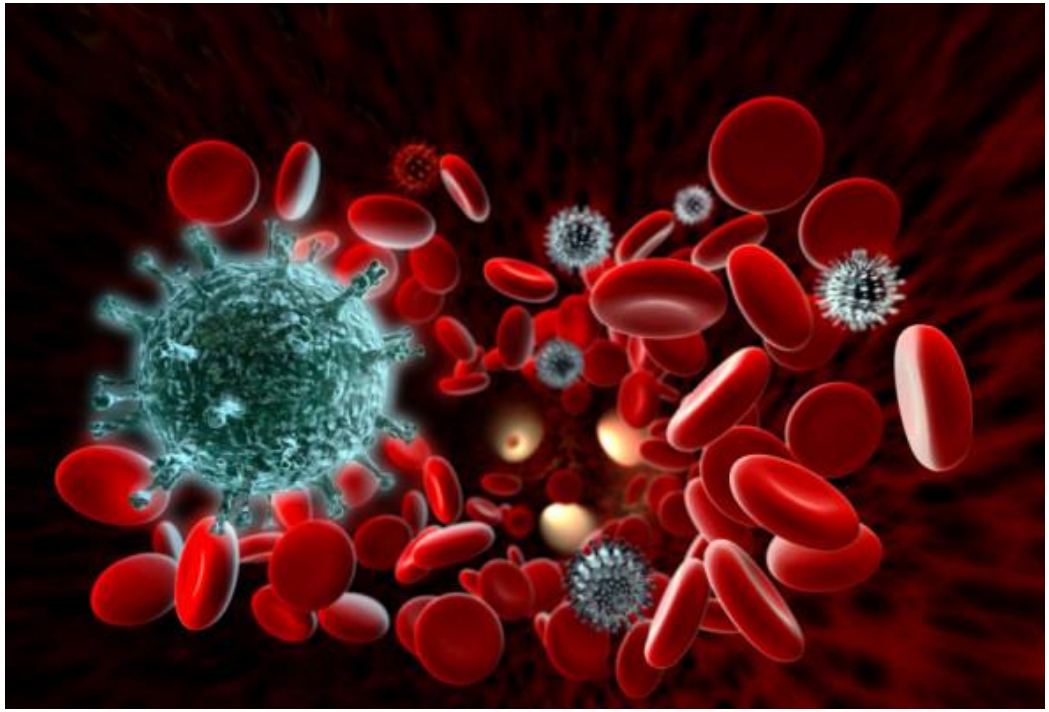
THE UNIVERSITY OF WESTERN AUSTRALIA

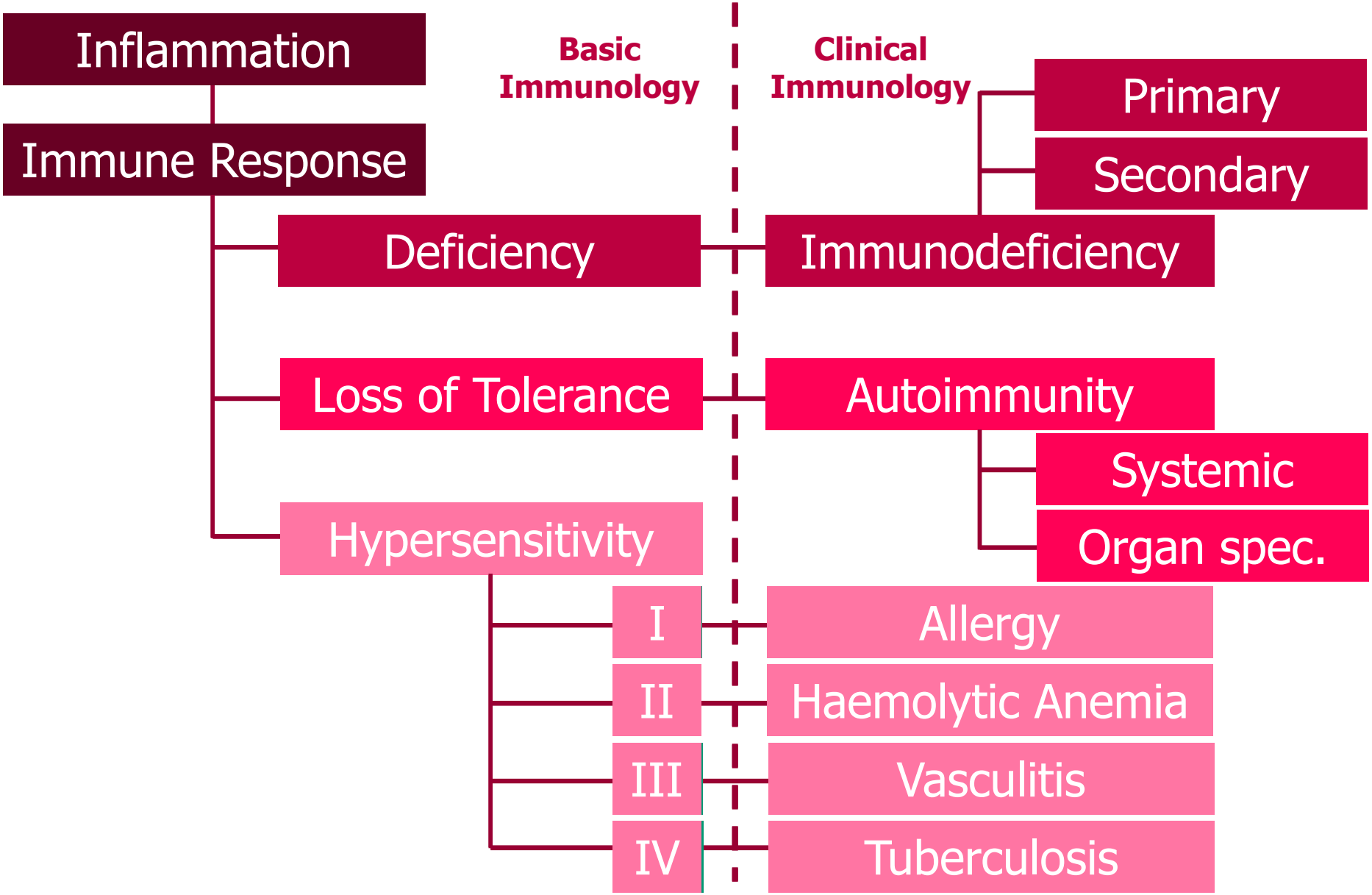
Clinical Immunology

Overview of the Immune System



Dr Sonia Fernandez

The Spectrum of Clinical Immunology



Some definitions…

- **Immunity**
  - our ability to protect ourselves from disease
  - Recognition & removal of foreign material entering body
  - relies on our ability to distinguish between self and non-self
  - can be innate or acquired
- **Immune system**
  - the cells and molecules responsible for immunity and their collective and coordinated response to the introduction of foreign substances (not just infectious)
- **Immunology**
  - study of cells, organs, molecules responsible for immunity & how they respond & interact
  - effects & consequences (desirable/undesirable)
  - can the response be advantageously increased/reduced

The immune system deals with a variety of pathogens

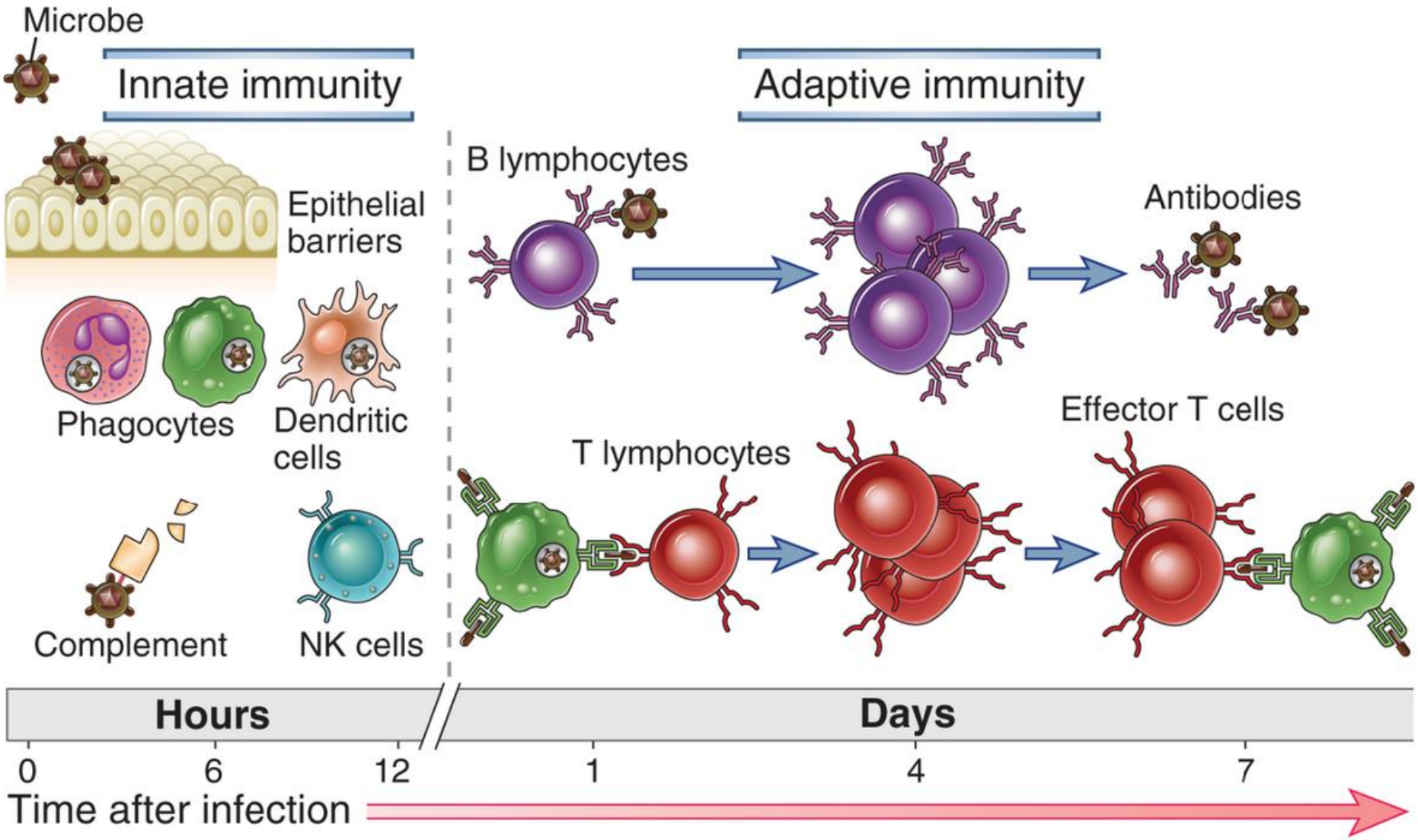
Type of pathogen	Examples	Diseases
Extracellular bacteria, parasites, fungi	*Streptococcus pneumoniae* *Clostridium tetani* *Trypanosoma brucei* *Pneumocystis carinii*	Pneumonia Tetanus Sleeping sickness *Pneumocystis* pneumonia
Intracellular bacteria, parasites	*Mycobacterium leprae* *Leishmania donovani*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

Figure 1.24 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

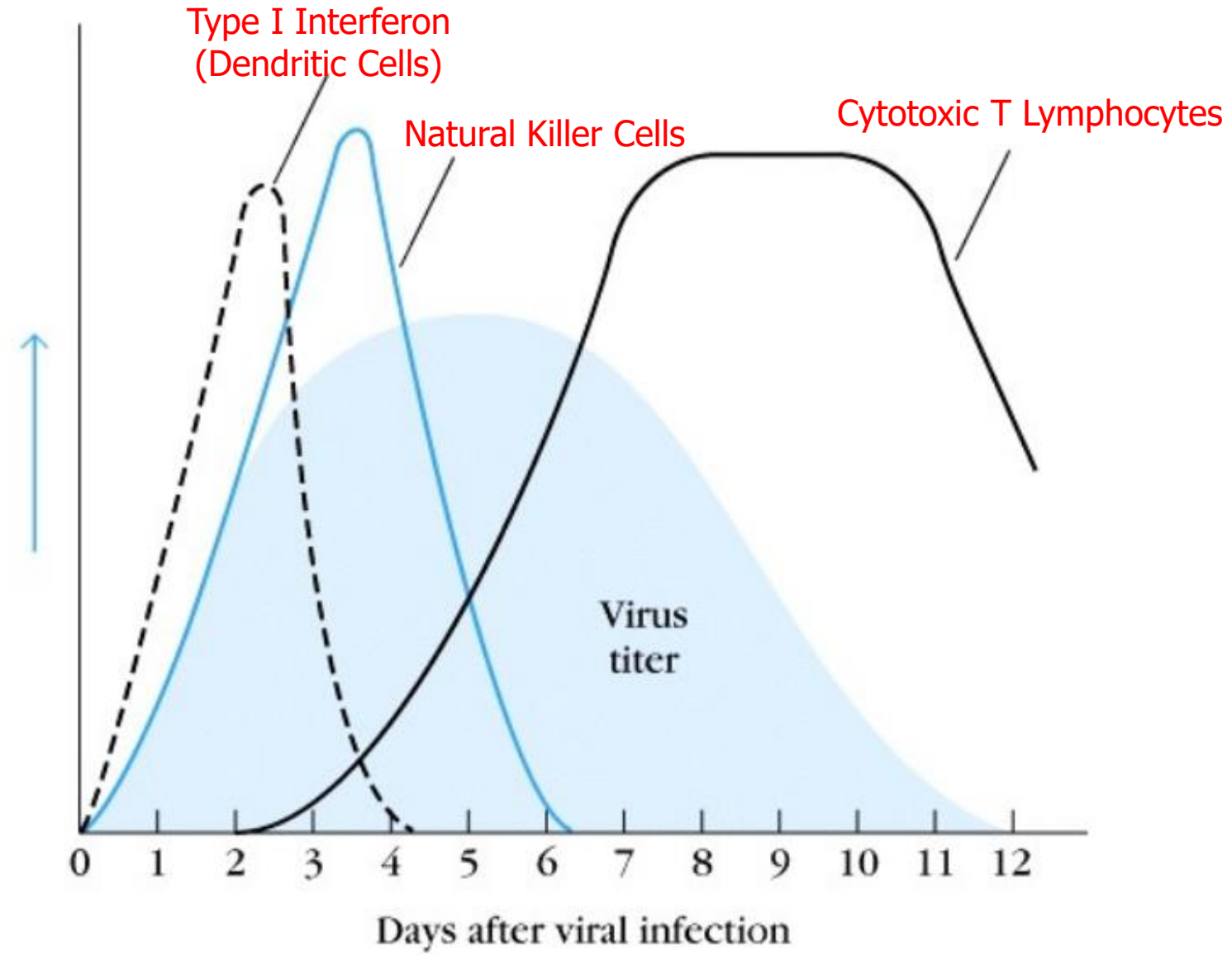
- The immune system has evolved different methods to deal with the wide variety of pathogens it has to deal with

- 2 key arms of the immune system are innate & adaptive immune responses

Two branches of the immune system



Time course of an immune response to viral infection



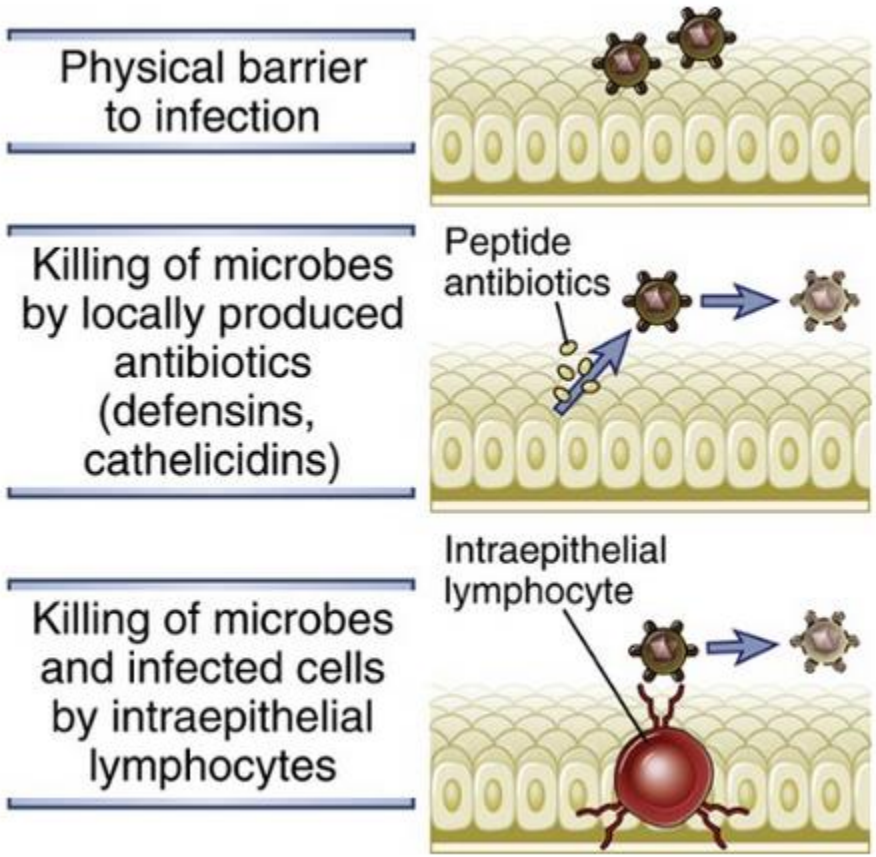
The Innate Immune System

- Why do we need innate immunity?
  - Microbes multiply at very high rates
  - Overwhelming infection can occur quickly
  - Need a system that detects infection rapidly

- Innate immunity is required to cover the time taken (7-10 days) for adaptive immunity to be generated

- Paramedics at an accident
  - React quickly & efficiently
  - Less specific actions than later “specialists”

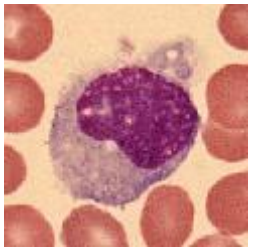
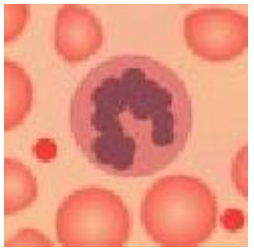
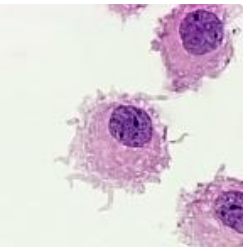
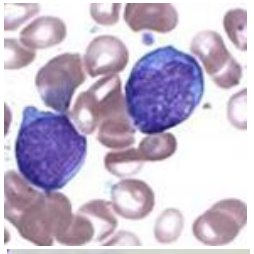
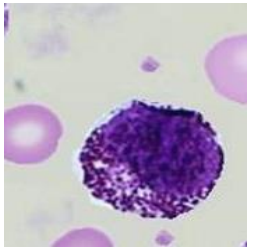
Physical components of innate immunity



- Physical barrier between microbes in external environment and host tissue
  - skin & mucosal surfaces
- Multiple levels of physical protection
  - Tight junctions
  - Keratin
  - Mucus assisted by cilia & peristalsis
- Epithelial cells also produce antimicrobial chemicals
  - defensins
  - further impede entry of microbes
- Intraepithelial T cells recognise and respond to a small number of common microbial structures

Cellular components of innate immunity

- Macrophages – large phagocytic tissue cells, responsible for removal of damaged tissue, cells, bacteria etc
- Neutrophils – short-lived scavenger blood cells containing granules of powerful bactericidal enzymes (80% luekocytes)
- Dendritic cells – present antigen to T cells to initiate adaptive immune responses
- Natural Killer (NK) cells – lymphocyte-like cells capable of killing virus infected and tumor cells without the specificity of true lymphocytes
- Mast cells – found in tissues, release inflammatory mediators when damaged and under the influence of IgE antibody

Soluble components of innate immunity

- Several molecules that recognize/respond to microbes and promote innate responses exist in soluble form in blood and ECF
- Provide early defense against pathogens present outside host cells at some stage of their life cycle
- Function in two major ways
  - bind to microbes & act as opsonins to enhance phagocytosis by macrophages, neutrophil & dendritic cells
  - promote inflammatory responses that bring more phagocytes to sites of infections and may also directly kill microbes
- Complement, cytokines, chemokines, defensins, acute phase proteins

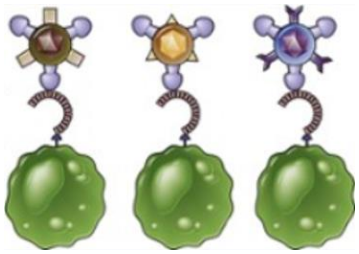
Various components of innate immunity work at different stages of infection

- Epithelial barriers impair microbial entry into the host
- Resident and recruited phagocytes in subepithelial and other tissues provide protection if the barriers are breached
- Plasma proteins and circulating phagocytes provide protection if microbes reach the blood stream

What does innate immunity recognise?

- Molecular structures that are produced by microbial pathogens – often shared by classes of microbes
  - Pathogen associated molecular patterns (**PAMPs**)
  - Essential for survival of microbes - ensures the target of the immune response can't just be discarded by the microbe to evade recognition

- Endogenous molecules that are produced by or released from damaged and dying cells
  - Damage associated molecular patterns (**DAMPs**)
  - Can be produced as a result of cell damage caused by infection
  - Also produced in response to sterile injury to cells
    - chemical toxins, burns, trauma or low blood supply
  - generally not released by cells dying from apoptosis



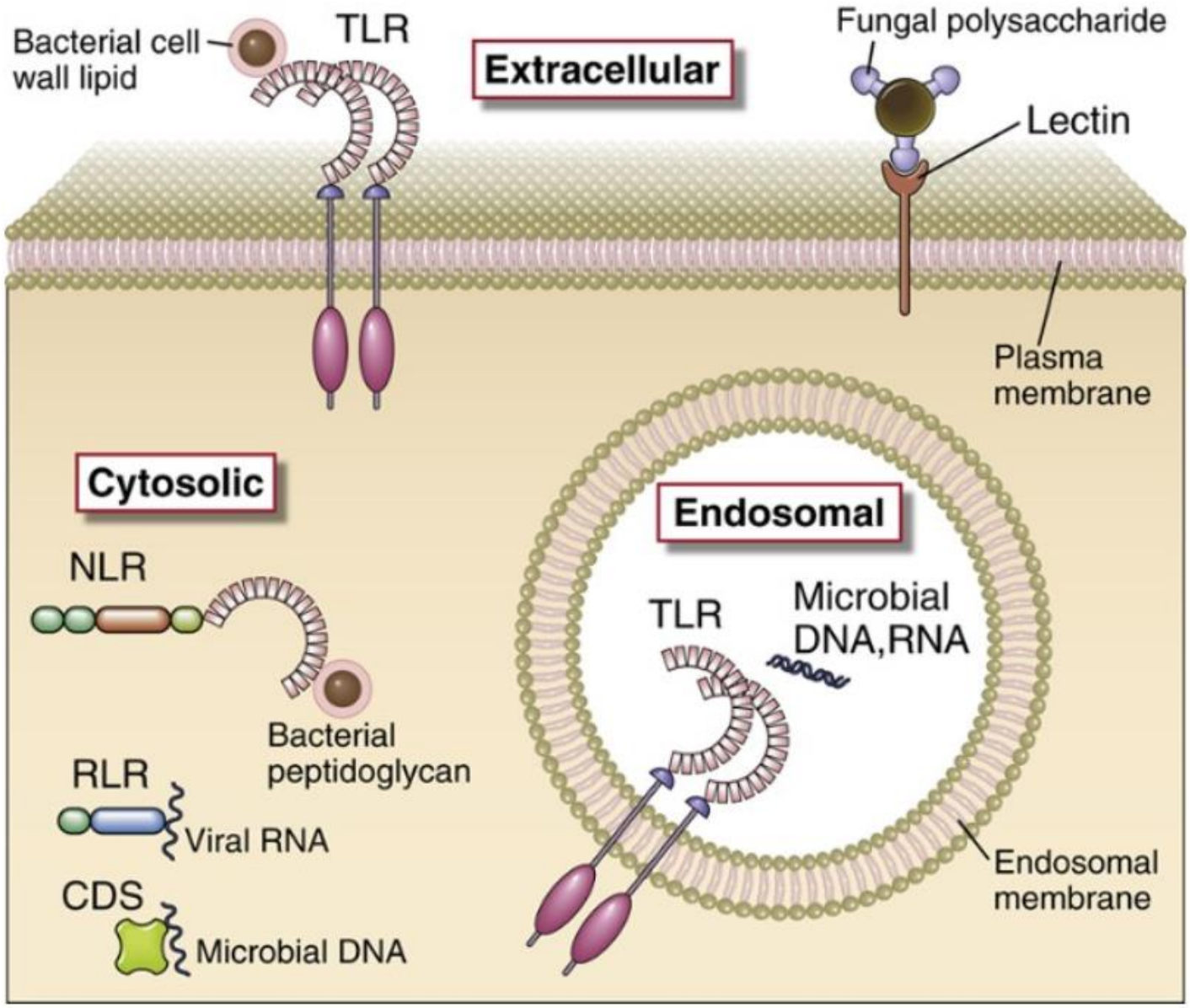
Examples of PAMPs and DAMPs

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	

How are PAMPs & DAMPs recognized?

- Pattern Recognition Receptors (PRR)
- Most cell types express PRR and are capable of participating in innate immune responses
- Phagocytes & dendritic cells express the widest variety and greatest amount of these receptors in keeping with their fundamental roles
- Expressed on cell surfaces, in phagocytic vesicles and in the cytosol of cells - all of which are locations where microbes may be present
- When these receptors bind PAMPs and DAMPs they activate signal transduction pathways that promote antimicrobial and proinflammatory functions of the cells in which they are expressed

Pattern Recognition Receptors

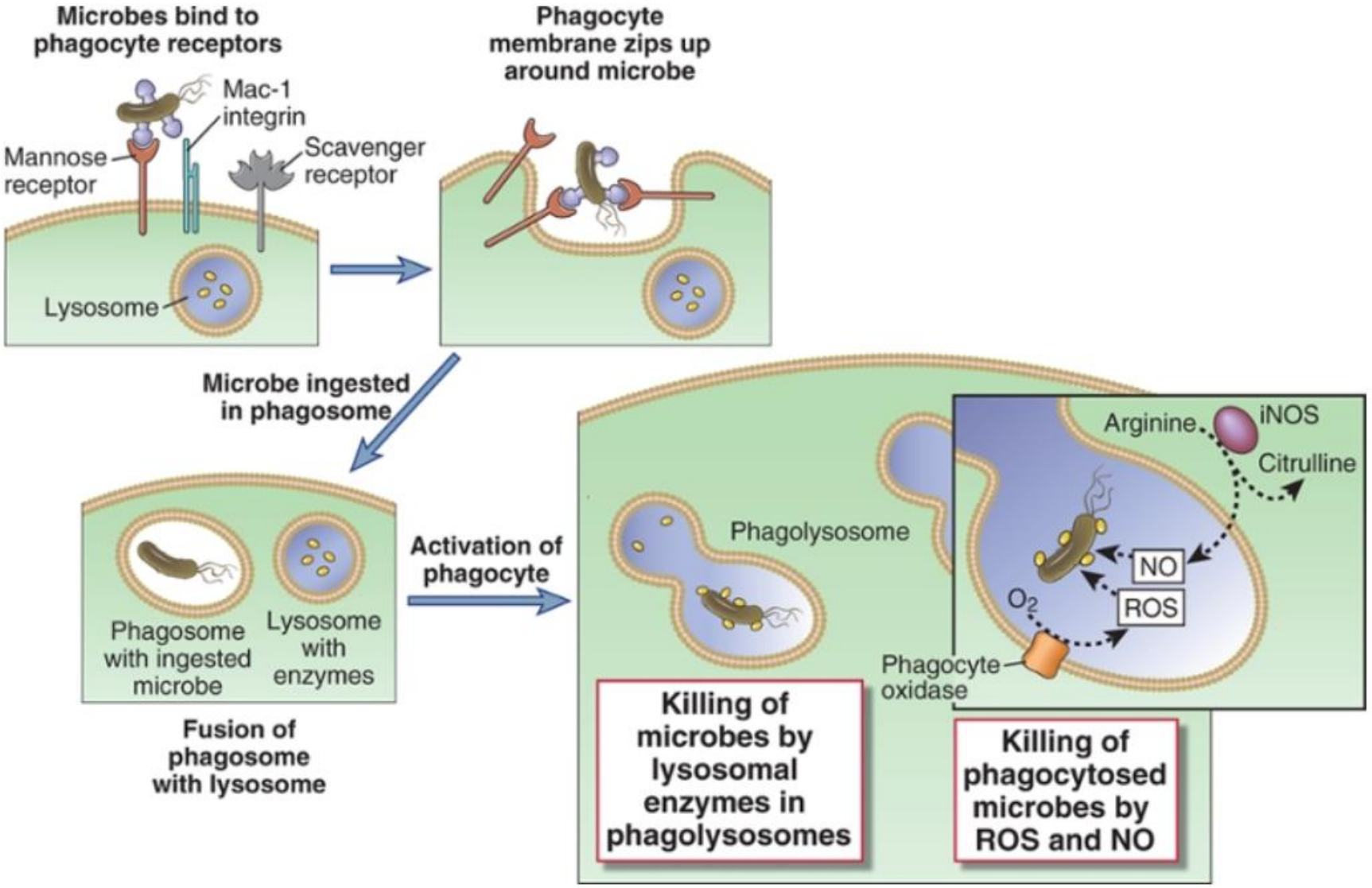


Effector mechanisms of innate immunity

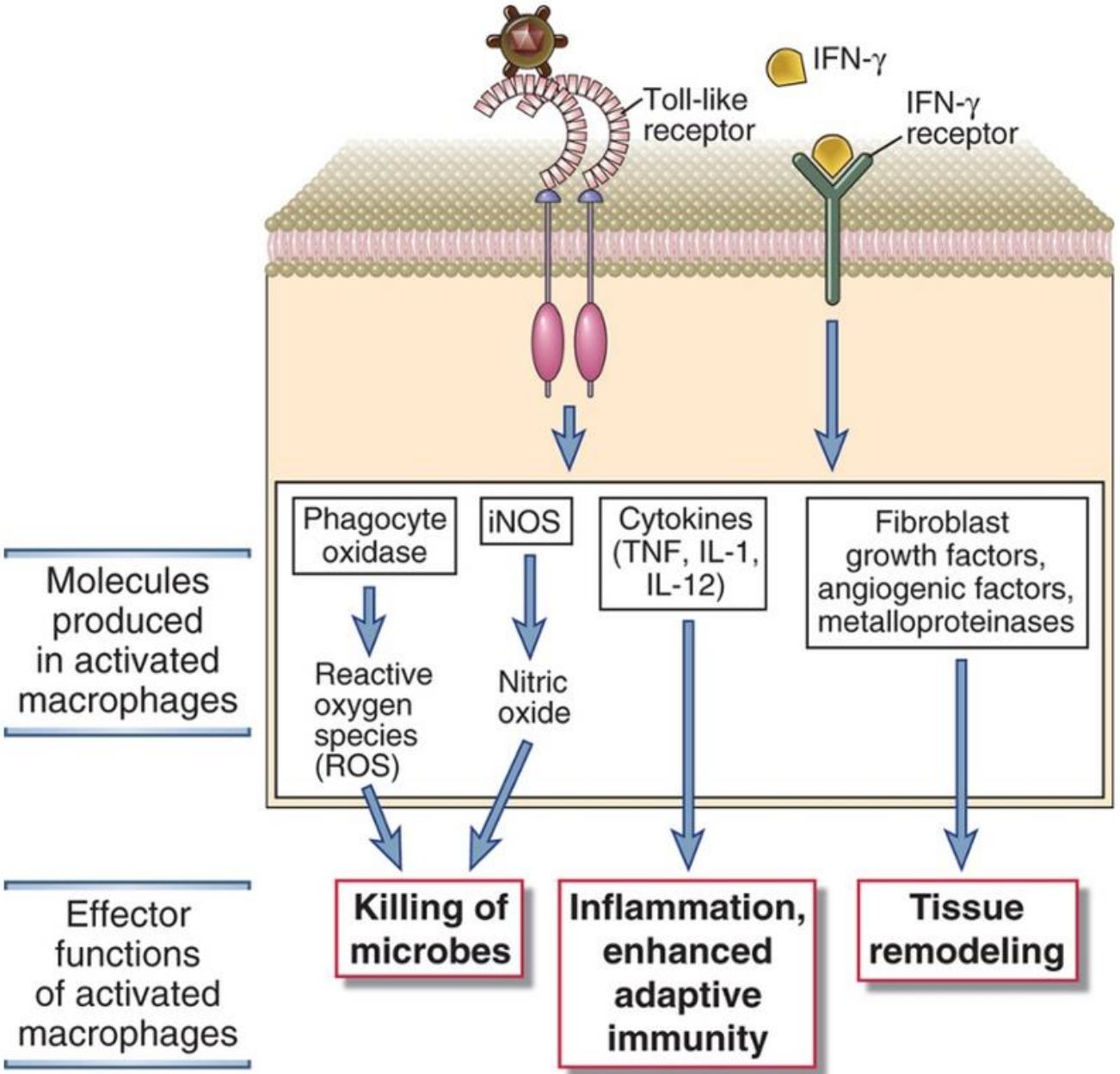
- Inflammation
  - the process by which leukocytes and circulating plasma proteins are brought into sites of infection and activated to destroy and eliminate the offending agents
  - also the major reaction to damaged or dead cells and to accumulations of abnormal substances in cells and tissues

- Anti-viral defense
  - consists of changes in cells that prevent virus replication and increase susceptibility

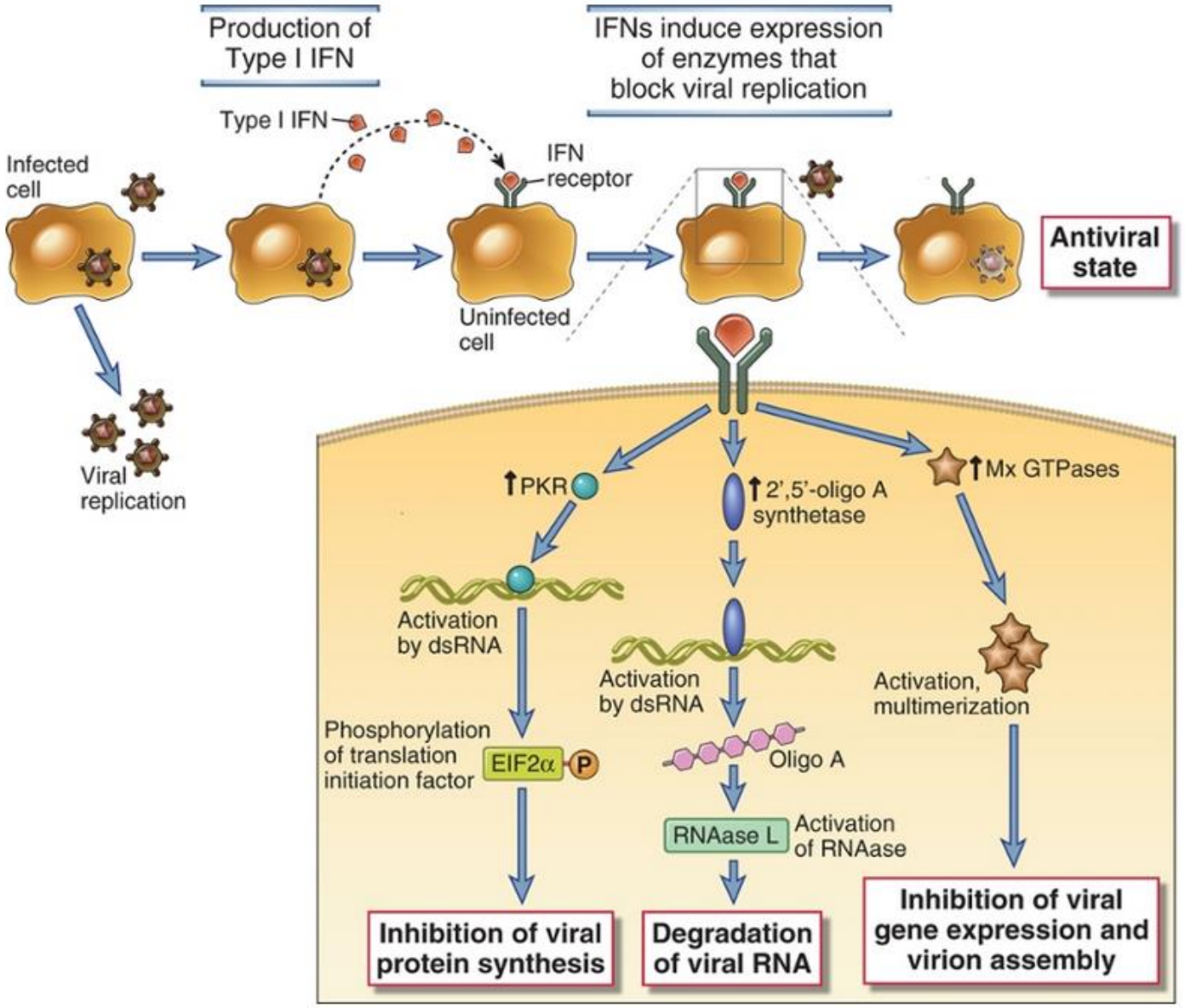
Phagocytosis and intracellular destruction of microbes



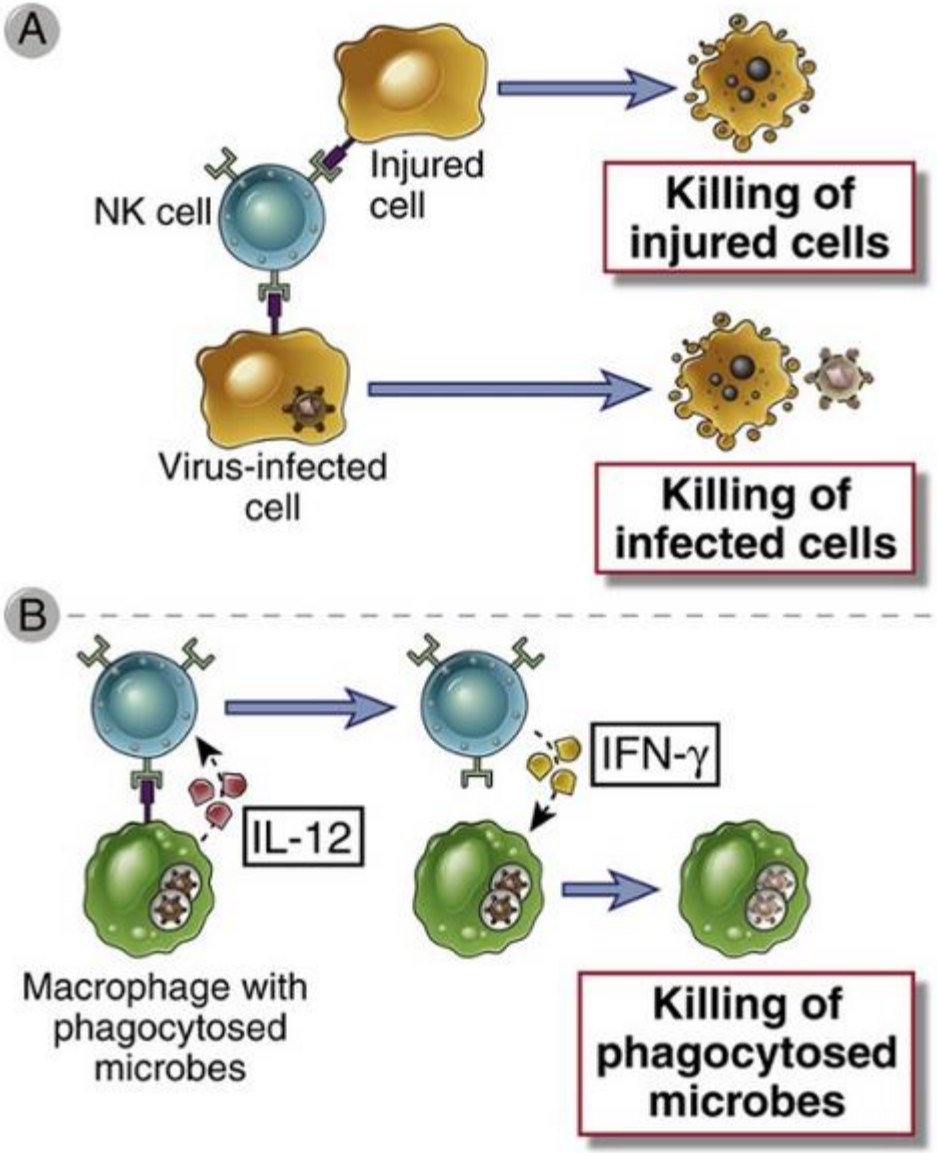
Effector functions of macrophages



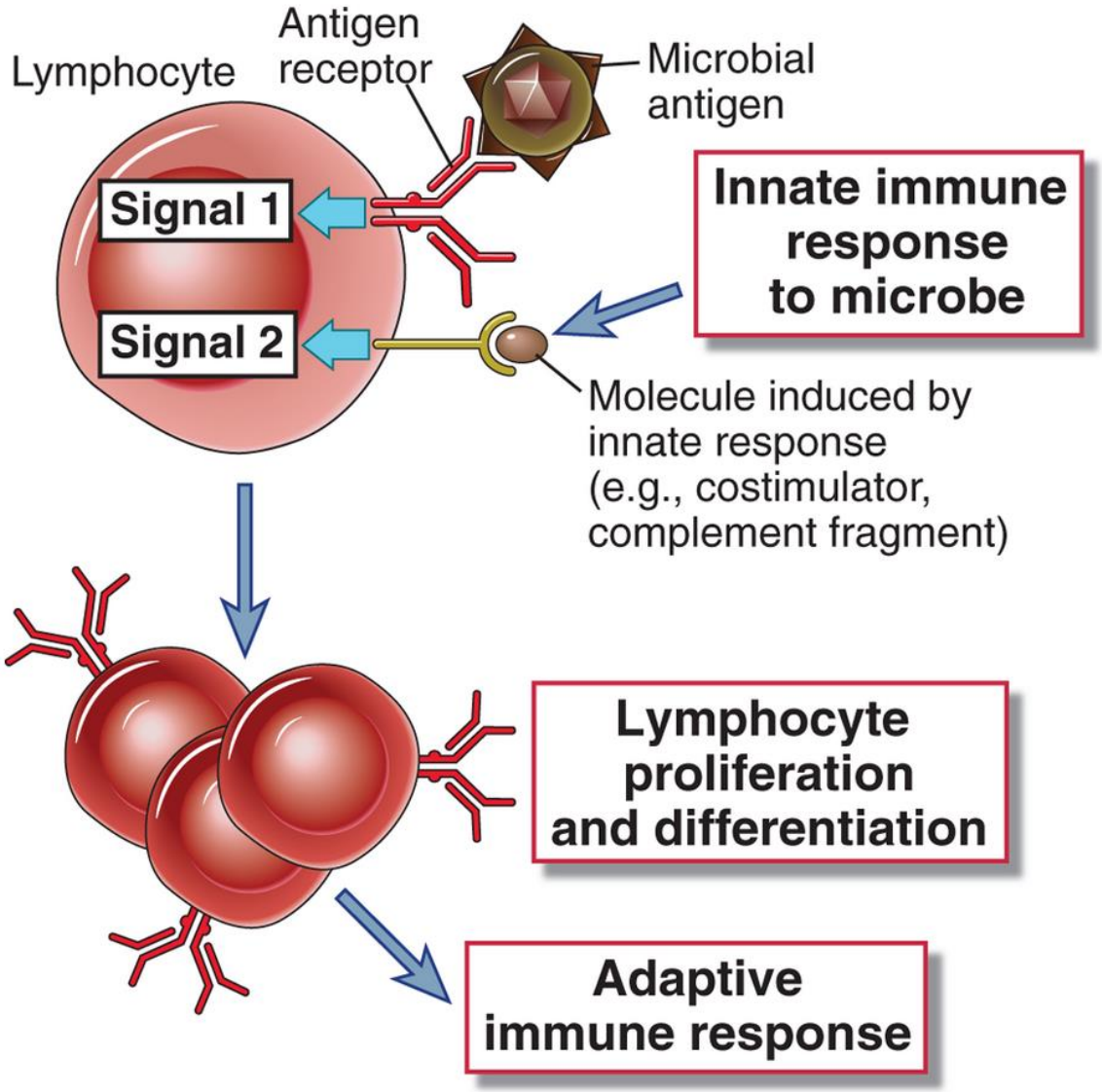
Anti-viral actions of type I interferons

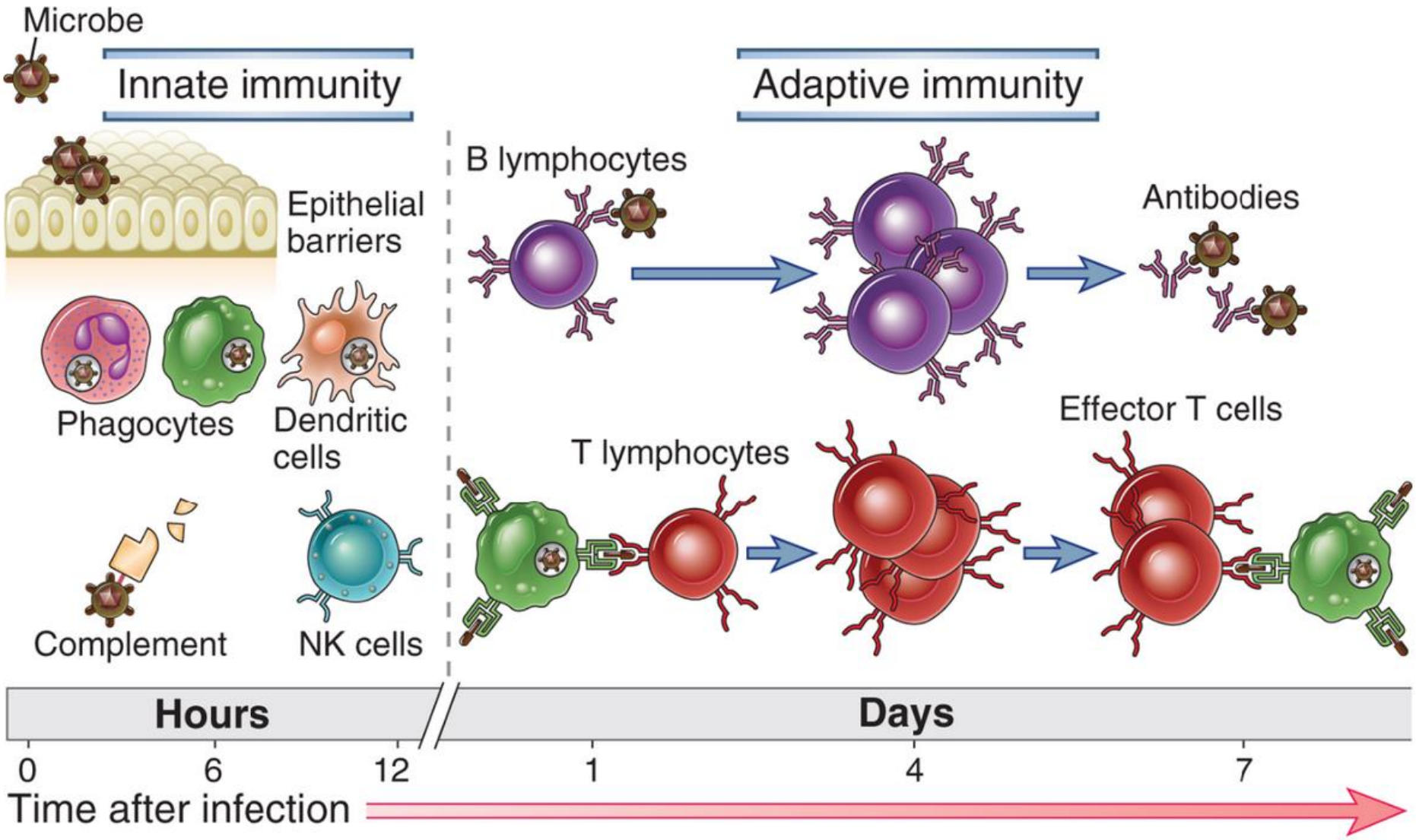


Effector functions of NK cells



Stimulation of adaptive immunity



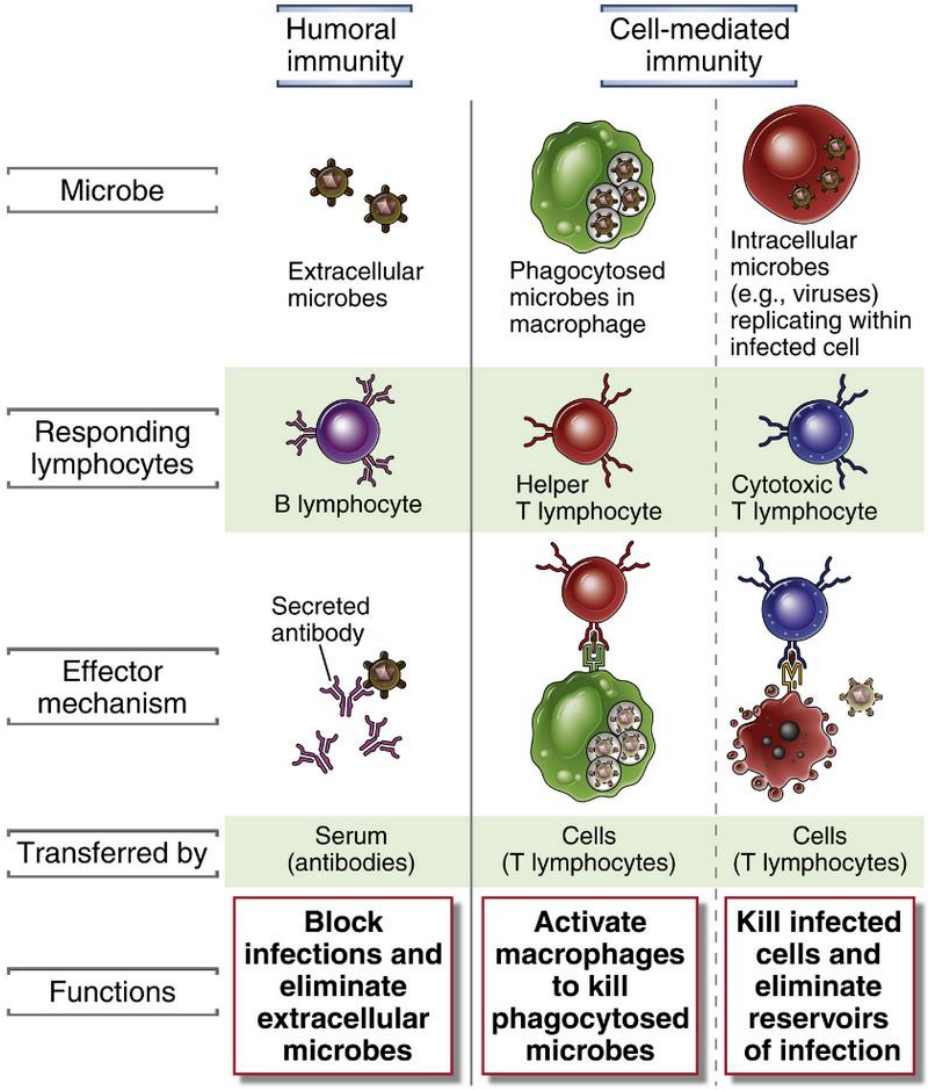

Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
B lymphocytes
Antibodies
Phagocytes
Dendritic cells
T lymphocytes
Effector T cells
Complement
NK cells
Hours
Days
0
6
12
1
4
7
Time after infection

The Adaptive Immune System

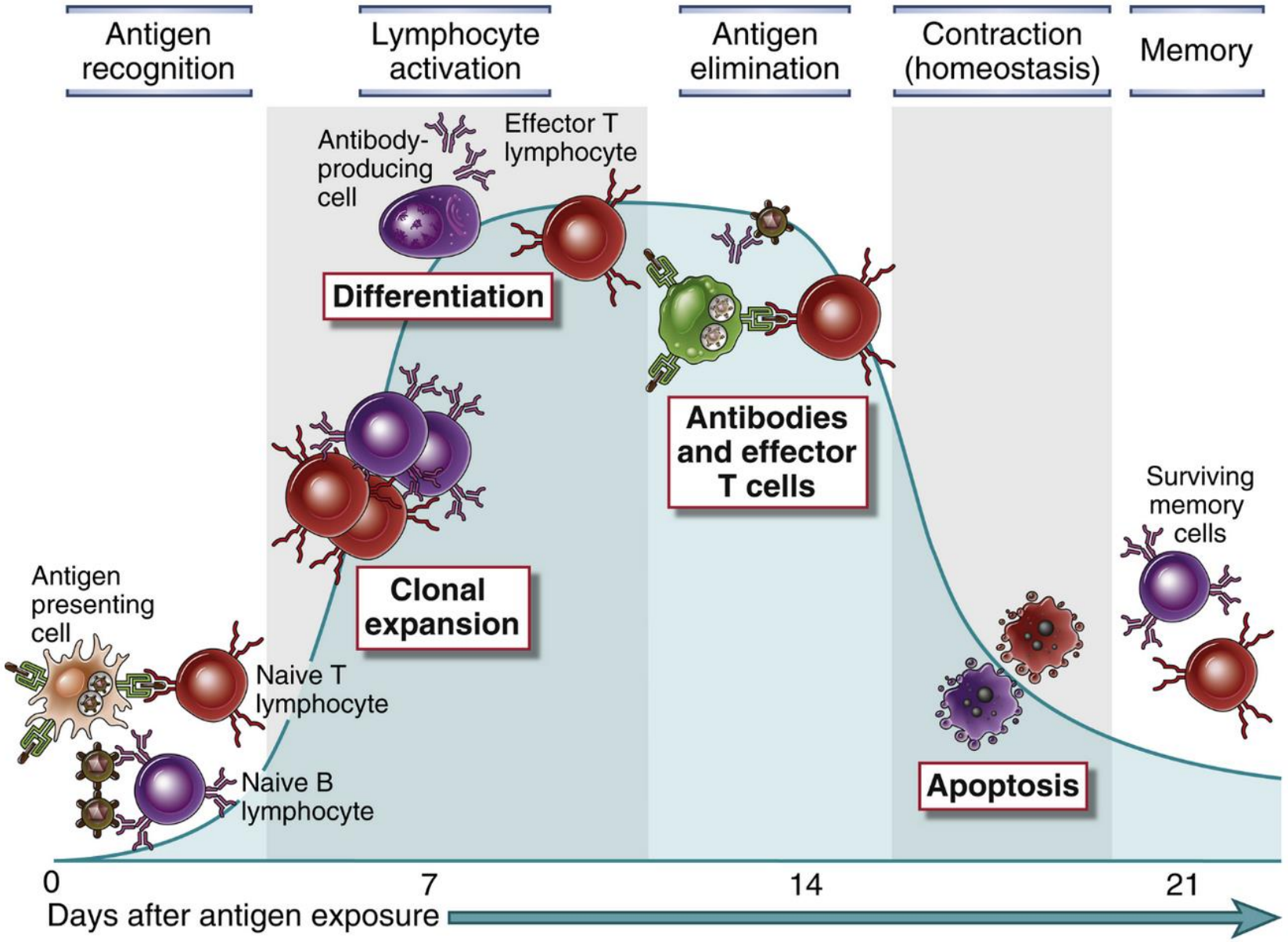
- Key cells are T and B lymphocytes
- Lymphocytes express highly diverse membrane receptors
  - Recognise a wide variety of foreign substances
  - Distinguish subtle differences in structure
  - Receptors generated by rearrangement of antigen receptor genes during the development of mature B and T cells from precursor cells
- Provides **diversity** –can respond to a large variety of antigens which is essential to defend against the many potential pathogens in the environment
- Takes about a week to develop but then provides long-term **memory** which ensure a faster, better response when next encountering the same pathogen

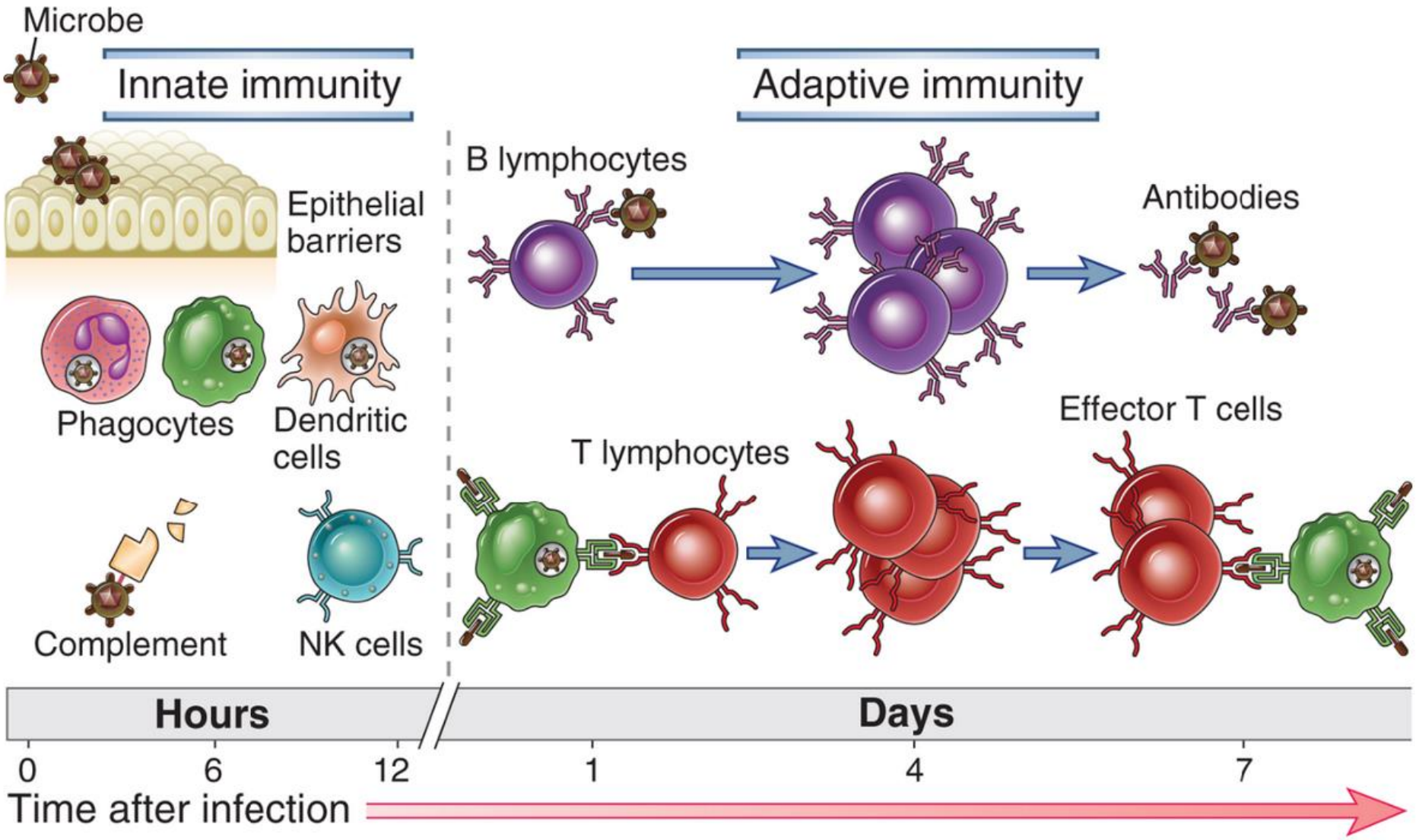
Types of adaptive immunity

- Humoral immunity
  - Mediated by secreted antibodies
  - Defense against extracellular microbes
  - Antibodies recognise microbial antigens, neutralise their infectivity and target microbes for elimination
  - Antibodies are specialised →activate different effector functions
- Cell-mediated immunity
  - Mediated by T cells themselves & their products (cytokines)
  - Defense against intracellular microbes



Phases of adaptive immune responses

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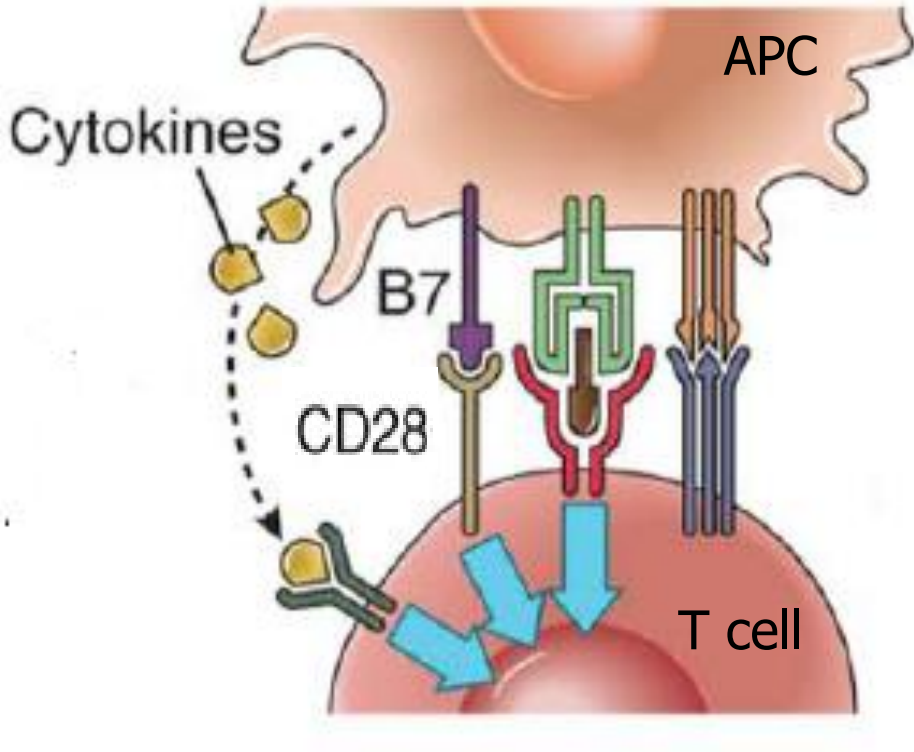
How are T cells activated?

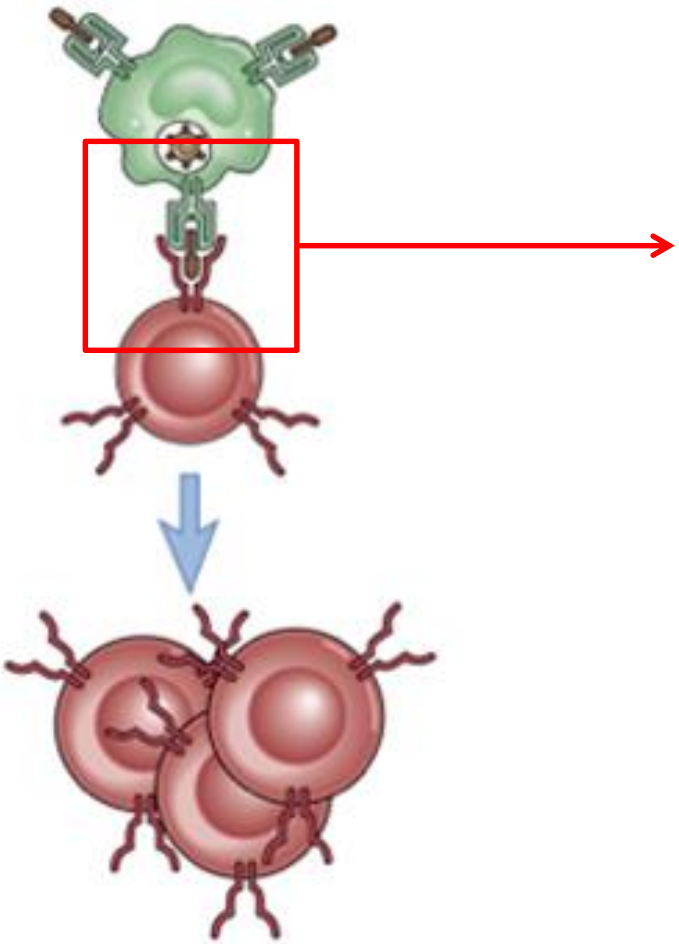
- They need to recognise the foreign pathogen
- T-cells can not directly "see" microbes - only recognise antigens (short peptides) that are presented on the surface of host cells
  - Infected cells
  - Antigen presenting cells
- They need a second costimulatory signal
  - Binding of B7 to CD28



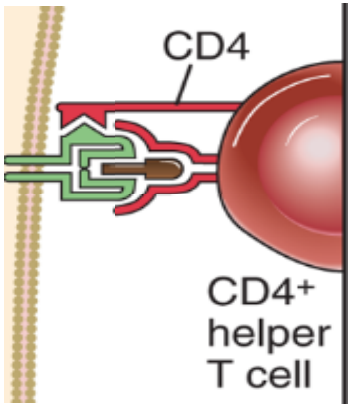
How do T cells recognise antigen?

APC

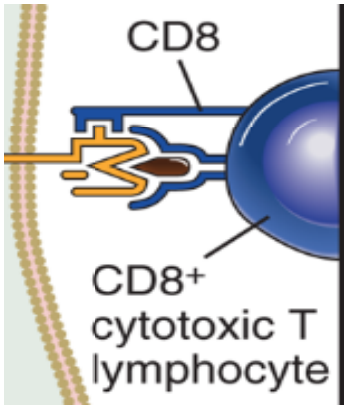
T cell



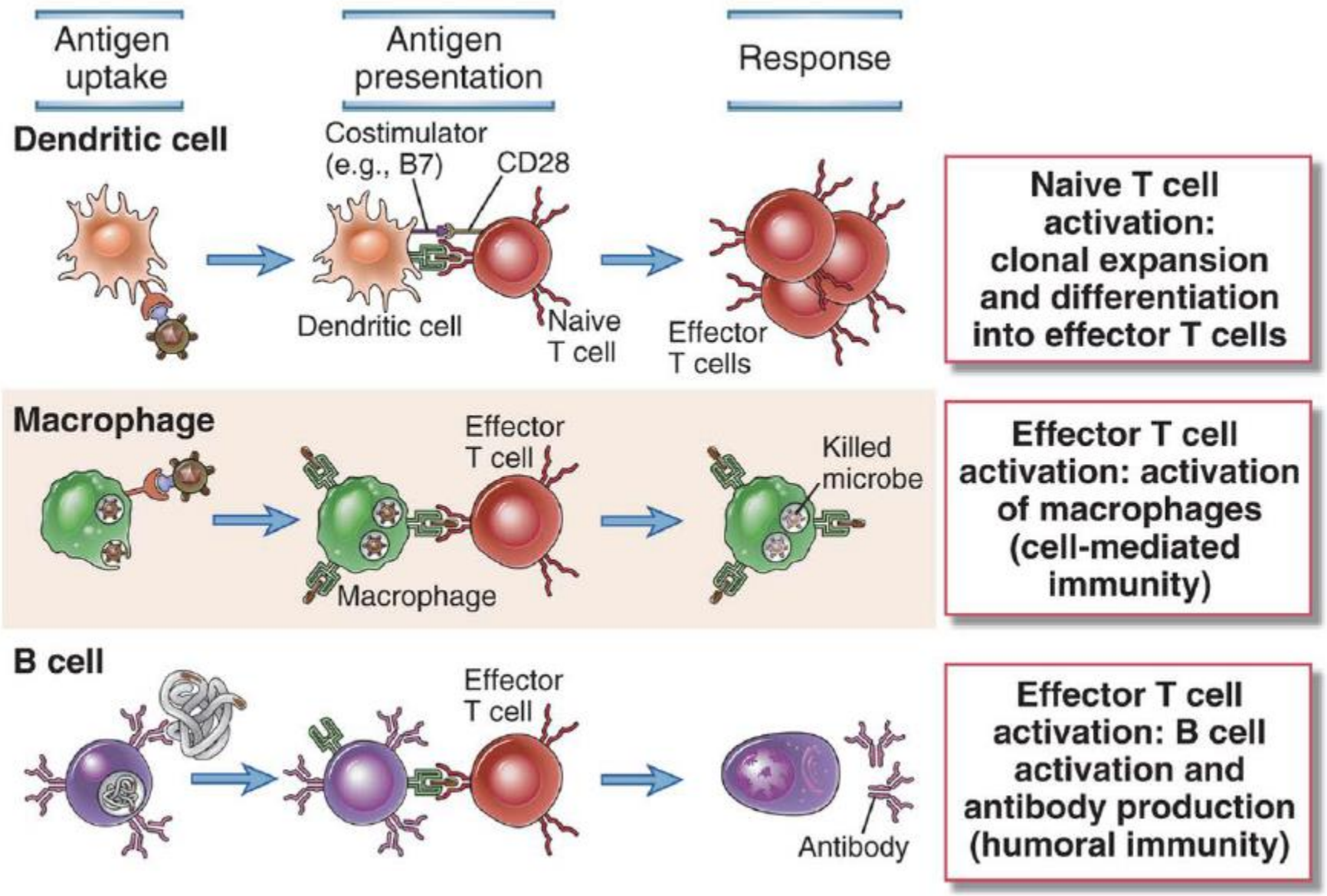
MHC class II present peptides to $CD4^+$ T-cells



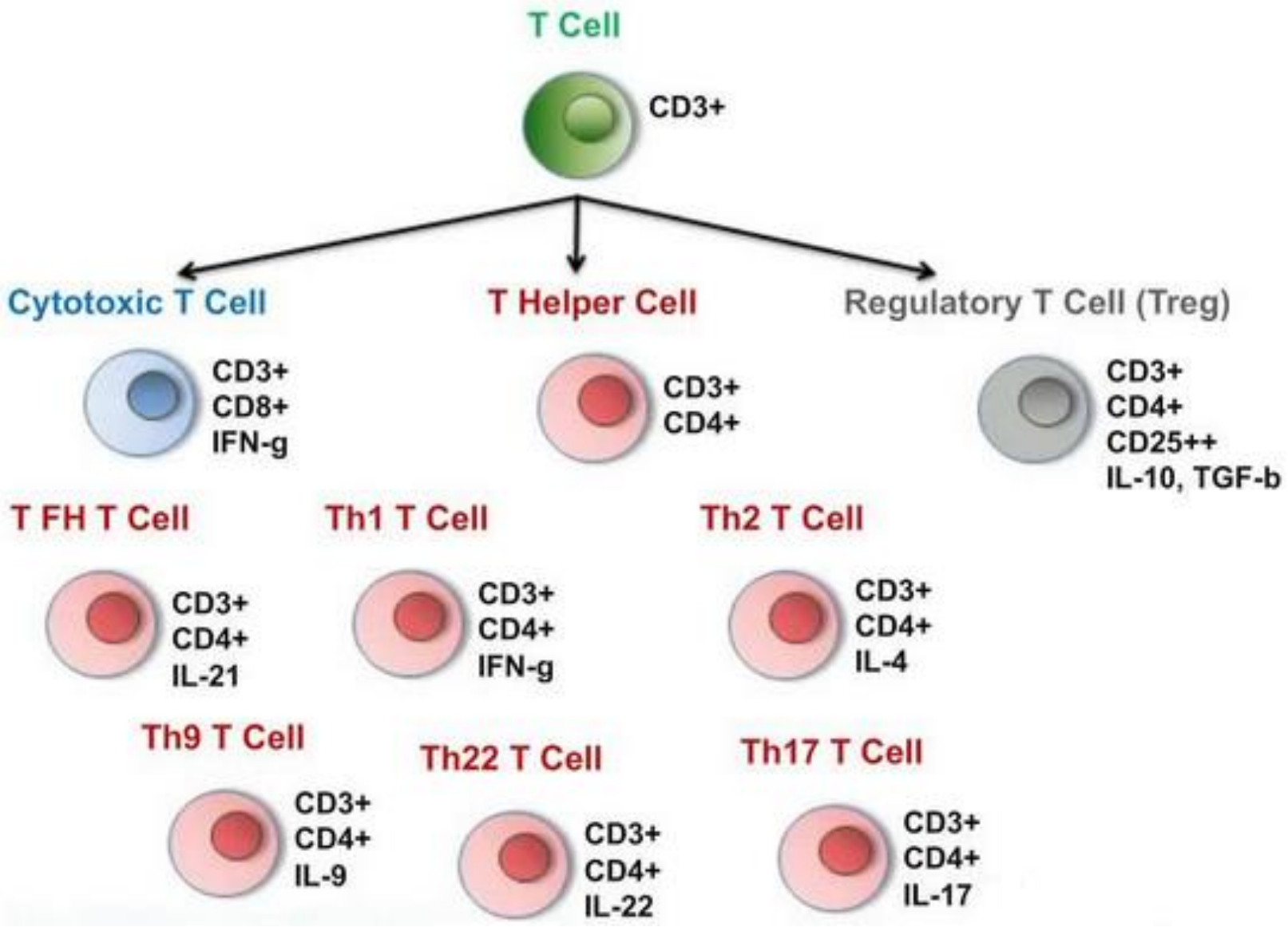
MHC class I present peptides to $CD8^+$ T-cells



Antigen Presenting Cells

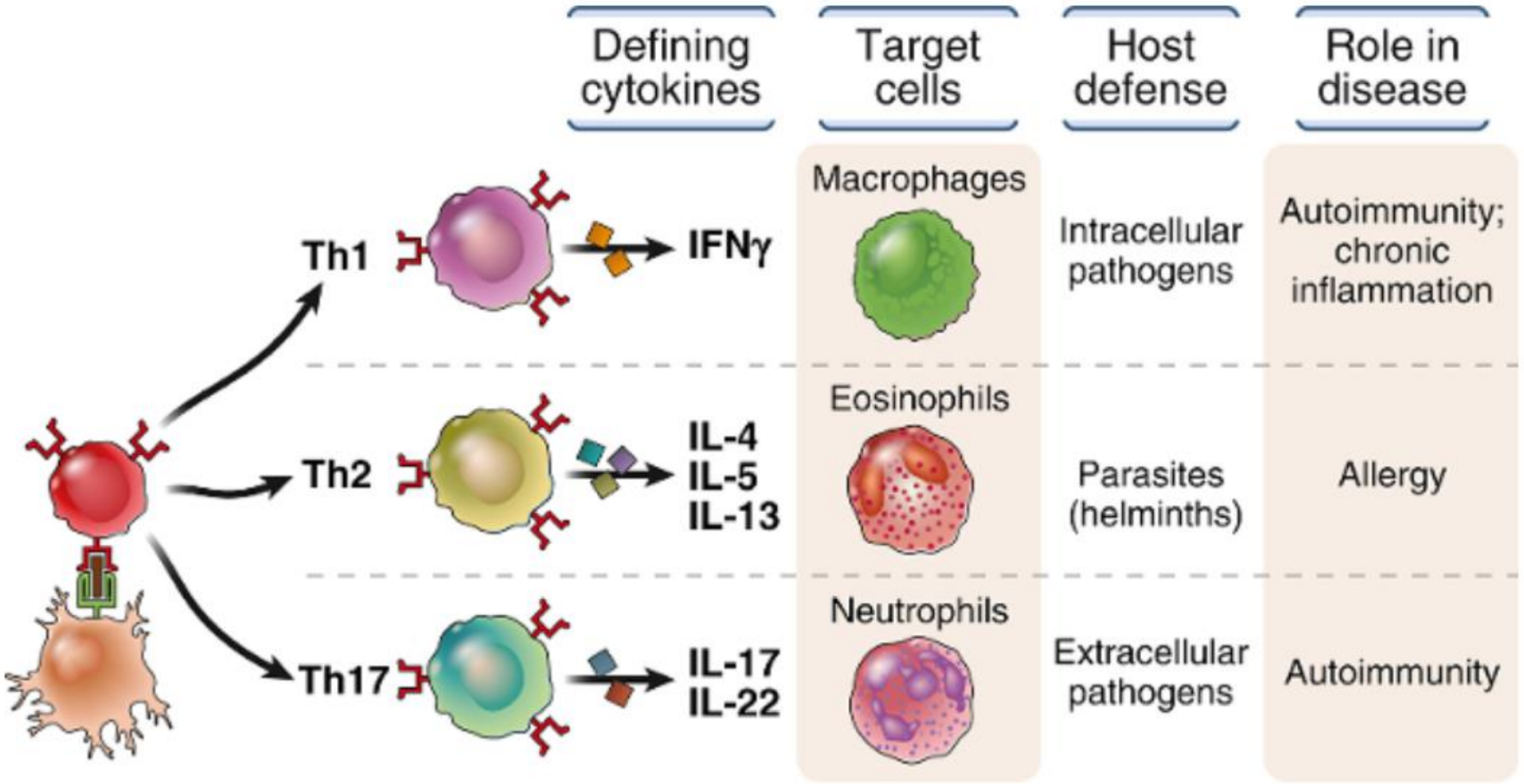


T cell subsets



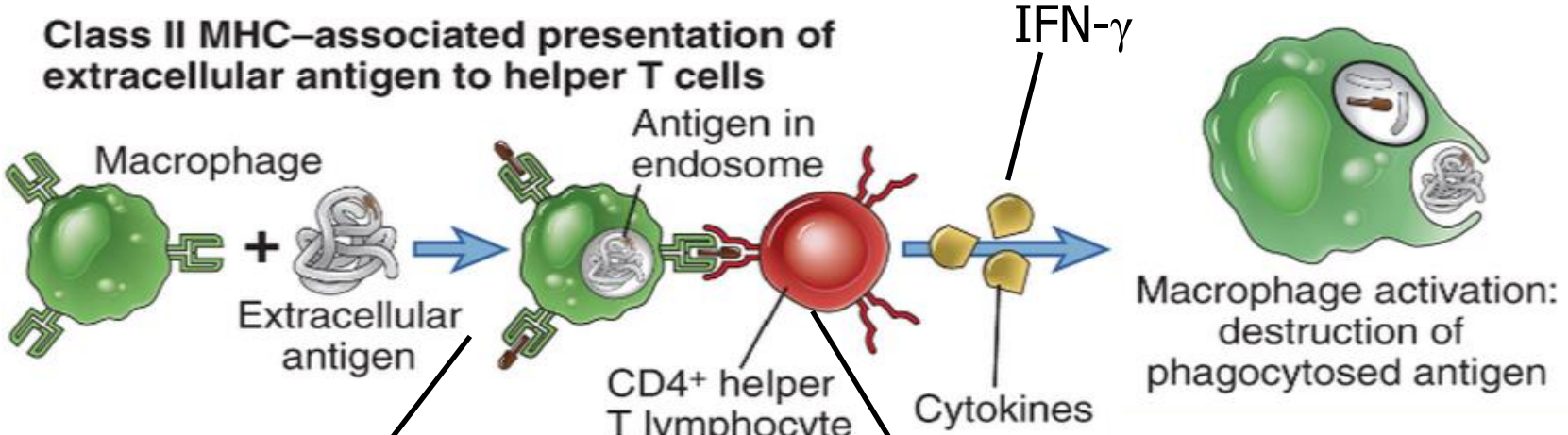
Effector CD4$^+$ T cell Subsets

- Express surface molecules and secrete cytokines
- Activate other cells
- Distinct subsets arise in response to different antigens



Functions of Th1 Cells

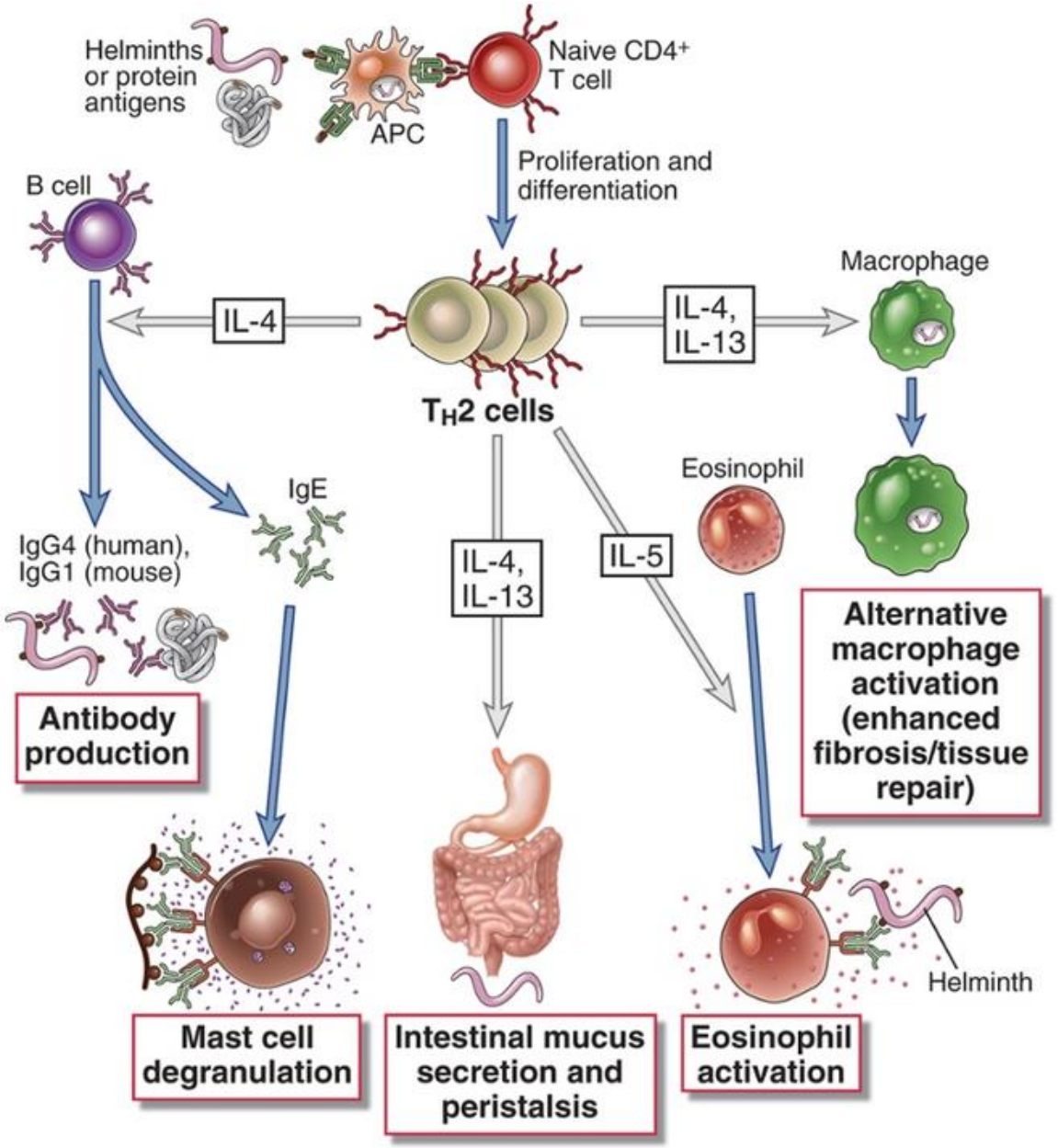
Activate macrophages to ingest and destroy internalised microbes



Extracellular antigens (e.g. bacteria) usually end up in endosomal vesicles

T cell recognition of peptide-MHC-II complex

Functions of Th2 Cells



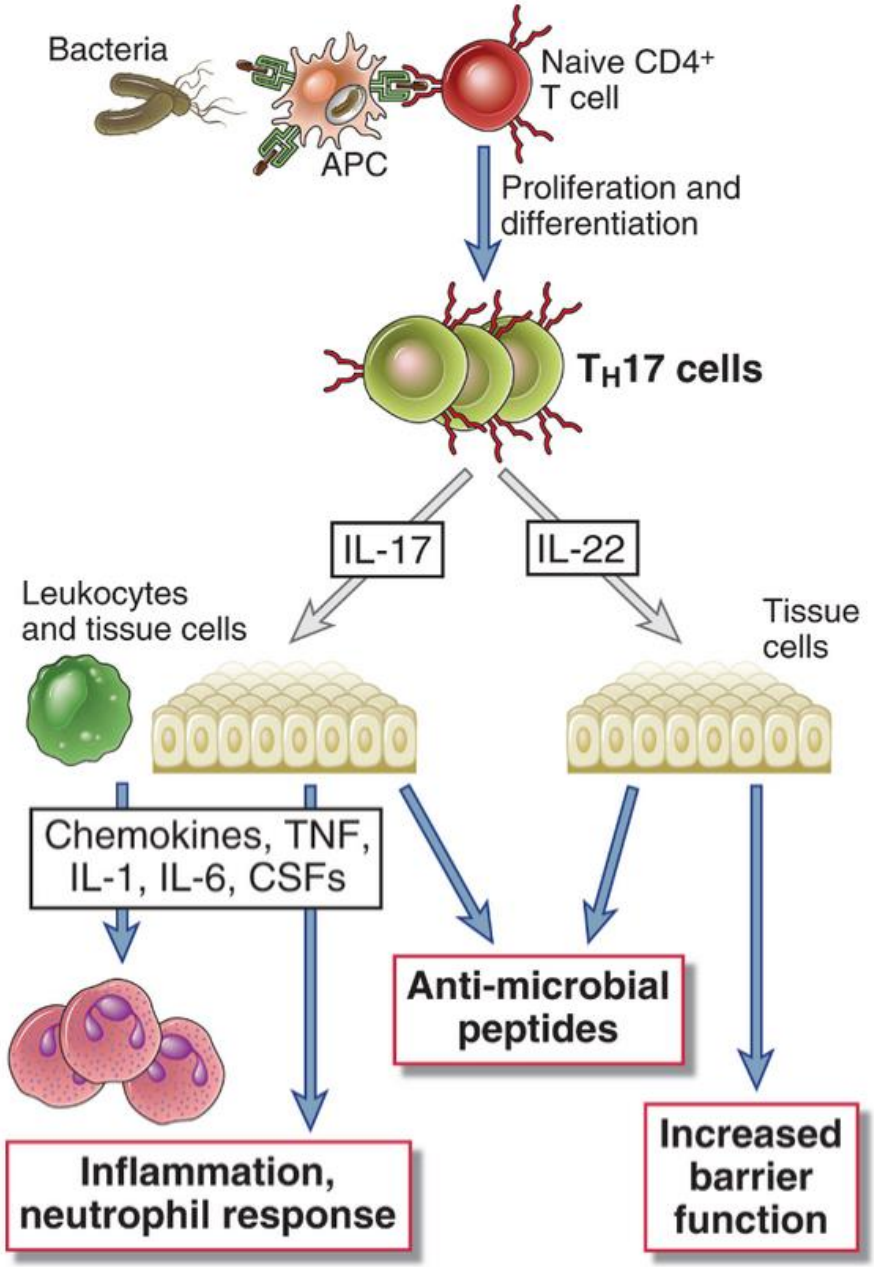
Stimulate reactions that serve to eradicate helminthic infections

IL-4 induces IgE antibody responses

IL-5 activates eosinophiles

IL-13 has diverse functions

Functions of Th17 Cells

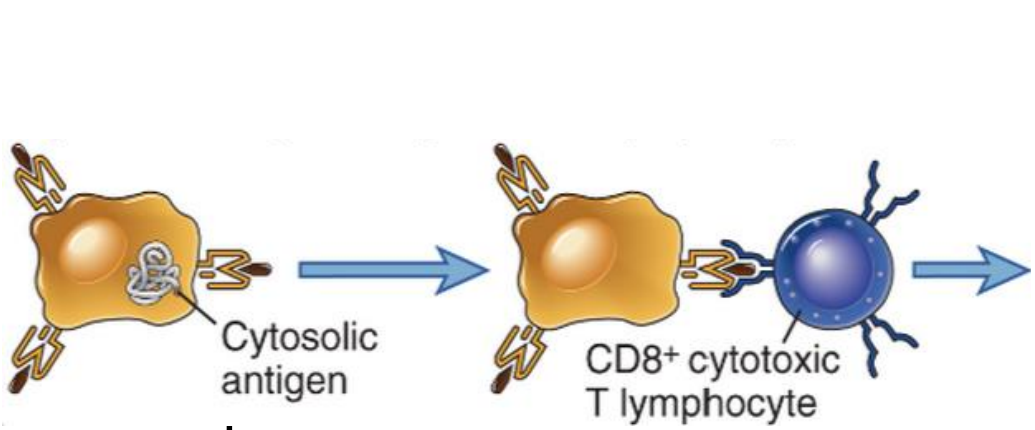


Secrete cytokines that recruit neutrophils to sites of infection

Neutrophils are a major defense mechanism against extracellular bacteria and fungi

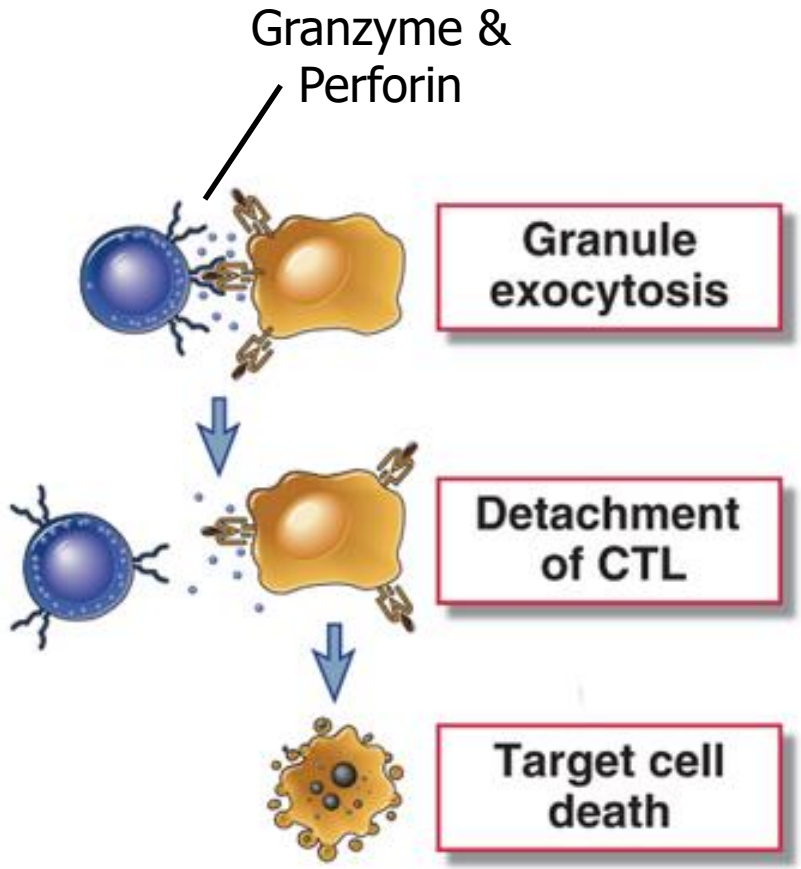
Cytotoxic T-cell responses

Eliminate intracellular microbes mainly by killing infected cells

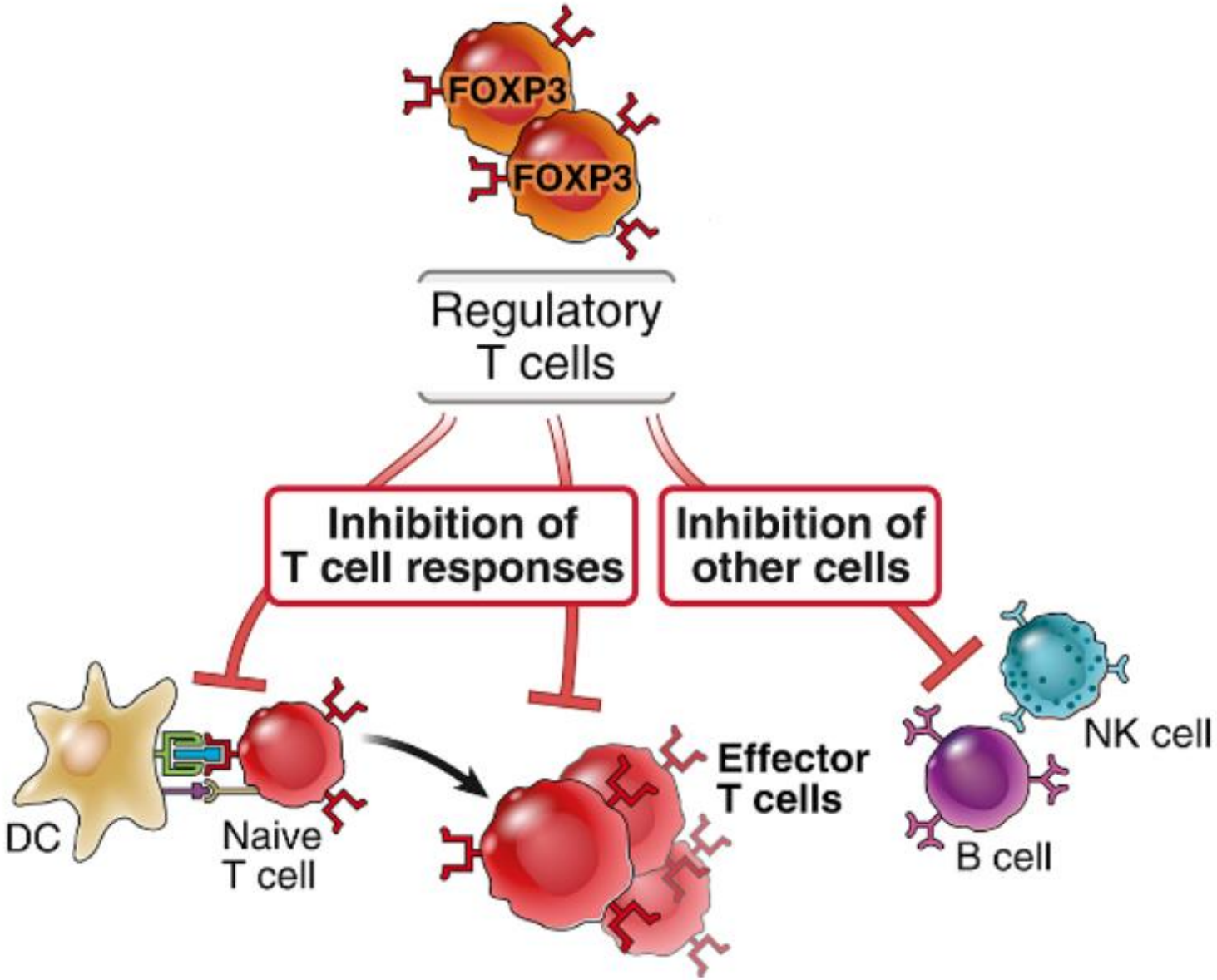


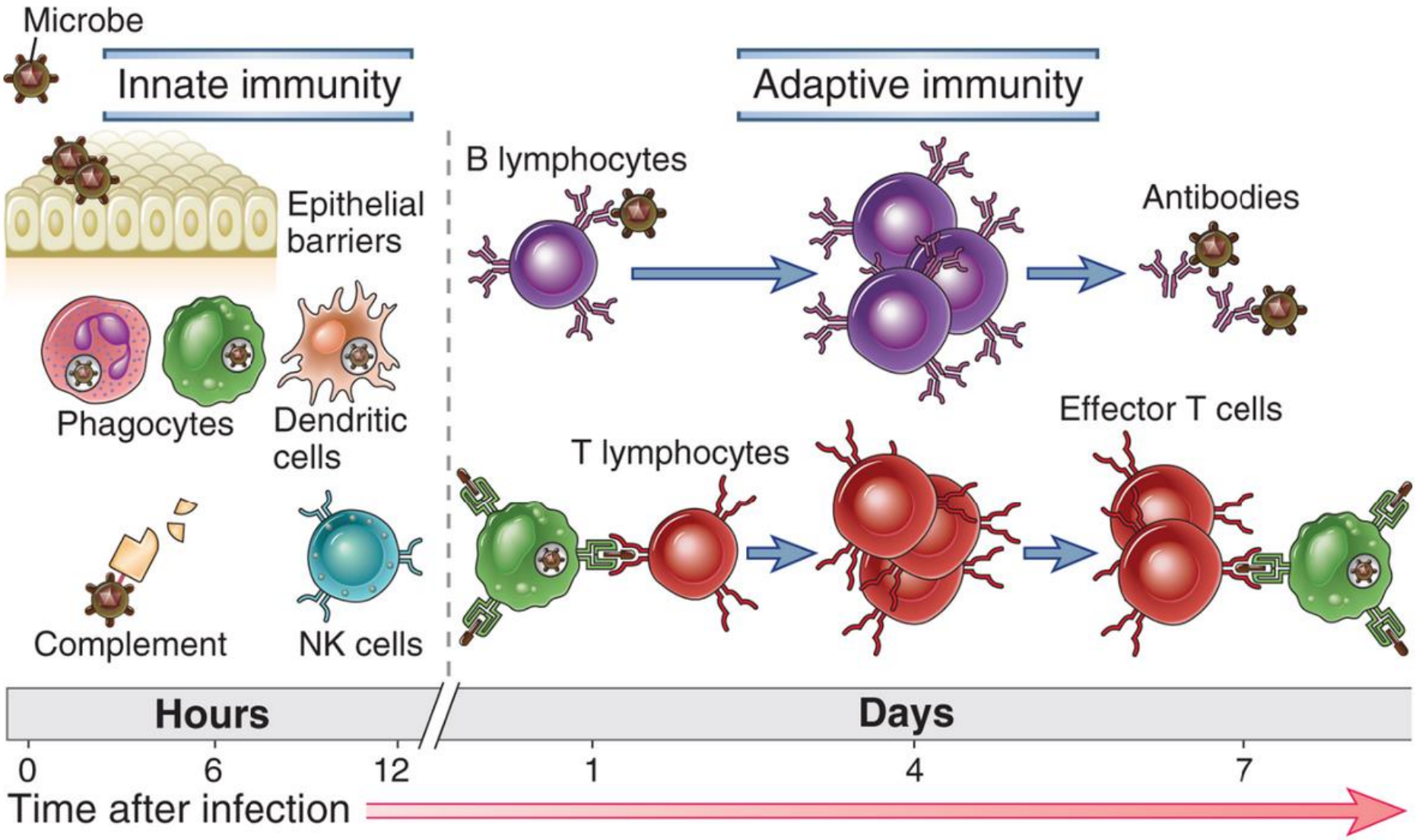
Endogenously synthesized antigens in nucleated cell (viral or tumor)

Recognise peptide-MHC-I complex



Treg suppress immune responses

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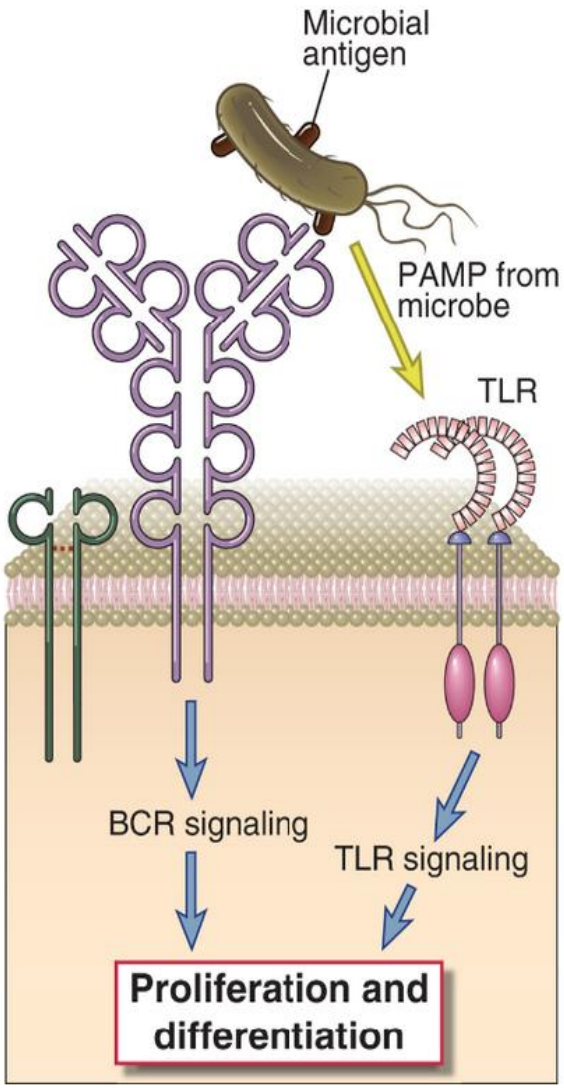
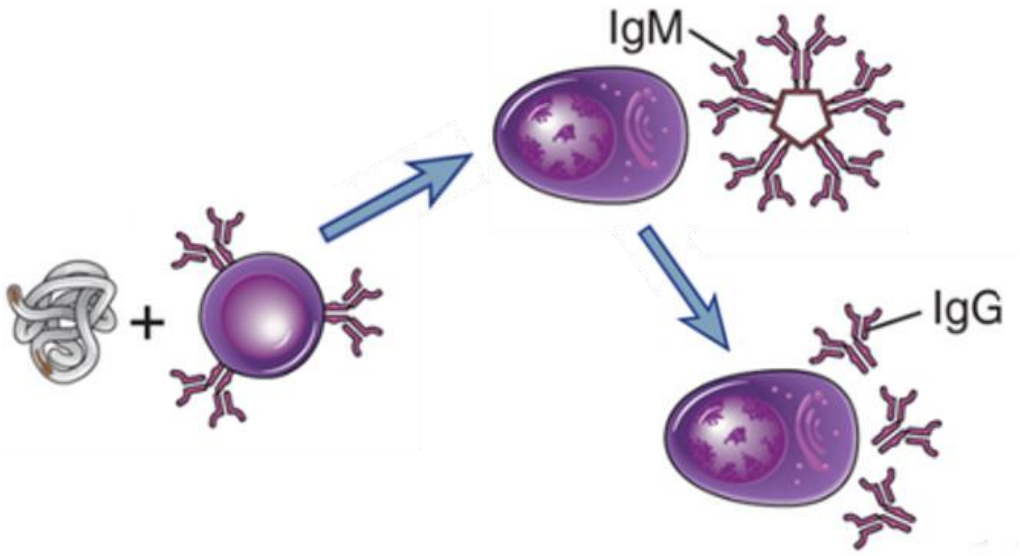
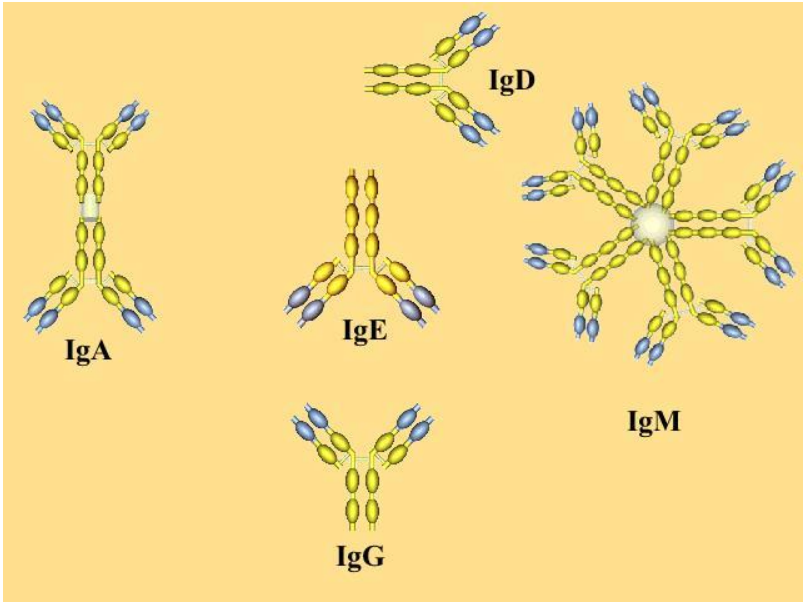
How are B cells activated?



- Recognise antigen in its intact, native conformation and do not require antigen to be processed by APC or presented in MHC molecules
- Antibody molecules expressed on the surface of the B cell act as the B cell receptor (BCR)
- Secondary signals promote increased activation and signalling
- Once activated, B cells differentiate into plasma cells that secrete antibody molecules

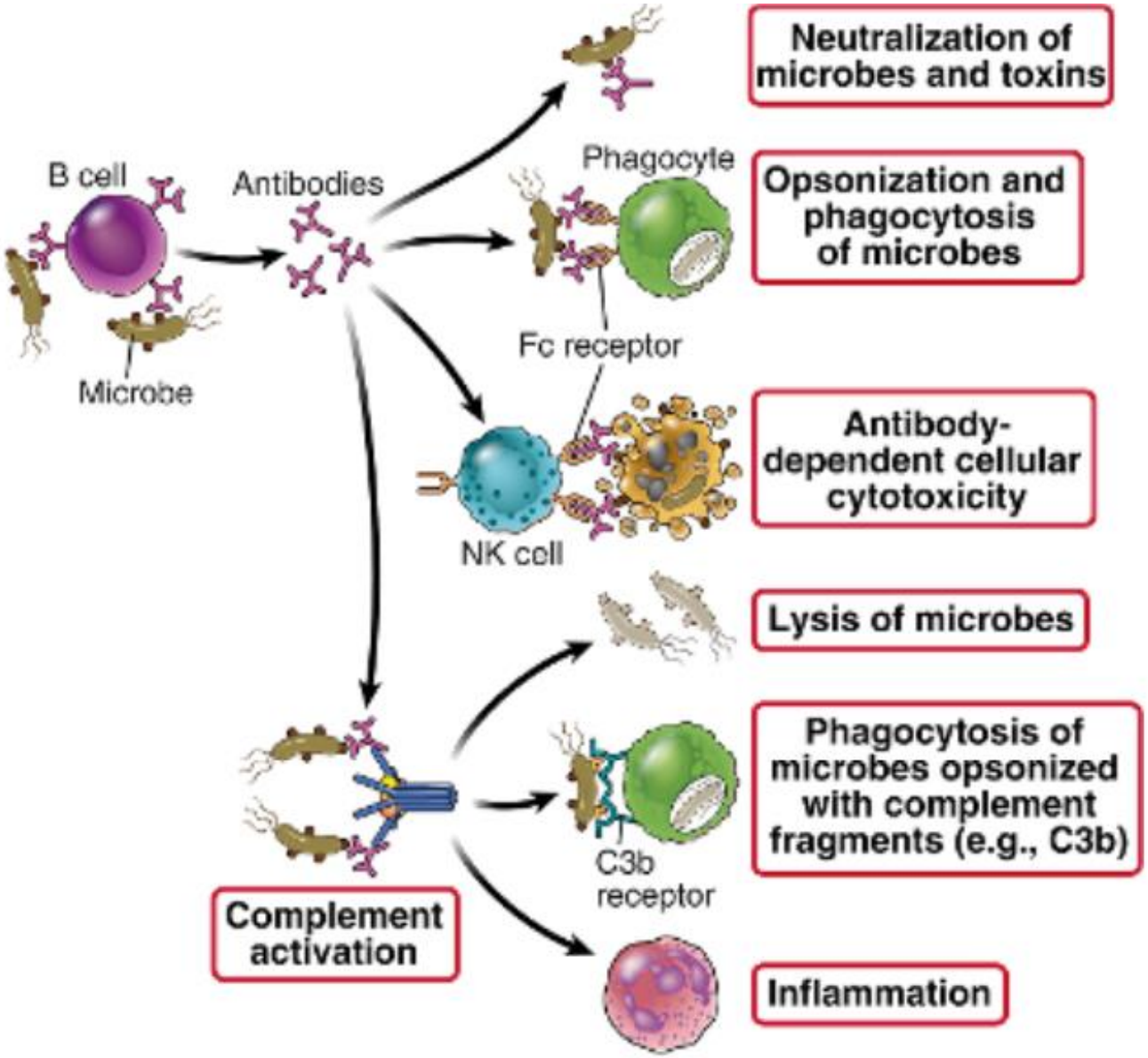
How are B cells activated?



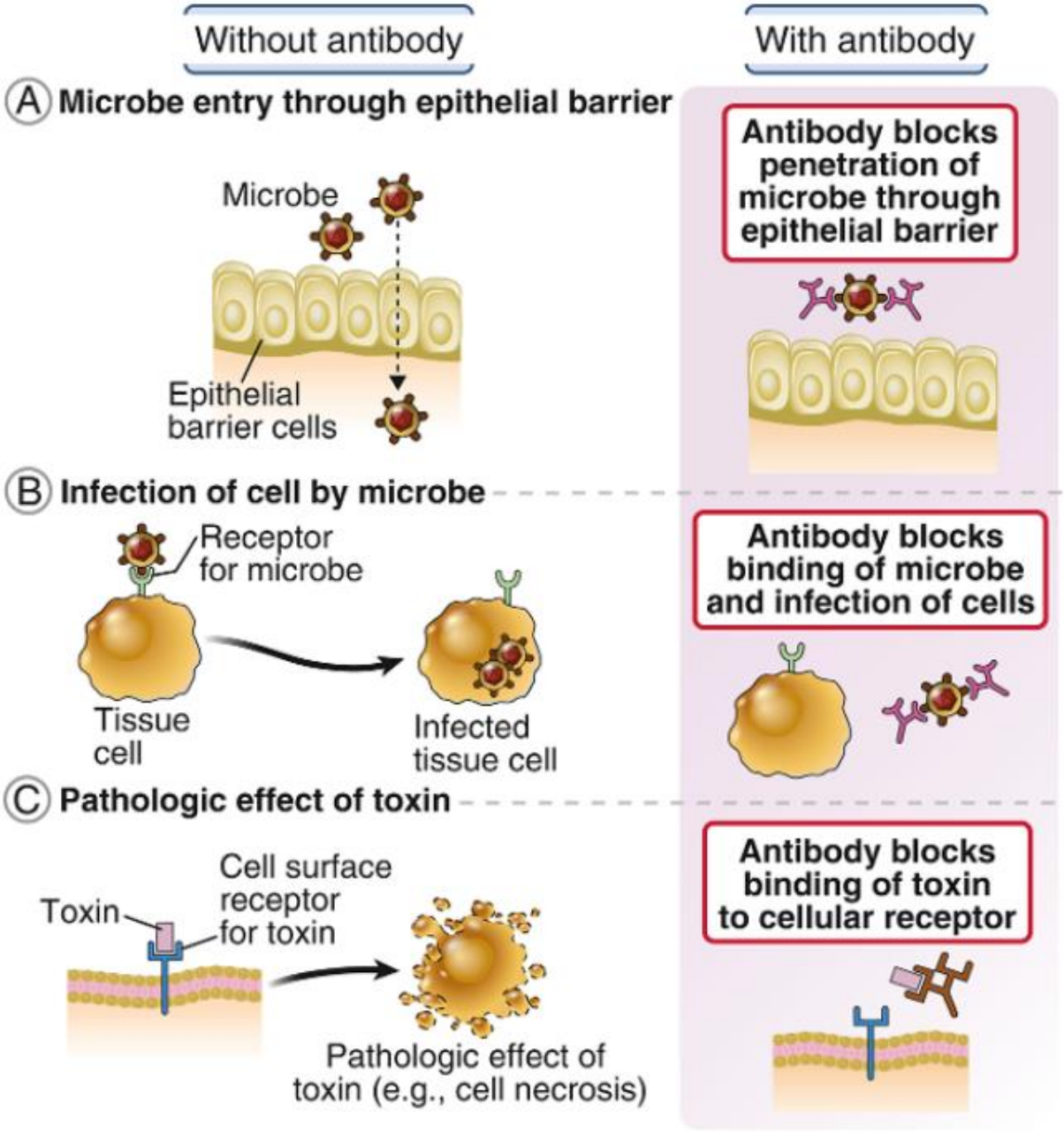


- Antibodies exist as different isotypes
- They have different functions at different locations and for different pathogens
- IgM is the first Ab made, switch to IgG and others later in the response

Functions of antibodies



Neutralisation



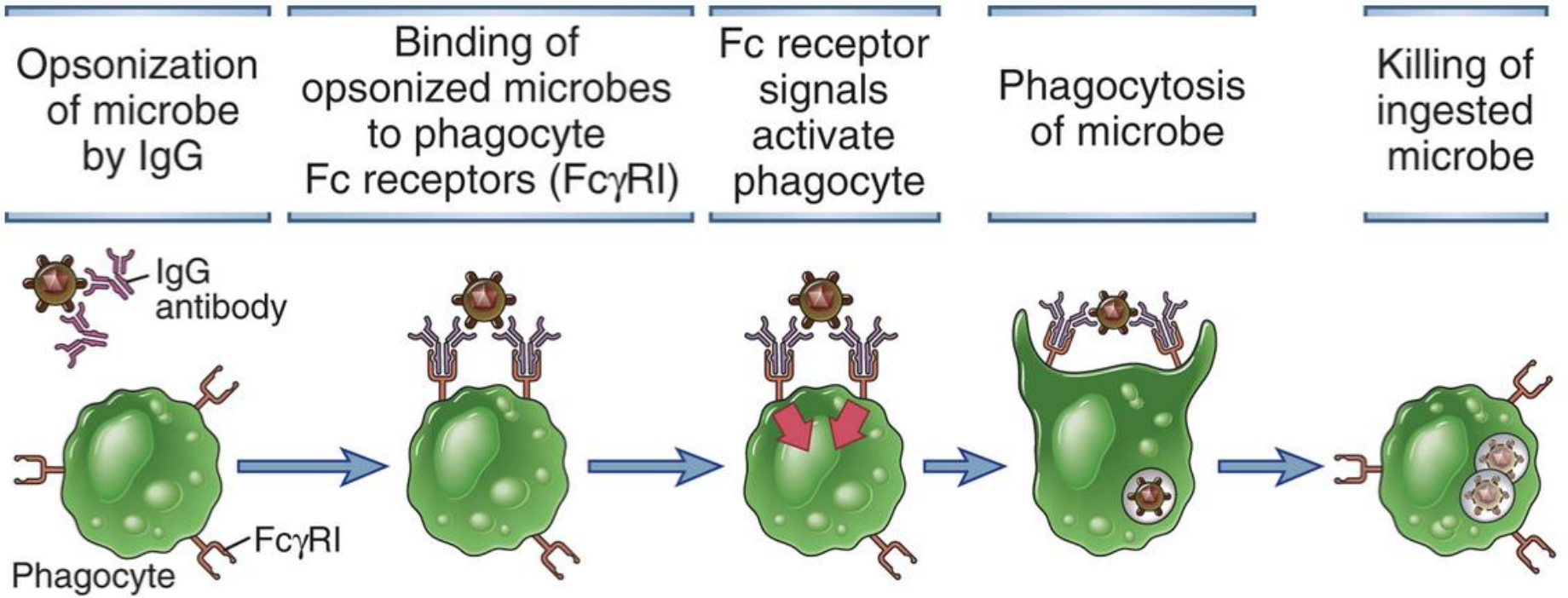
A. Antibodies prevent the binding of microbes to cells and so inhibit infection of host cells.

B. Antibodies inhibit the spread of microbes from an infected cell to adjacent uninfected cells.

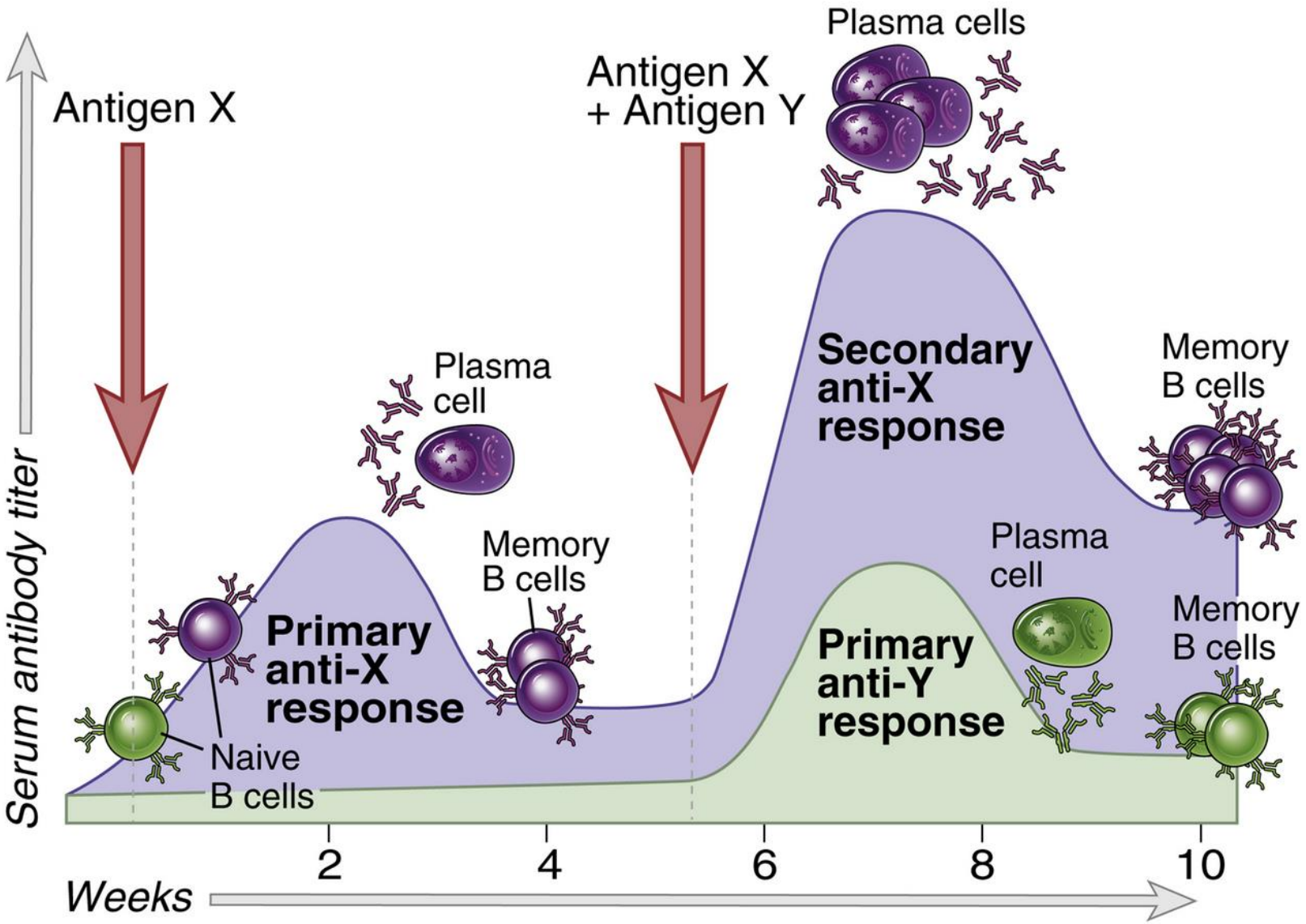
C. Antibodies block the binding of toxins to cells and thus inhibit the pathologic effects of the toxins.

Opsonisation

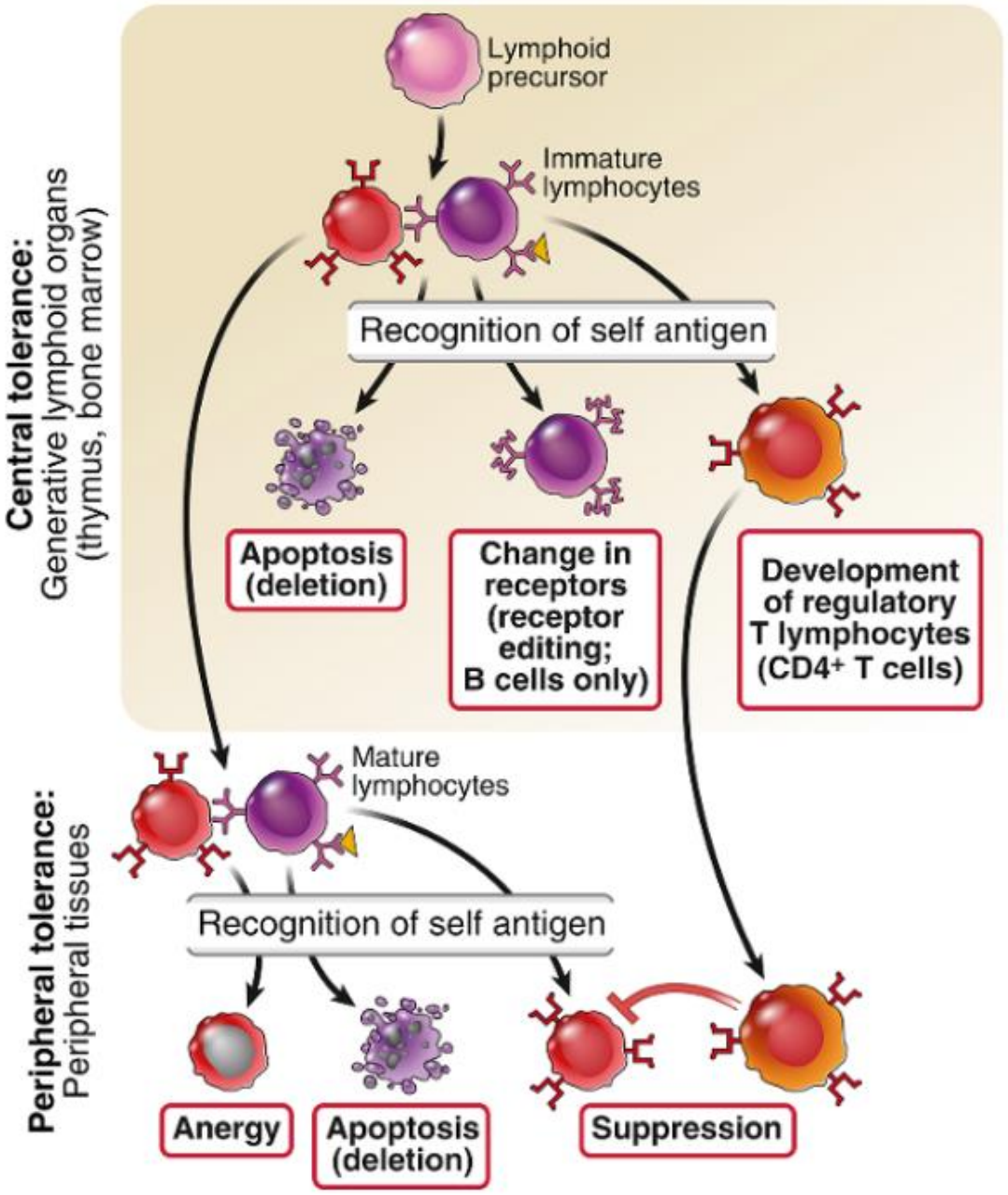
- Antibodies of certain IgG subclasses bind to microbes and are then recognized by Fc receptors on phagocytes.
- Signals from the Fc receptors promote the phagocytosis of the opsonized microbes and activate the phagocytes to destroy these microbes.



Specificity, memory and contraction of adaptive immune responses



Tolerance



Central Tolerance

mechanism by which immature T cells that recognise self antigens are deleted during development in the thymus, sometimes referred to as "thymic education"

Peripheral Tolerance

mechanism by which mature T cells that recognise self antigens in peripheral tissues are rendered incapable of subsequently responding to those antigens

The Spectrum of Clinical Immunology