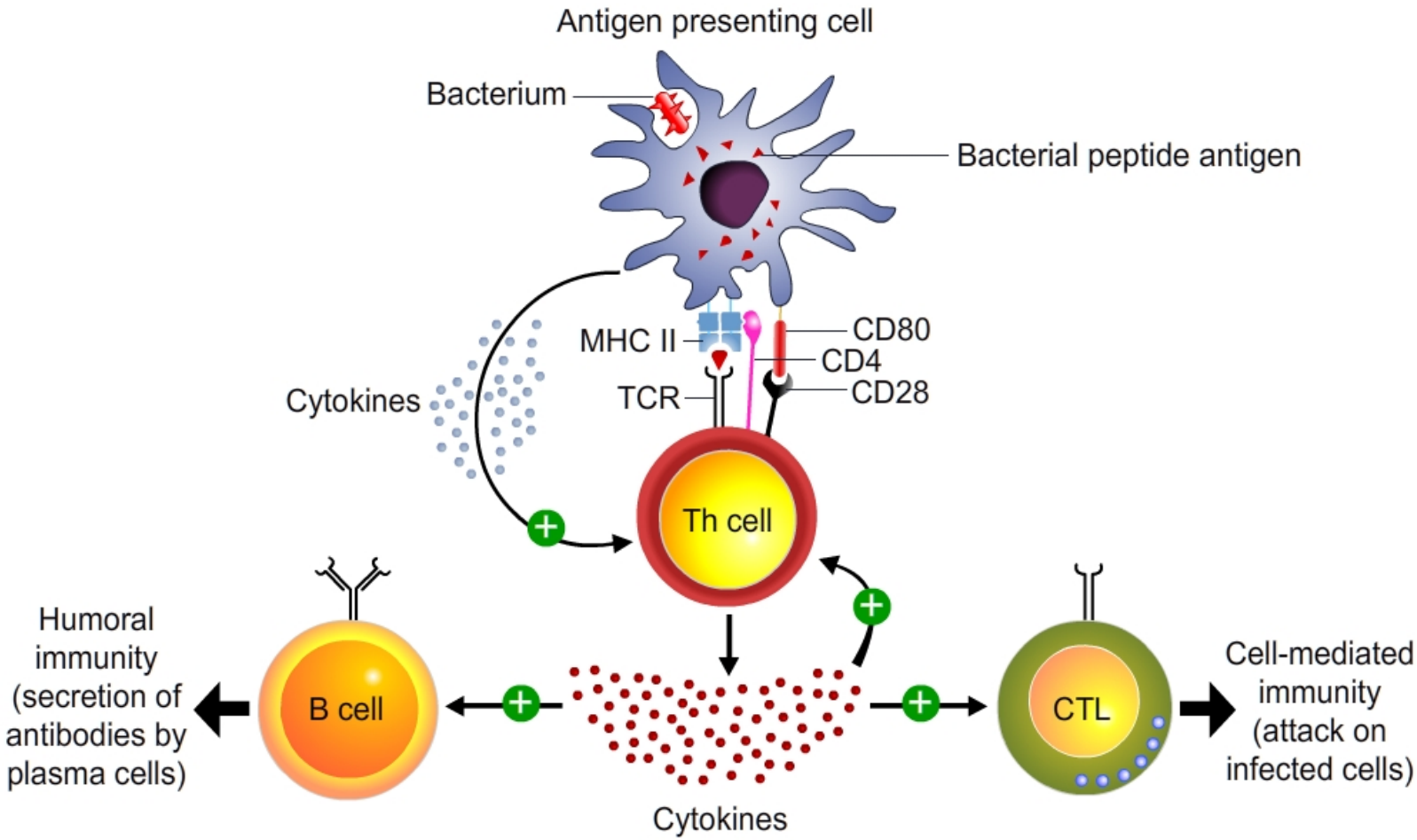
Second contact with an antigen activates memory B cells.

- shorter lag period (1-3 days)
- higher magnitude
- IgG > IgM (high affinity)

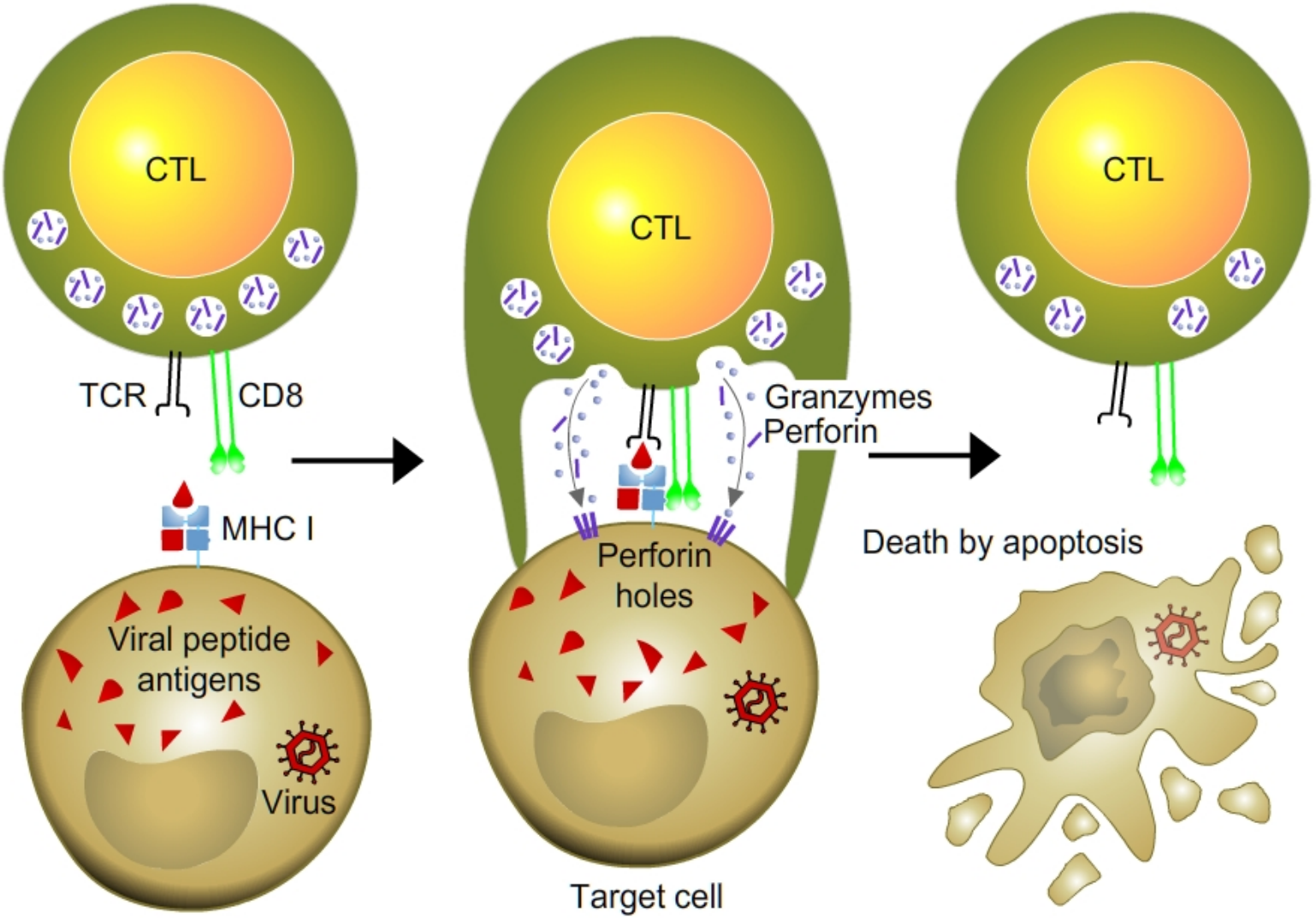
An overview of the acquired immune response



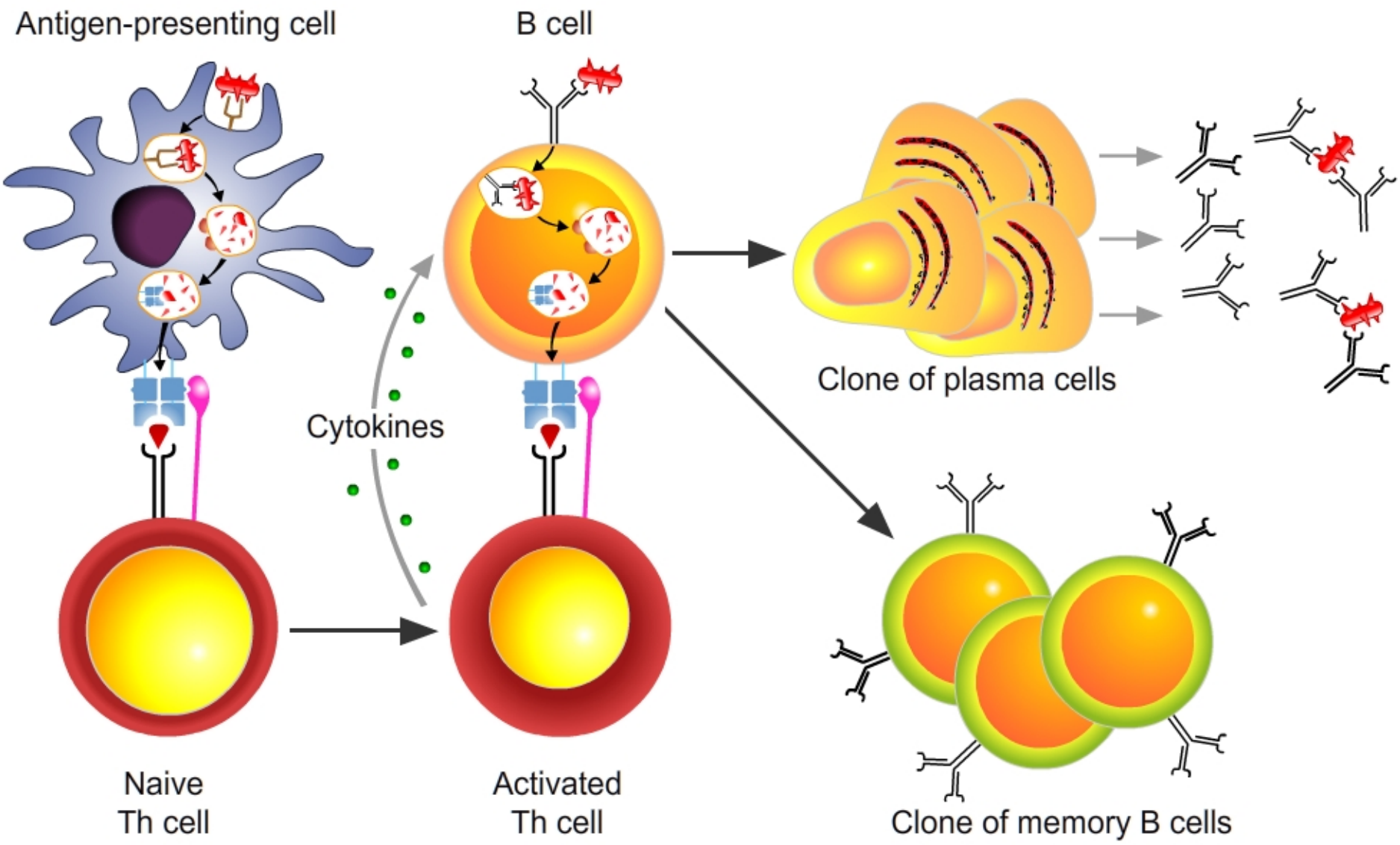
1. The central role of helper T cells in humoral and cell-mediated immune responses



2. Cytotoxic T Cells: A Response to Infected Cells



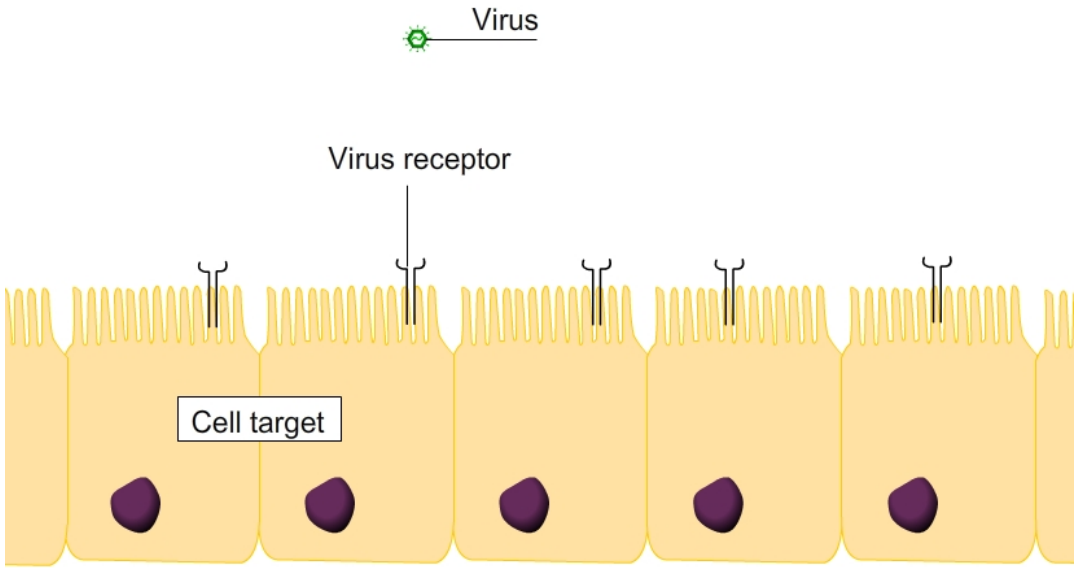
3. B cell activation in the humoral immune response



Defence against microbes

Viral infection		Bacterial infection		Parasitic infection	
Cytopathogenic	Non- cytopathogenic	Extracellular	Intracellular	Protozoan	Helminths
Antibodies	CTL	Antibodies	Antibodies + CTL	Antibodies + CTL	IgE antibodies

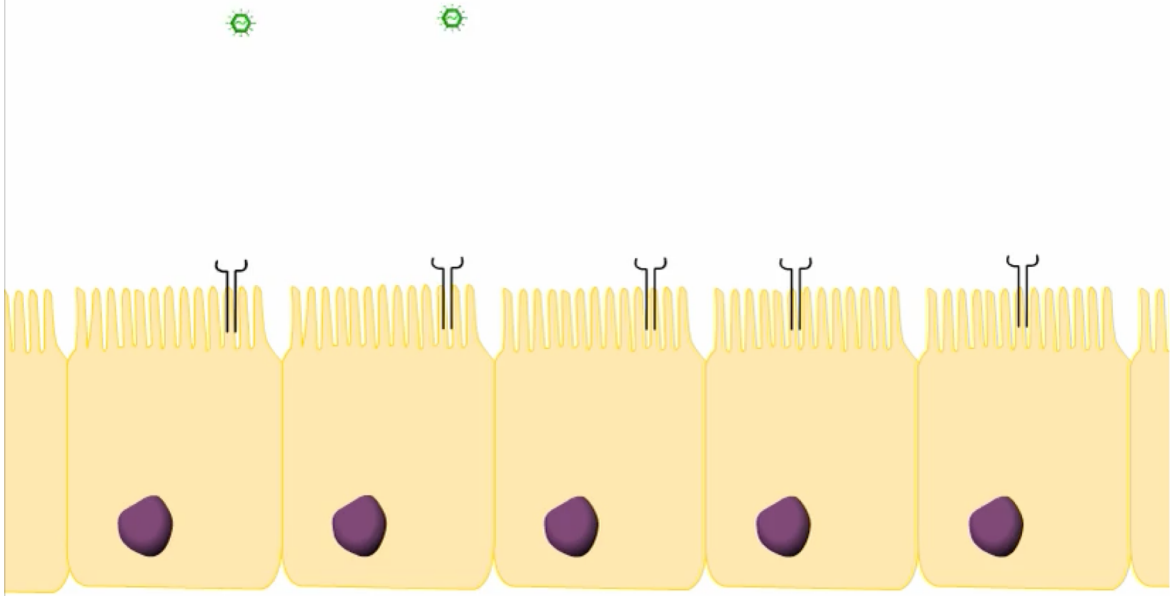
Cytopathogenic Virus



Defence against microbes

Viral infection		Bacterial infection		Parasitic infection	
Cytopathogenic	Non- cytopathogenic	Extracellular	Intracellular	Protozoan	Helminths
Antibodies	CTL	Antibodies	Antibodies + CTL	Antibodies + CTL	IgE antibodies

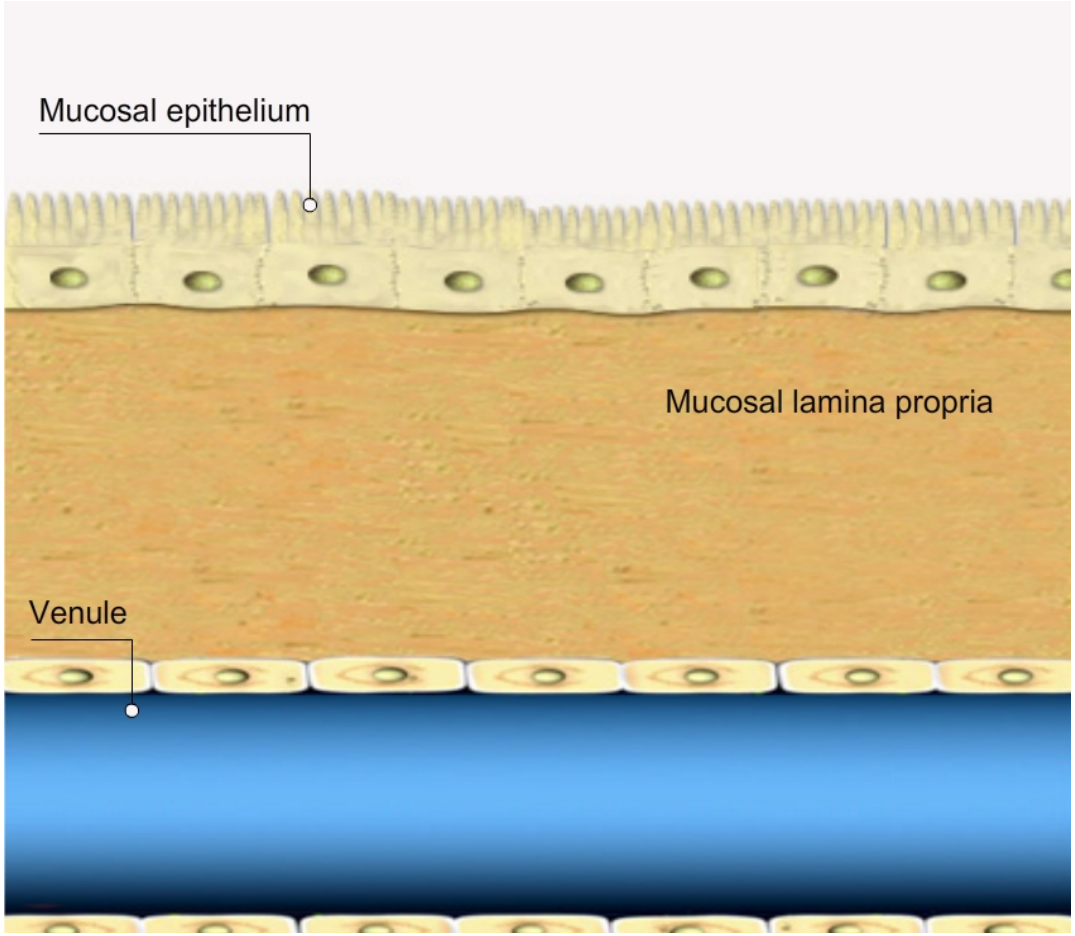
Non-cytopathogenic Virus



Defence against microbes

Viral infection		Bacterial infection		Parasitic infection	
Cytopathogenic	Non- cytopathogenic	Extracellular	Intracellular	Protozoan	Helminths
Antibodies	CTL	Antibodies	Antibodies + CTL	Antibodies + CTL	IgE antibodies

Neutralization



Defence against microbes

Viral infection		Bacterial infection		Parasitic infection	
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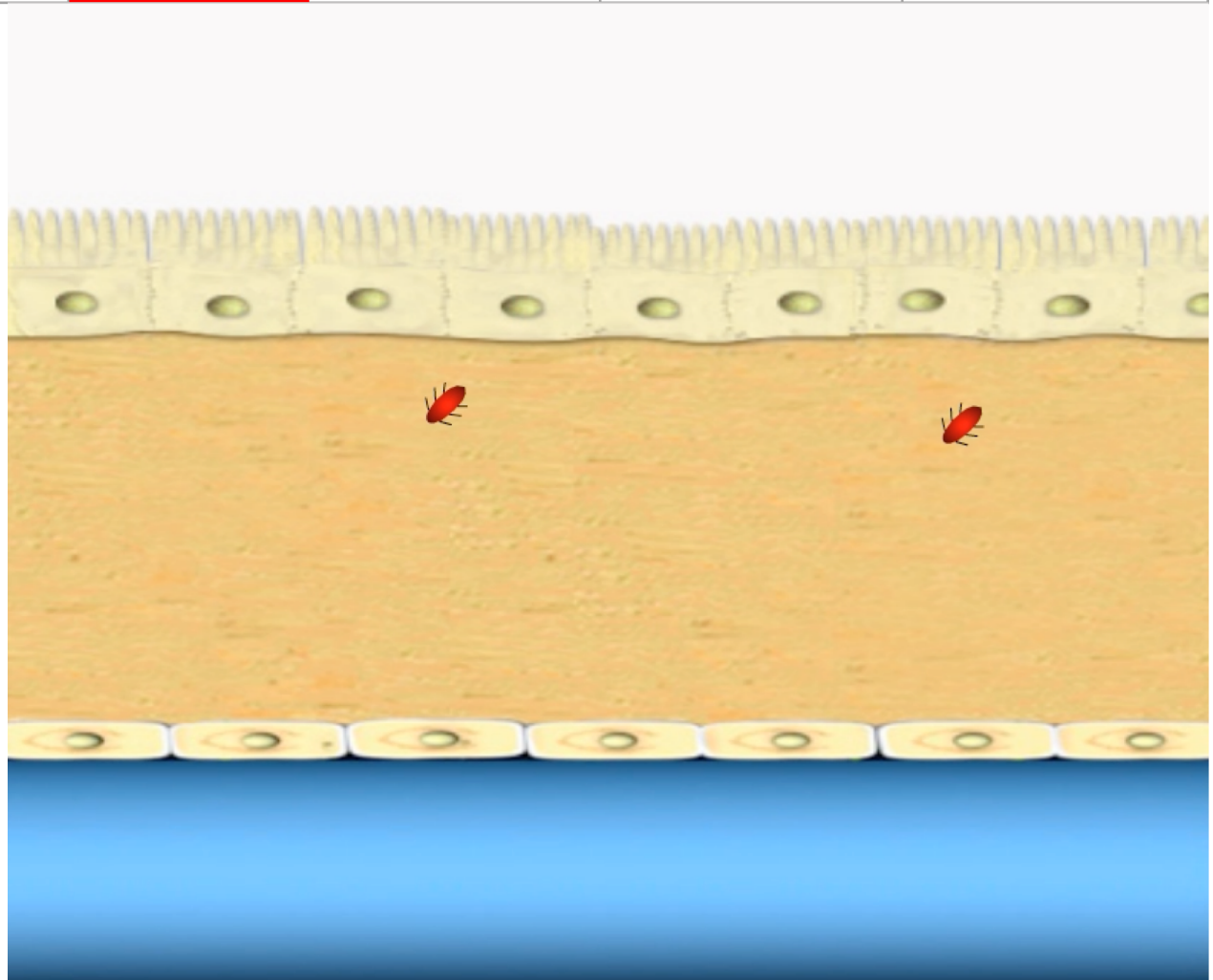
Phagocytosis



Conclusion 1C

- Adaptive immunity consists of humoral immunity, in which antibodies neutralize and eradicate extracellular microbes and toxins, and cell-mediated immunity, in which T lymphocytes eradicate intracellular microbes.
- Adaptive immune responses consist of sequential phases: antigen recognition by lymphocytes, activation of the lymphocytes to proliferate and to differentiate into effector and memory cells, elimination of the microbes, decline of the immune response, and long-lived memory.
- B lymphocytes are the only cells that produce antibodies. B lymphocytes express membrane antibodies that recognize antigens, and effector B cells secrete the antibodies that neutralize and eliminate the antigen.
- T lymphocytes recognize peptide fragments of protein antigens displayed on other cells. Helper T lymphocytes activate phagocytes to destroy ingested microbes and activate B lymphocytes to produce antibodies. CTLs are cytotoxic: they kill infected cells harboring microbes in the cytoplasm.
- APCs capture antigens of microbes that enter through epithelia, concentrate these antigens in lymphoid organs, and display the antigens for recognition by T cells.