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Pathophysiology of chronic inflammation, ethiopathogenesis, consequences, systemic inflammation, SIRS, MODS

Julie Dobrovolná

Immune system

- **Immune system** = cells, tissues and molecules that mediate resistance to infections
- **Immunology** = study of the structure and function of the immune system **Immunity** = host resistance to pathogens and their toxic effects
- **Immune response** = collective and coordinated response to the introduction of foreign substances into an individual mediated by cells and immune molecules system

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The role of the immune system

- Defense against microbes
- Defense against tumor cell growth kills tumor cell growth
- Homeostasis of destruction of abnormal or dead cells (e.g. dead red or white blood cells, antigen-antibody complex)

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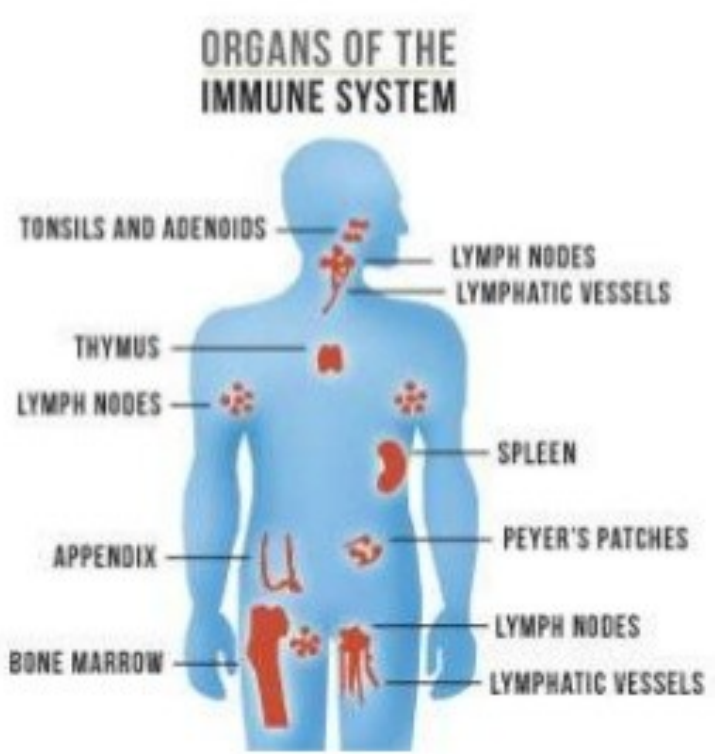
The components of the immune system

Major Components of the Immune System:



Organs related to our Immune System

- Tonsils
- Adenoids
- Lymph Nodes
- Lymphatic Vessels
- Thymus
- Spleen
- Appendix
- Peyer's Patches
- Bone Marrow

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The type of immune response

- **Innate (non-adaptive):** the first-line immune response relies on mechanisms that existed before infection

- **Acquired (adaptive) immunity:** The second line of response (if innate immunity fails) relies on mechanisms involving cellular memory of key T- and B-lymphocytes

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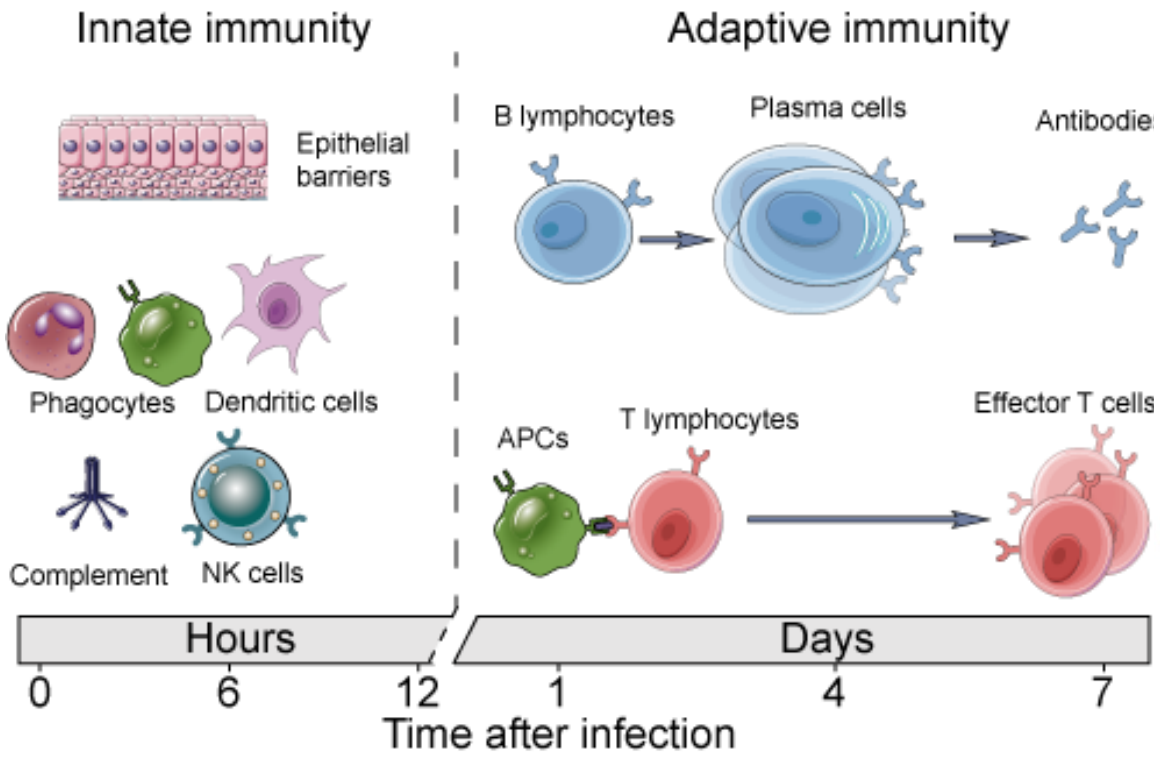
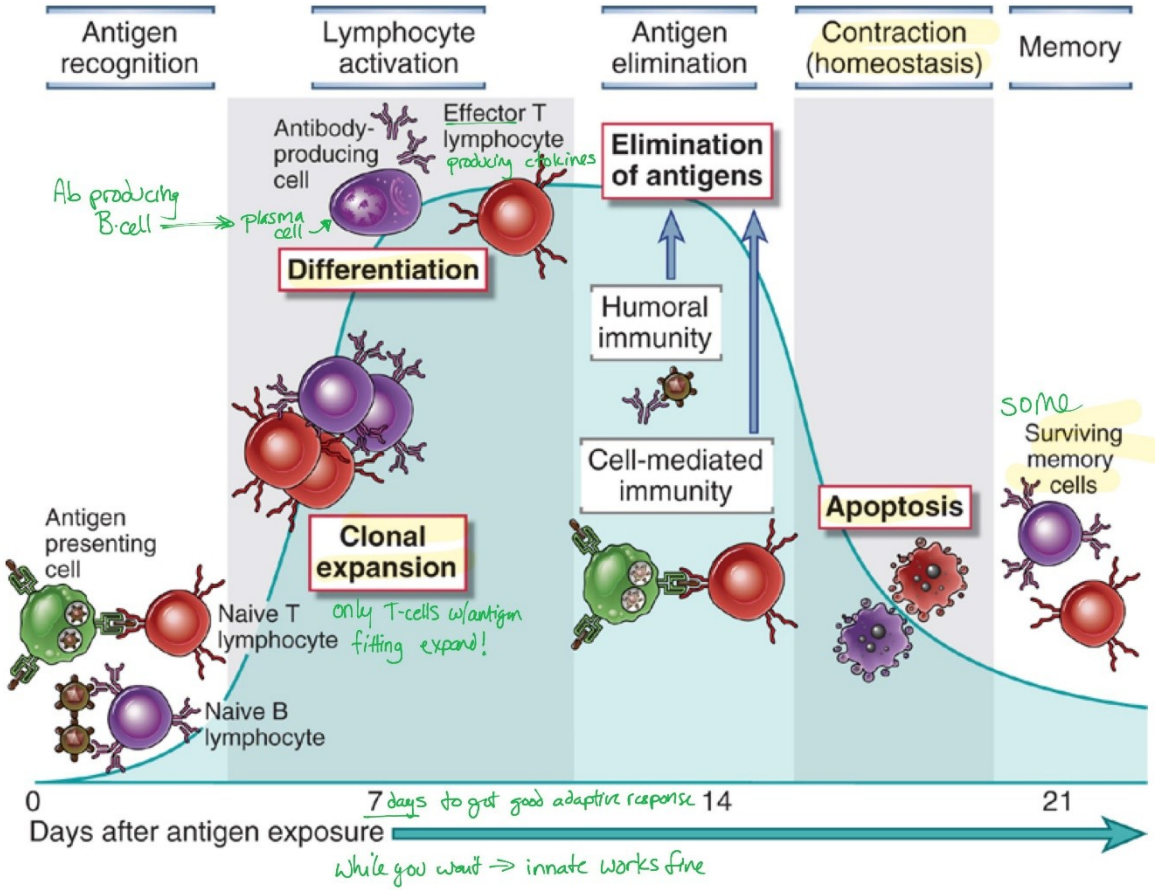
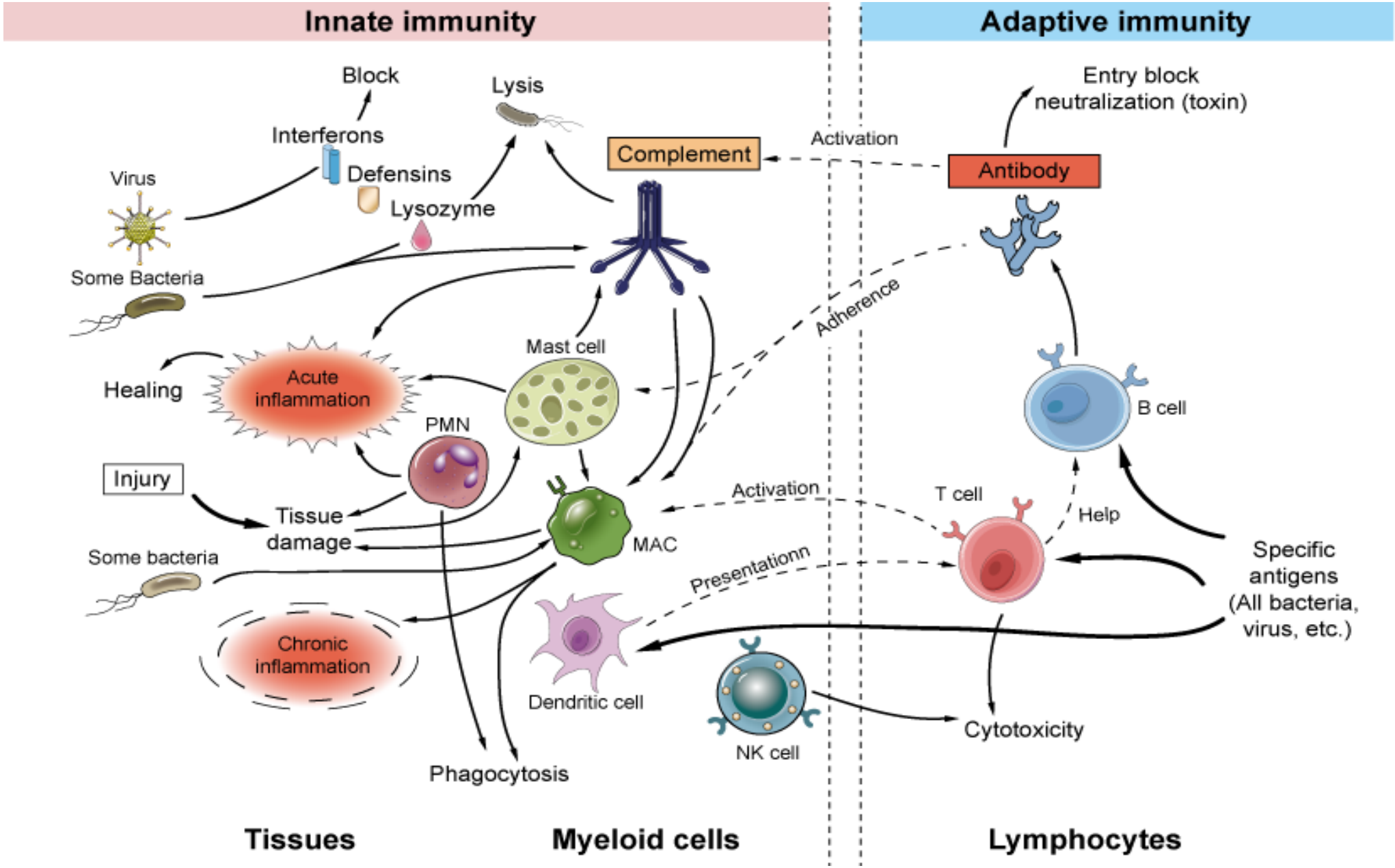
Timeline


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


Antigen recognition
Lymphocyte activation
Antigen elimination
Contraction (homeostasis)
Memory
Antibody-producing cell
Effector T lymphocyte
Elimination of antigens
Ab producing B-cell
plasma cell
Differentiation
Humoral immunity
Cell-mediated immunity
Apoptosis
Surviving memory cells
Clonal expansion
Antigen presenting cell
Naive T lymphocyte
only T-cells w/antigen fitting expand!
Naive B lymphocyte
0
7 days to get good adaptive response
14
21
Days after antigen exposure
while you wait → innate works fine


Innate immunity
Adaptive immunity
Block
Lysis
Interferons
Defensins
Lysozyme
Virus
Some Bacteria
Complement
Activation
Entry block
neutralization (toxin)
Antibody
Adherence
Mast cell
Healing
Acute
inflammation
PMN
B cell
Injury
Tissue
damage
Activation
T cell
Help
MAC
Some bacteria
Presentationn
Specific
antigens
(All bacteria,
virus, etc.)
Chronic
inflammation
Dendritic cell
NK cell
Cytotoxicity
Phagocytosis
Tissues
Myeloid cells
Lymphocytes

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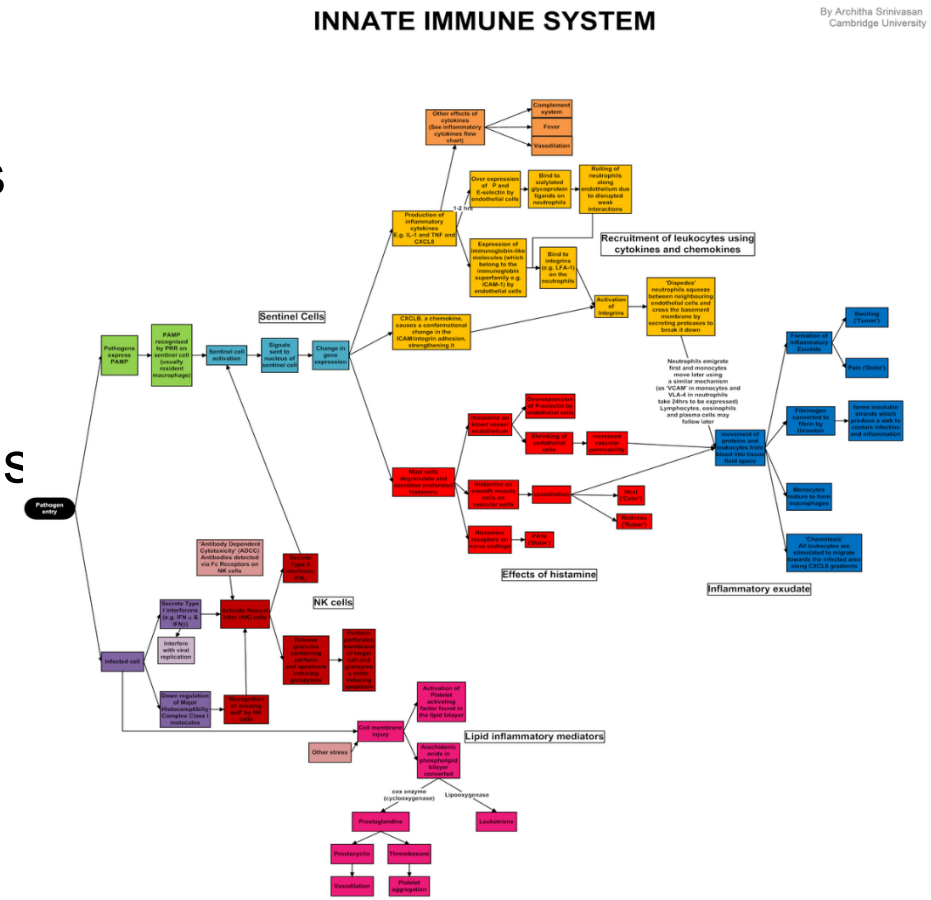
Innate immunity

- Based on genetic background
- Relies on existing system components
- Rapid response: within minutes of infection
- Not specific: the same molecules / cells respond to many pathogens
- No memory: the same response after repeated exposure
- Does not lead to clonal expansion



Innate immunity mechanisms

- Mechanical barriers / excretion on the skin surface, acidic pH in the stomach, cilia
- Humoral mechanisms
- Lysozymes, basic proteins, complement, interferons
- Mechanisms of cell defense by natural killers (NK cells) neutrophils, macrophages, mast cells, basophils, eosinophils

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Adaptive immunity

- Based on resistance acquired during life
- Relies on the genetic background of the individual and cell growth
- The reaction is slower, in a number of days
- It is specific
- Each cell responds to one epitope on the antigen
- It has anamnestic memory
- Repeated exposure leads to a faster and stronger reaction
- It leads to clonal expansion

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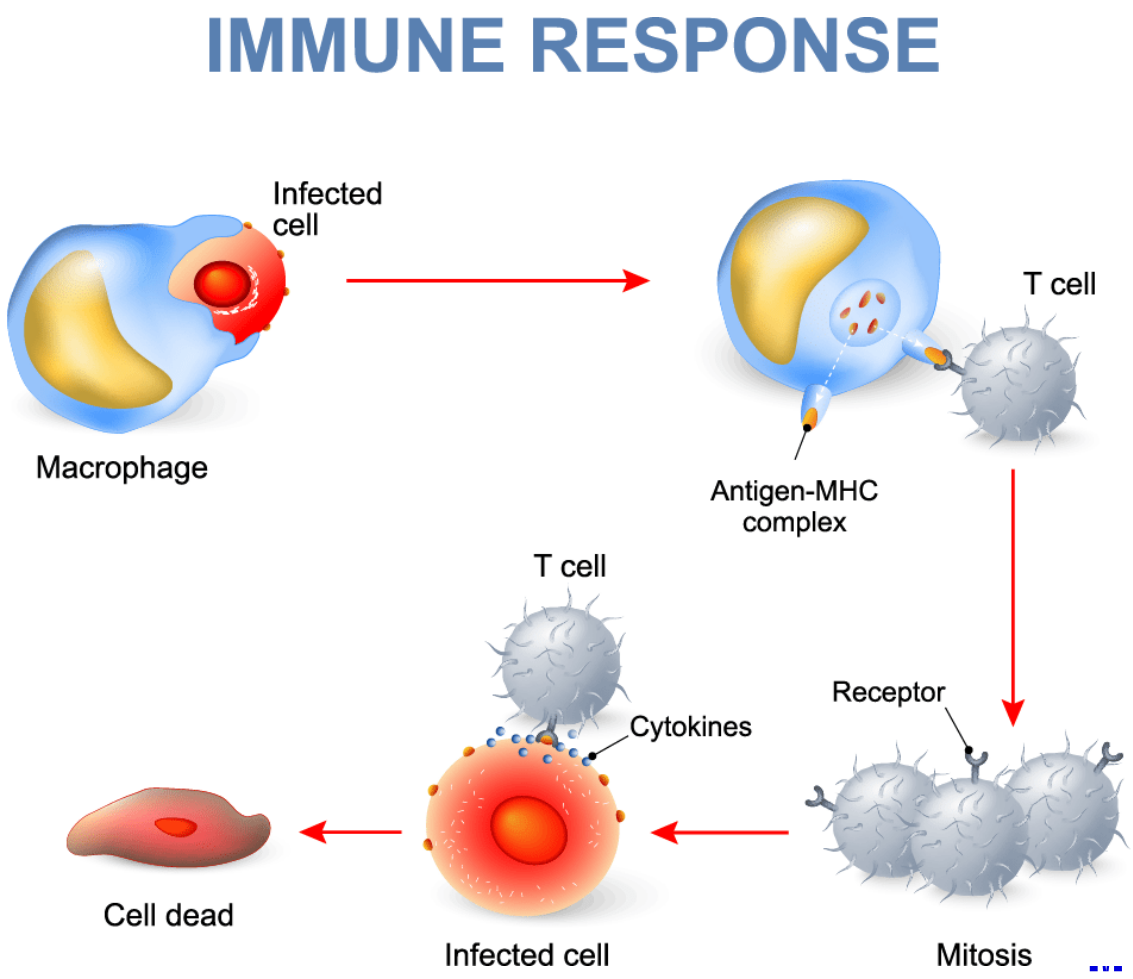
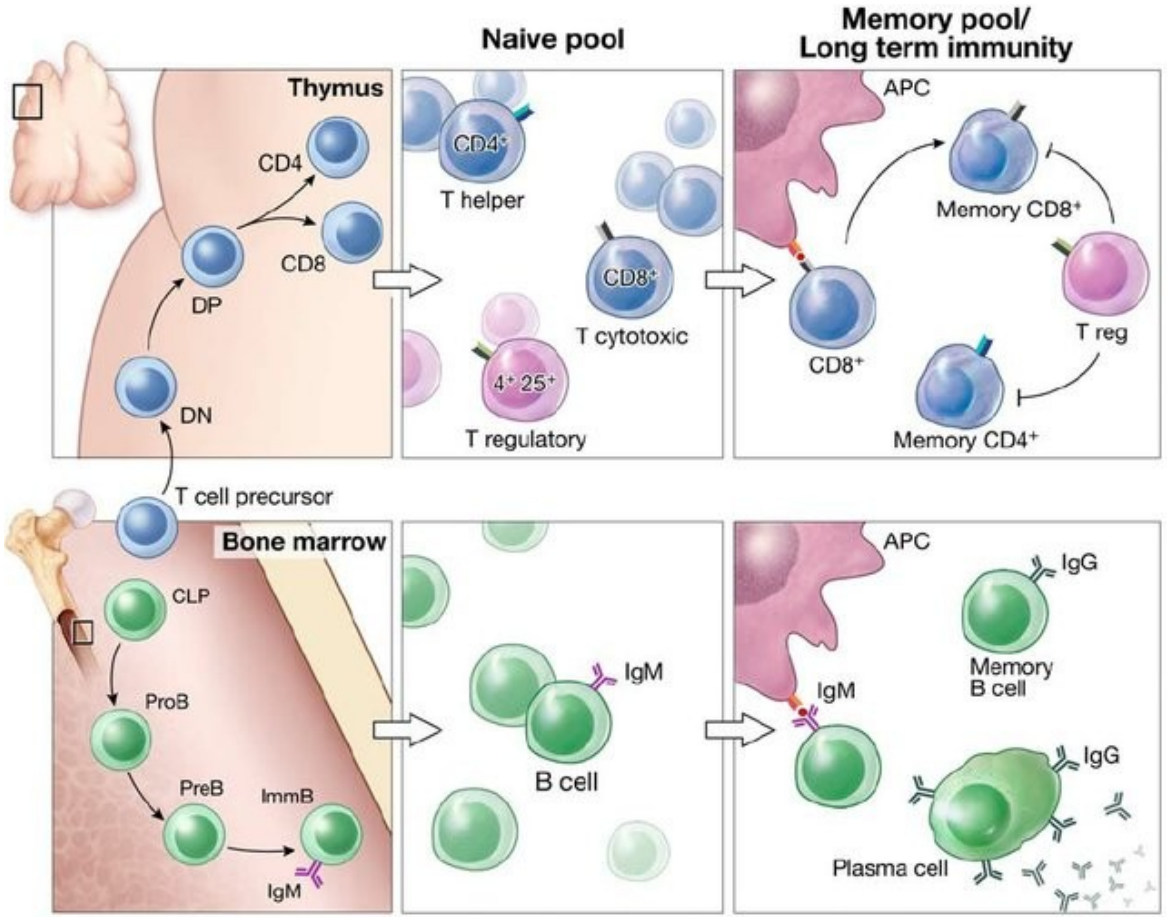
Adaptive immunity mechanisms

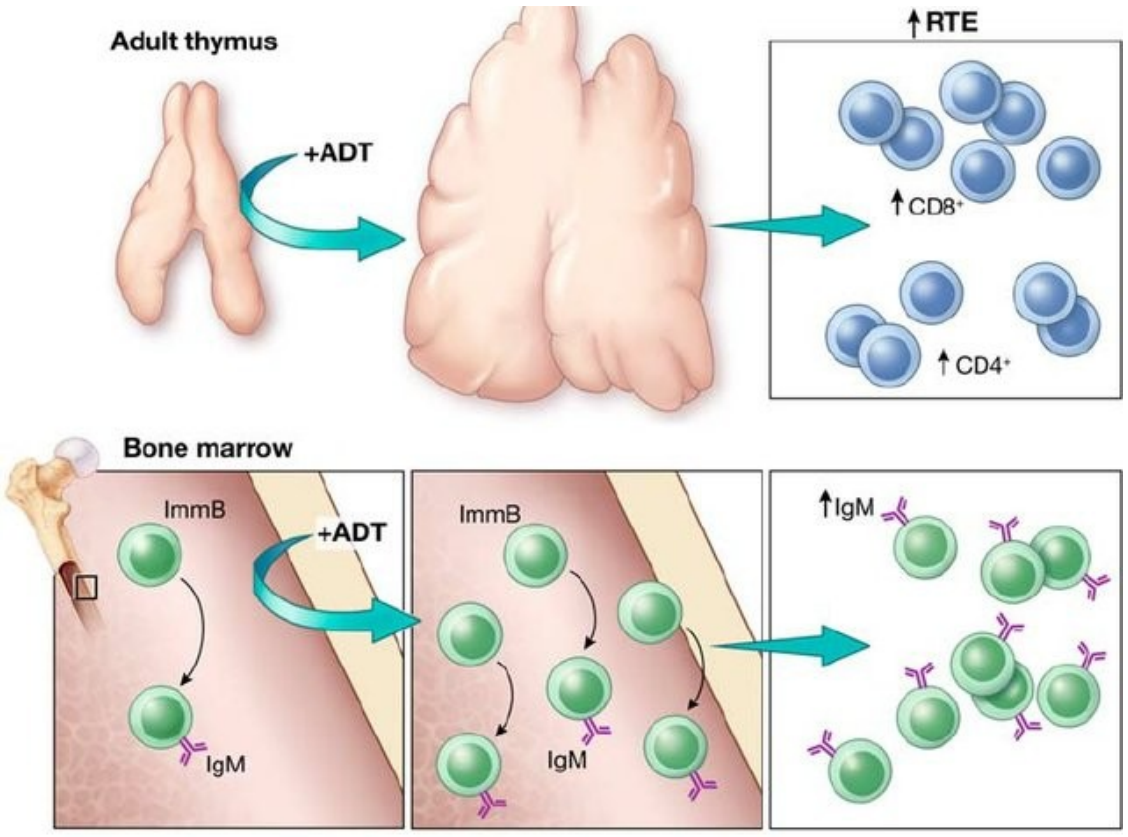
- **Cell-mediated immune response** (CMIR)
- T-lymphocytes
- Elimination of intracellular microbes that survive inside phagocytes or other infected cells

- **Humoral immune response (HIR)**
- B-lymphocytes
- antibody-mediated
- Elimination of intracellular microbes or their toxins



Adaptive immunity: mechanisms





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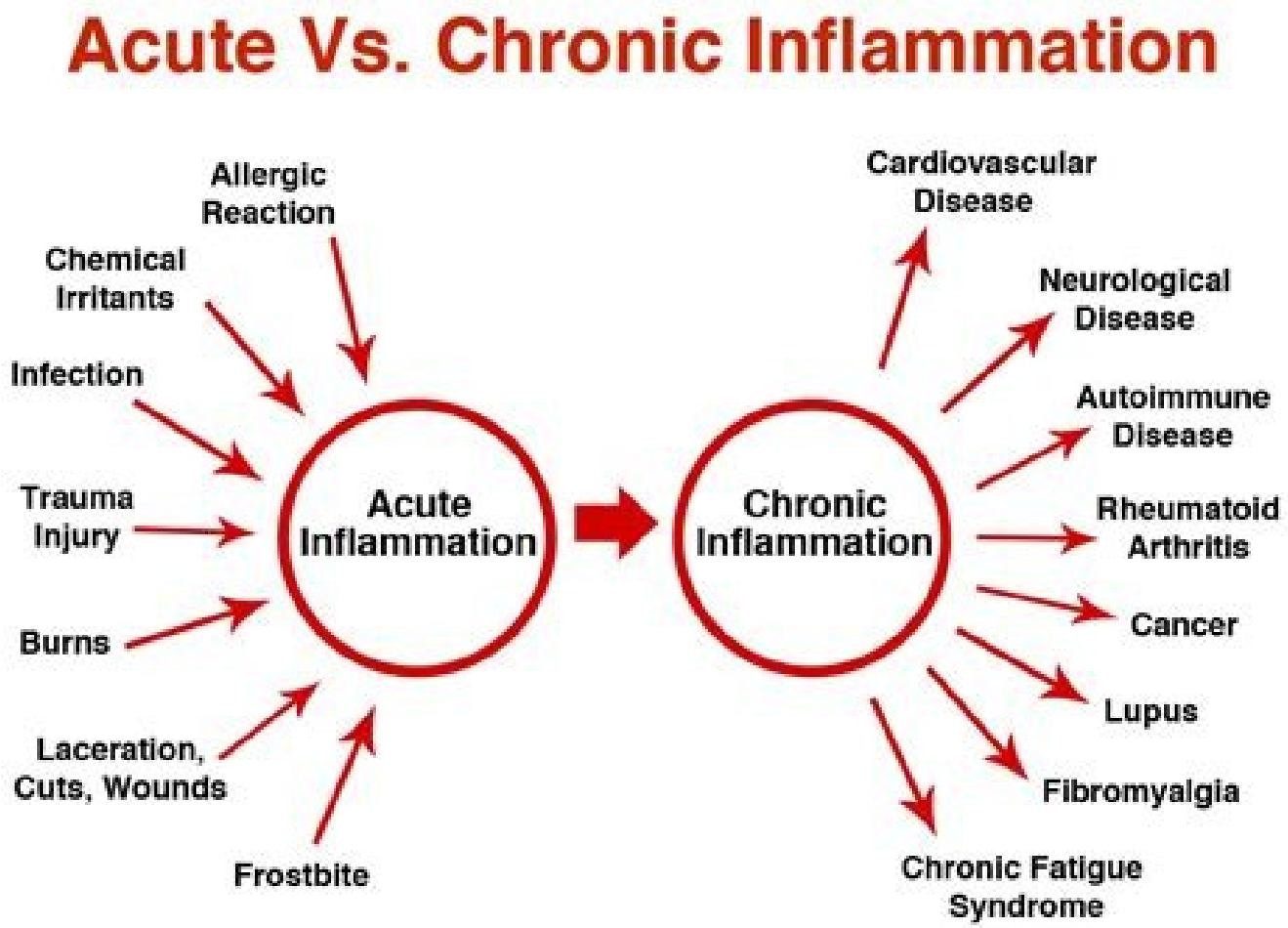
Inflammation



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Inflammation

Inflammation is a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult

The reaction of vascularized living tissue to local injury.

How inflammation accomplishes its protective mission?

How to accomplishes protective mission?

Inflammation serves to destroy, dilute or isolate the injurious agent (microbes, toxins) and eliminate the necrotic cells and tissues.
Inflammation is part of a broader protective response (*innate immunity*)

It starts a series of events which leads as far as possible to the healing and reconstitution of the damaged tissue.

Inflammation

During repair, the injured tissue is replaced by :

- Regeneration of native parenchyma cells
- Filling of the defect by fibroblastic tissue or both

Inflammation and repair are protective response

Can Inflammation cause considerable harm to the body?

They may induce harm
e.g. anaphylactic reaction
rheumatoid arthritis
atherosclerosis
pericarditis

How?

- The components of the inflammatory reaction that destroy and eliminate microbes and dead tissues are capable of also injuring normal tissues.
  - This may accompany
    entirely normal, beneficial inflammatory reactions, (e.g., when the infection is severe),
    prolonged (e.g., when the eliciting agent resists eradication)
    inappropriate (e.g., when it is directed against self-antigens in autoimmune diseases)
    against usually harmless environmental antigens (allergic disorders)

Then what happens?

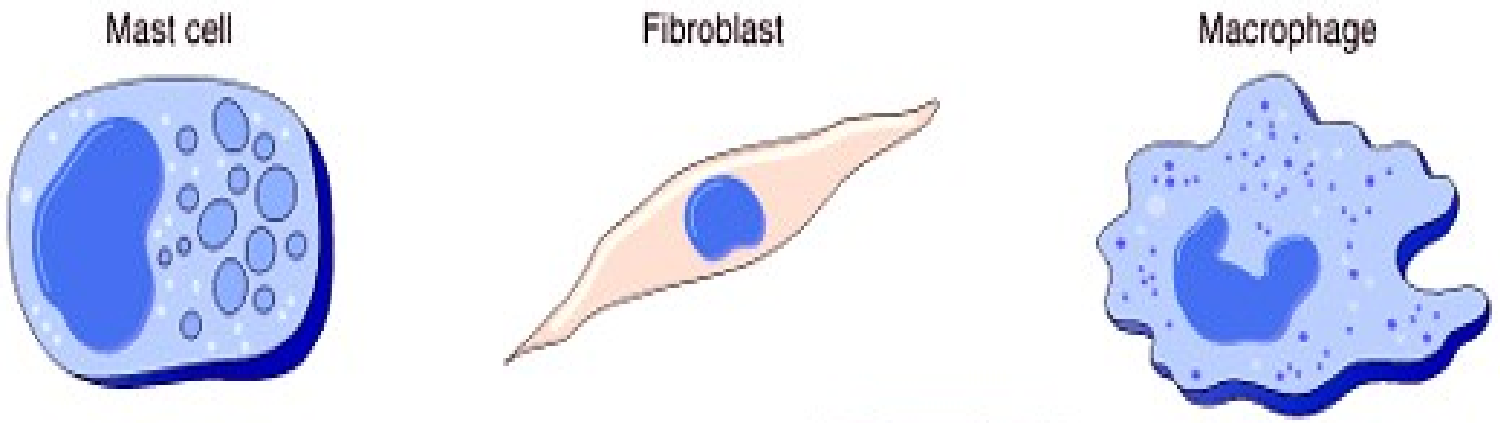
Inflammation is terminated when the offending agent is eliminated and the secreted mediators are broken down or dissipated.

There are active anti-inflammatory mechanisms that serve to control the response and prevent it from causing excessive damage to the host.

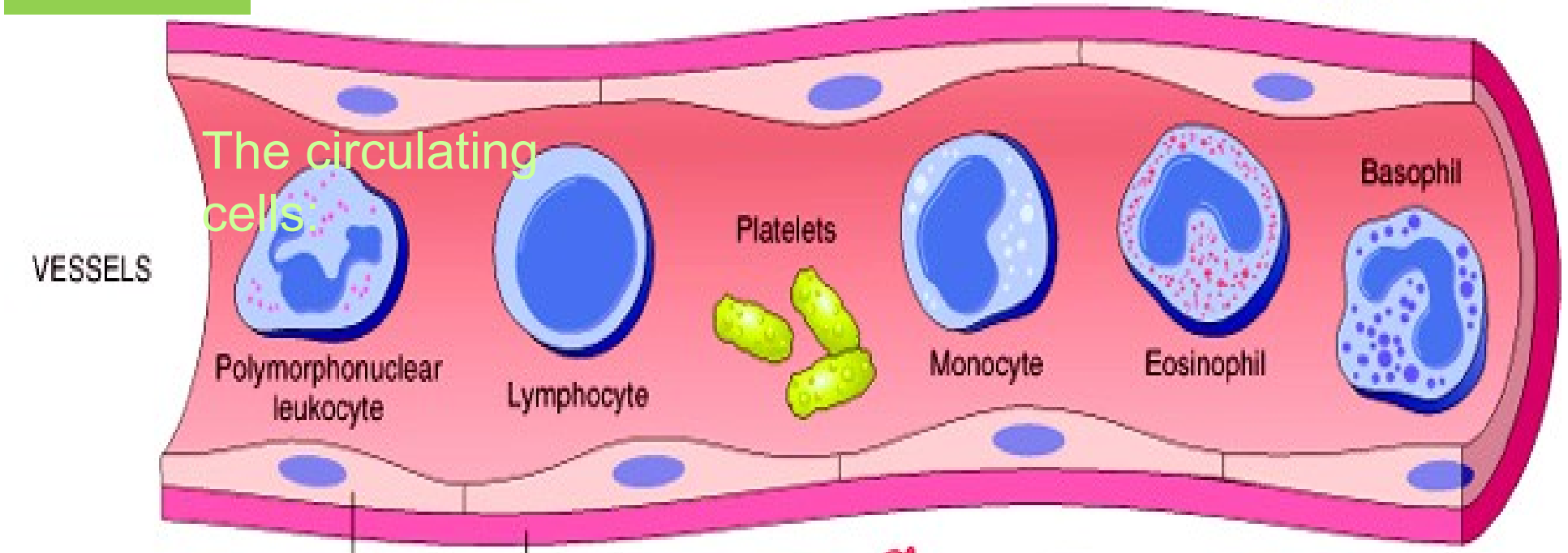
What are the cells and molecules that play important roles in inflammation?

blood leukocytes
plasma proteins
cells of vascular walls
cells of the surrounding connective tissue
extracellular matrix (ECM) of the surrounding connective tissue

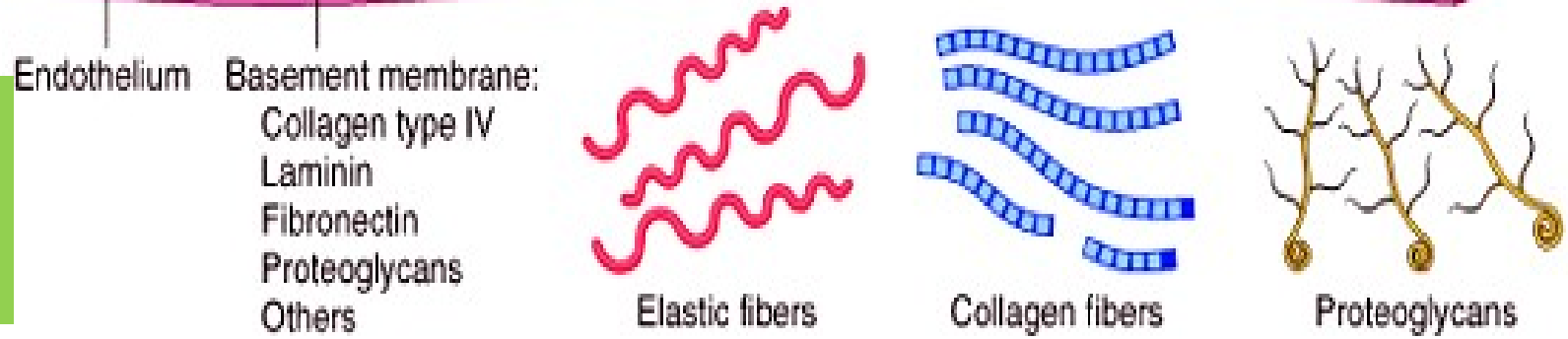
The connective tissue cells



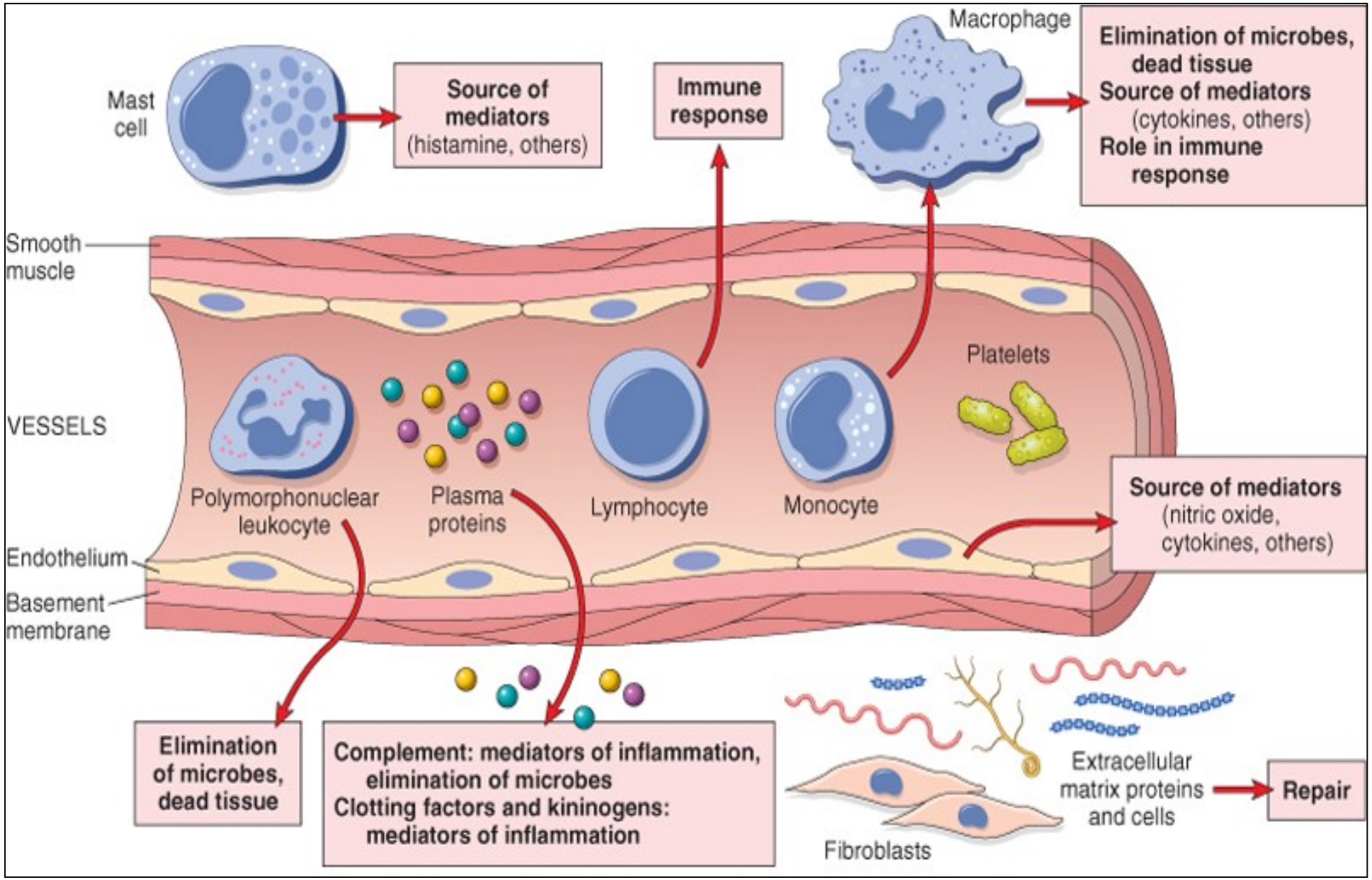
The circulating cells:



The extracellular matrix



Cells and molecules that play important roles in inflammation



Tissues and cells involved in inflammatory response :

The fluid and proteins of plasma, circulating cells, blood vessels and connective tissue

- The circulating cells: *neutrophils, monocytes, eosinophils, lymphocytes*, *basophils*, and *platelets*.

- The connective tissue cells are the *mast cells,* the connective tissue *fibroblasts*, resident *macrophages* and *lymphocytes*.

- The extracellular matrix, consists of the structural fibrous proteins *(collagen*, *elastin)*, adhesive glycoproteins (*fibronectin, laminin*, *nonfibrillar collagen, tenascin,* and others), and proteoglycans

What are types of inflammation?

What is the difference between these types of inflammation?

Acute inflammation

- rapid in onset (seconds or minutes)
- relatively short duration, lasting for minutes, several hours, or a few days
- its main characteristics:
  - the exudation of fluid and plasma proteins (edema)
  - the emigration of leukocytes, predominantly neutrophils.

Chronic inflammation

- is of longer duration
- associated histologically with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis, and tissue necrosis.
- Less uniform.

What is the source of chemical mediators in inflammation?

What is the action of chemical mediators in inflammation?

Some of mediators act on small blood vessels

Promote the efflux of plasma

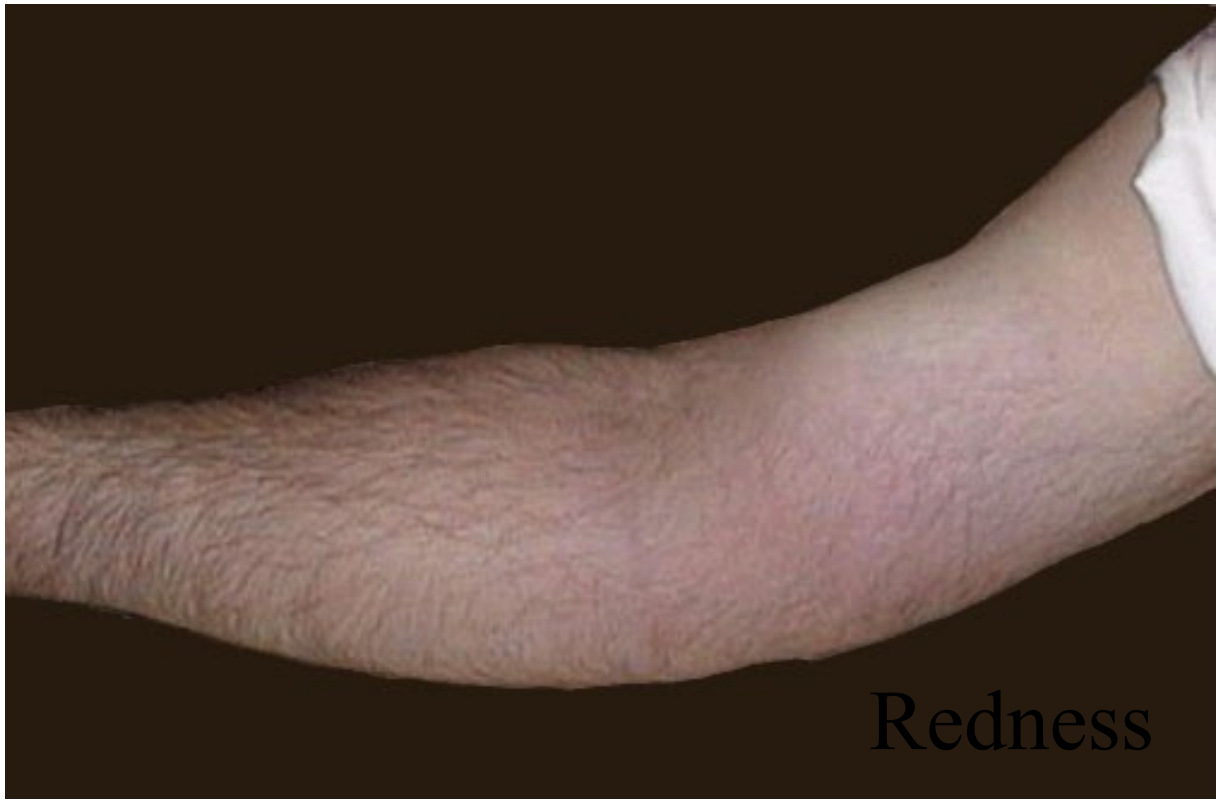
Recruitment of circulating leukocytes to the site where the offending agent is located

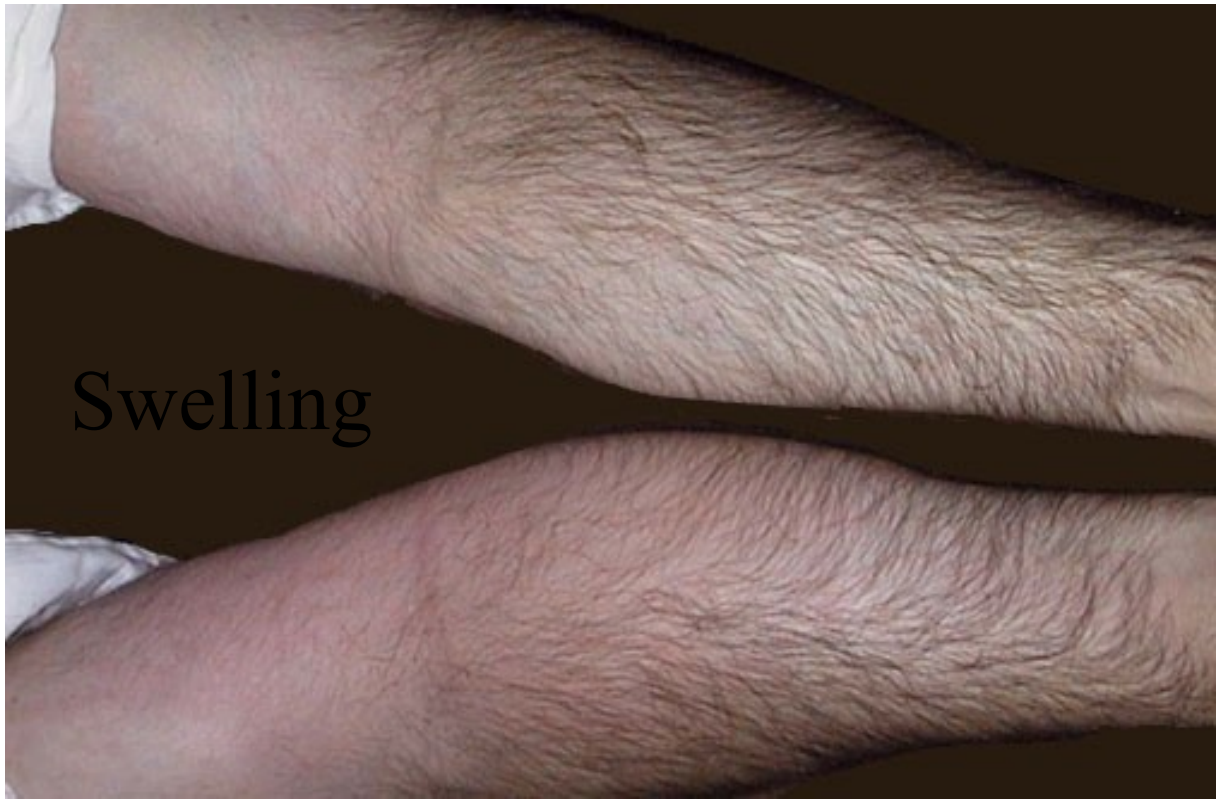
What are the cardinal signs of inflammation?

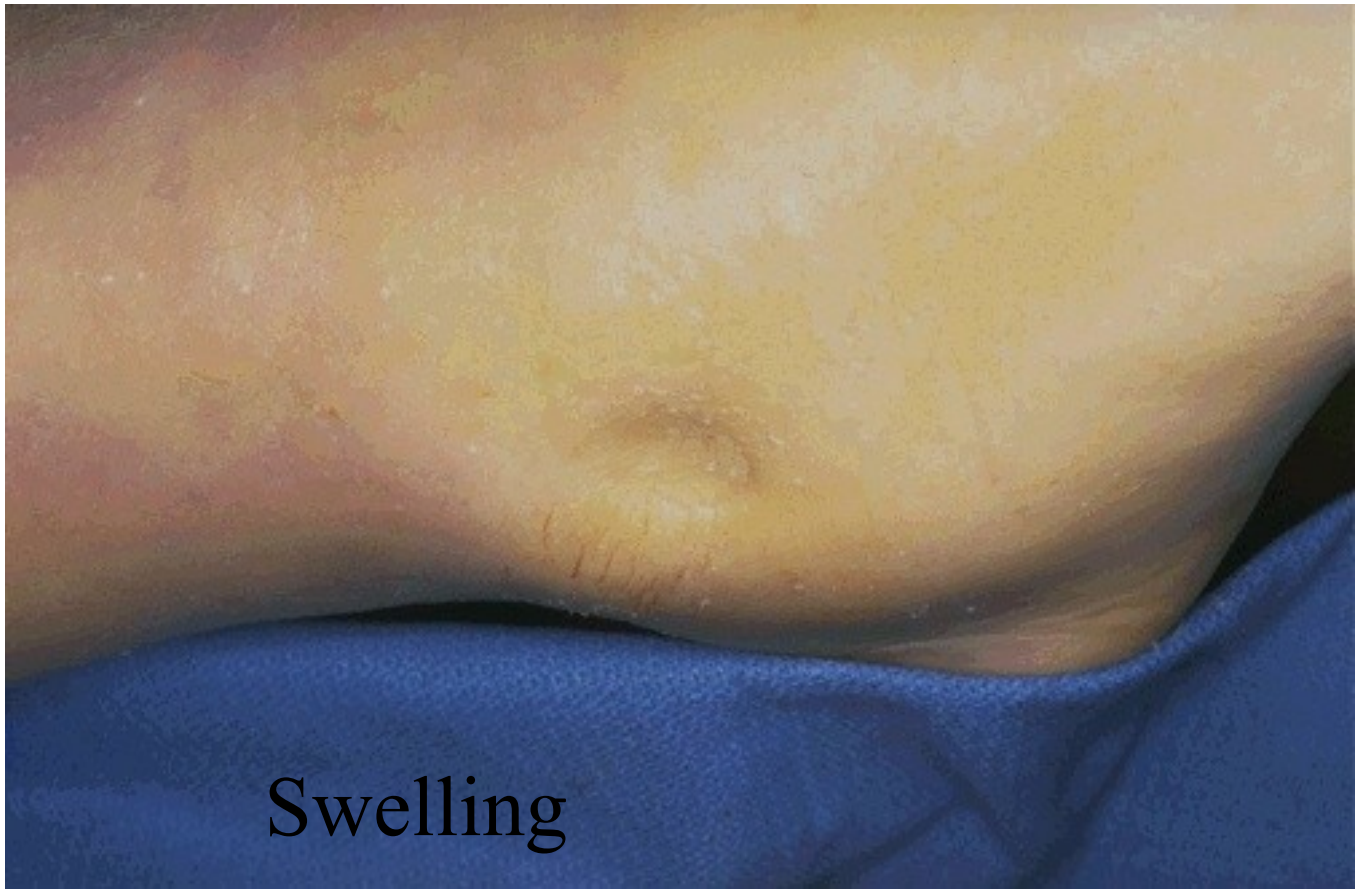
Acute Inflammation

Local clinical signs of acute inflammation:

- Heat
- Redness
- Swelling
- Pain
- Loss of function


Redness


Swelling


Swelling

What are the steps of the inflammatory response which can be remembered as the five Rs?

Steps of the inflammatory response

(1) Recognition of the injurious agent
(2) Recruitment of leukocytes
(3) Removal of the agent
(4) Regulation (control) of the response
(5) Resolution

Learning Objectives:

1. Define inflammation, its causes and clinical appearance.
2. Describe the sequence of vascular changes in acute inflammation (vasodilation, increased permeability) and their purpose.
3. Know the mechanisms of increased vascular permeability.
4. Define the terms edema, transudate, and exudate.

What are the two major components of acute inflammation?

Components of acute inflammation

VASCULAR CHANGES

- *Vasodilation:* alterations in vessel caliber resulting in increased blood flow
- *Increased vascular permeability:* permit plasma proteins to leave the circulation

CELLULAR EVENTS

- Emigration of the leukocytes from the microcirculation and accumulation in the focus of injury
- Principal leukocytes in acute inflammation are neutrophils (polymorphonuclear leukocytes).

Chronic inflammation

- Is a pathogenic process of chronic duration (weeks, months, years)
- Where attempts at healing, inflammation and persistent tissue damage occur in different proportions

Causes of chronic inflammation

- Persistent infection
- Toxic agents (pollutants, etc)
- Immune-mediated inflammatory diseases

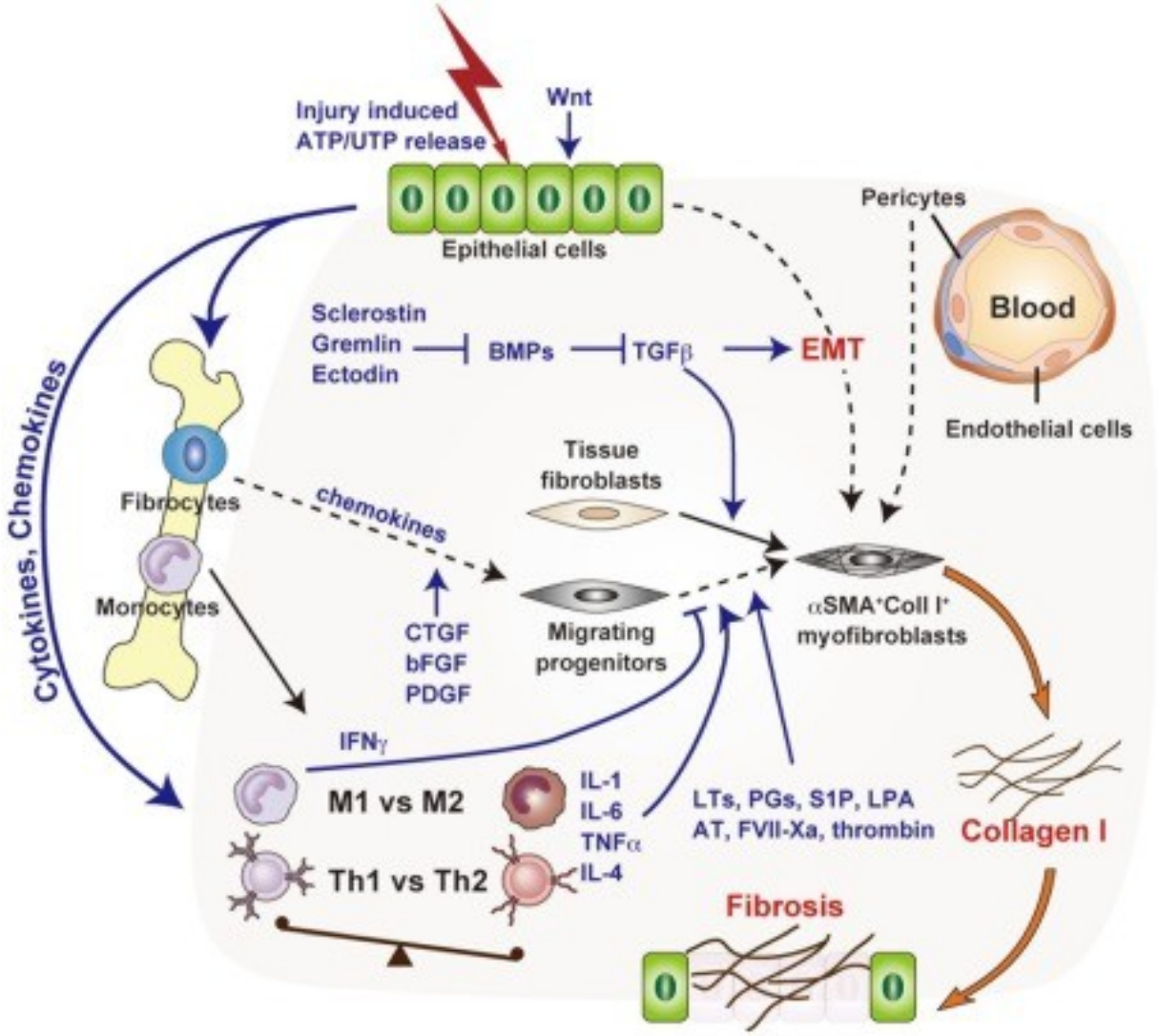
Primary chronic inflammation

- Is the cause of tissue damage in some of the most common and disabling human diseases

- Rheumatoid arthritis
- Atherosclerosis
- Primary pulmonary fibrosis
- Tuberculosis

- Also, the chronic inflammation has been implicated in progression of cancerous lesions

Mechanisms of chronic inflammation



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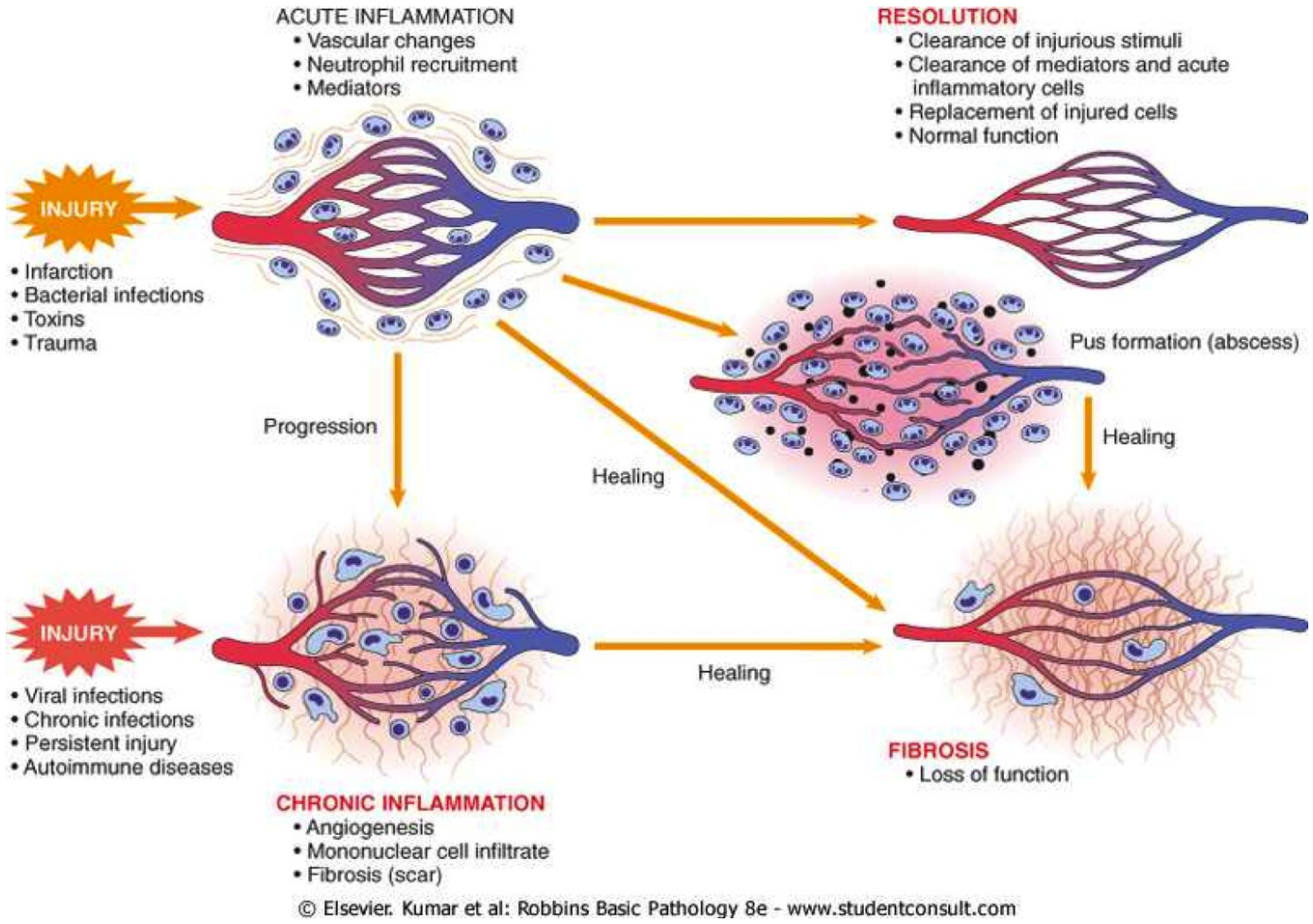
Morphological features of chronic inflammation



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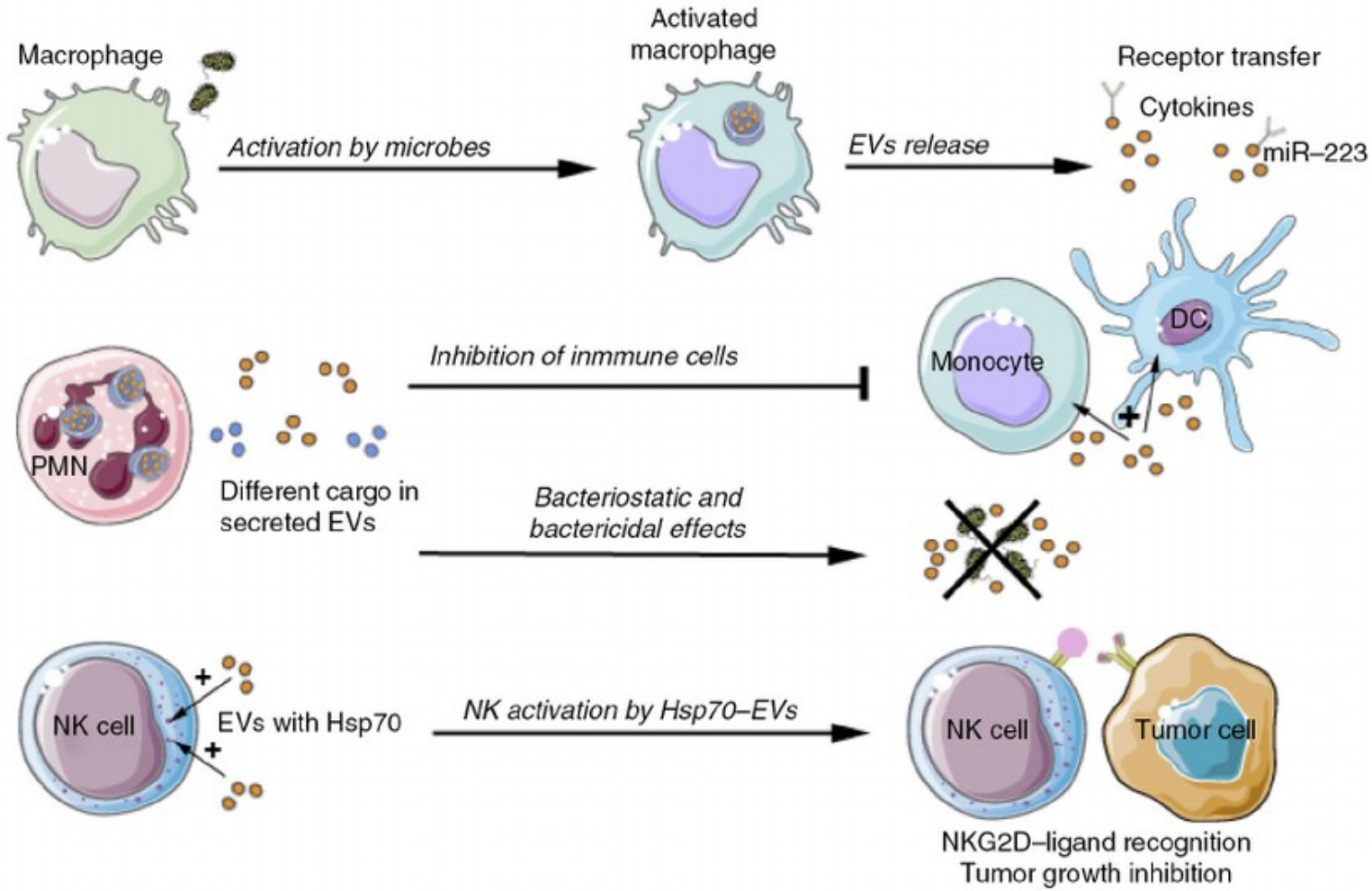
The role of macrophages in chronic inflammation



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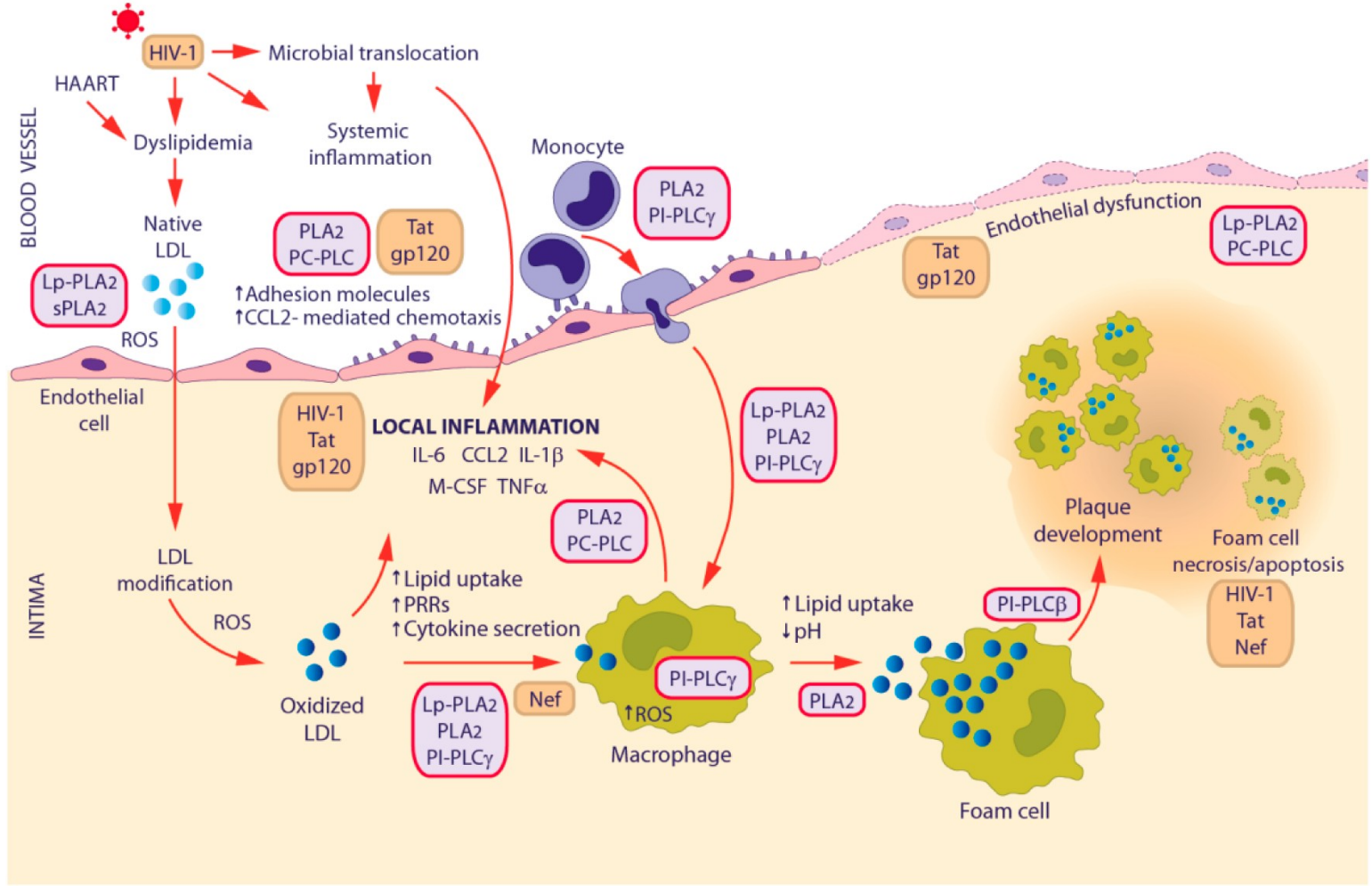
The role of macrophages in chronic inflammation



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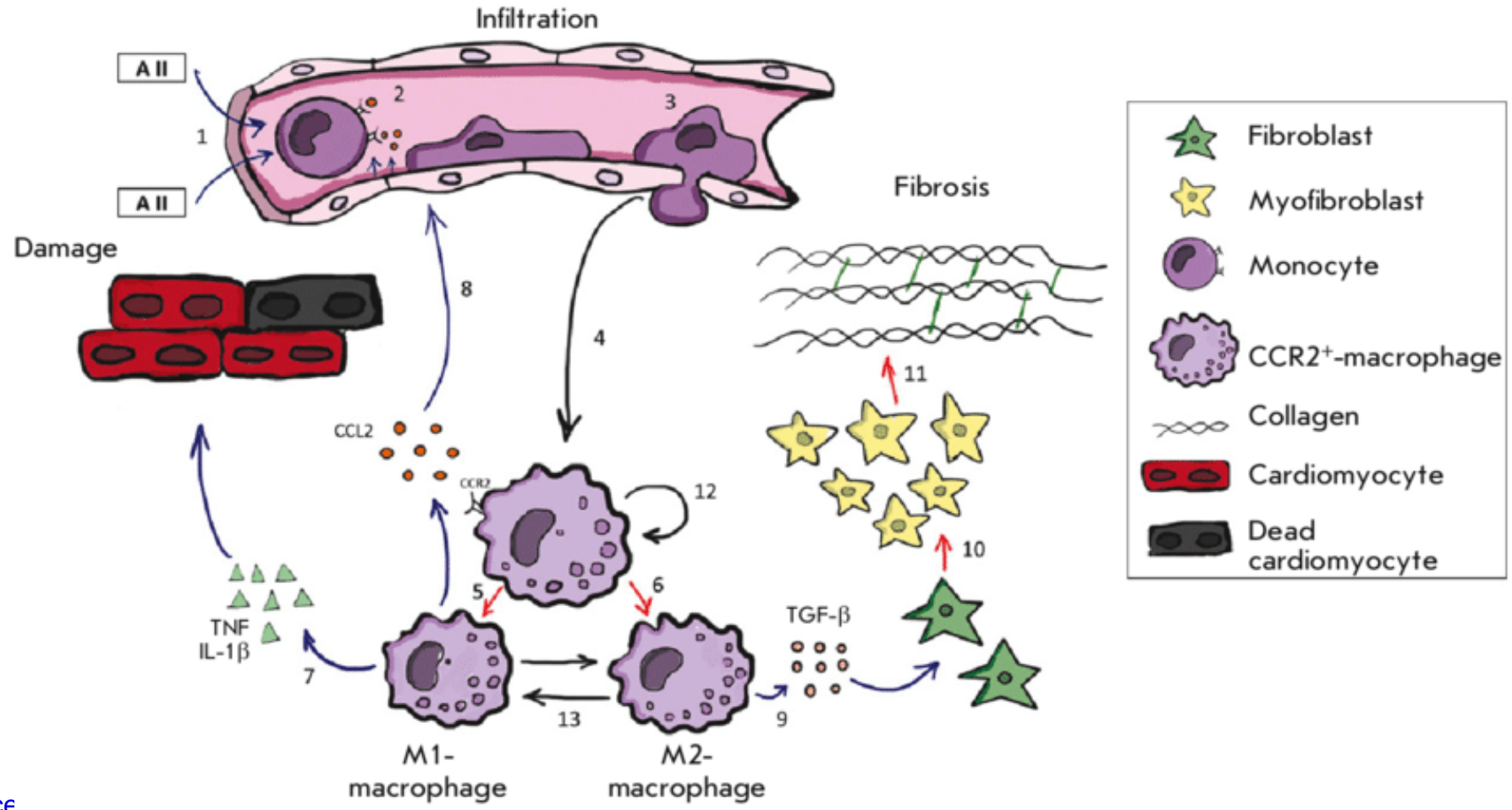

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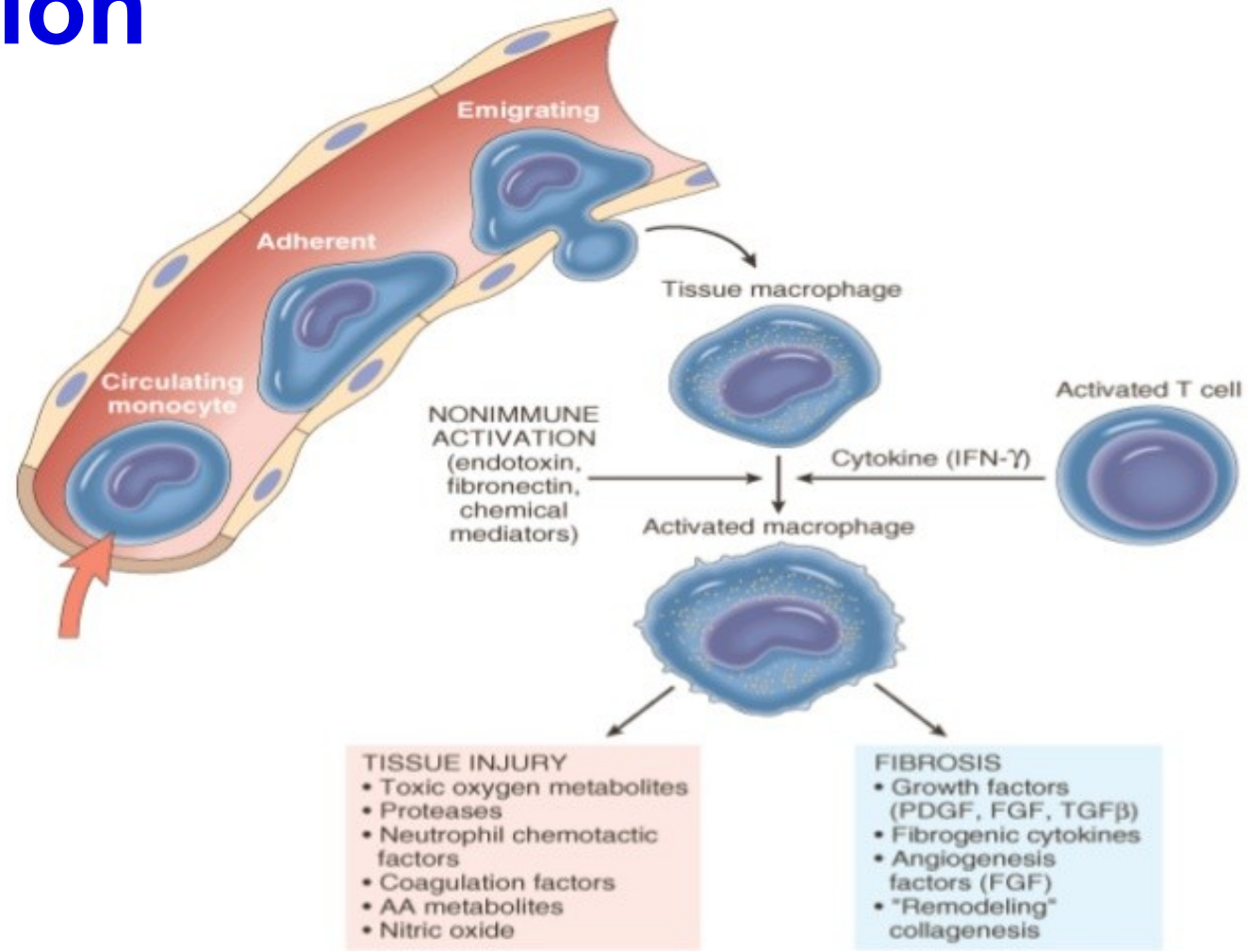
The role of macrophages in chronic inflammation



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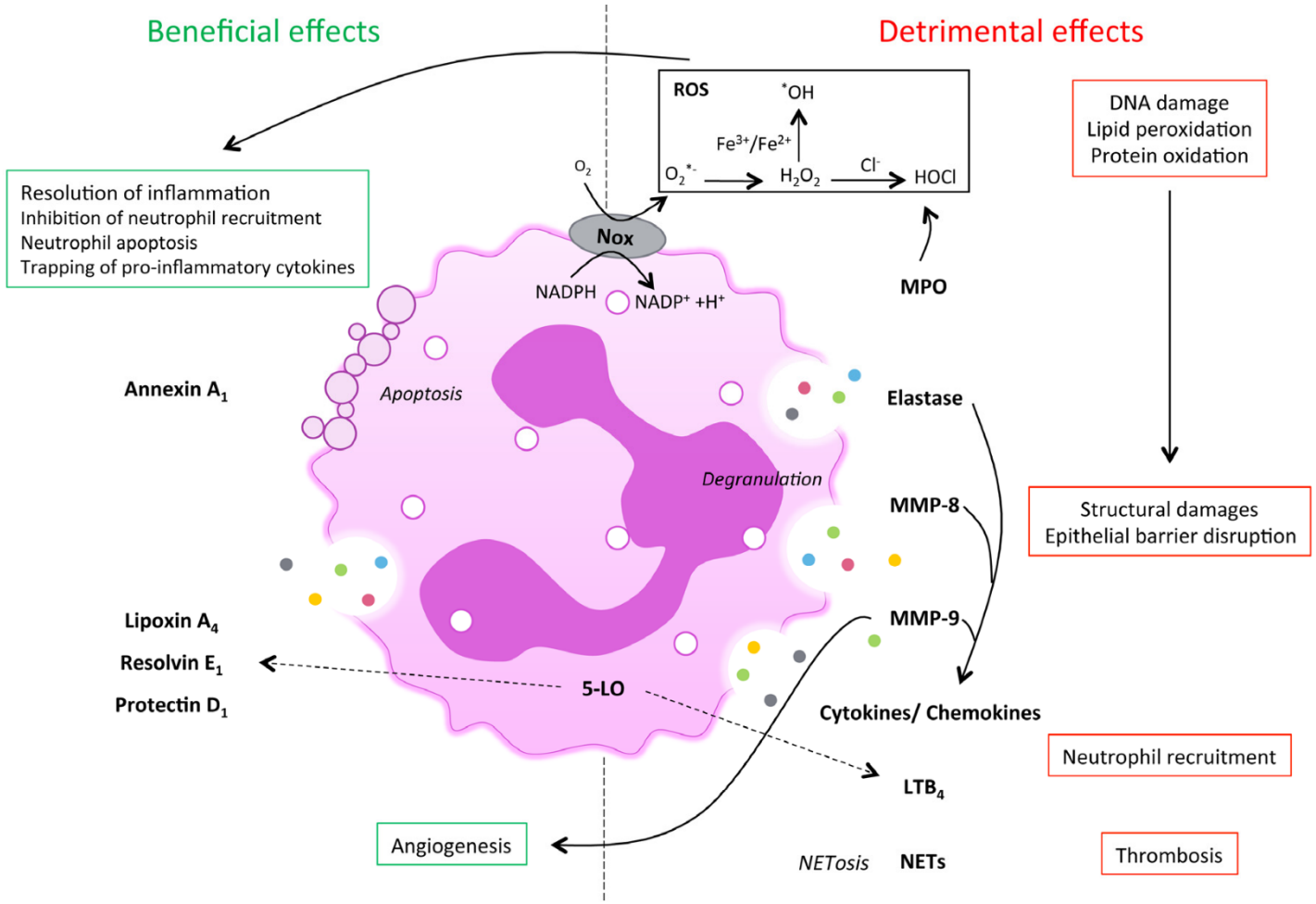
The role of neutrophils in chronic inflammation



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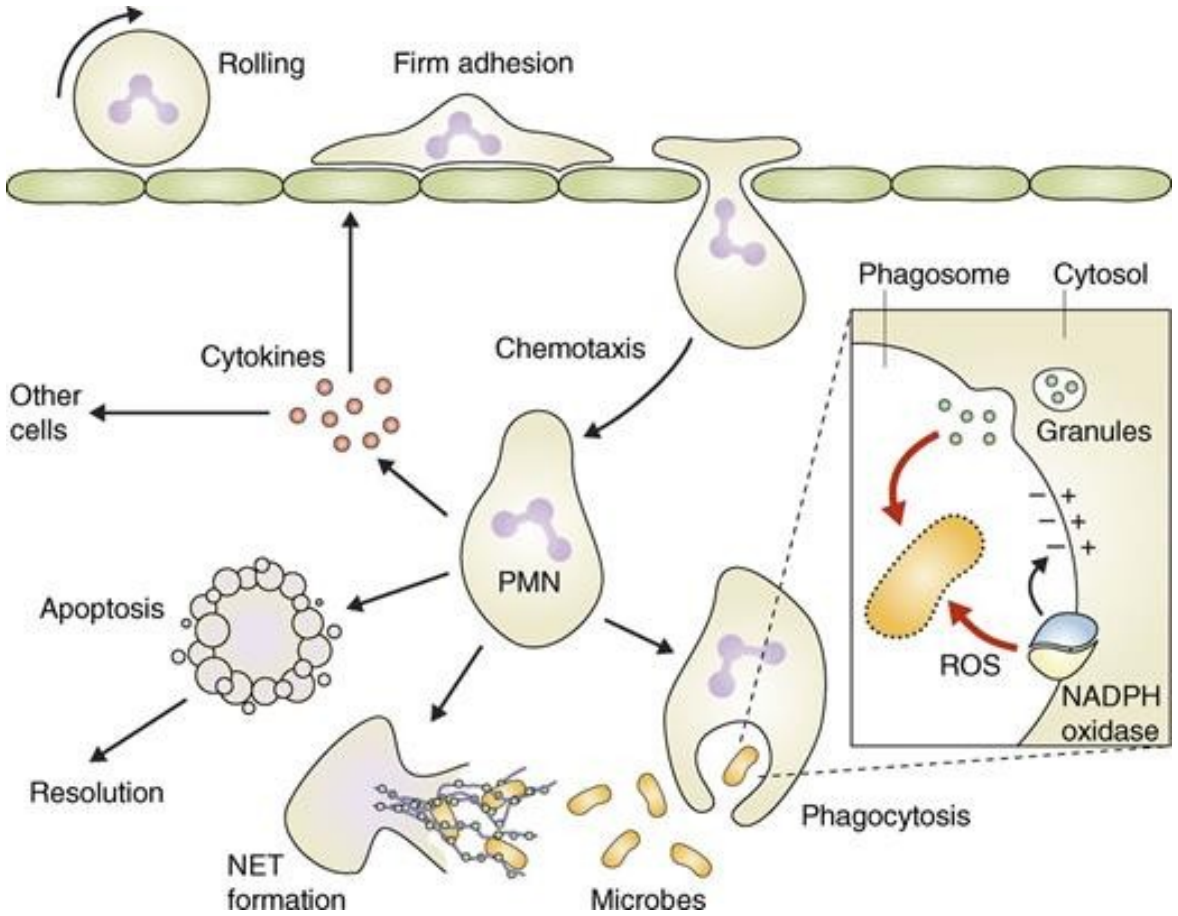
The role of neutrophils in chronic inflammation



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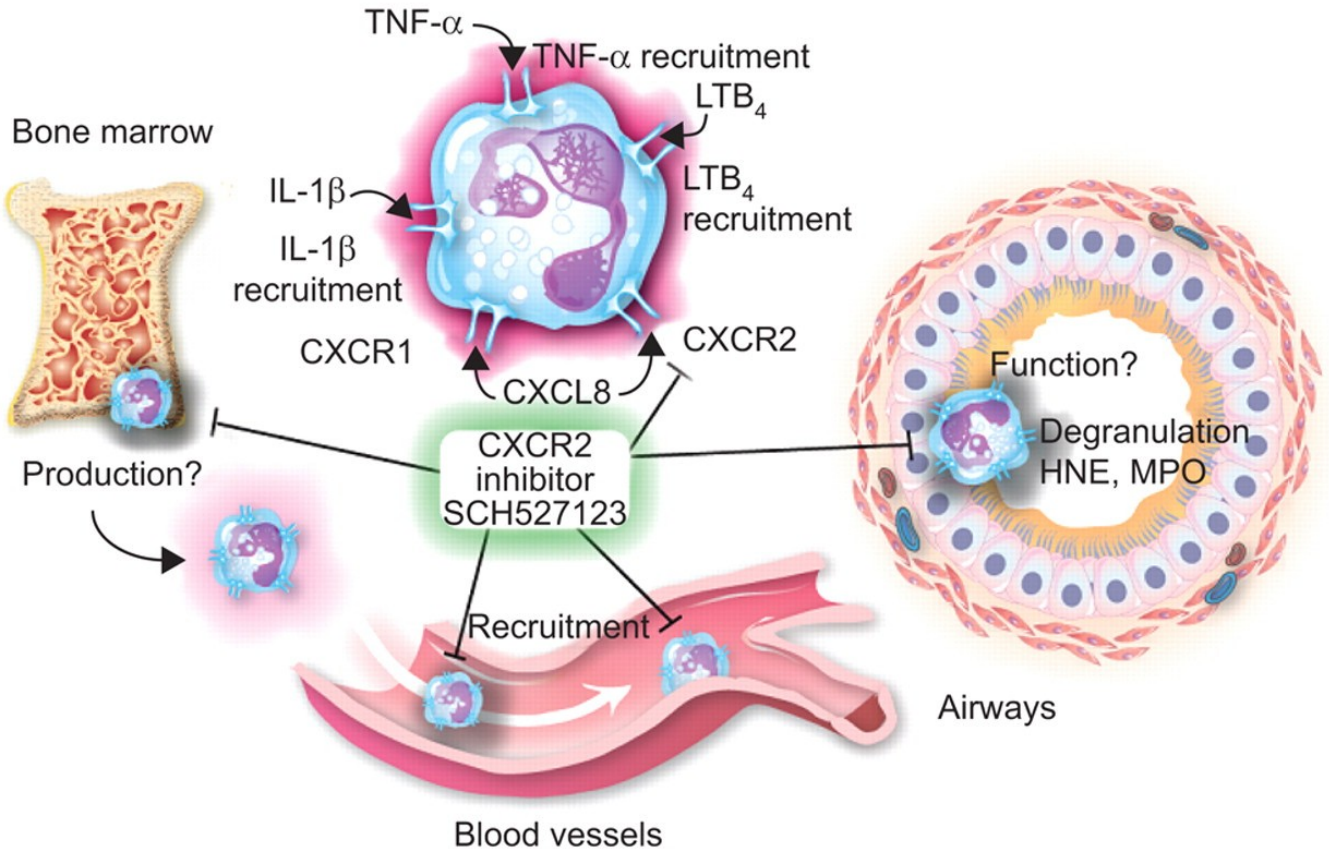
The role of neutrophils in chronic inflammation



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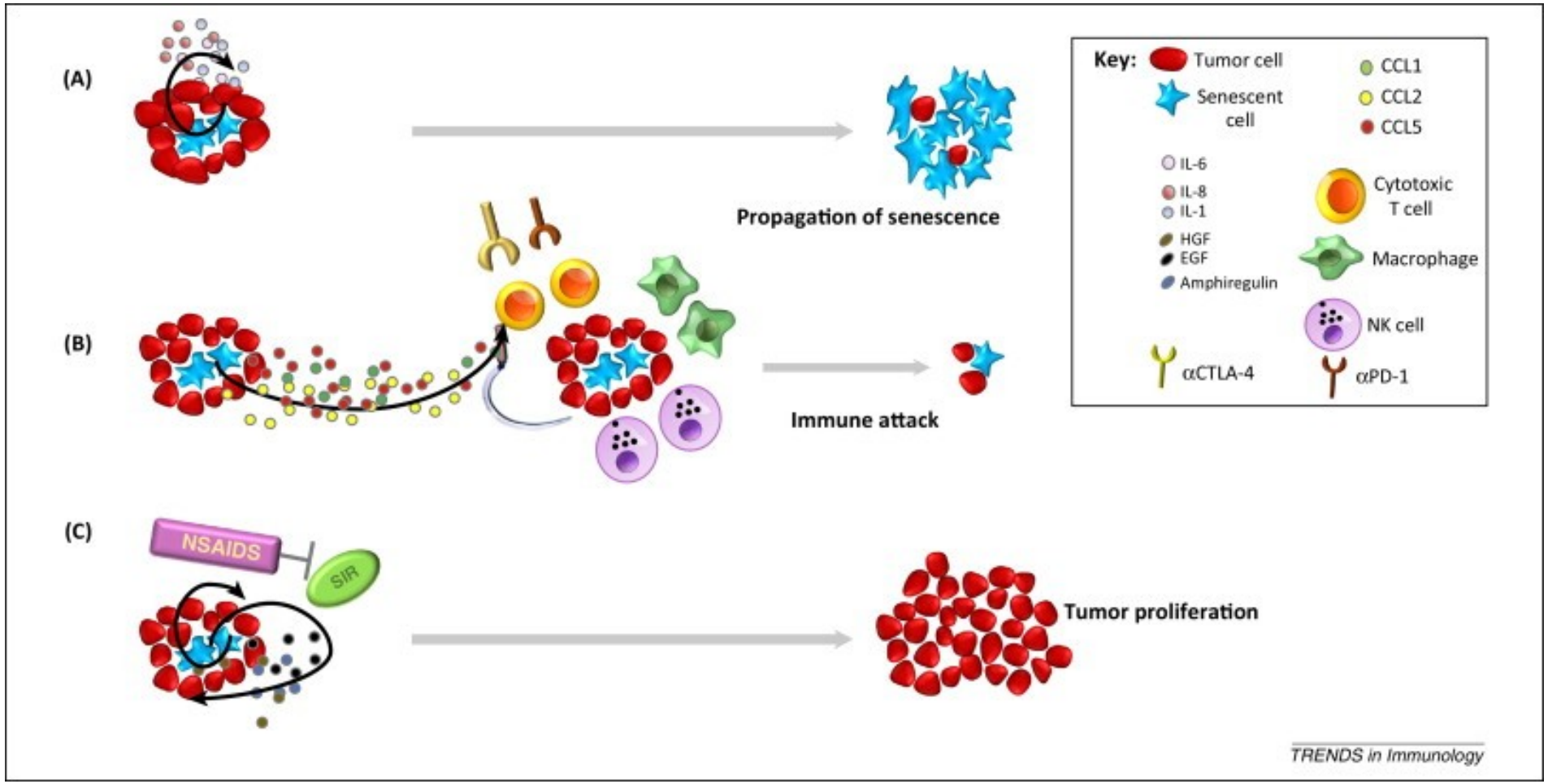
Age-dependent consequences



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SIRS – systemic inflammatory response syndrome

- Generalized acute inflammatory reaction that spreads throughout the body
- Intense inflammatory response to primary local, multiple or otherwise complex damage
- In SIRS, subsequent inflammation is not limited to the area where the inflammation occurred, but spreads throughout the body
- Even common inflammation spreads throughout the body - the difference from SIRS is that in SIRS, the mechanisms of inflammation control stop working

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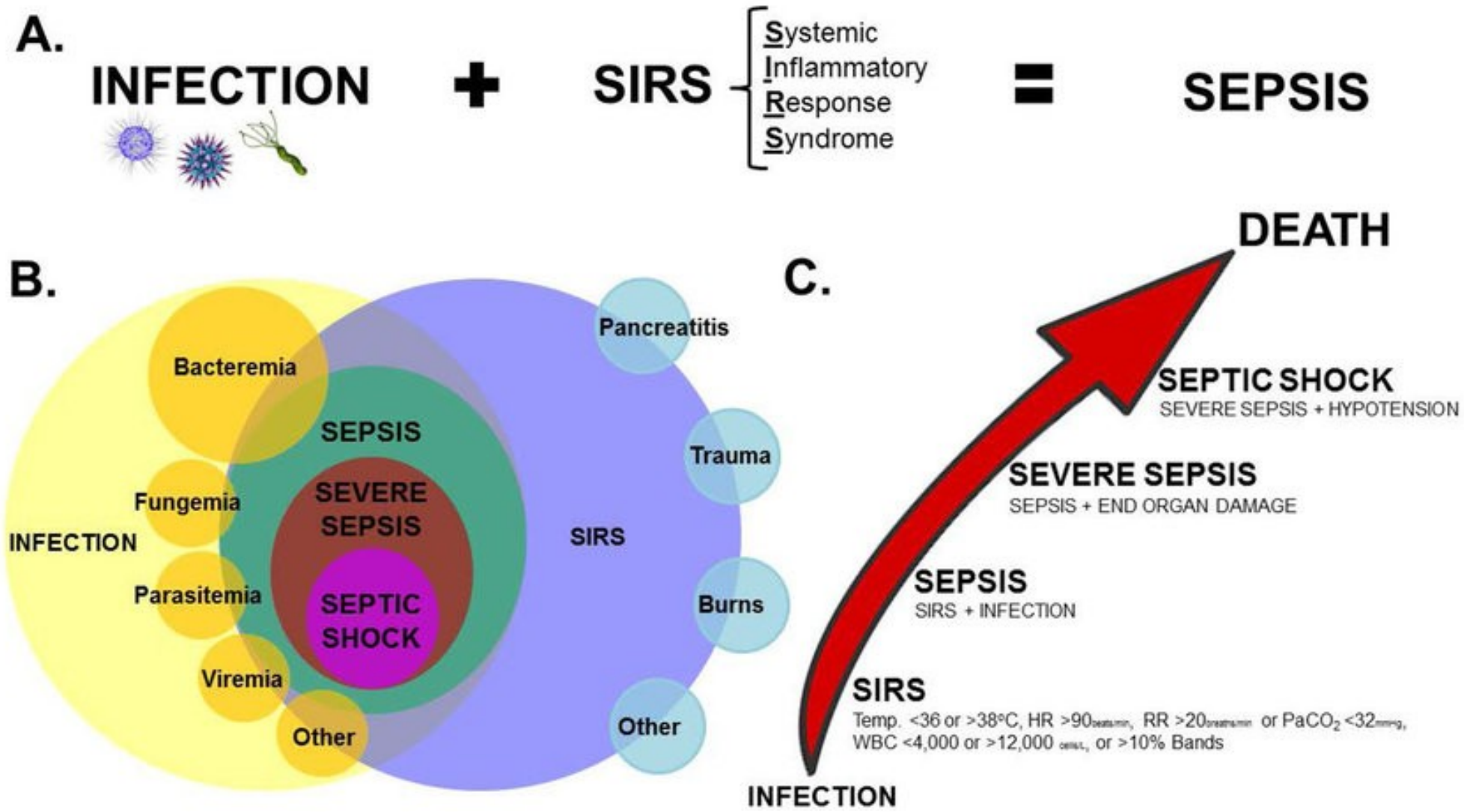

A.
INFECTION
SIRS
Systemic
Inflammatory
Response
Syndrome
SEPSIS
B.
Bacteremia
Pancreatitis
SEPSIS
Trauma
Fungemia
SEVERE
SEPSIS
INFECTION
SIRS
Parasitemia
SEPTIC
SHOCK
Burns
Viremia
Other
Other
C.
DEATH
SEPTIC SHOCK
SEVERE SEPSIS + HYPOTENSION
SEVERE SEPSIS
SEPSIS + END ORGAN DAMAGE
SEPSIS
SIRS + INFECTION
SIRS
Temp. <36 or >38°C, HR >90, RR >20 or PaCO2 <32,
WBC <4,000 or >12,000 , or >10% Bands
INFECTION

Pathogenesis of Covid-19 disease

- Coronaviruses belong to the Coronaviridae family in the Nidovirales order
- Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus
- Coronaviruses are enveloped viruses, minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length

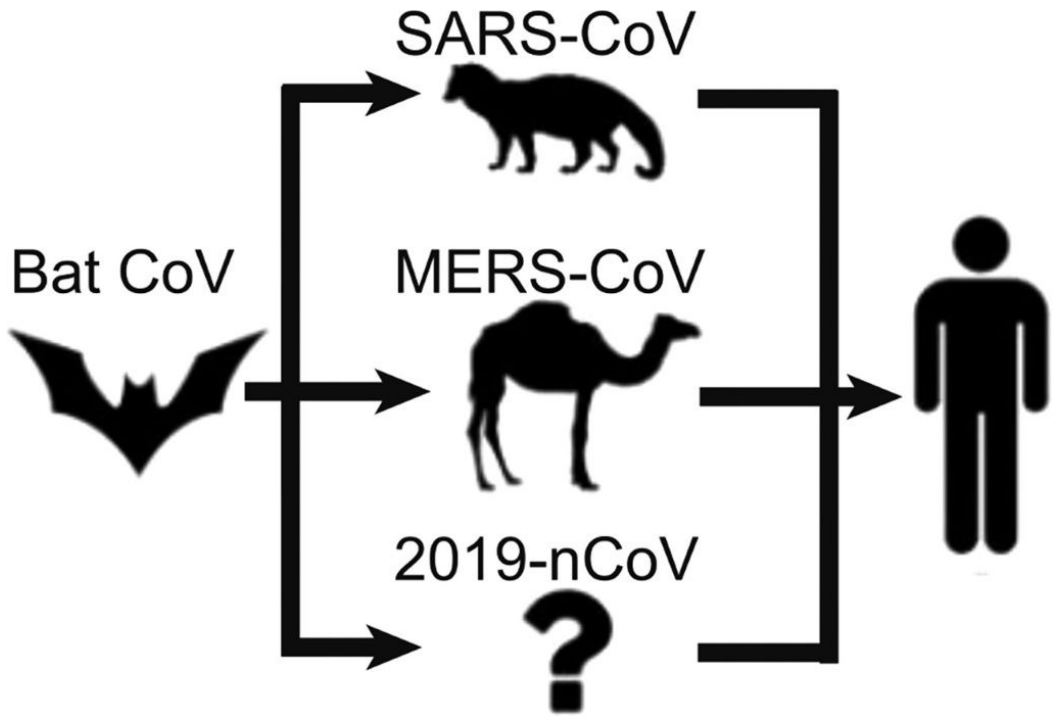
Covid-19

- The virus that causes COVID-19 is known as SARS-CoV-2

  It appears to have first emerged in Wuhan, China, in late 2019.
- The outbreak has since spread across China to other countries around the world. By the end of January, the new coronavirus had been declared a public health emergency of international concern by the WHO.
- The most commonly reported symptoms include a fever, dry cough and tiredness, and in mild cases people may get just a runny nose or a sore throat.
- In the most severe cases, people with the virus can develop difficulty breathing, and may ultimately experience organ failure. Some cases are fatal.

Human coronaviruses

- The most likely ecological reservoirs for coronaviruses are bats, but it is believed that the virus jumped the species barrier to humans from another intermediate animal host.
- This intermediate animal host could be a domestic food animal, a wild animal, or a domesticated wild animal which has not yet been identified.



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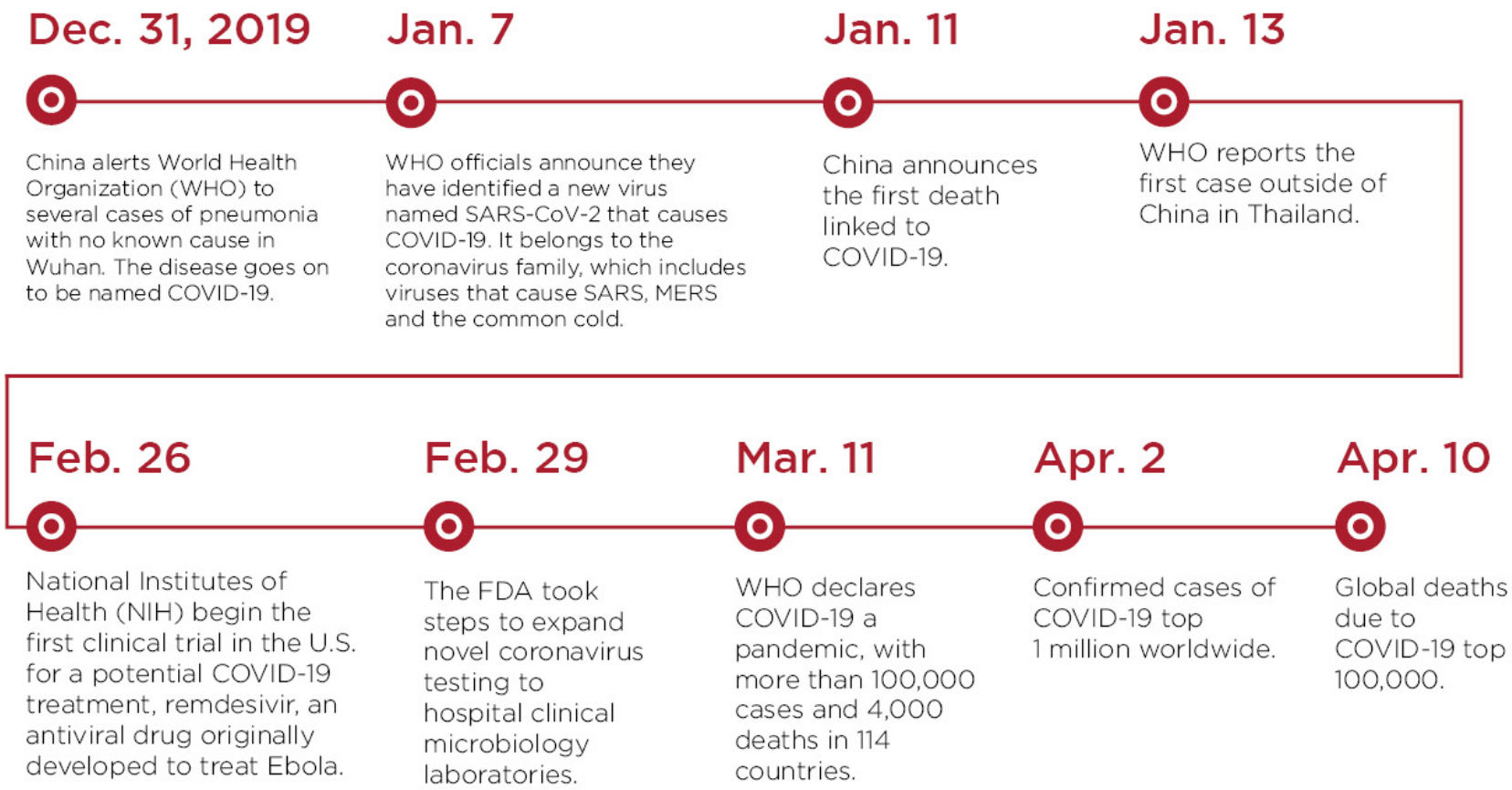
Covid-19 timeline



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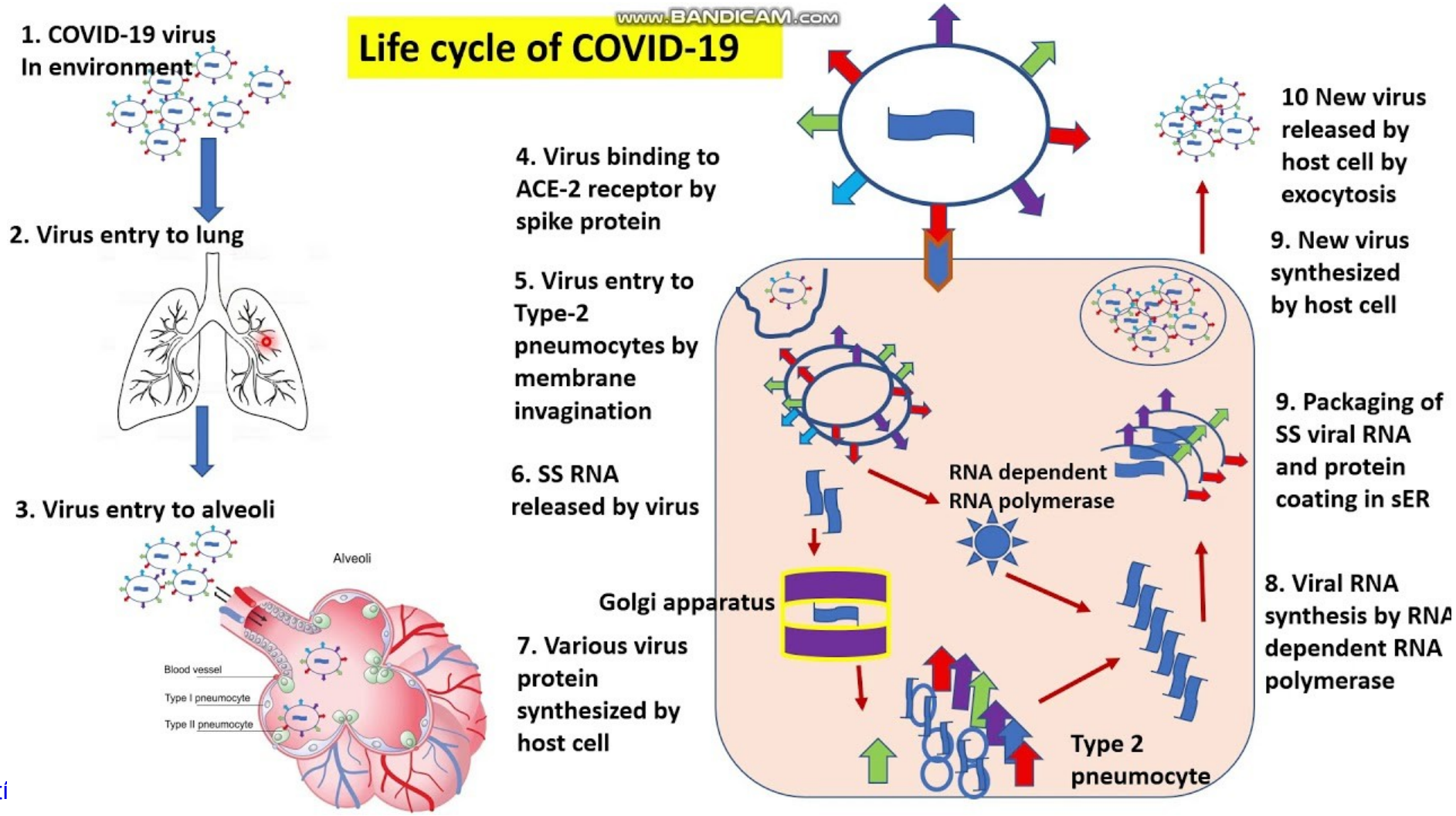
Pathogenesis of Covid-19 disease



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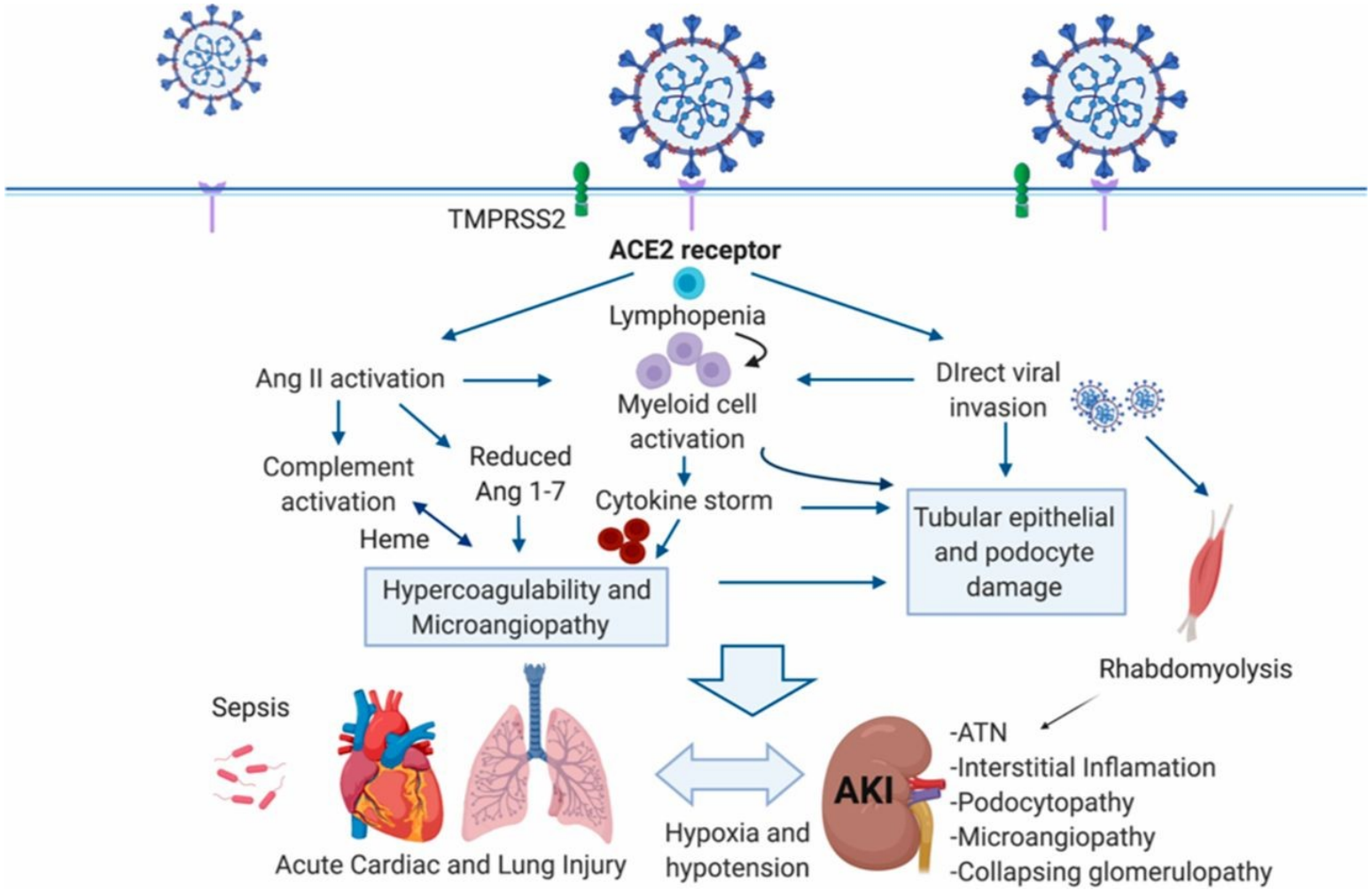
Pathogenesis of Covid-19 disease



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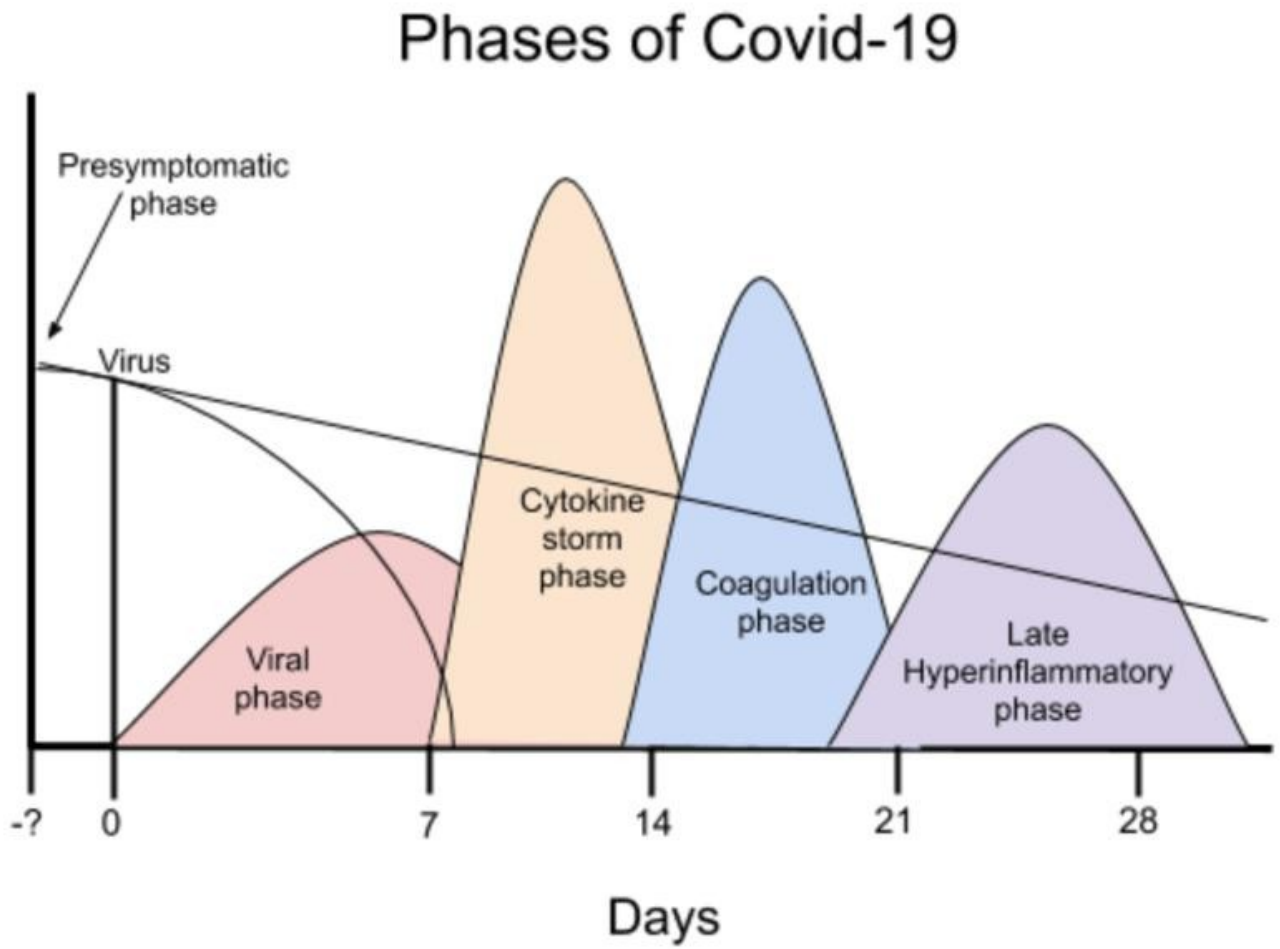
Pathogenesis of Covid-19 disease

- Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology.

Pathogenesis of Covid-19 disease



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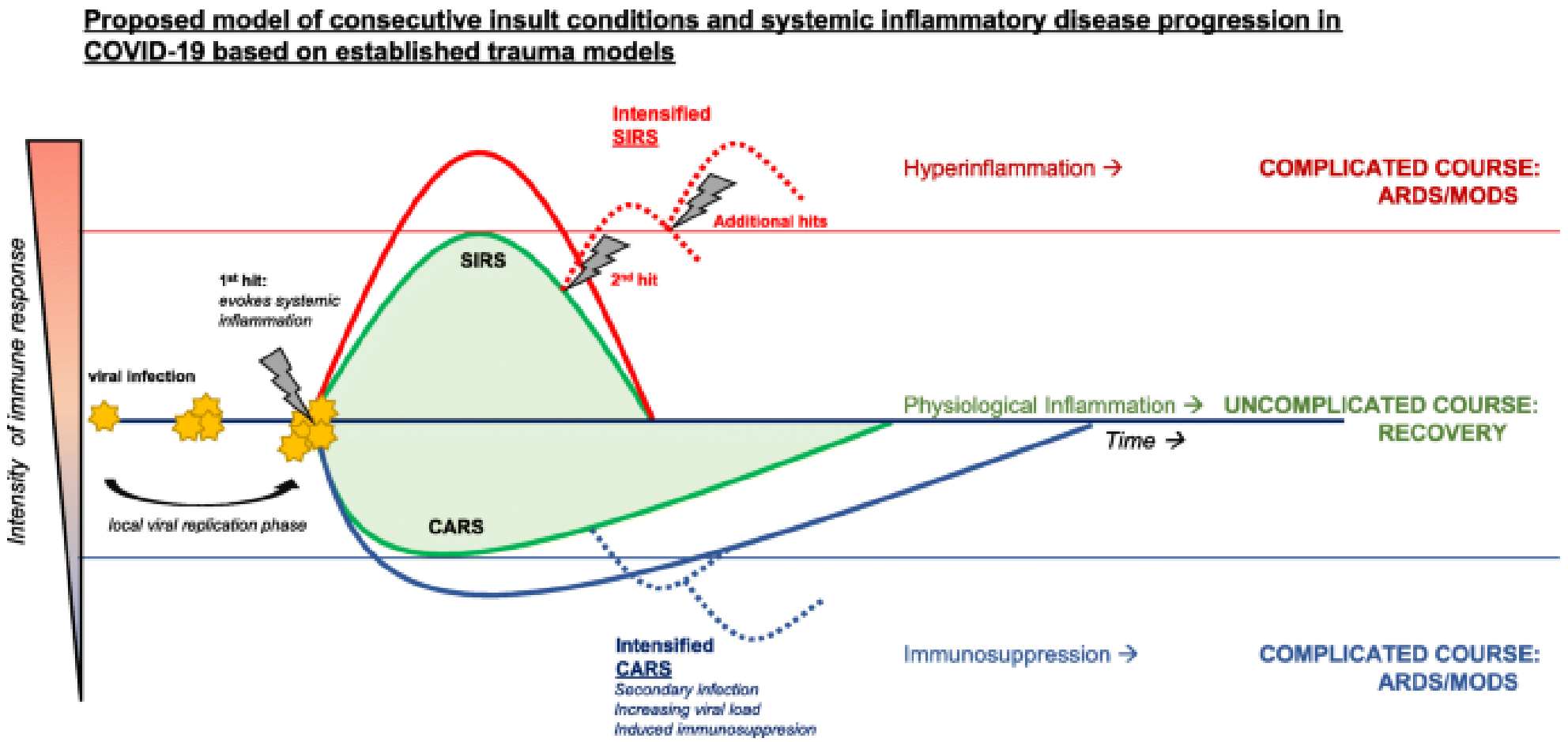
SIRS and Covid-19



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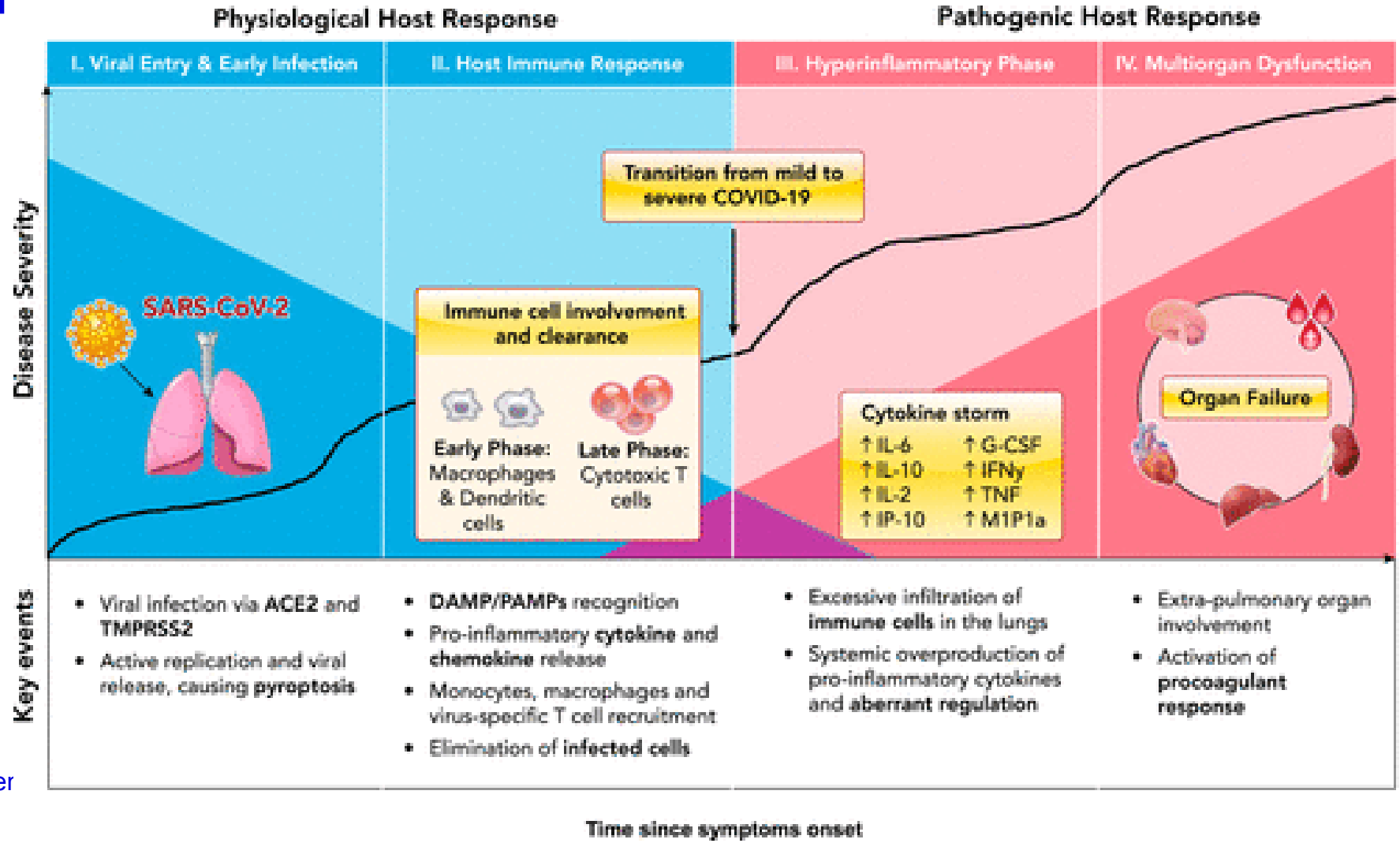
Pathogenesis of Covid-19 disease – key steps



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SIRS

- Generalized deregulated destructive process
- Often associated with the devastation of distant organs
- In hypersensitivity individuals, SIRS may occur even with very small amounts of antigen
- Classification:
- 1) septic SIRS - associated with infection
- 2) unseptic SIRS - after severe trauma, hypoxemia, burns, poisoning, incompatible transfusion

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Septic SIRS

- Disseminated microbial infection
- 50% - gram-positive bacteria, 30% - gram-negative bacteria, 5% - polymicrobial infections, 5% yeasts and fungi and 1% anaerobes
- 1/3 of those affected die

Primary SIRS
Secondary SIRS

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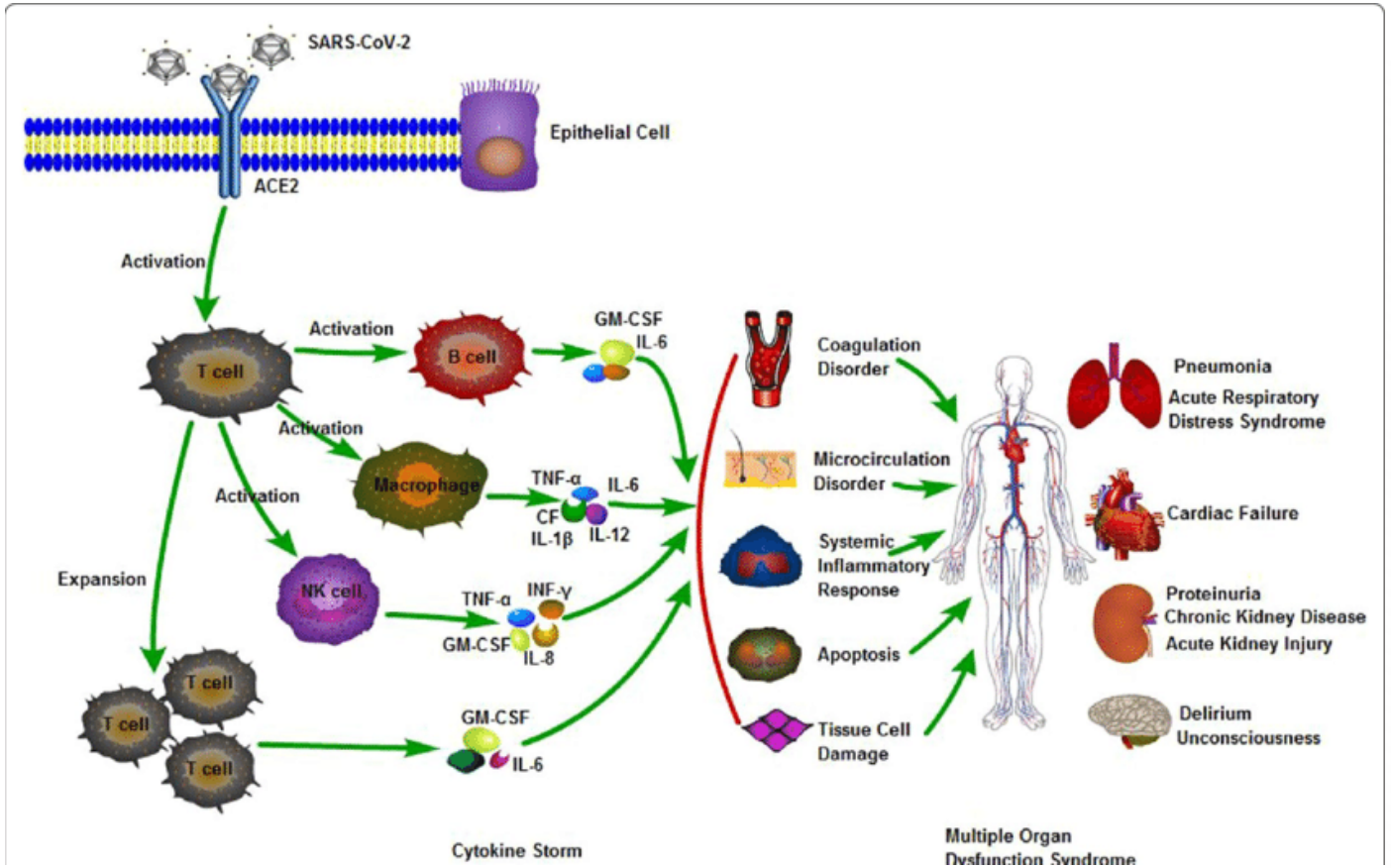
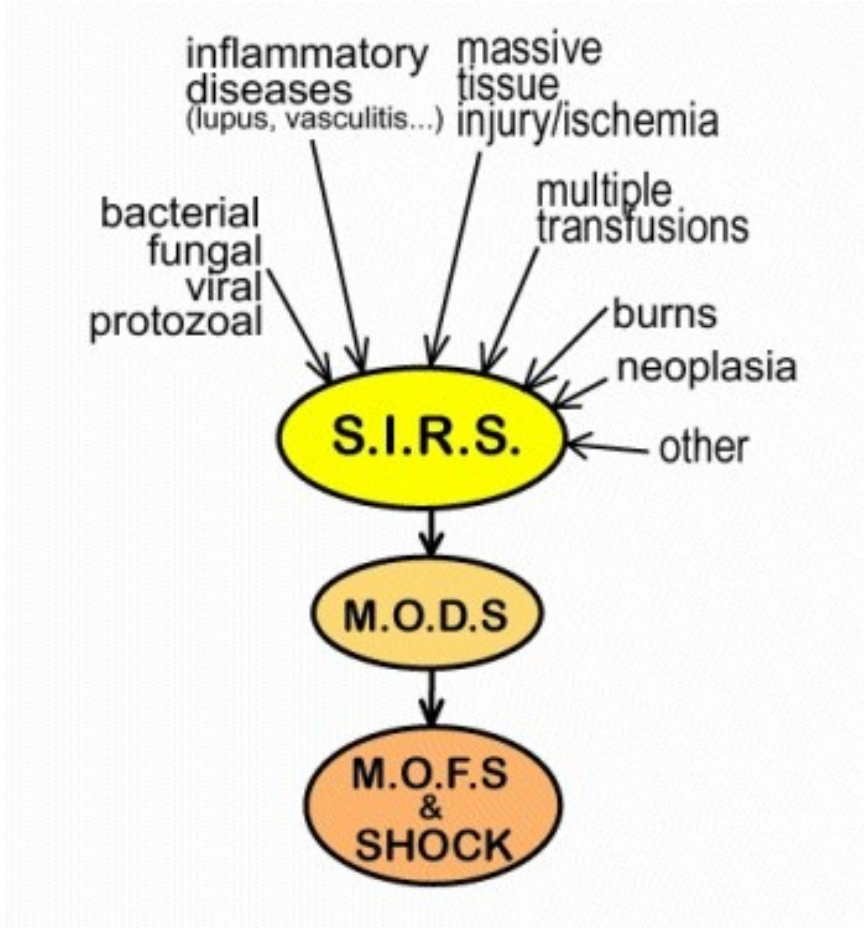
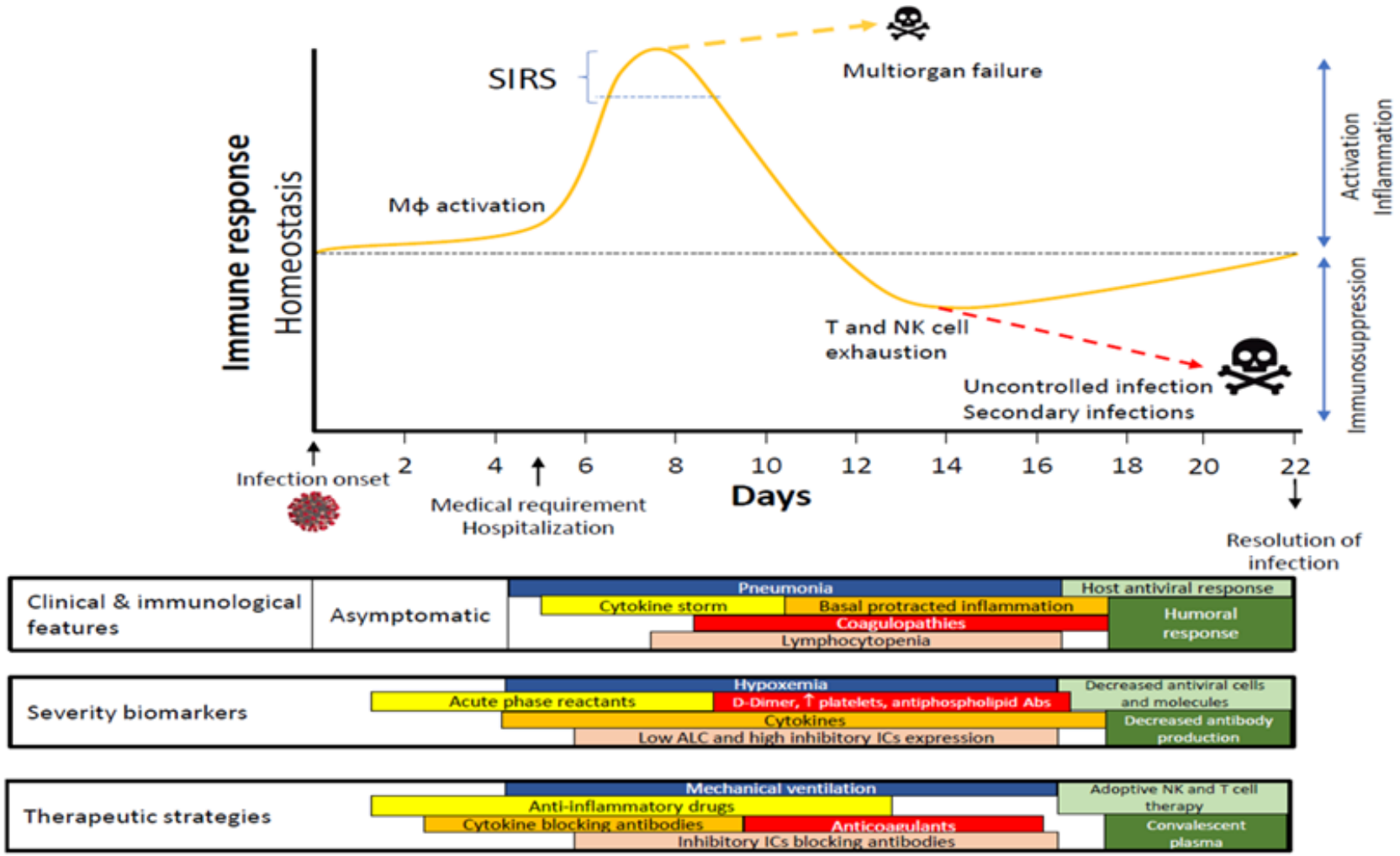
MED

MODS

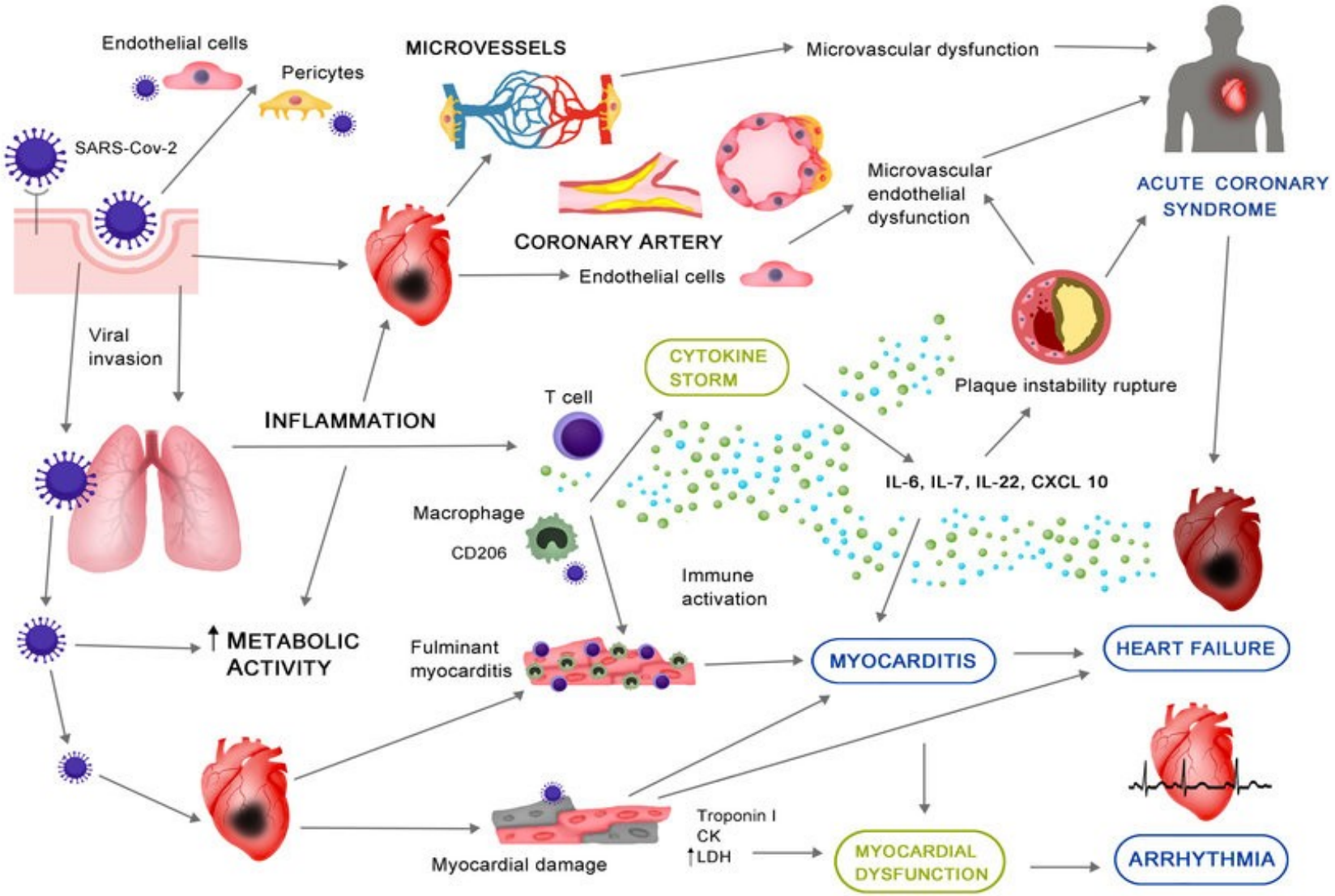

SARS-CoV-2
Epithelial Cell
ACE2
Activation
T cell
Activation
B cell
GM-CSF
IL-6
Activation
Macrophage
TNF-α
IL-6
CF
IL-1β
IL-12
Activation
NK cell
TNF-α
INF-γ
GM-CSF
IL-8
Expansion
T cell
T cell
T cell
GM-CSF
IL-6
Cytokine Storm
Coagulation Disorder
Microcirculation Disorder
Systemic Inflammatory Response
Apoptosis
Tissue Cell Damage
Pneumonia
Acute Respiratory Distress Syndrome
Cardiac Failure
Proteinuria
Chronic Kidney Disease
Acute Kidney Injury
Delirium
Unconsciousness
Multiple Organ Dysfunction Syndrome


inflammatory diseases (lupus, vasculitis...)
massive tissue injury/ischemia
bacterial
fungal
viral
protozoal
multiple transfusions
burns
neoplasia
other
S.I.R.S.
M.O.D.S
M.O.F.S & SHOCK

SIRS, MODS and Covid-19

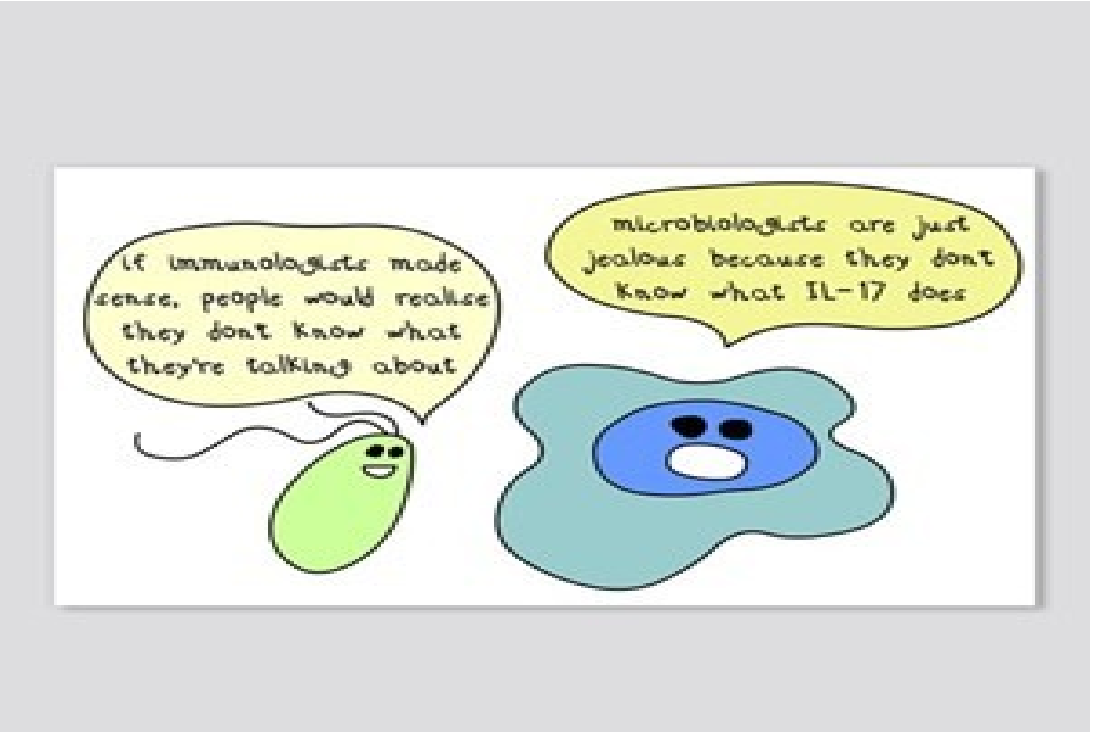


MUNI MED


Endothelial cells
Pericytes
MICROVESSELS
Microvascular dysfunction
SARS-Cov-2
CORONARY ARTERY
Endothelial cells
Microvascular endothelial dysfunction
ACUTE CORONARY SYNDROME
Viral invasion
CYTOKINE STORM
Plaque instability rupture
INFLAMMATION
T cell
IL-6, IL-7, IL-22, CXCL 10
Macrophage
CD206
Immune activation
METABOLIC ACTIVITY
Fulminant myocarditis
MYOCARDITIS
HEART FAILURE
Troponin I
CK
LDH
Myocardial damage
MYOCARDIAL DYSFUNCTION
ARRHYTHMIA

MUNI MED

Thank you for you attention



MUNI MED