Immunity

- Immunity is body's ability to resist or eliminate potentially harmful foreign materials or abnormal cells

History: what imparts Immunity?

- Emil von Behring and Kitasato (1890)
  - Serum from vaccinated animals was protective (diptheria)

- Metchinkoff (1880)
  - Cell based Immunity

- Merrill Chase (1940)- Transfer of WBC (immunity to tuberculosis)

Both serum and cells contribute to immunity

Immunology- nobel prizes

- Since 1901 there have been 19 Nobel Prizes for immunology-related research.

The immune system

A functional system – **NOT** an organ system:

Complex system – includes

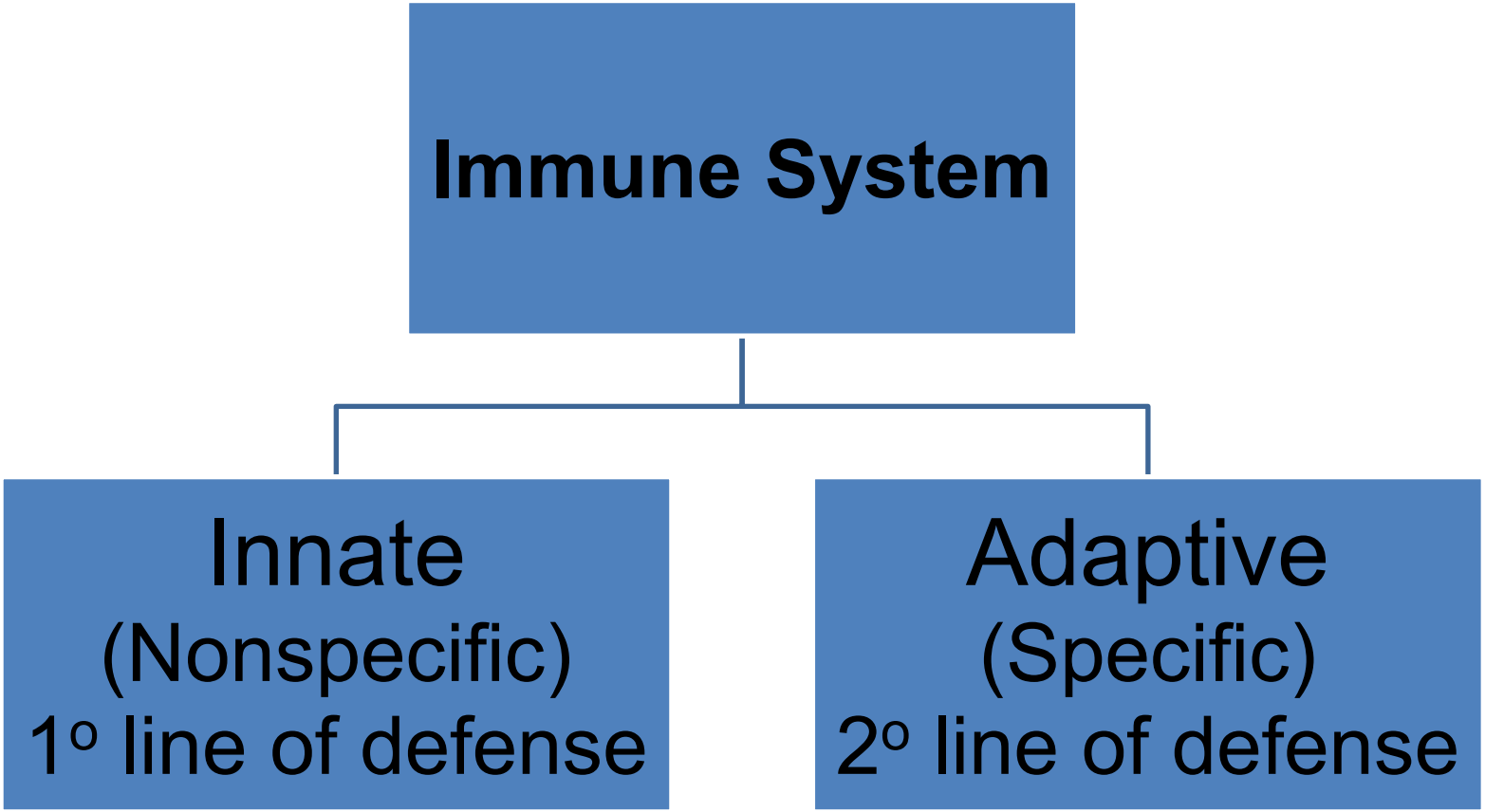
- Skin – physical barrier
- Lining of mucus membranes – physical barrier
- Secretions – tears, mucus etc - antimicrobial
- Blood cells and vasculature – WBCs
- Bone marrow
- Liver – makes complement proteins
- Lymphatic system and lymphoid organs
- Most tissues – have resident immune cells

Immunity

- Immunity (immunis- Latin-exempt, state of protection from infectious diseases)
- Immunity is body's ability to resist or eliminate potentially harmful foreign materials or abnormal cells
- consists of following activities:
  - Defense against invading pathogens (viruses & bacteria)
  - Removal of 'worn-out' cells (e.g., old RBCs) & tissue debris (e.g., from injury or disease)
  - Identification & destruction of abnormal or mutant cells (primary defense against cancer)
  - Rejection of 'foreign' cells (e.g., organ transplant)
  - Inappropriate responses:
    - Allergies - response to normally harmless substances
    - Autoimmune diseases

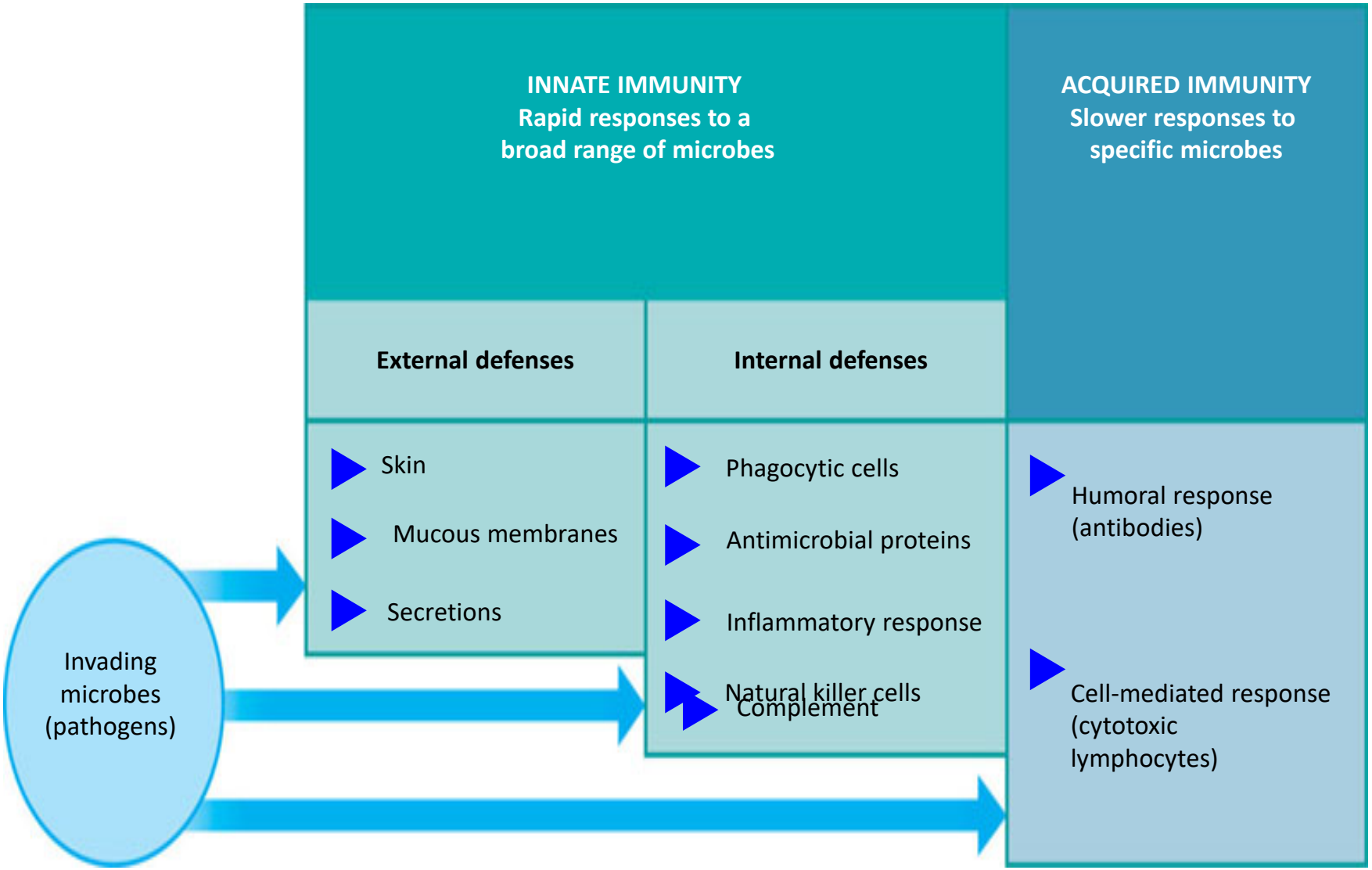
The Immune System

Overview of the Immune System



Interactions between the two systems

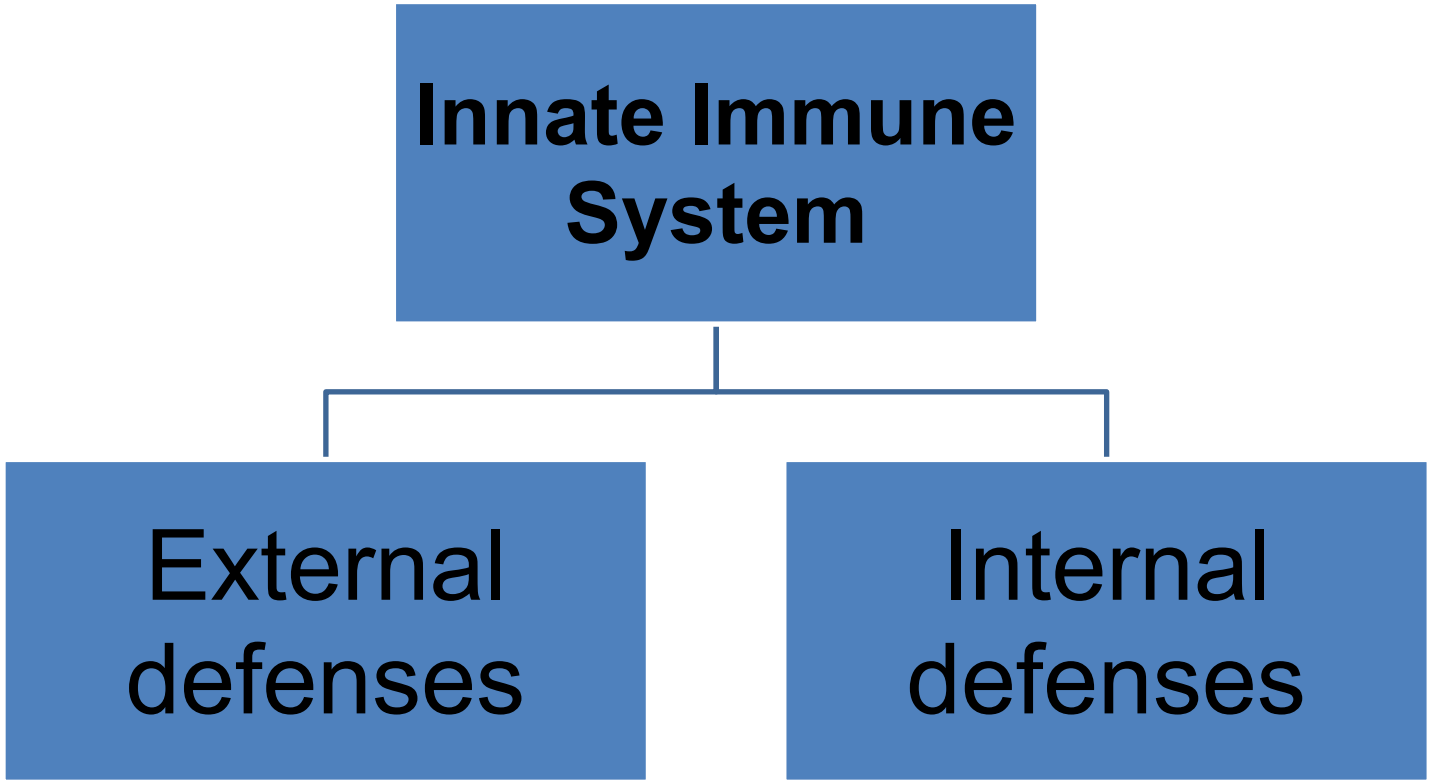
A typical immune response



Innate immunity vs Adaptive Immunity

Innate Immunity (first line of defense)	Adaptive Immunity (second line of defense)
• No time lag	• A lag period
• Not antigen specific	• Antigen specific
No memory	• Development of memory

The innate immune System

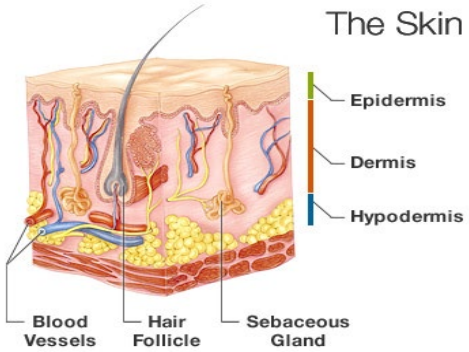


Interactions between the two systems

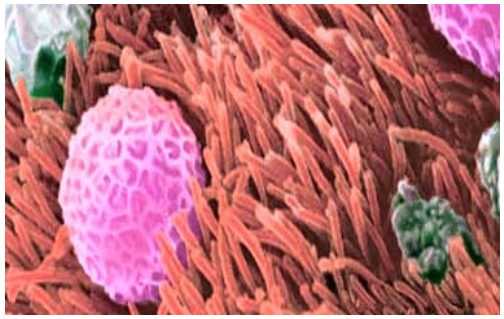
Innate immune system
External defenses

Anatomical Barriers - Mechanical Factors

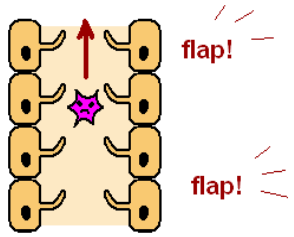
- Skin



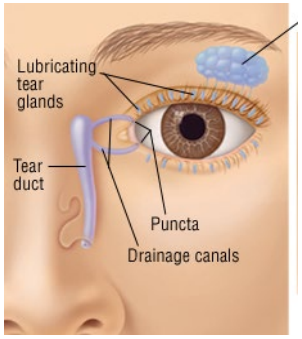
- Mucociliary escalator



The MUCOCILIARY ESCALATOR!



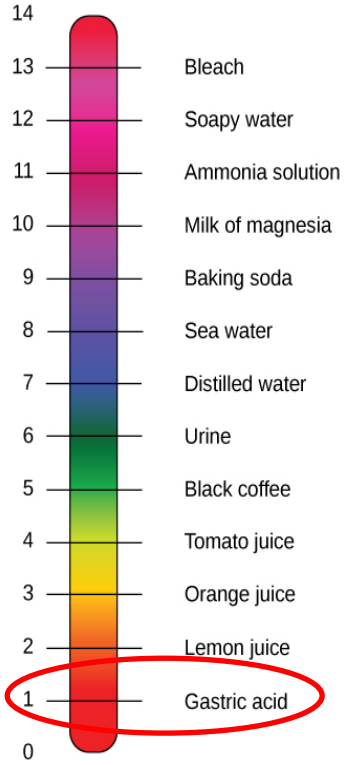
- Flushing action of saliva, tears, urine



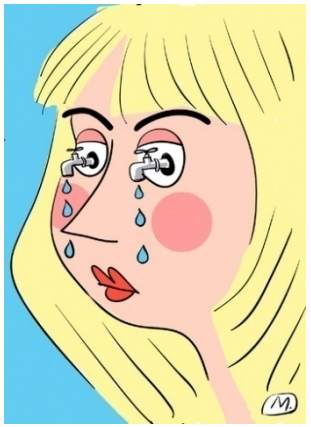
Anatomical Barriers – Chemical factors

Antimicrobial Peptides in sweat

HCl in stomach



Lysozyme in tears /saliva

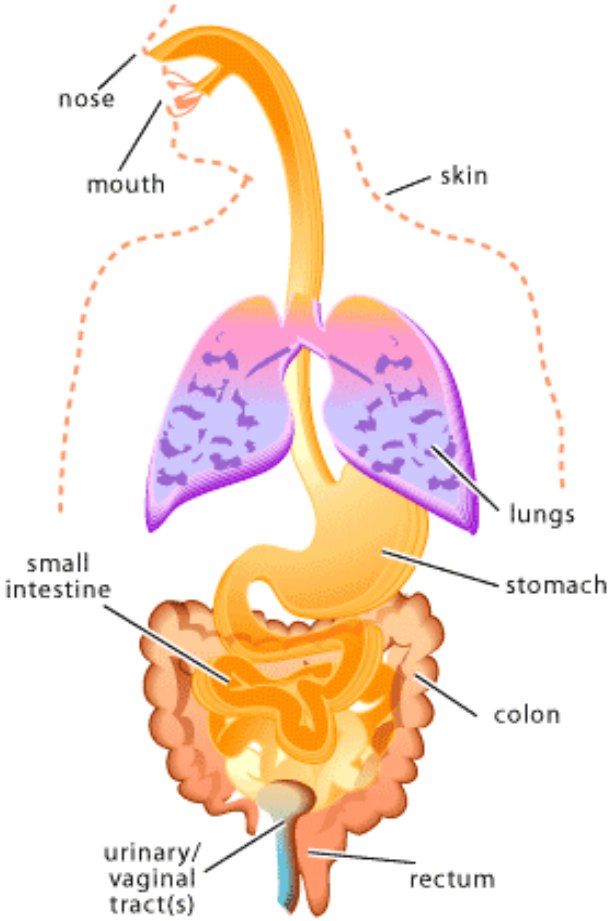


Anatomical Barriers – Biological factors

Normal flora – microbes in many parts of the body

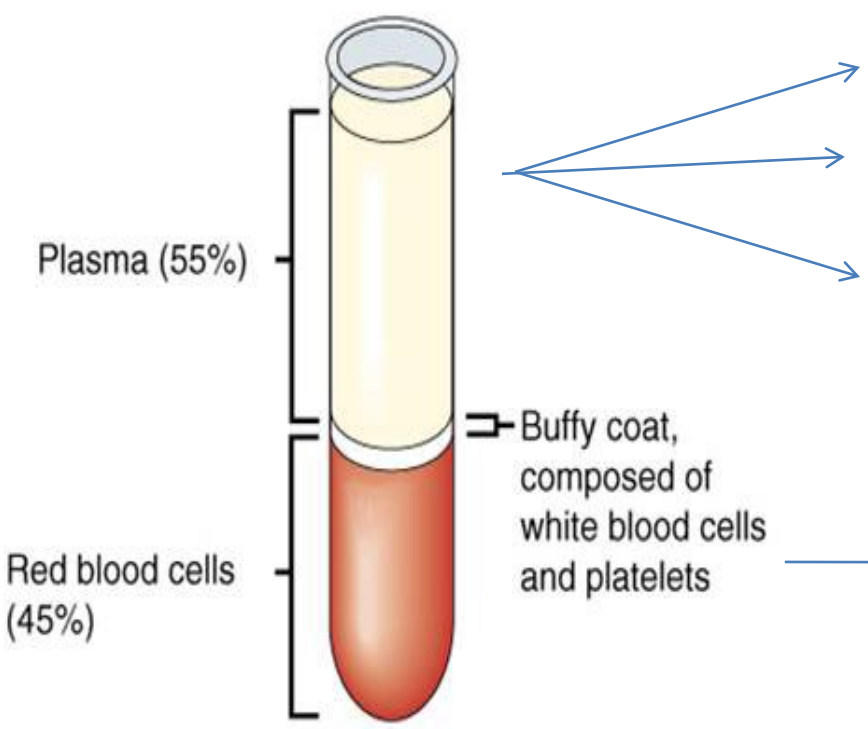
Normal flora – > 1000 species of bacteria

Normal flora – competes with pathogens for nutrients and space



Innate immune system internal defenses

Innate immune system: components of Blood



Complement proteins

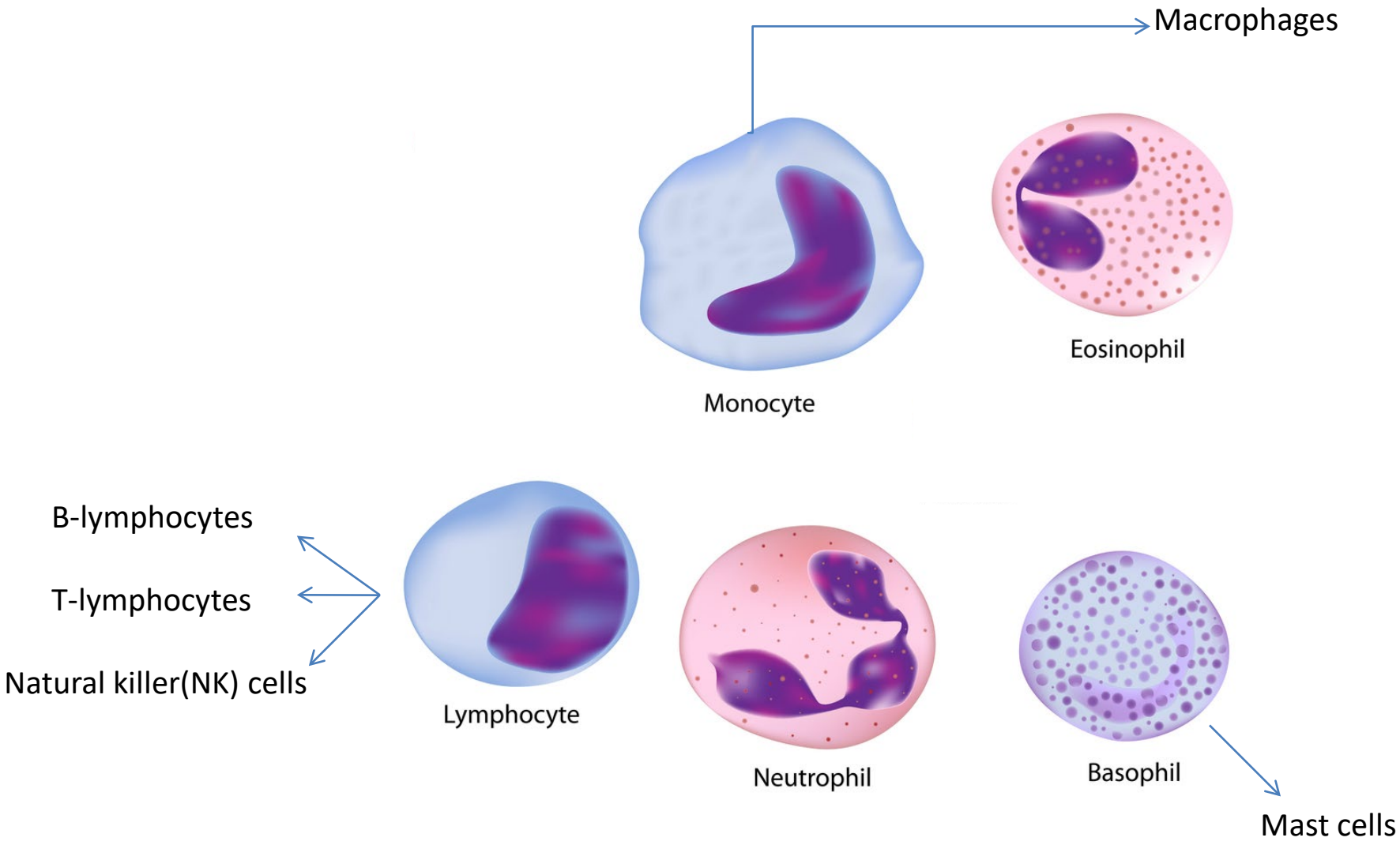
Coagulation proteins

Cytokines

Extracellular

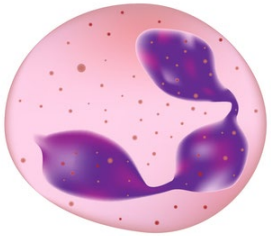
WBCs

White blood cells (WBCs)



Neutrophils in innate immune response

- Most abundant WBCs (~50-60%)
- Efficient phagocytes
- Most important cells of the innate immune system



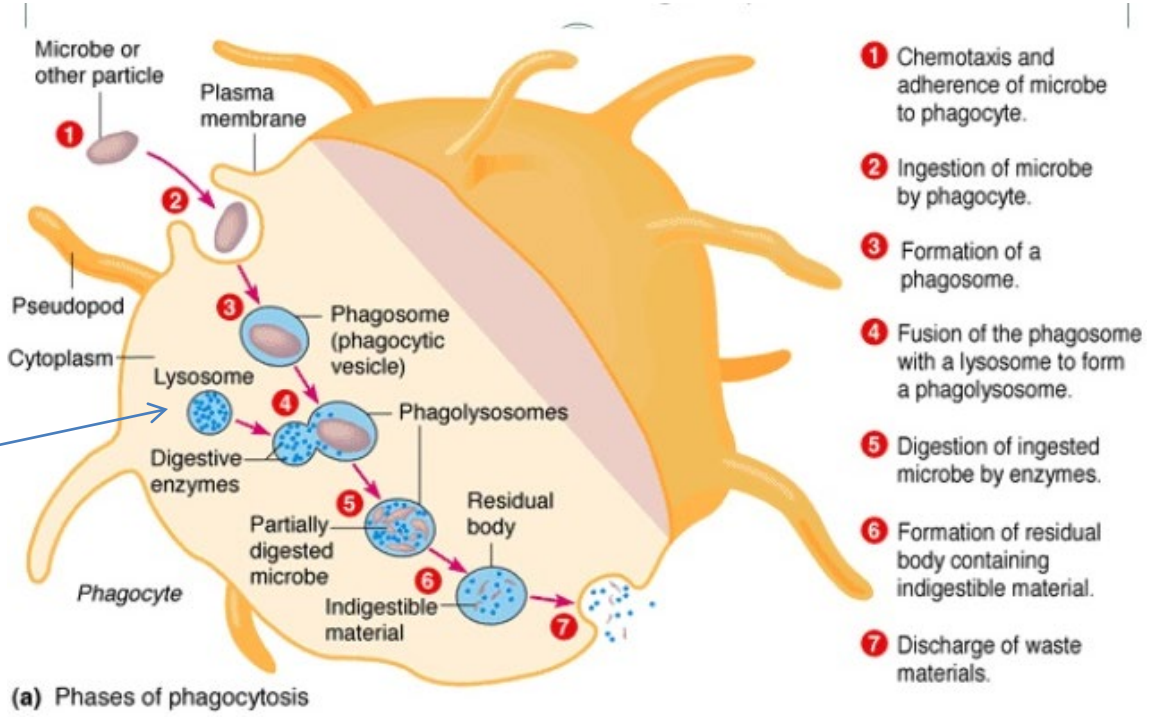
Neutrophil

Phagocytosis

- Phago = to eat
- Cyte = cell

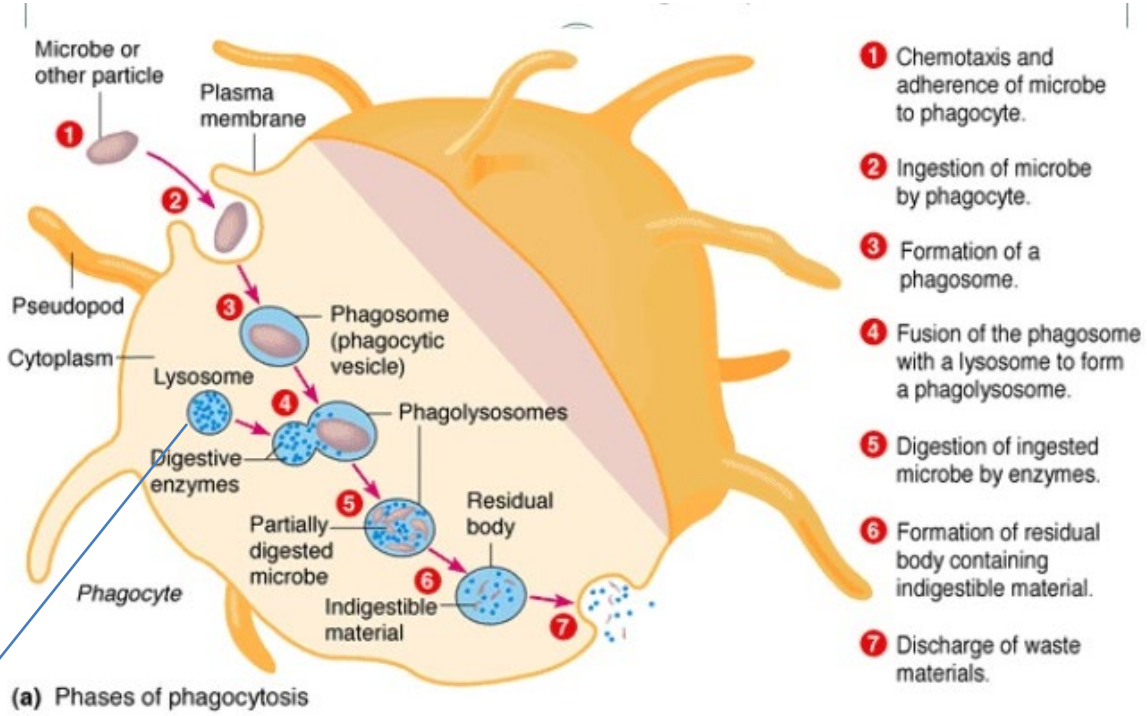
- WBCs (eg. Neutrophils) – find, eat and digest microbes !

How do neutrophils eat and digest microbes ?



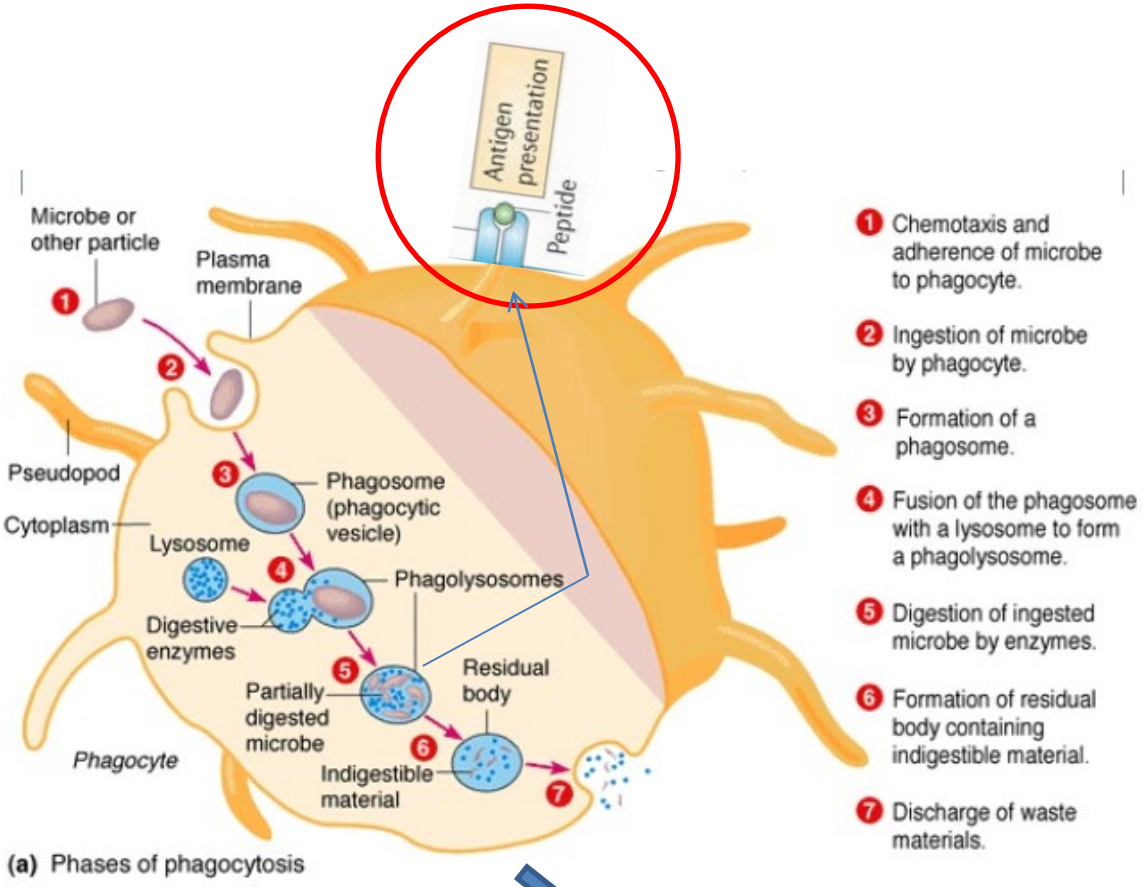
Granules

What's in the granules ?



Lysozyme – digests bacterial cell wall;
other antimicrobial proteins

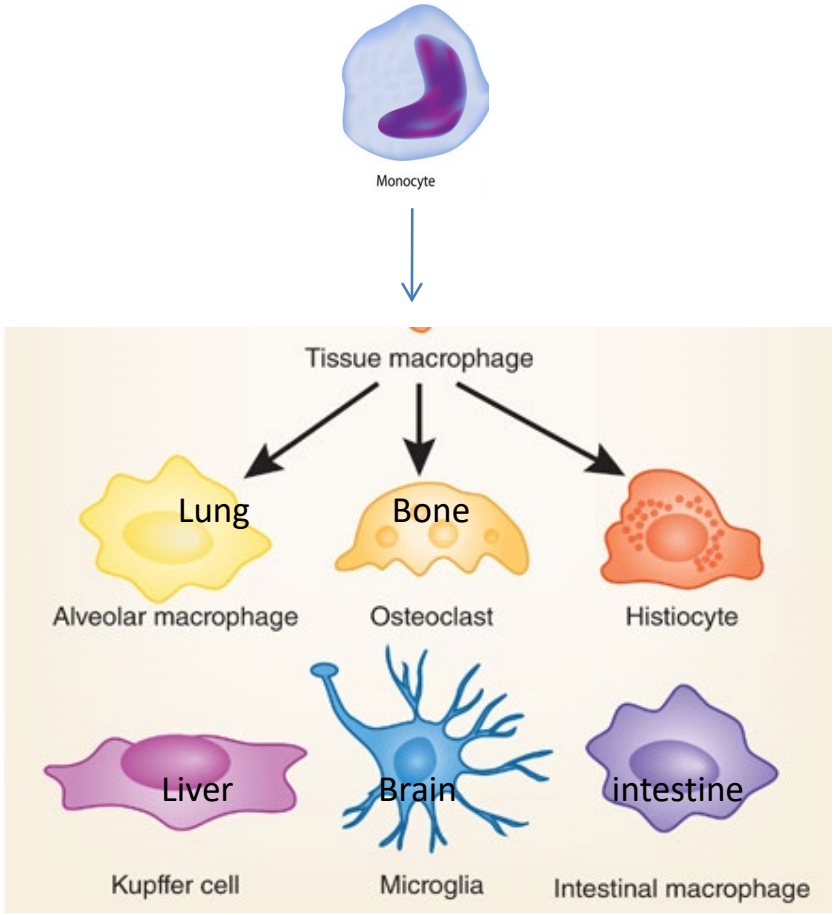
Additional role of neutrophils



Triggers inflammatory response

Monocytes

- Monocytes (~5% of WBCs)
- Migrate into the tissues and become Macrophages

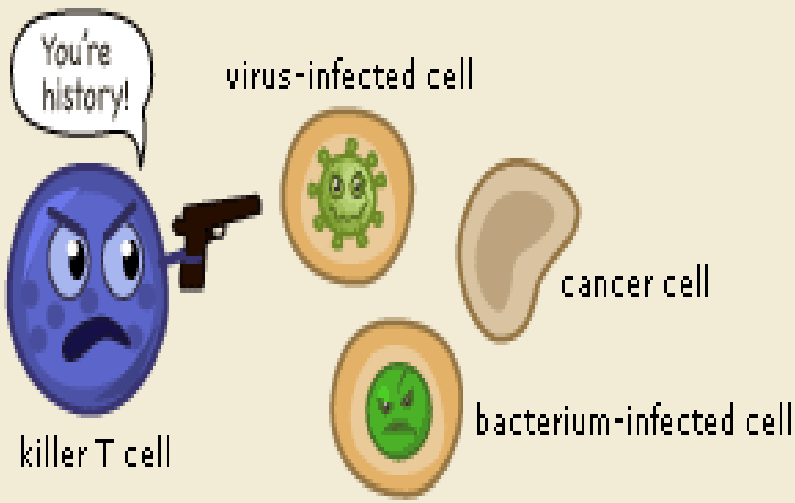


Macrophages

- “Big eaters”
- Phagocytosis of microbes in tissue
  (neutrophils are present only in blood)
- Antigen presentation

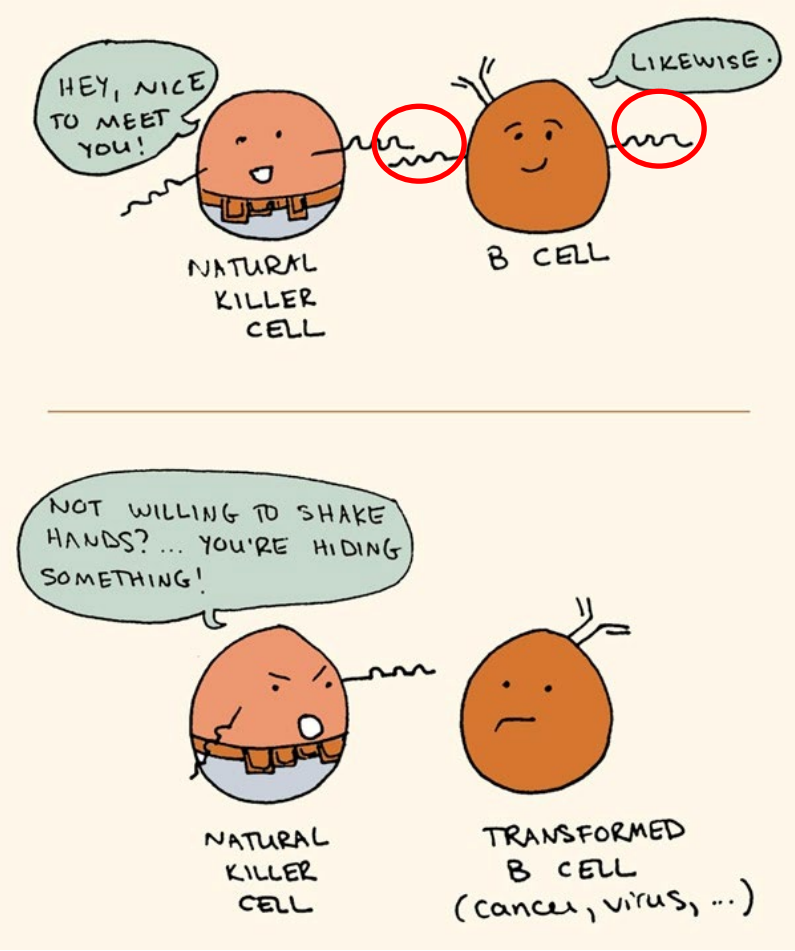
Natural killer cells

- Not B-lymphocytes / T-lymphocytes
- Important part of the innate immune system
- Kill virus /bacteria infected cells (Intracellular pathogens)
- Kills cancer cells



The killer T cells terminate cancer cells and cells infected by a virus or bacterium.

NK cells differentiate choose cells to kill ?

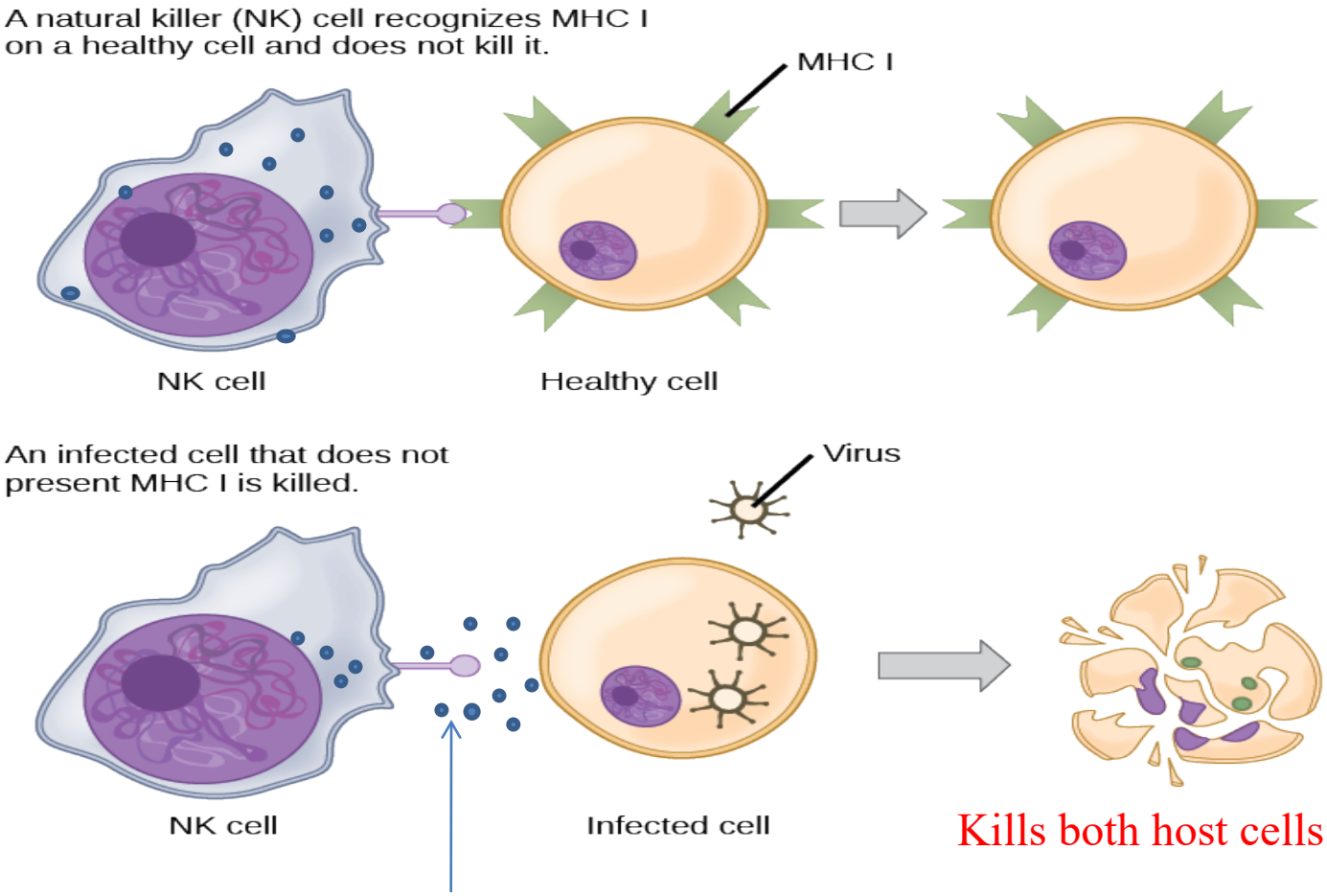


Uninfected cell / Normal cell

Microbe infected cell / cancer cell

Some cell surface proteins are missing

How does the killer kill ?



Toll-like receptors (TLRs)

- Transmembrane proteins
- Present on macrophages / few other cells
- Conserved across vertebrates
- Important part of innate immune system

TLRs – What do they do ?

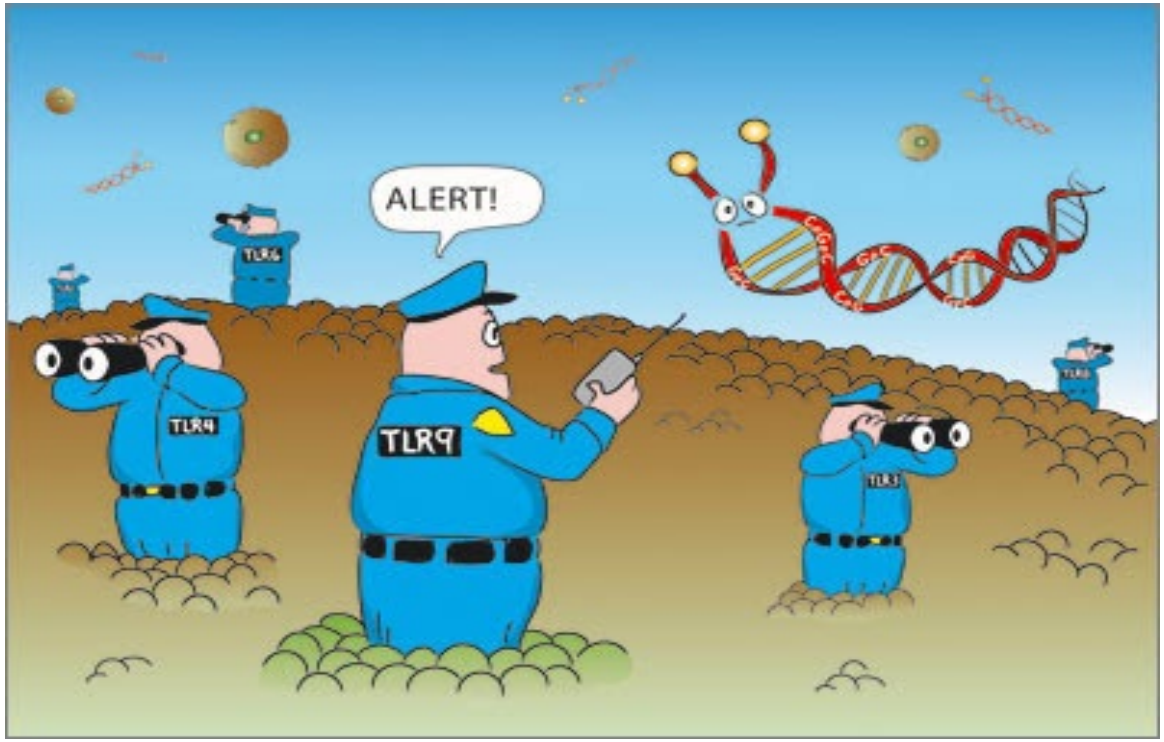
They look out for microbes (or their components)

They bind to the microbes (or their components)

They trigger a cascade of events to kill or protect against pathogens

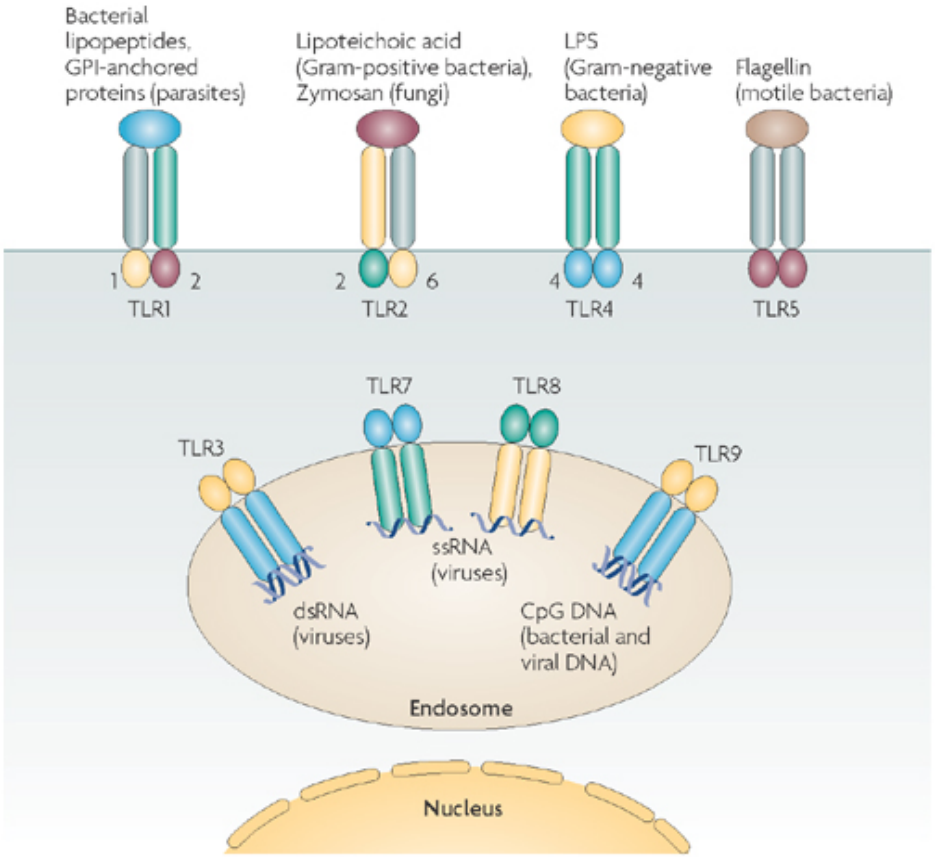
THEY ARE INNATE IMMUNE SENSORS

TLRs – look out for microbes



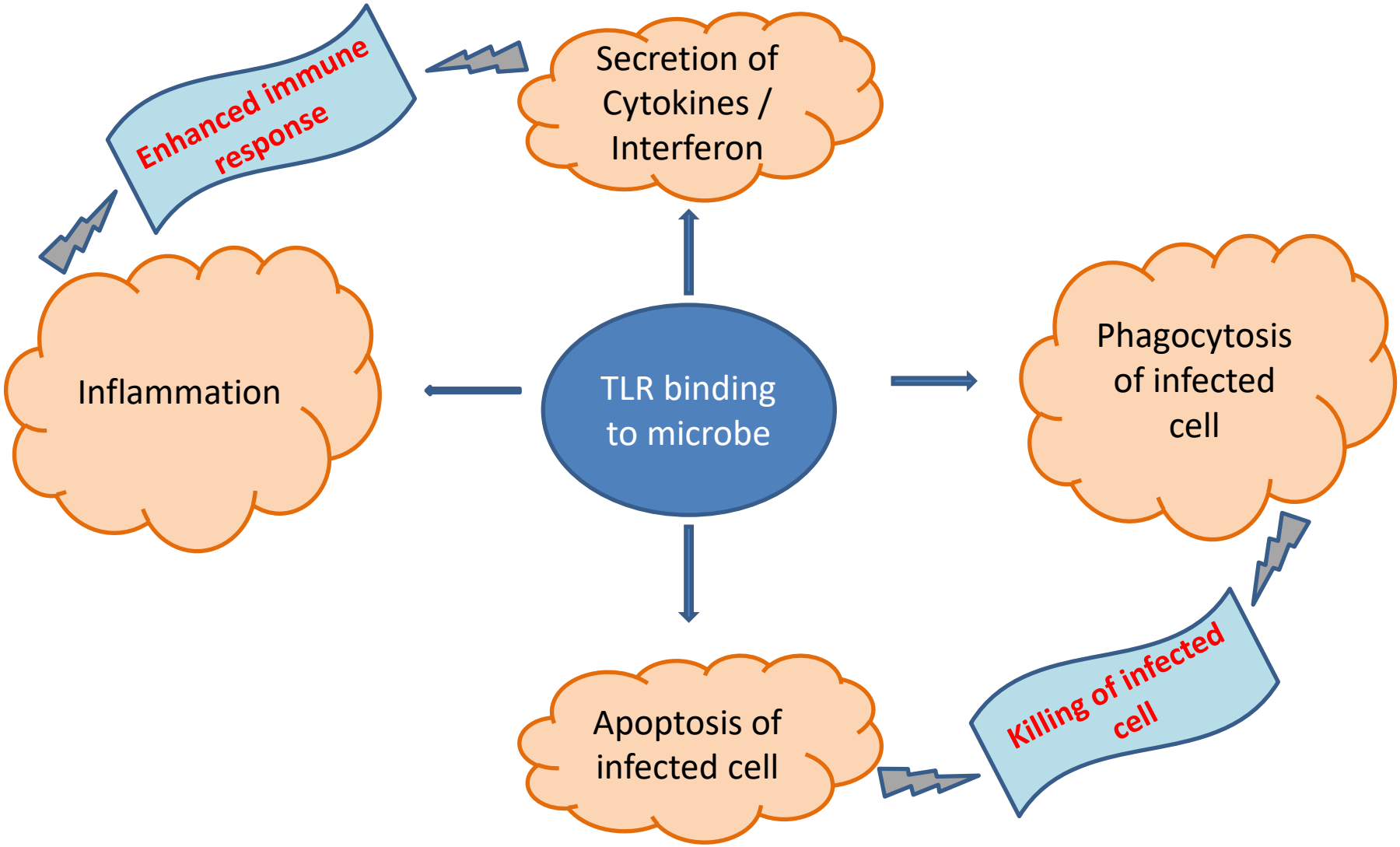
TLRs – bind to microbes / components of microbes

Which microbial components are recognized by TLRs ?



Nature Reviews | Drug Discovery

What happens when a TLR bind to a microbe ?

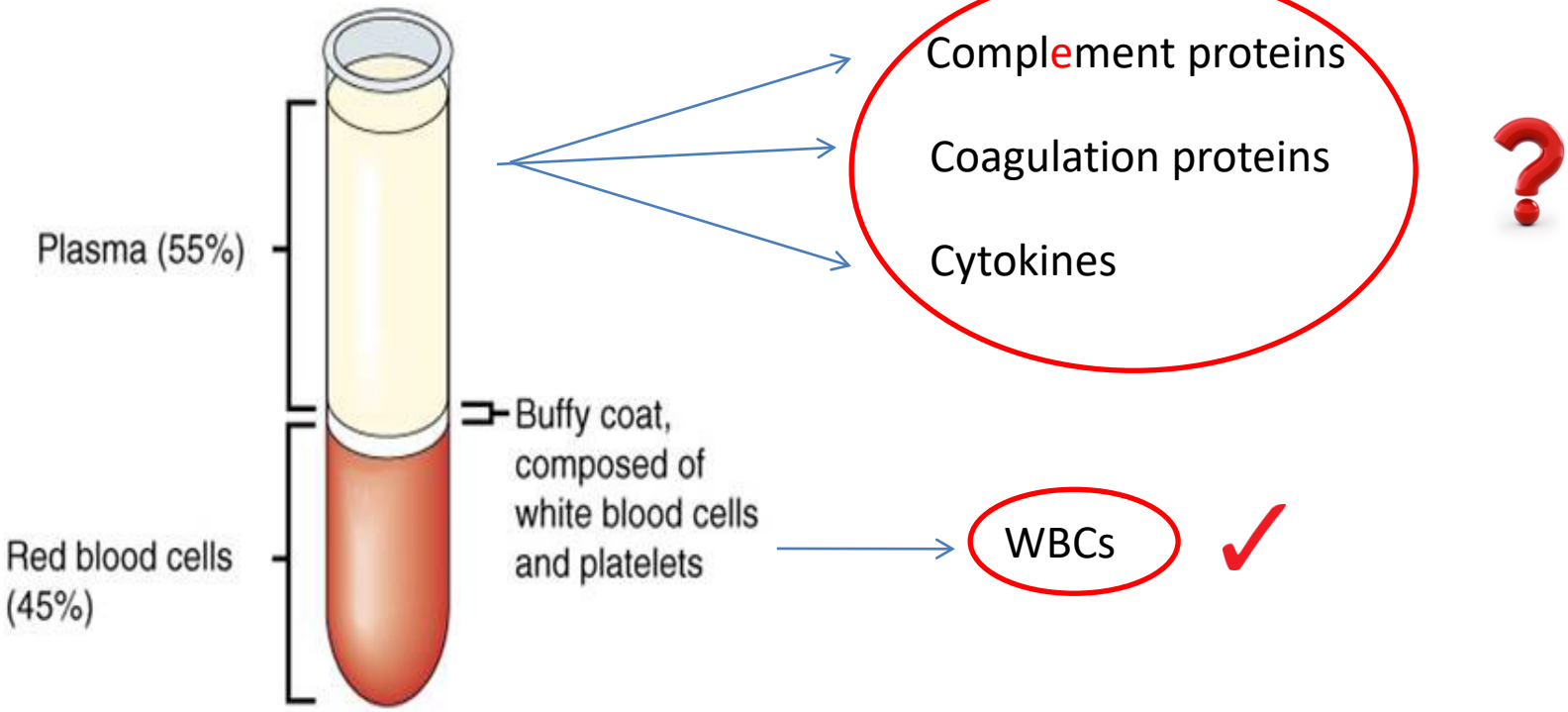


Summary: innate response – internal defenses – Cellular (WBCs)

Come into play when the external defenses are breached

- Neutrophils
- Monocytes /macrophages
- NK cells
- TLRs

Innate immune system: components of Blood



Cytokines

- Small proteins – secreted by cells of the immune system
- Affect the behaviour of other cells
- signalling molecules
- Key players in innate and acquired immunity

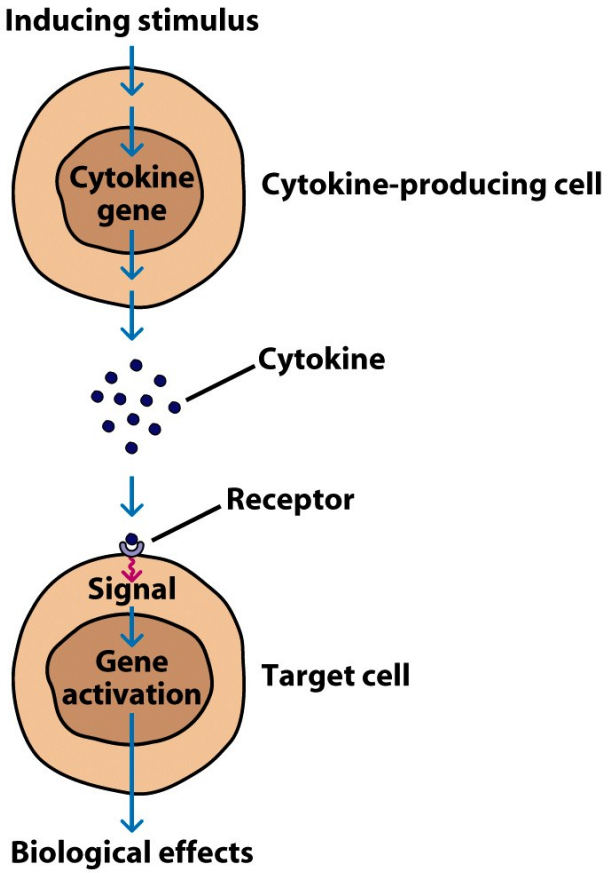


Figure 12-1a
Kuby IMMUNOLOGY, Sixth Edition

Which cells release cytokines ?

Cells of the immune system:

- Neutrophils – when they encounter a pathogen
- Macrophages – when they encounter a pathogen
- TLRs – bind to microbe / components of a microbe
- NK cells – on encountering a microbe infected cell /tumour cell
- Lymphocytes – when they are activated

Examples of cytokines

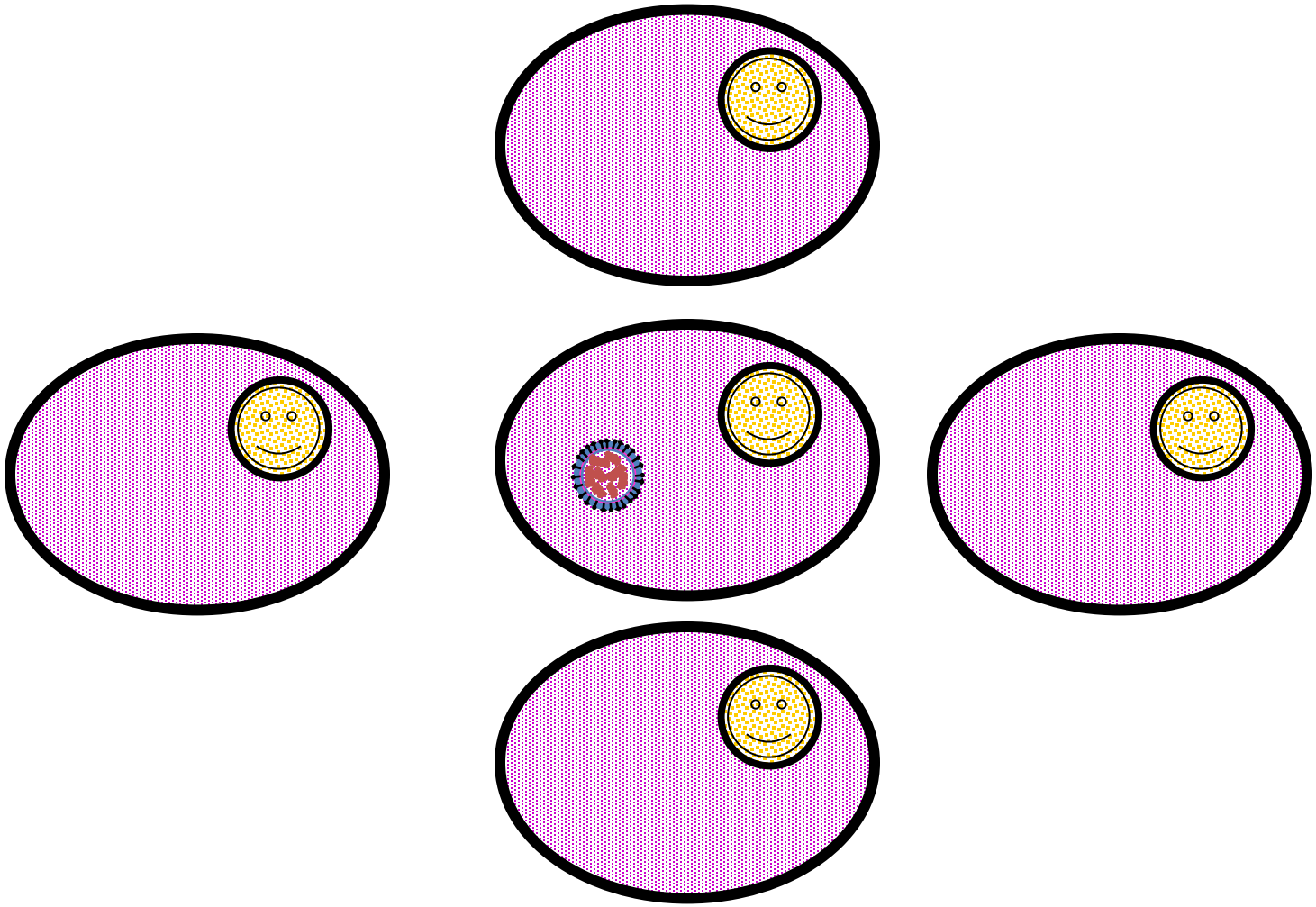
- **Interferons**
- **Interleukins**
- **Tumour necrosis factor (TNF)**

Interferons (IFN)

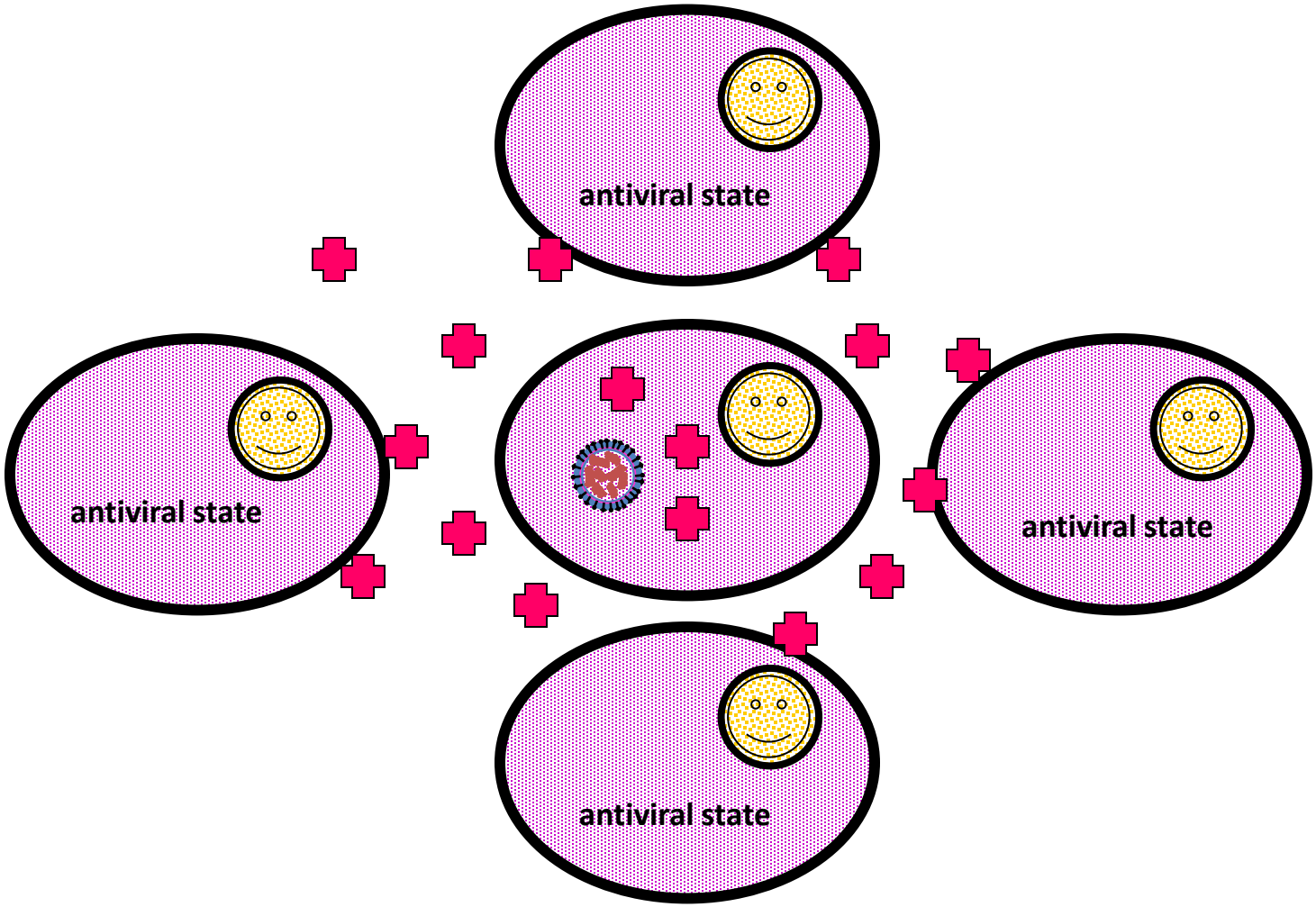
- Signalling proteins produced by by virus infected monocytes and lymphocytes
- Secreted proteins – Key anti-viral proteins
- “Interfere” with virus replication
- Warn the neighbouring cells that a virus is around...

- If we did not have IFNs – most of us may die of influenza virus infection

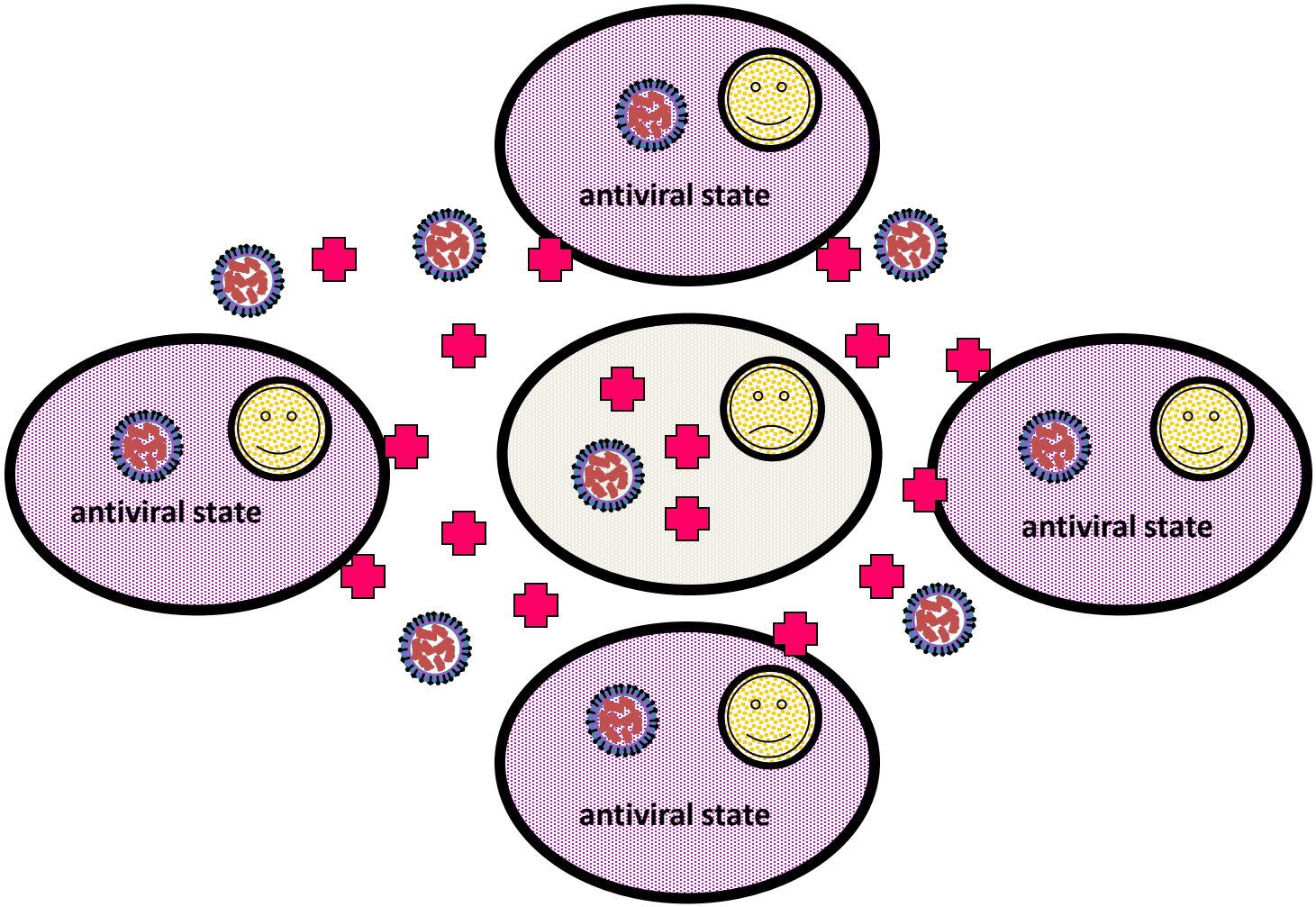
How does IFN warn the neighbouring cells ?



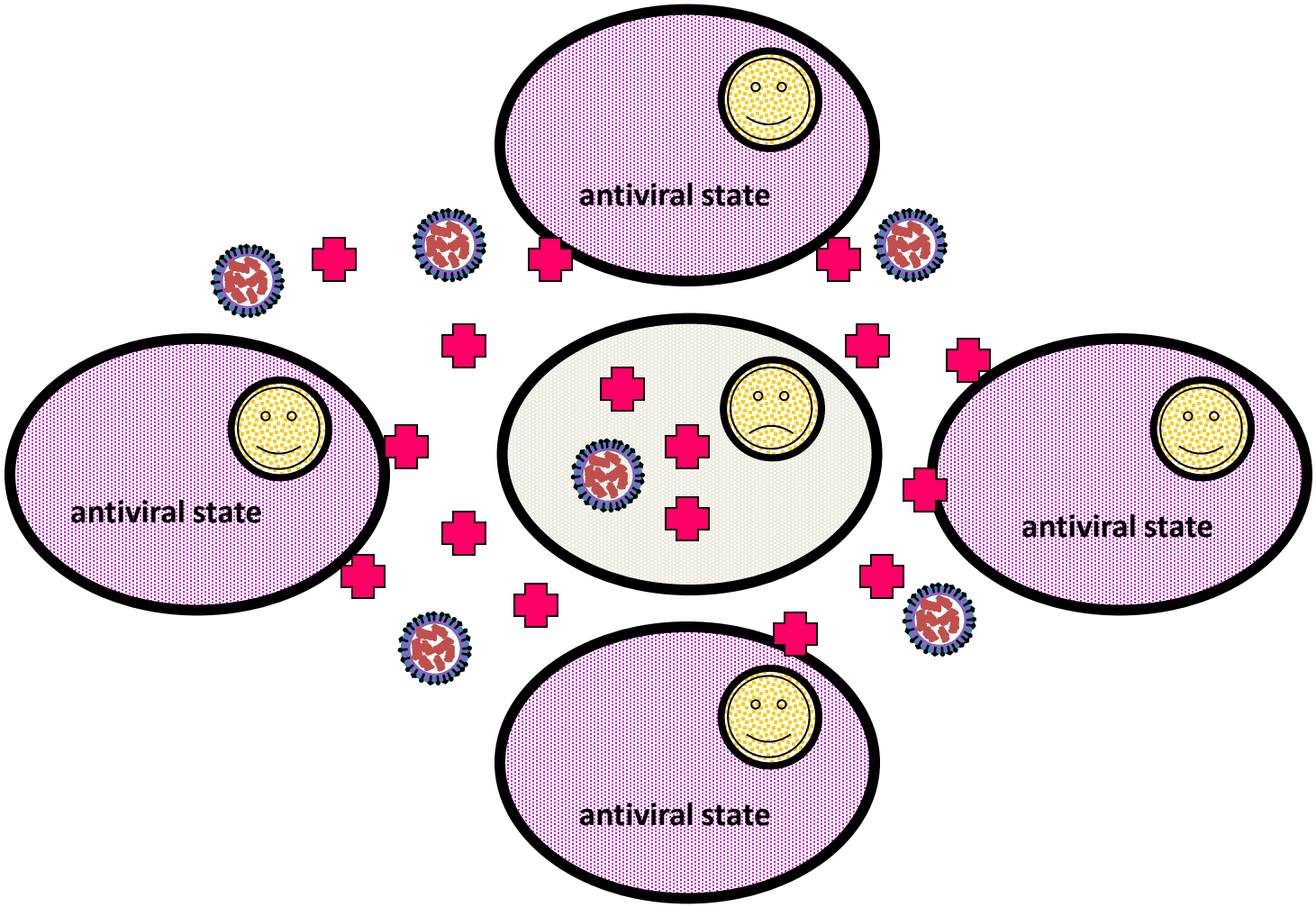
The infected cells release IFN



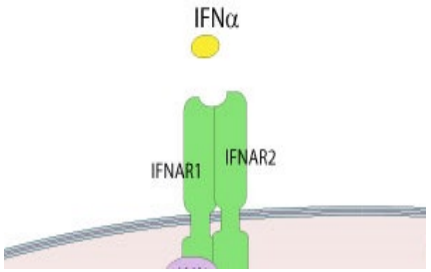
Virus infects the neighbouring cells



Prewarned cells are able to quickly inhibit the virus



How do interferons inhibit viruses ?



Induction

Host protein

Virus ds-RNA

Inactive host protein

Activation

Active host protein

Cascade of events

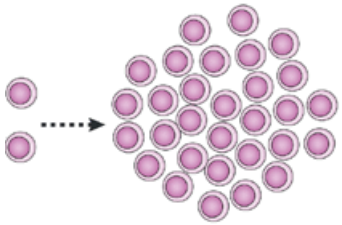
Inhibition of host protein synthesis

Virus cannot replicate

Interleukins

- Interleukins – 1-37
- Not stored inside cells
- Quickly synthesized and secreted in response to infection
- Key modulators of behaviour of immune cells
- Mostly secreted by T-lymphocytes & macrophages

What to interleukins do ?



Proliferation of immune cells

Inflammation

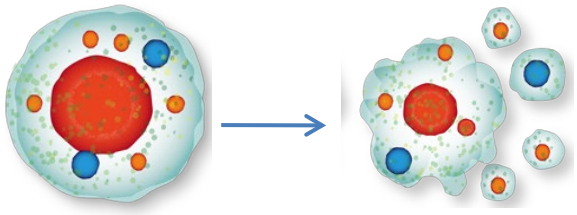
Interleukins

Increase antibody production

Activation of immune cells

Tumour necrosis factor (TNF)

TNF



Killing of cancer

Fever

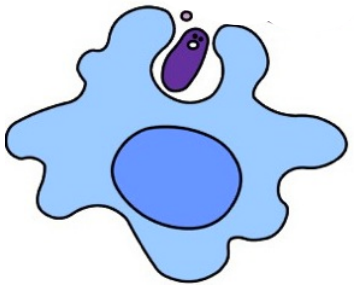
Inflammation

Complement (C`)

- a large number of distinct plasma proteins that react with one another (C1 thro' C9)
- Complement can bind to microbes and coat the microbes
- Essential part of innate immune response
- Enhances adaptive immune resposne (taught later)

Complement proteins: role in innate immune system

C`proteins

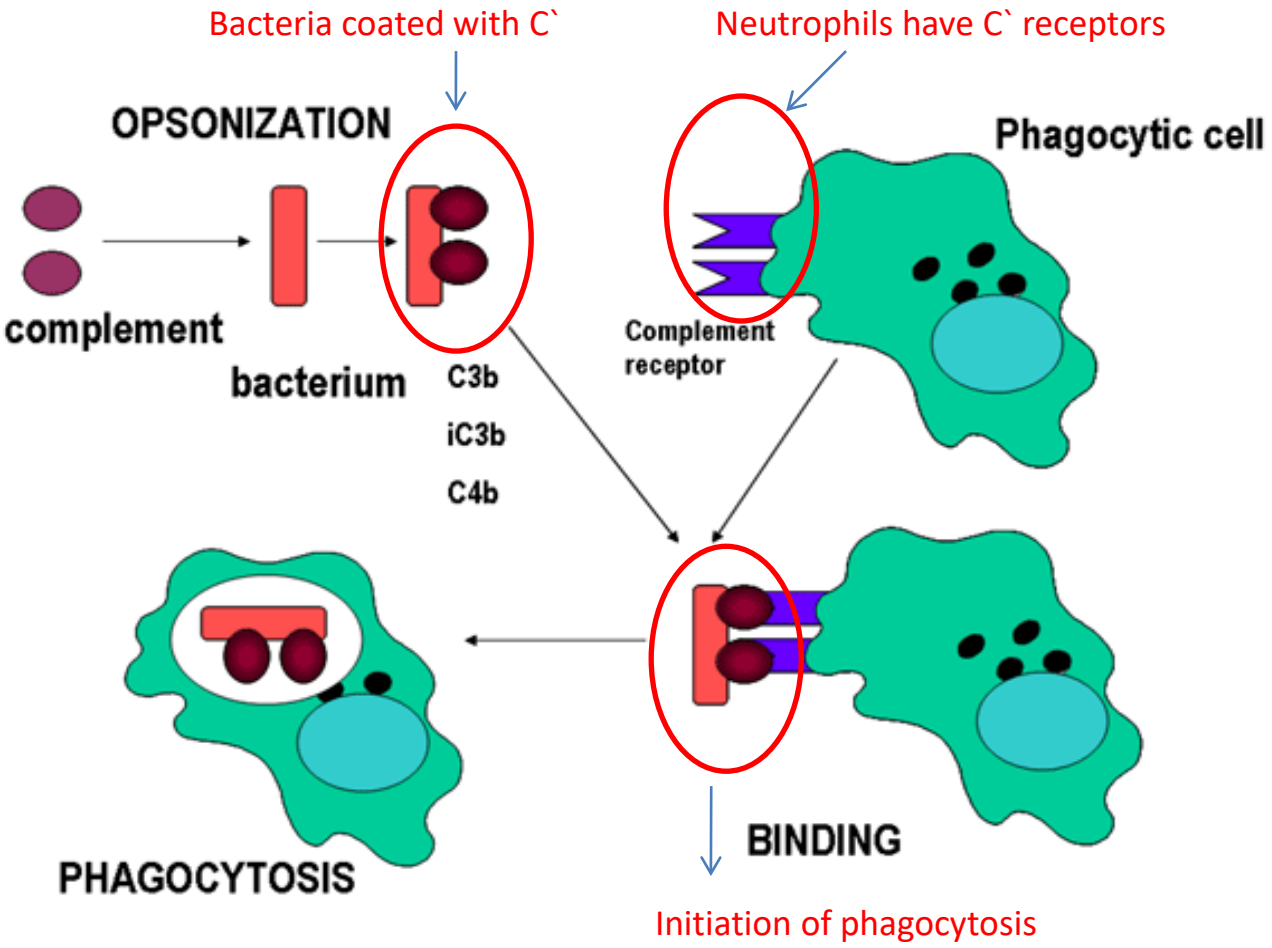


Facilitates phagocytosis

Direct lysis of pathogens

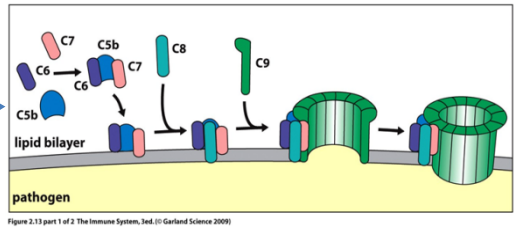
Inflammation

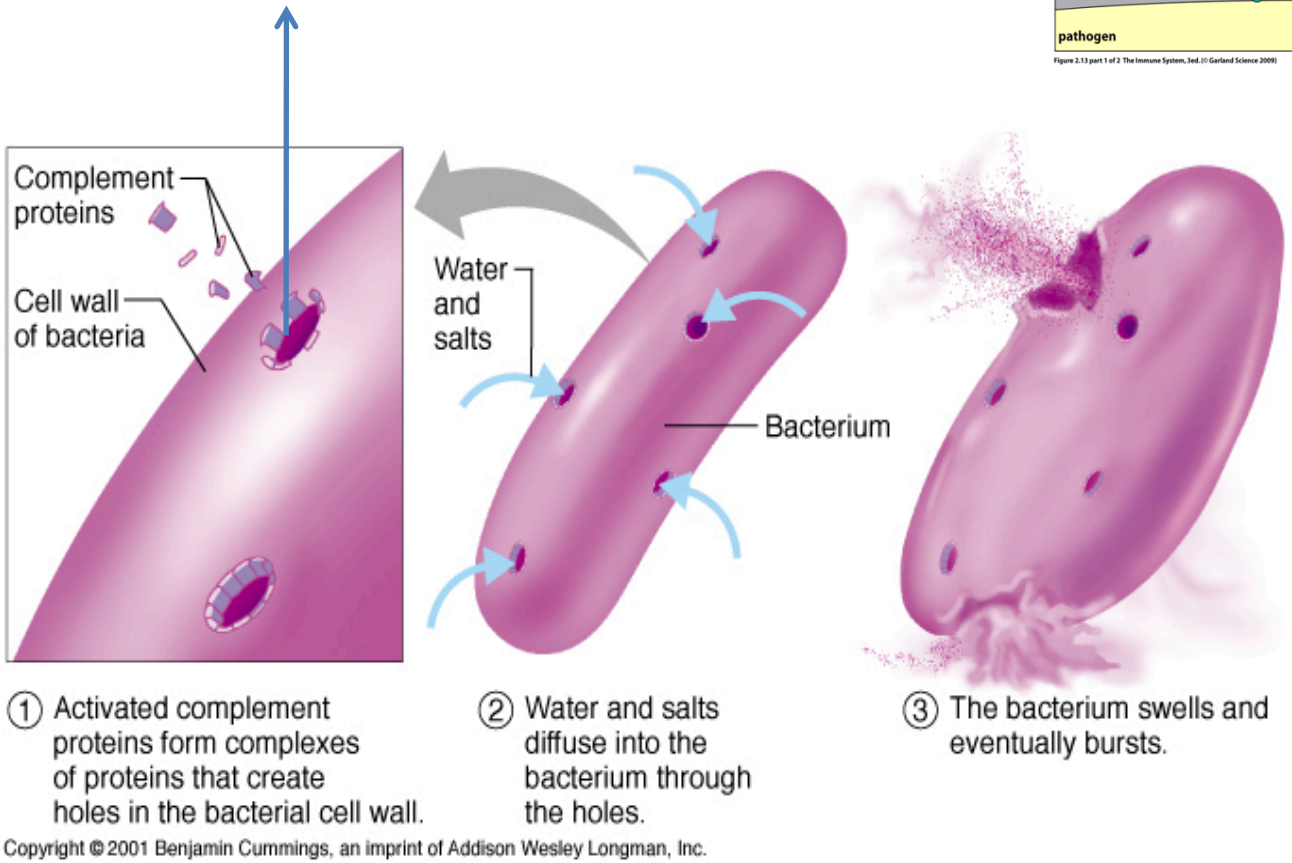
How do C` proteins facilitate phagocystosis ?



How do C` proteins lyse pathogens?

Membrane attack complex formed by c` proteins





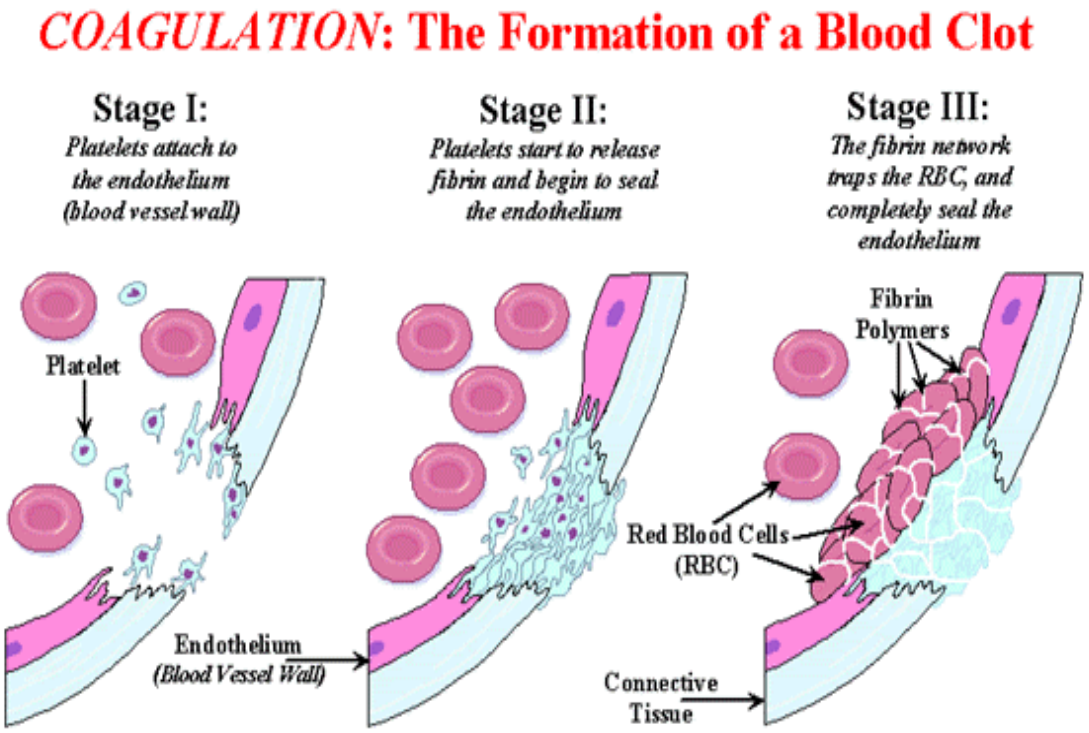
Coagulation proteins

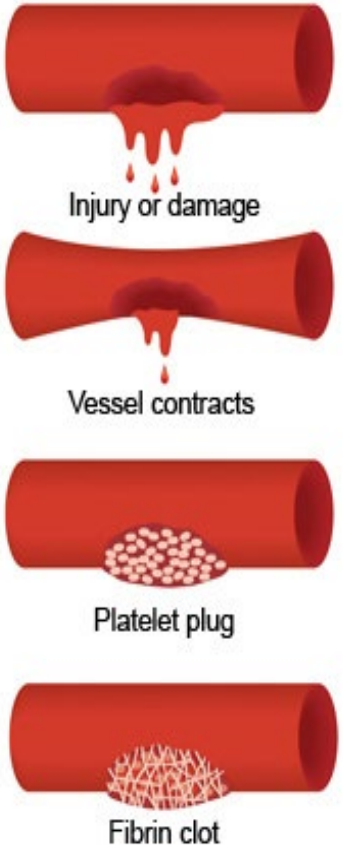
- Coagulation: mechanism to stop bleeding after injury to blood vessels

Complex pathway involves

- Platelets
- Coagulation factors
- Vitamin K

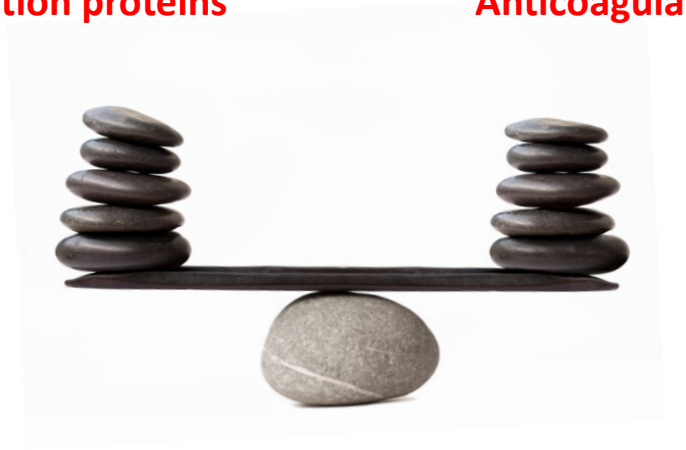
How does blood clot ?





Coagulation: Delicate balance

Coagulation proteins **Anticoagulants**



Blood clotting
Inflammation
Apoptosis (prog. Cell death)

Prevent blood clotting
Inhibit inflammation
Inhibit apoptosis

Too much of clotting – Problem
Too little clotting - Problem

→ **Maintenance of a balance**

Coagulation and innate immunity

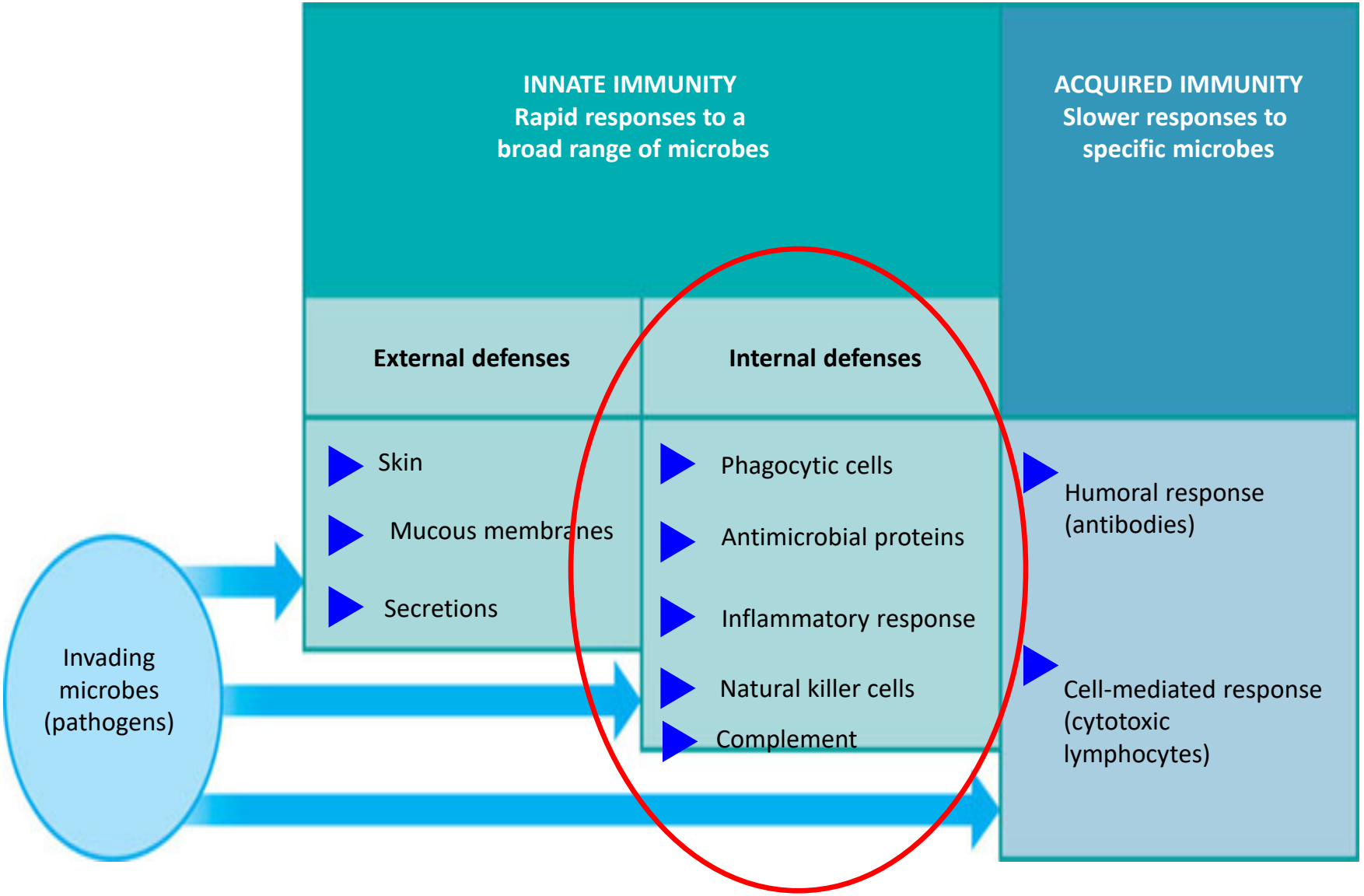
Pathogens and cytokines

Anticoagulants

Coagulation proteins

Increased inflammation and increased apoptosis of infected cells

Summary: what happens when external defenses fail ?



Summary: innate response – internal defenses

Cellular

- Neutrophils
- Monocytes /macrophages
- NK cells
- TLRs

Extracellular

- Cytokines
- Complement
- Coagulation

Introduction to the immune system

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Immunology: lecture 3

Inflammation

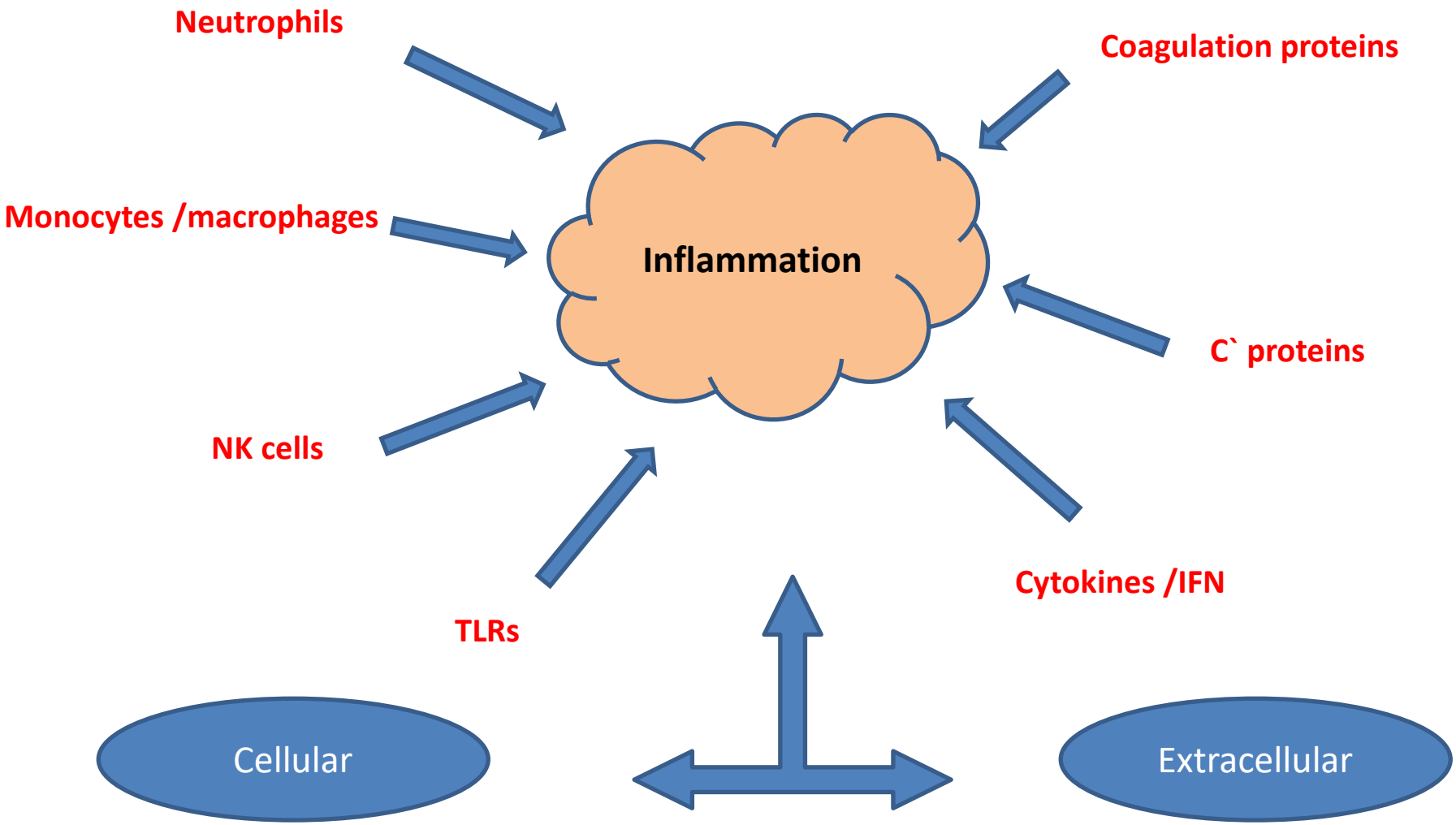
Antigens

Antibody

Inflammation

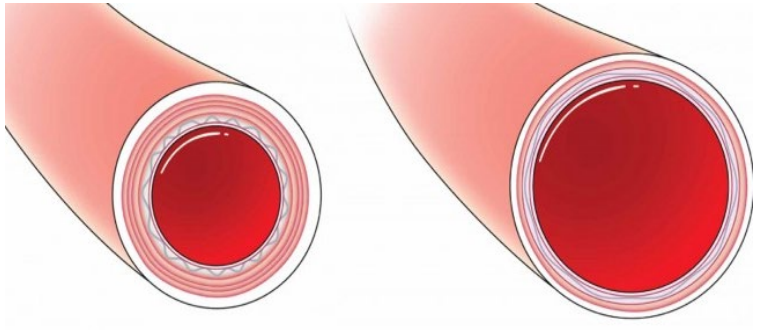
- Complex biological process by which body responds to pathogens and irritants
- Associated with swelling of tissue
- Key player in innate immune repsone

All roads lead to inflammation



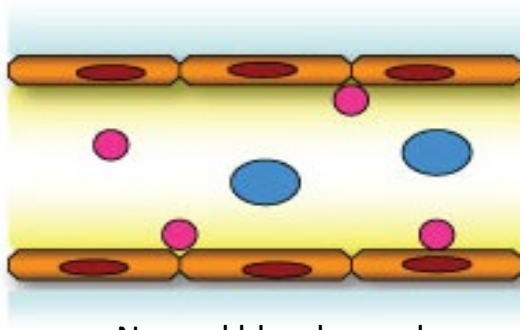
Inflammation and vascular changes

- **Vasodilatation**

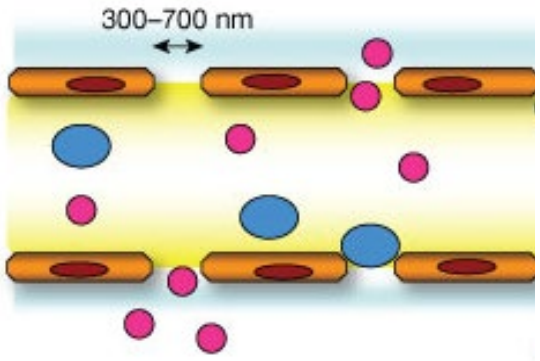


Normal blood vessel Dilated blood vessel

- **Increased capillary permeability**

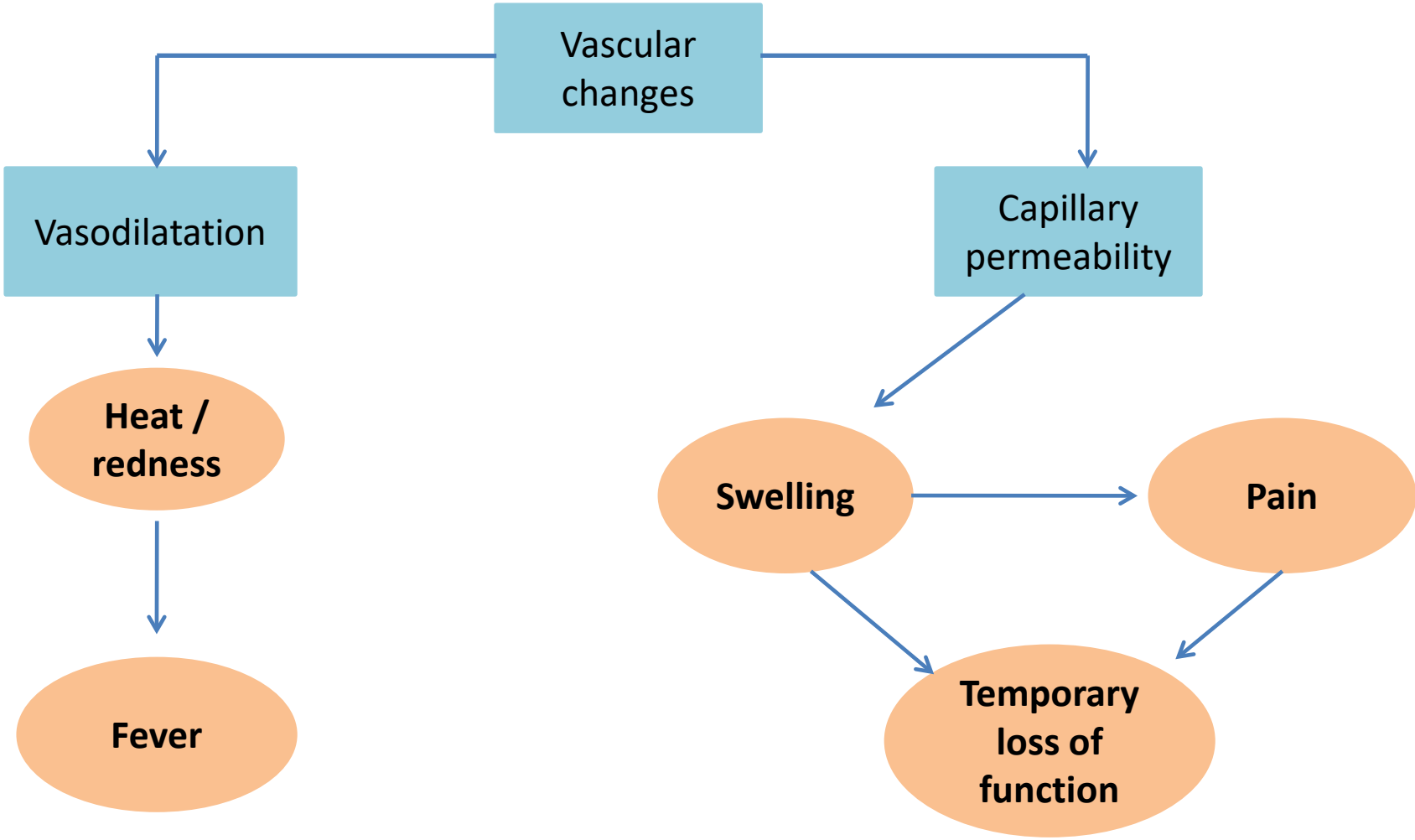


Normal blood vessel

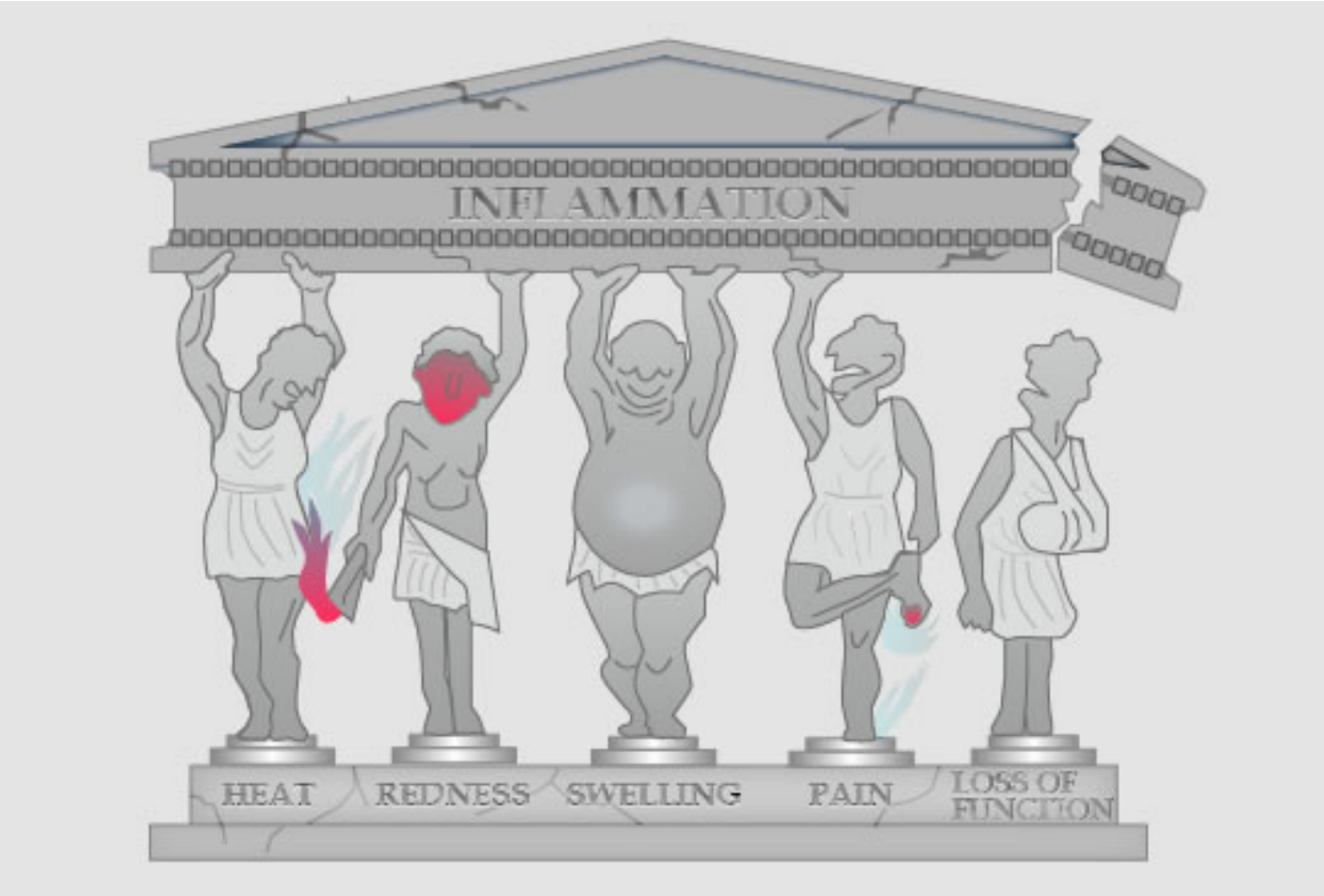


Leaky blood vessel

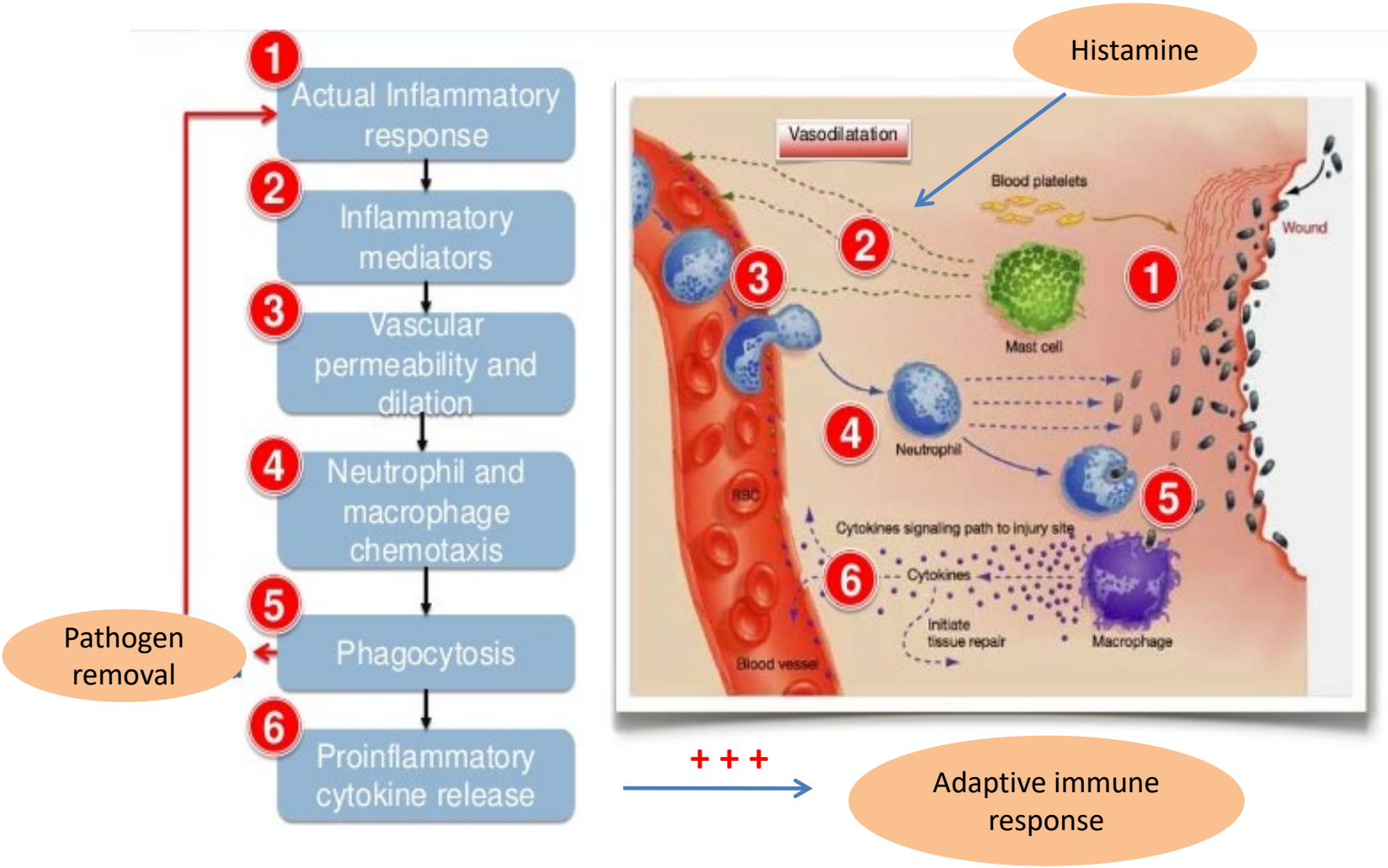
Signs of inflammation



Signs of inflammation



Inflammation and innate immunity



Mast cells – similar to basophils in blood;
mast cells are present in tissues and release histamines in response to wound / infection /irritant

Summary: role of Inflammation in innate immunity

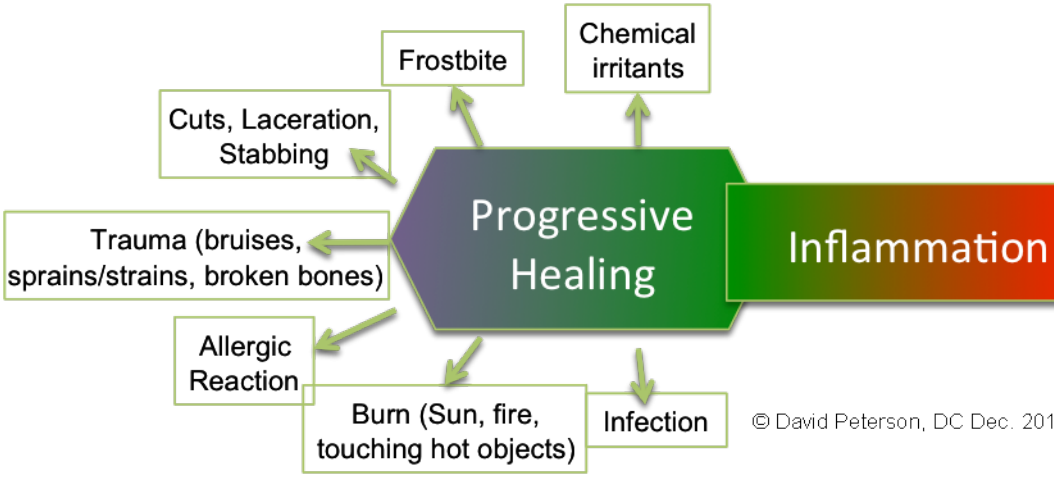
- Initiation of phagocytosis – killing of pathogen
- Limiting the spread of infection
- Stimulate adaptive immune response
- Initiate tissue repair

Not everything about Inflammation is good

The good and bad about inflammation

Acute /short-term -Good

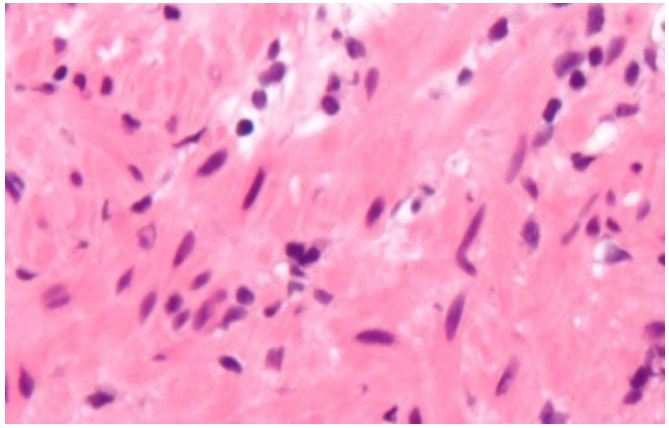
chronic /long-term - Bad



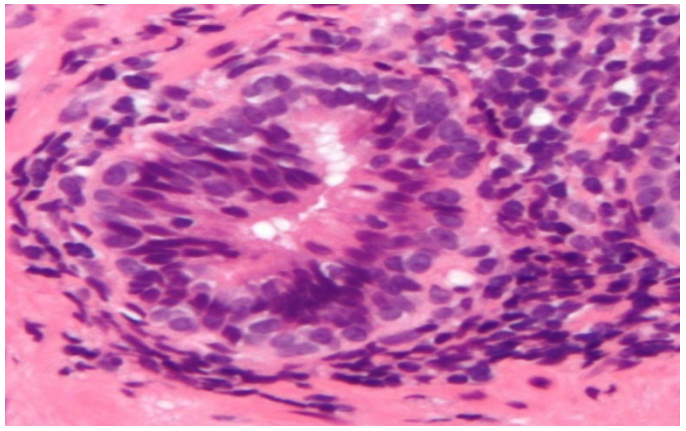
Chronic inflammation = tissue damage

- Chronic inflammation - macrophages in the injured tissue.
- Macrophages release toxins (including reactive oxygen species or ROS) that injure tissues
- chronic inflammation is almost always accompanied by tissue destruction.

Normal tissue

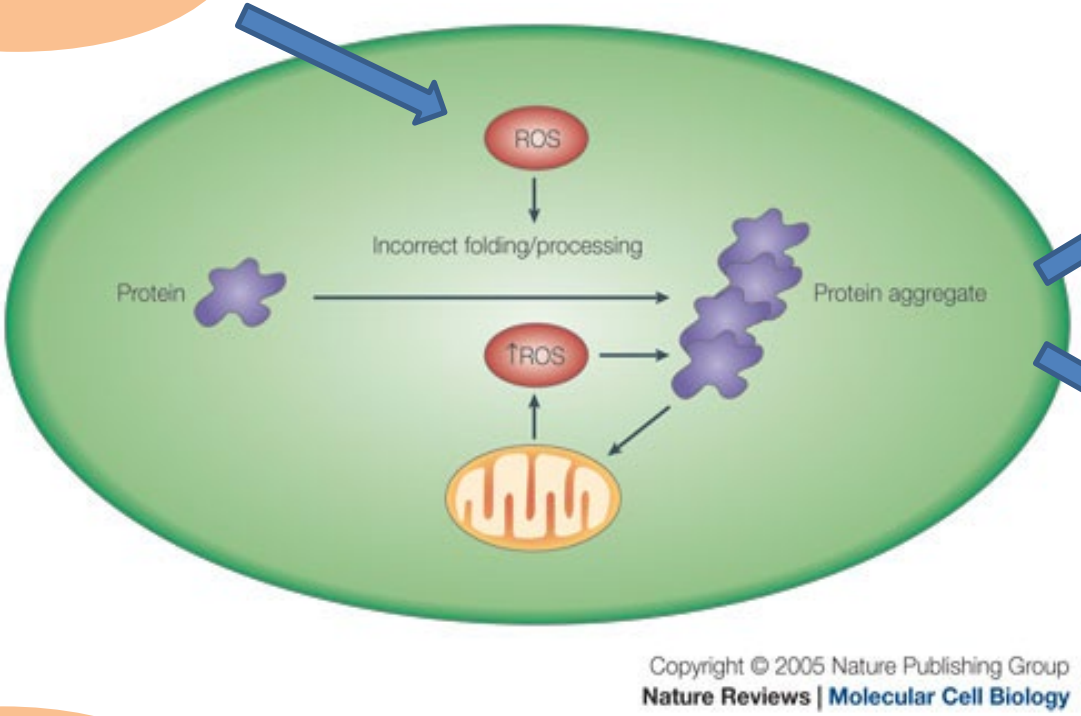


Tissue : chronic inflammation



Chronic inflammation and tissue damage

Chronic inflammation



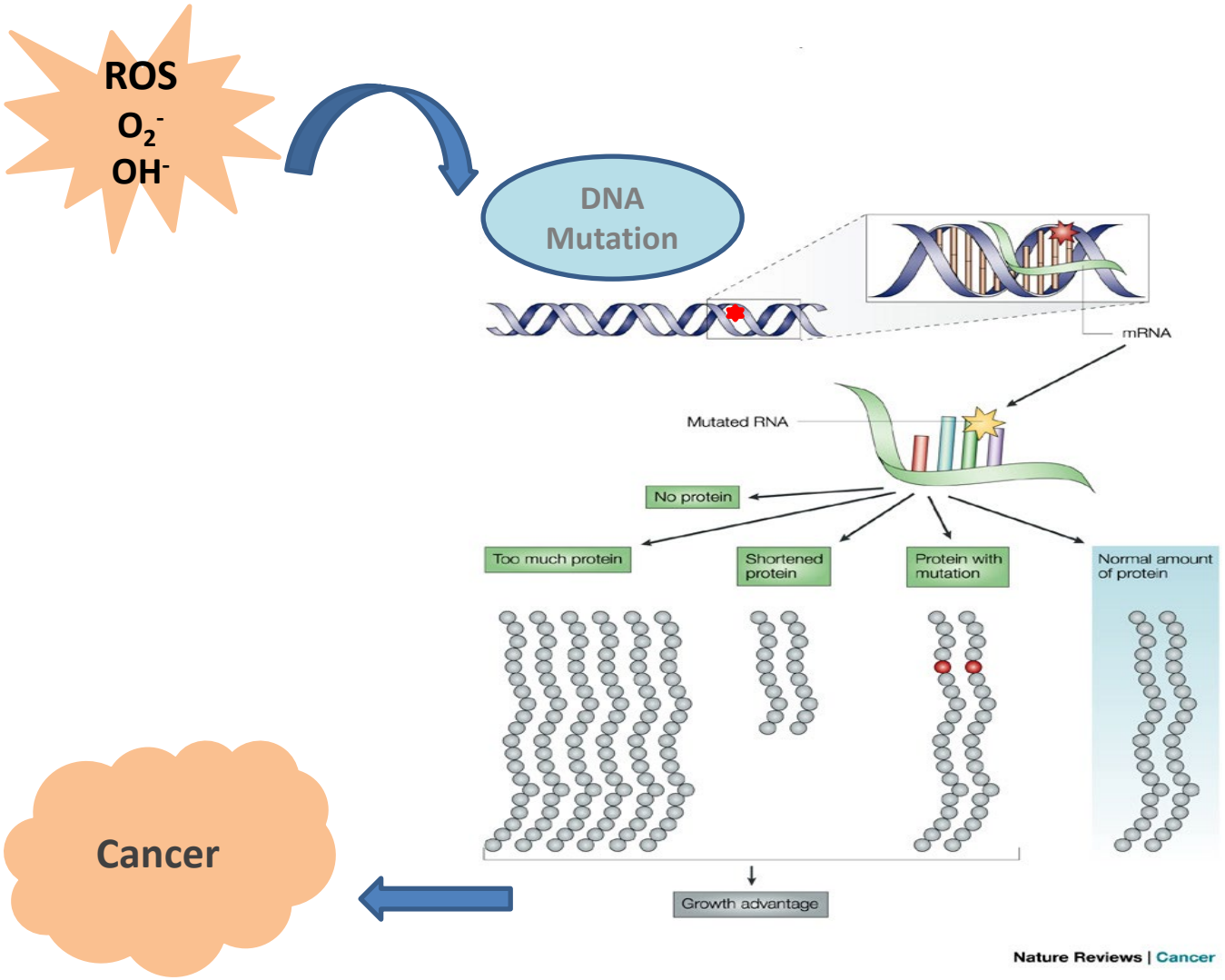
Reduced tissue function

Tissue damage

Activation of immune cells

Killing of host cells

Chronic inflammation and Cancer



Immunogens / Antigens

Immunogens and antigens

- **Immunogen / antigen:** a substance that elicits an immune response [i.e. a humoral (antibody response) or cell-mediated immune response]

⇨ **Immune** response **gen**erator

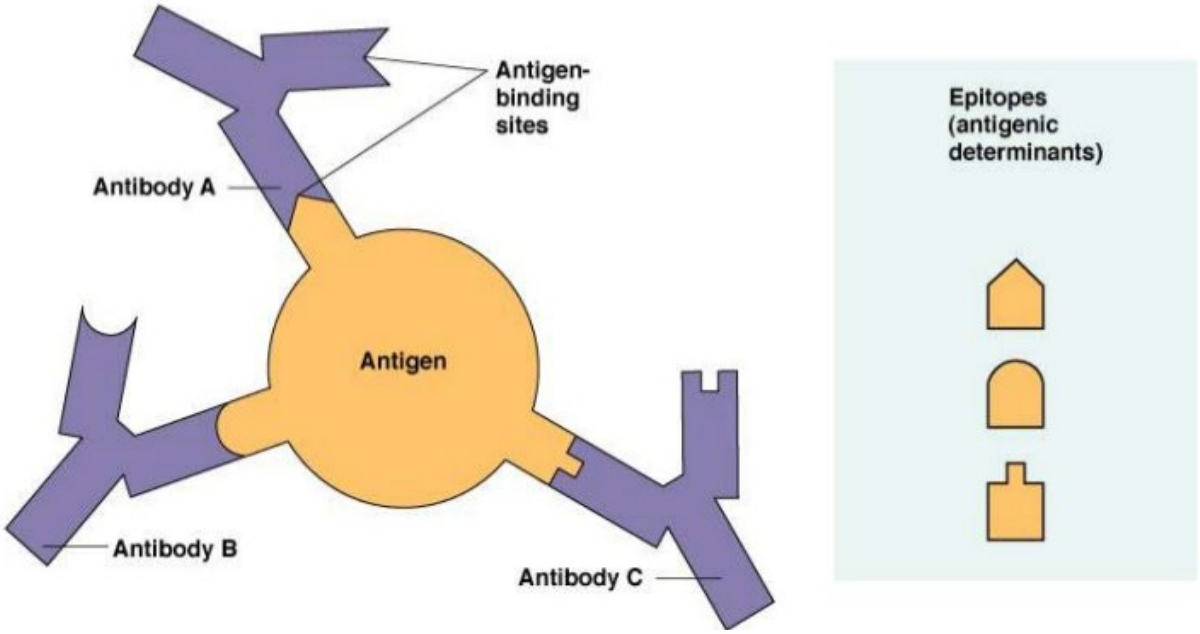
Though the two terms are used interchangeably – there are differences between the two

Epitope

- **Epitope:** the portion of an antigen that is recognized and bound by an antibody (Ab) or a T-cell receptor (TCR)

- epitope = antigenic determinant

Epitopes



- **Epitope: the portion of an antigen that is recognized and bound by an Ab or a T Cell receptor**

One protein may have multiple antigenic determinant

Epitopes

- B-cell Epitopes – recognized by B-cells
- T-cell Epitopes – recognized by T cells

Immunogenicity

- **Immunogencity:** is the ability to induce a humoral (antibody) and/or cell-mediated immune response.

- Weak immunogens
- Strong immunogens

What determines immunogenicity ?

- **Foreignness:** essential for immunogenicity (self-responsive immune cells are eliminated during lymphocyte development)
- **Size:** Bigger>Smaller
- **Chemical composition:** Proteins > nucleic acids / polysaccharides / lipids
- **Structure:** Primary /secondary /tertiary structures play a role
- **Physical form:** Particulate> Soluble

Host factors affecting immunogencity

- Difference across species (interspecies)

- Differences within a species (intraspecies)
  - Responders / non-responders to vaccine
  - differences in disease severity in epidemics

⇨ **Genetics**

⇨ **Age**

Isoantigens

- **Isoantigens:** Antigens present in some but not all members of a species
- Blood group antigens – basis of blood grouping
- MHC (major histocompatibility complex)- cell surface glycoproteins

Autoantigens

- Autoantigens are substances capable of immunizing the host from which they are obtained.
- Self antigens are ordinarily non-antigenic
- Modifications of self-antigens are capable of eliciting an immune response

Haptens

- **Haptens are small molecules which are non-immunogenic, thus could never induce an immune response by themselves.**

Examples of haptens

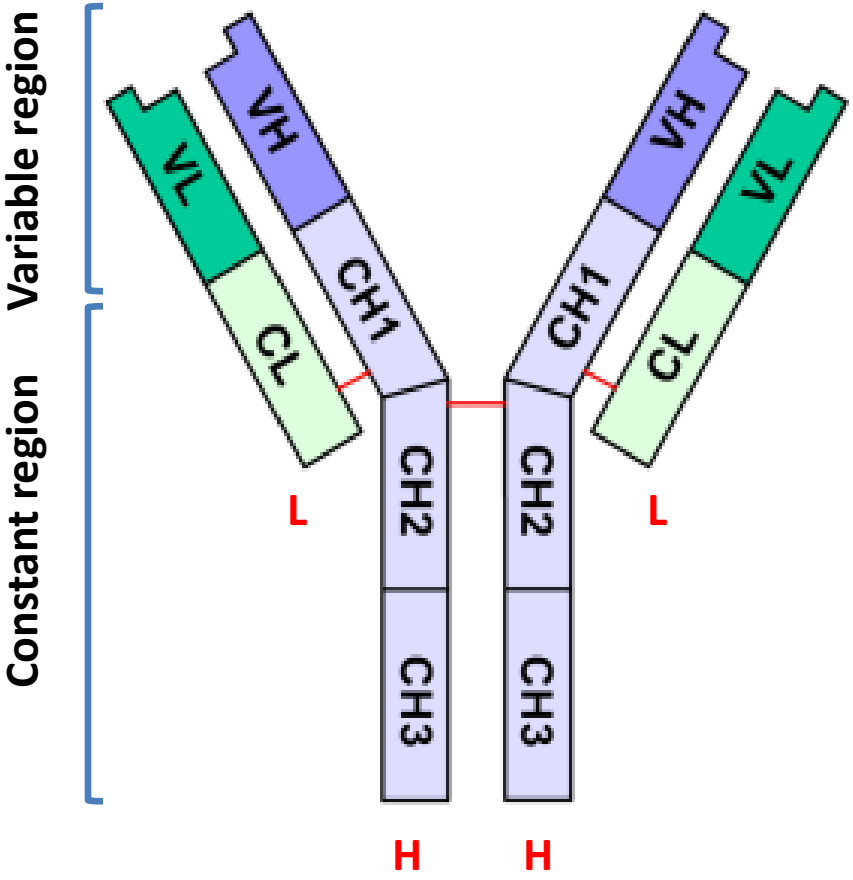
⇨ **DO NOT ELICIT an immune response by themselves**

Immunogens / Antigens

What is an antibody?

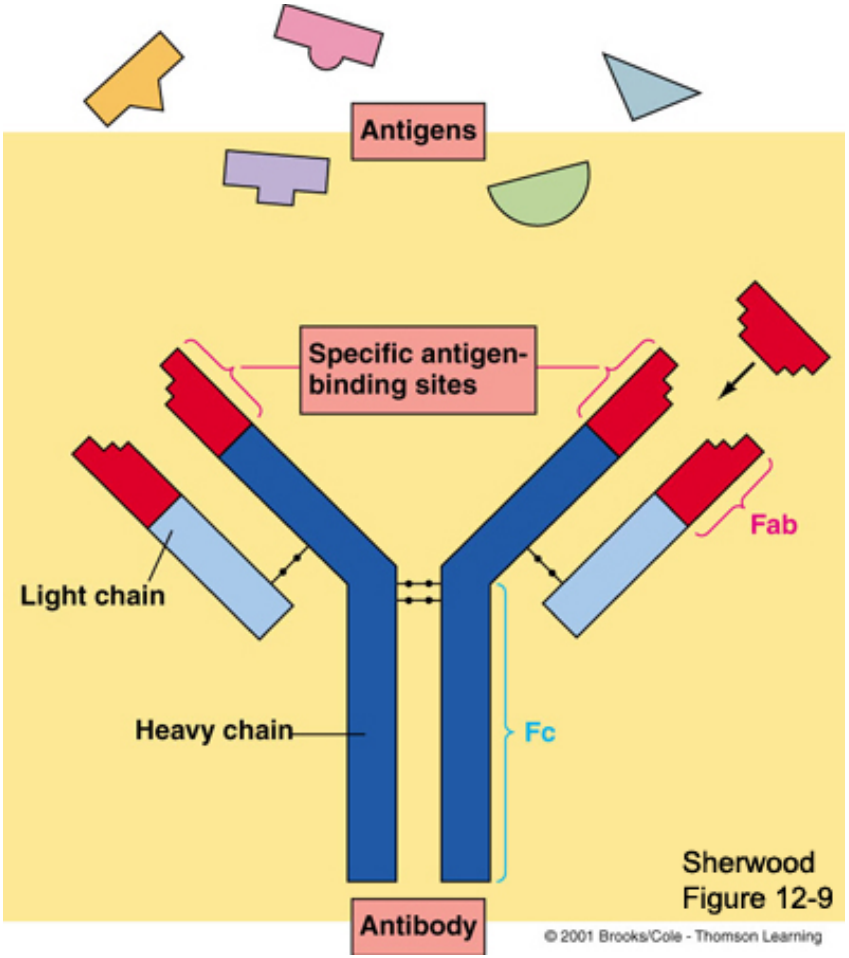
- Produced by Plasma cell (B-lymphocytes producing Ab)
- Essential part of adaptive immunity
- Specifically bind a unique antigenic epitope (also called an antigenic determinant)
- Possesses antigen binding sites
- Members of the class of proteins called immunoglobulins

What does an antibody look like ?



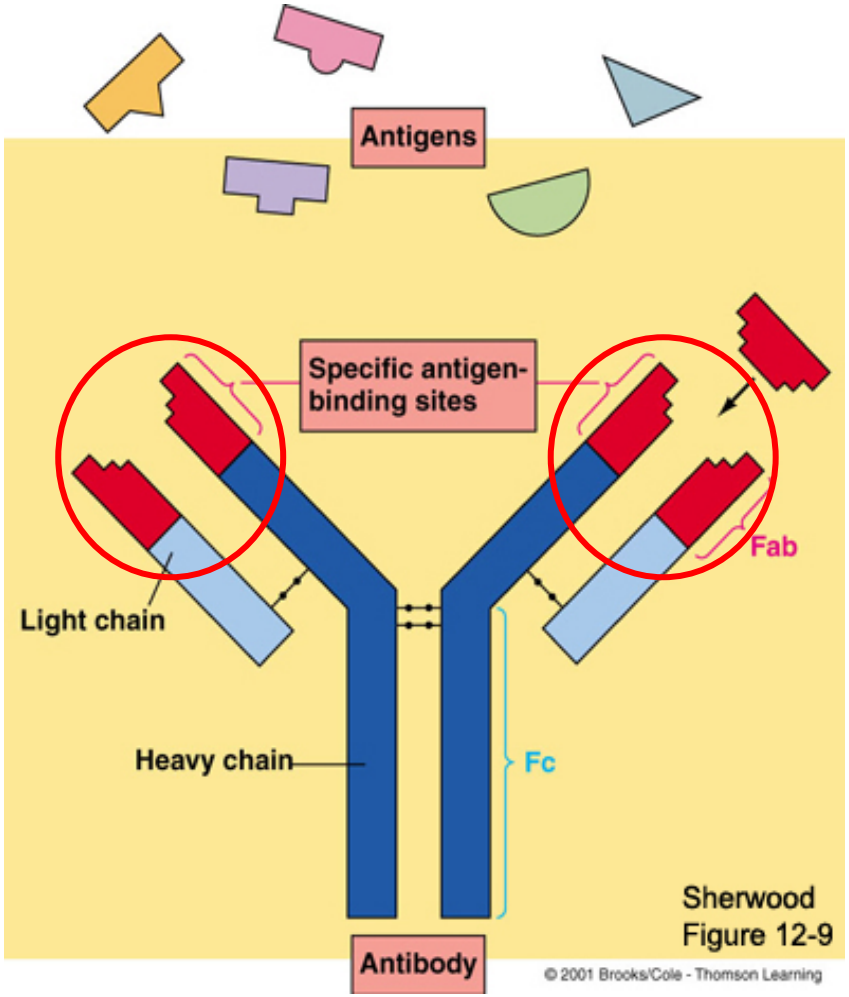
- 2 identical heavy chains
- 2 identical light chains
- Each heavy chain – has a constant and a variable region
- Each light chain has a constant and a variable region

Antibody: structure and function



- Fab – fragment antigen binding
- Fc- Fragment constant

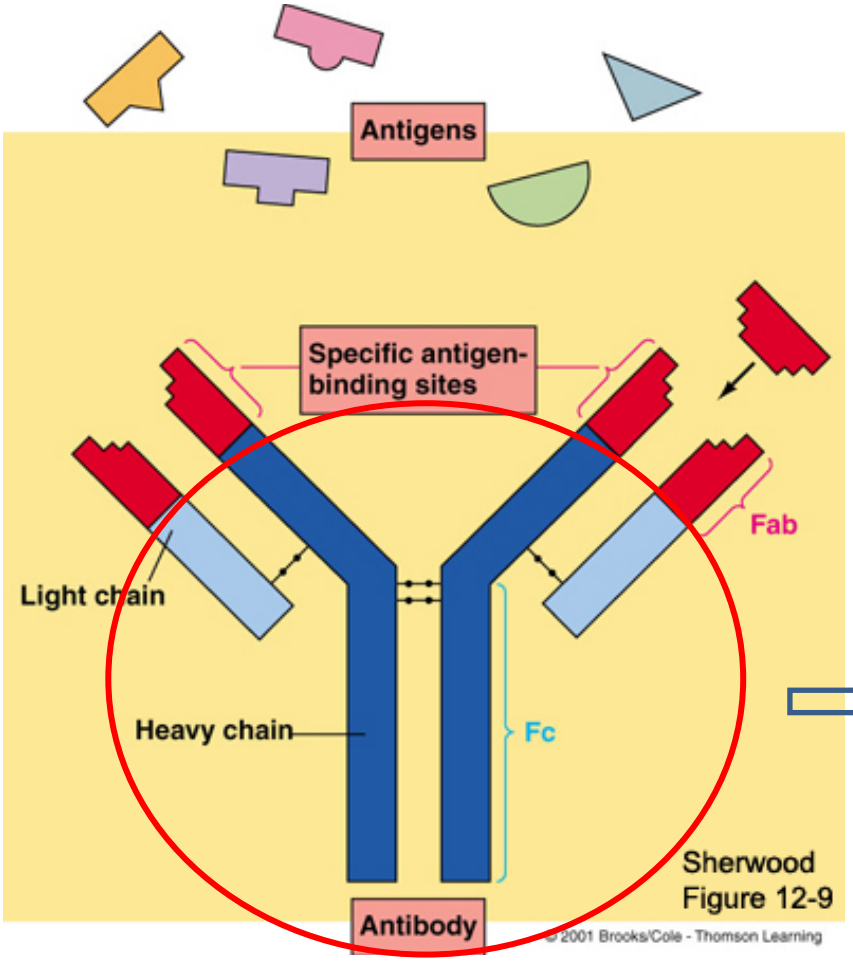
Antibody: Fab



Fab region

- Variable region of the antibody
- Tip of the antibody
- Binds the antigen
- Specificity of antigen binding determined by V_H and V_L

Antibody: Fc



Fc region

- Constant region
- Base of the antibody
- Can bind cell receptors and complement proteins

Antibodies exist in two forms

- Antibodies occur in 2 forms
  - Soluble Ag: secreted in blood and tissue
  - Membrane-bound Ag: found on surface of B-cell, also known as a B-cell receptor (BCR)