

M U N I
M E D

**Pathophysiology of chronic inflammation,
etiopathogenesis, consequences,
systemic inflammation, SIRS, MODS**

Immune system

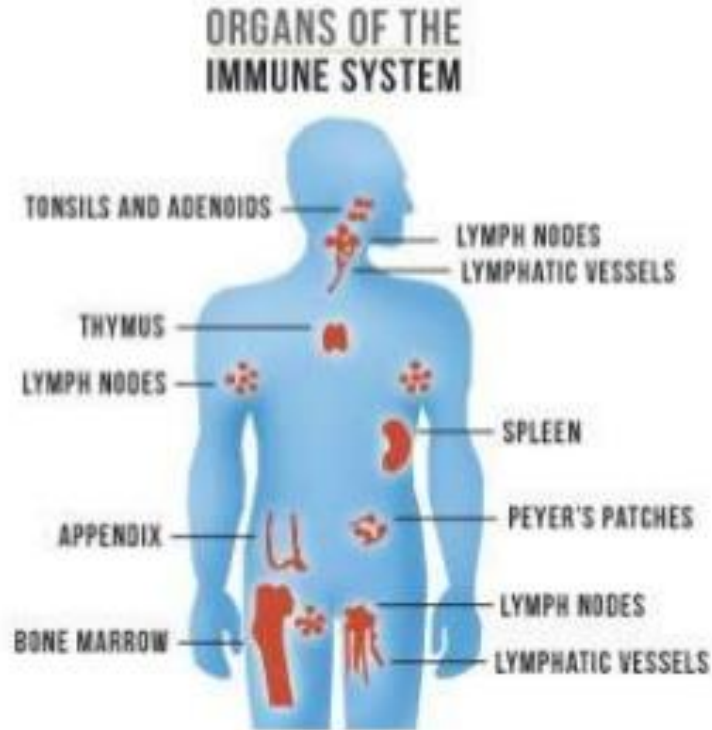
- **Immune system** = cells, tissues and molecules that mediate resistance to infections
- **Immunology** = study of the structure and function of the immune system **Immunity** = host resistance to pathogens and their toxic effects
- **Immune response** = collective and coordinated response to the introduction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

The role of the immune system

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

The components of the immune system

Major Components of the Immune System:



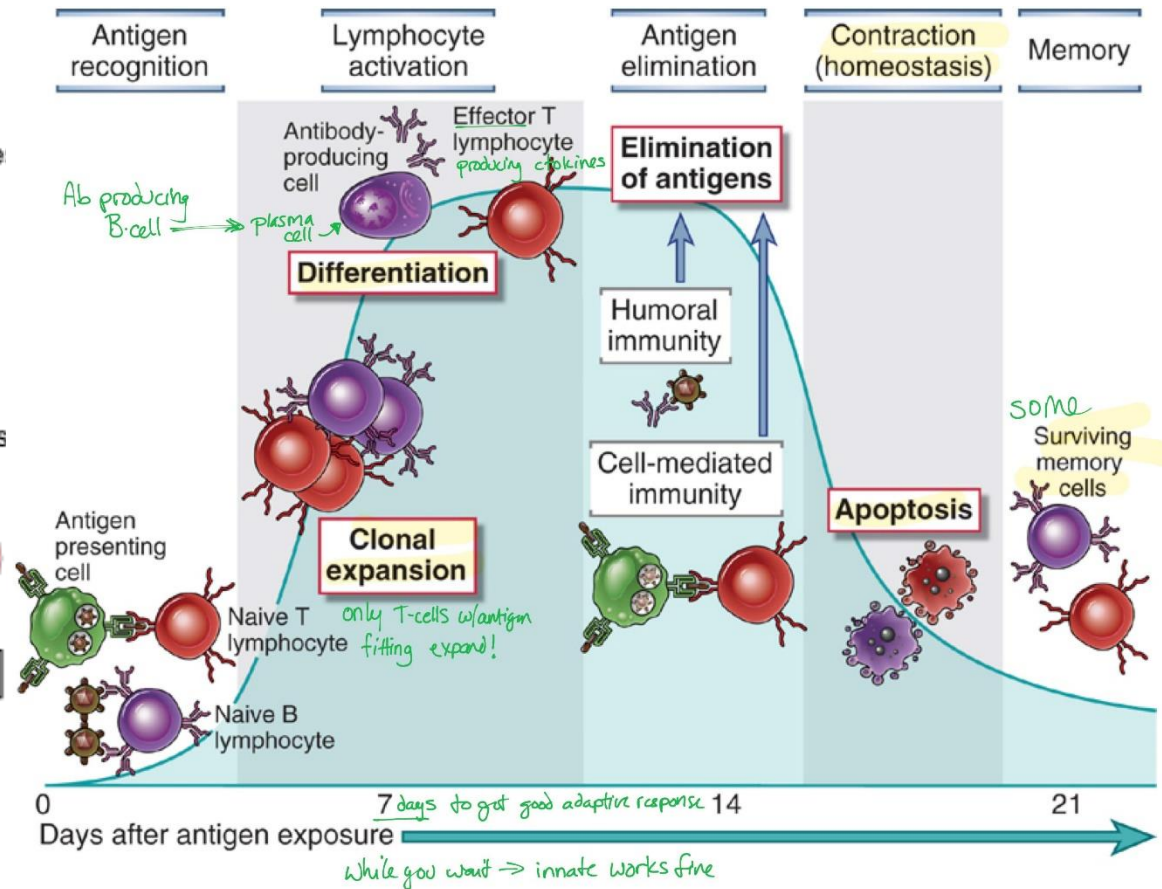
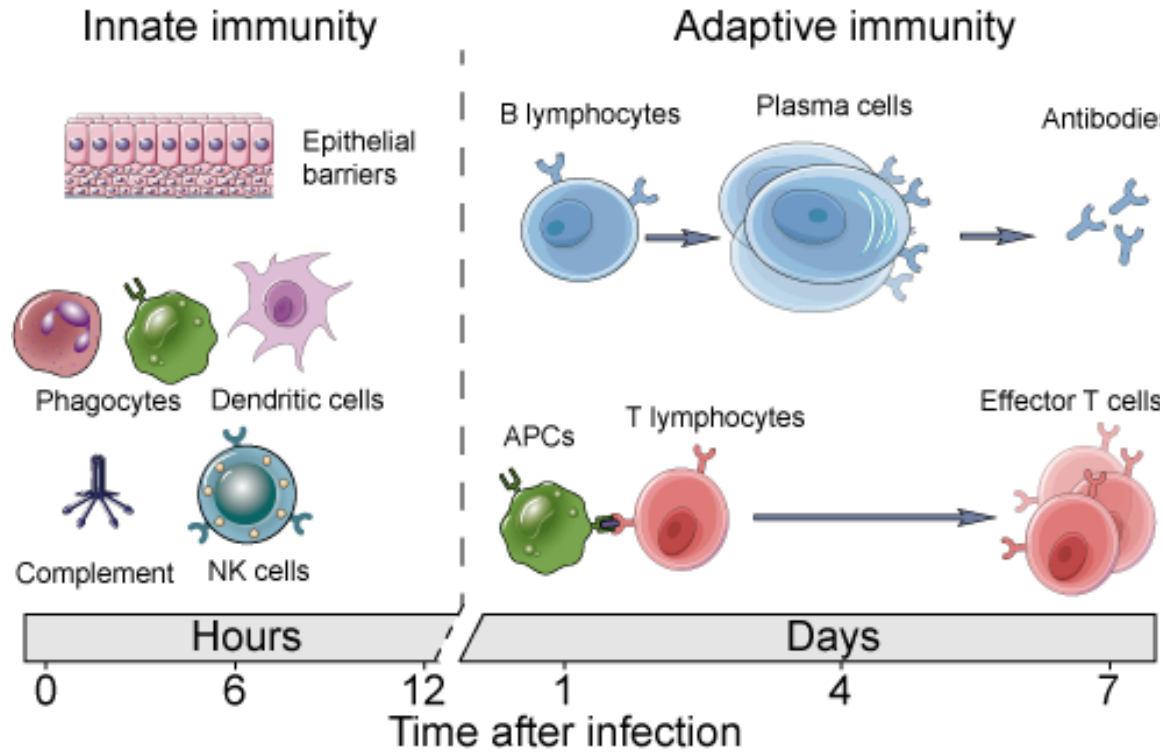
Organs related to our Immune System

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

The type of immune response

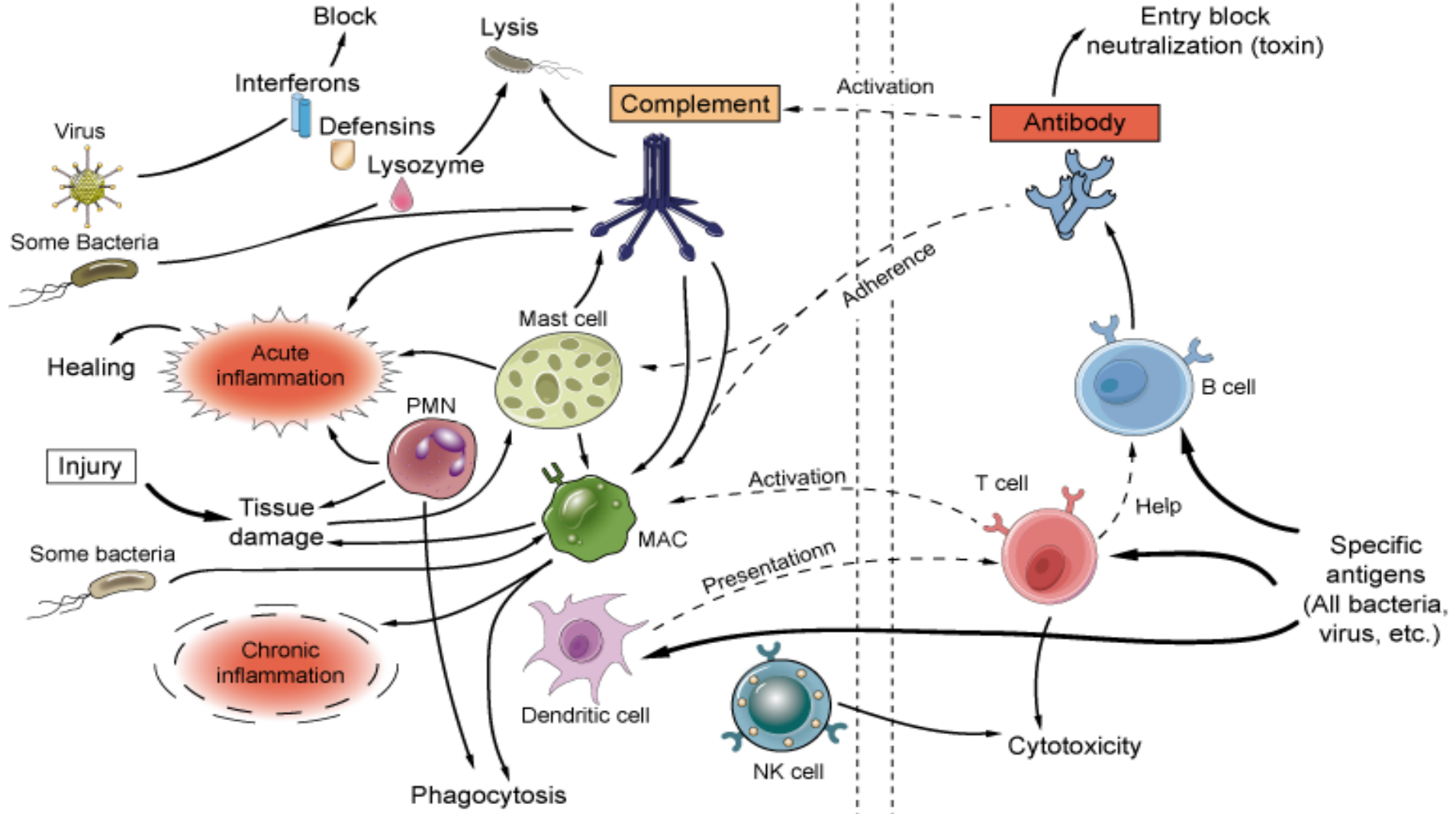
- **Innate (non-adaptive):** the first-line immune response relies on mechanisms that existed before infection
- **Acquired (adaptive) immunity:** The second line of response (if innate immunity fails) relies on mechanisms involving cellular memory of key T- and B-lymphocytes

Timeline



Innate immunity

Adaptive immunity



Tissues

Myeloid cells

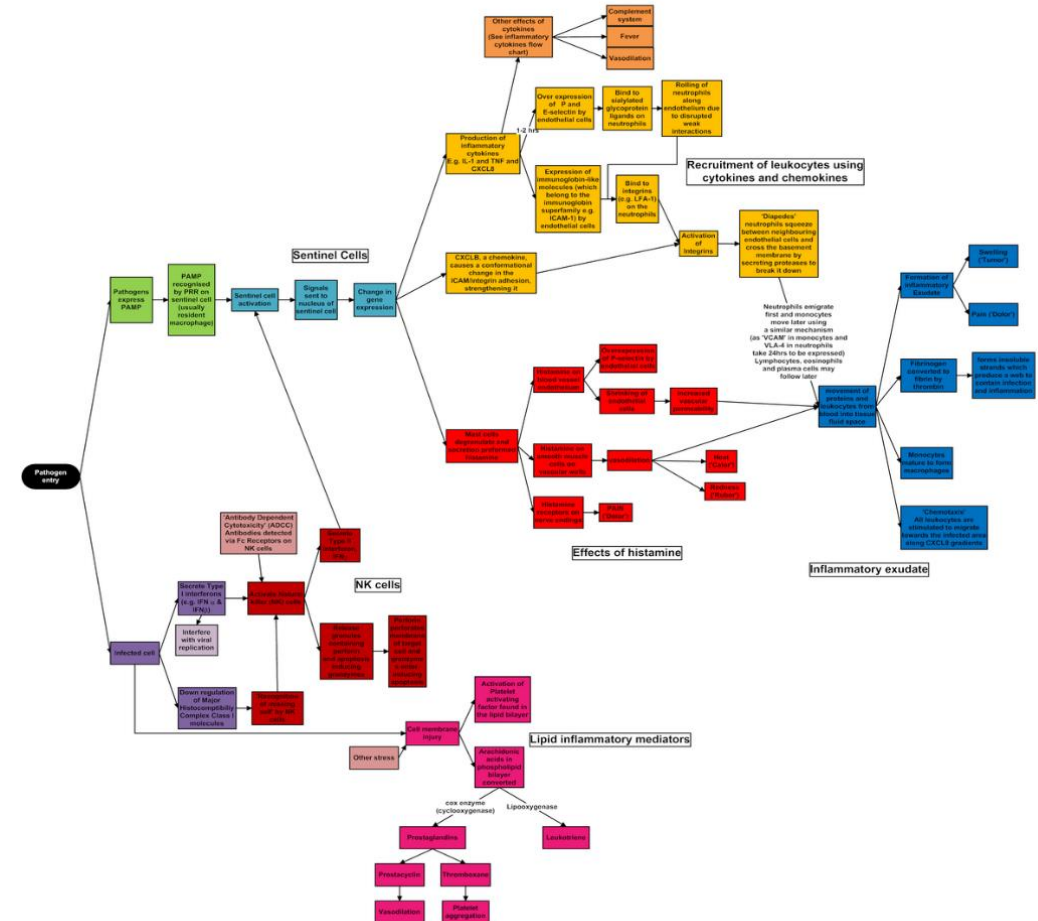
Lymphocytes

Innate immunity

INNATE IMMUNE SYSTEM

By Architha Srinivasan
Cambridge University

- 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

Adaptive immunity

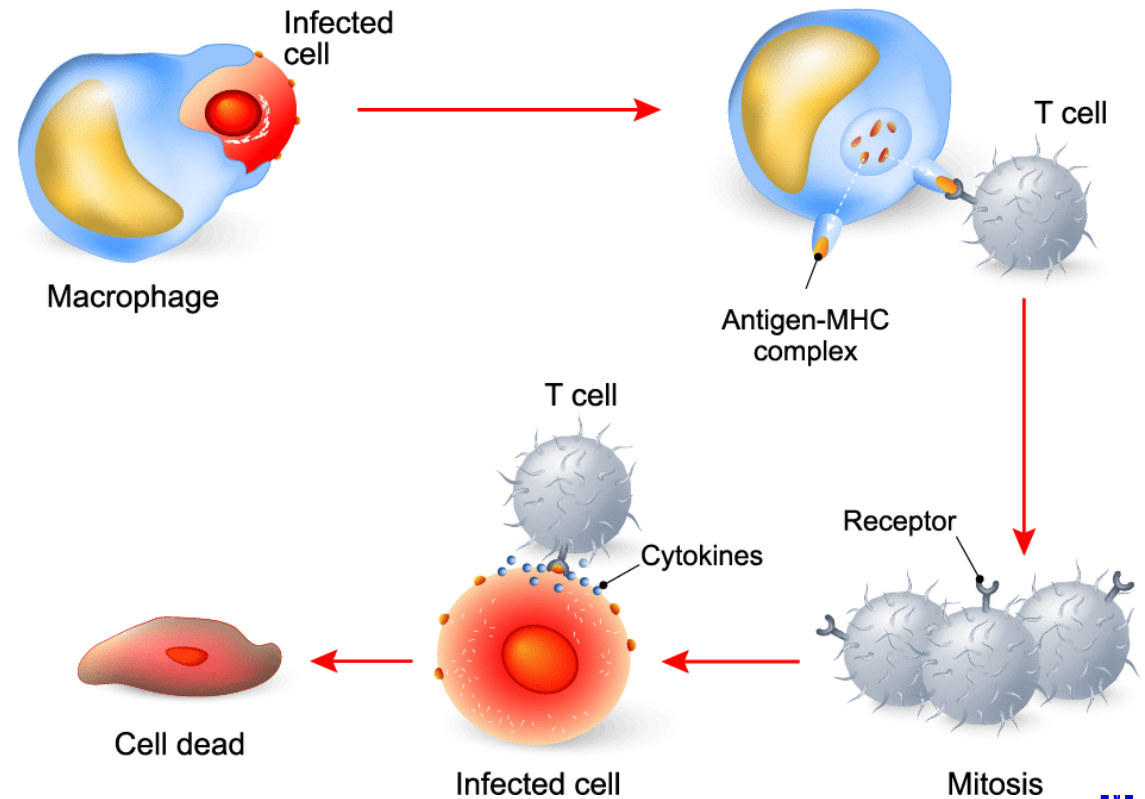
- Based on resistance acquired during life
- Relies on the genetic background of the individual and cell growth
- The reaction is slower, in a number of days
- It is specific
- Each cell responds to one epitope on the antigen
- It has anamnestic memory
- Repeated exposure leads to a faster and stronger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

Adaptive immunity mechanisms

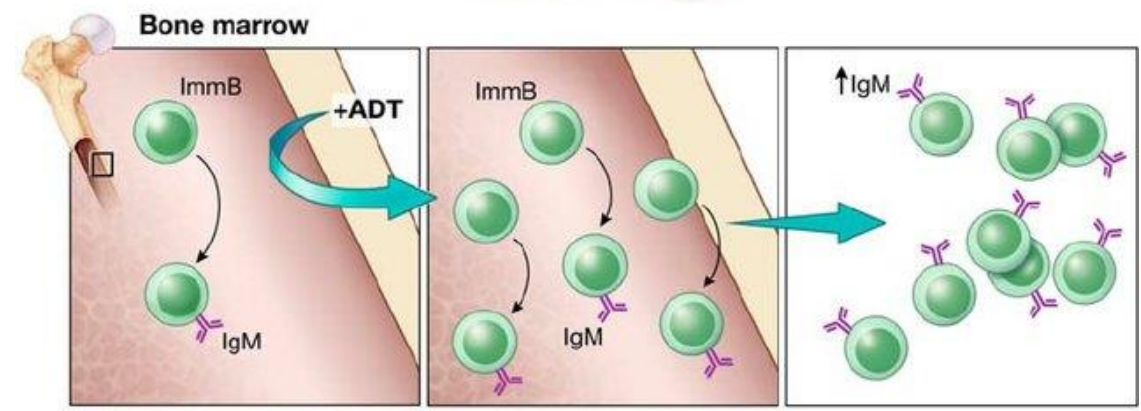
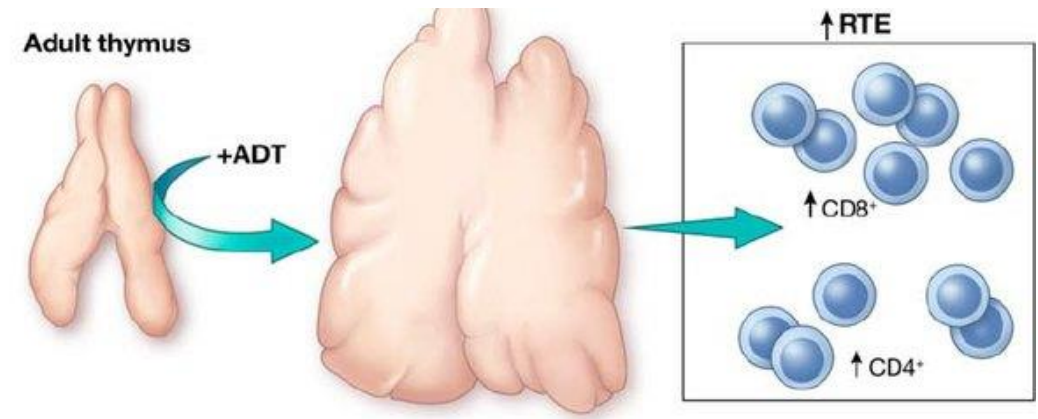
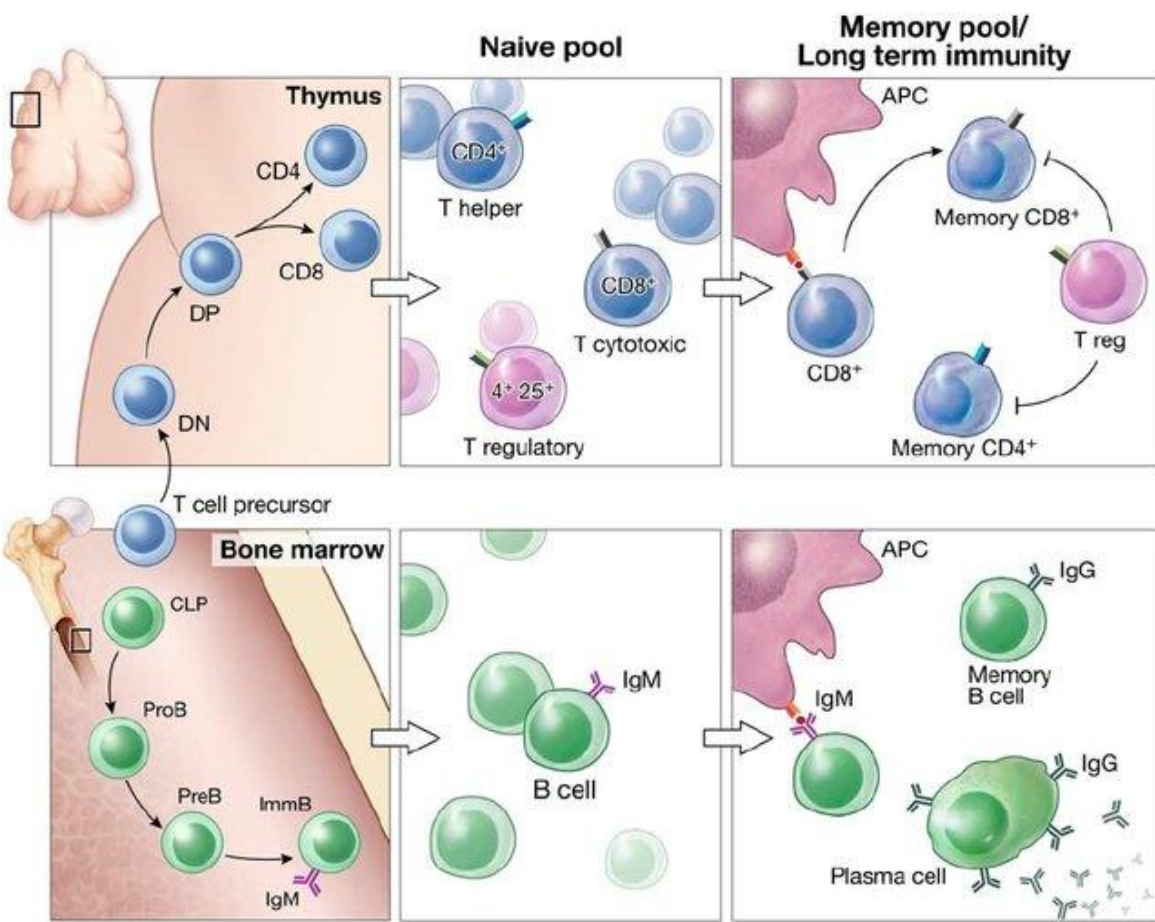
- **Cell-mediated immune response (CMIR)**
- T-lymphocytes
- Elimination of intracellular microbes that survive inside phagocytes or other infected cells

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

IMMUNE RESPONSE



Adaptive immunity: mechanisms



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.

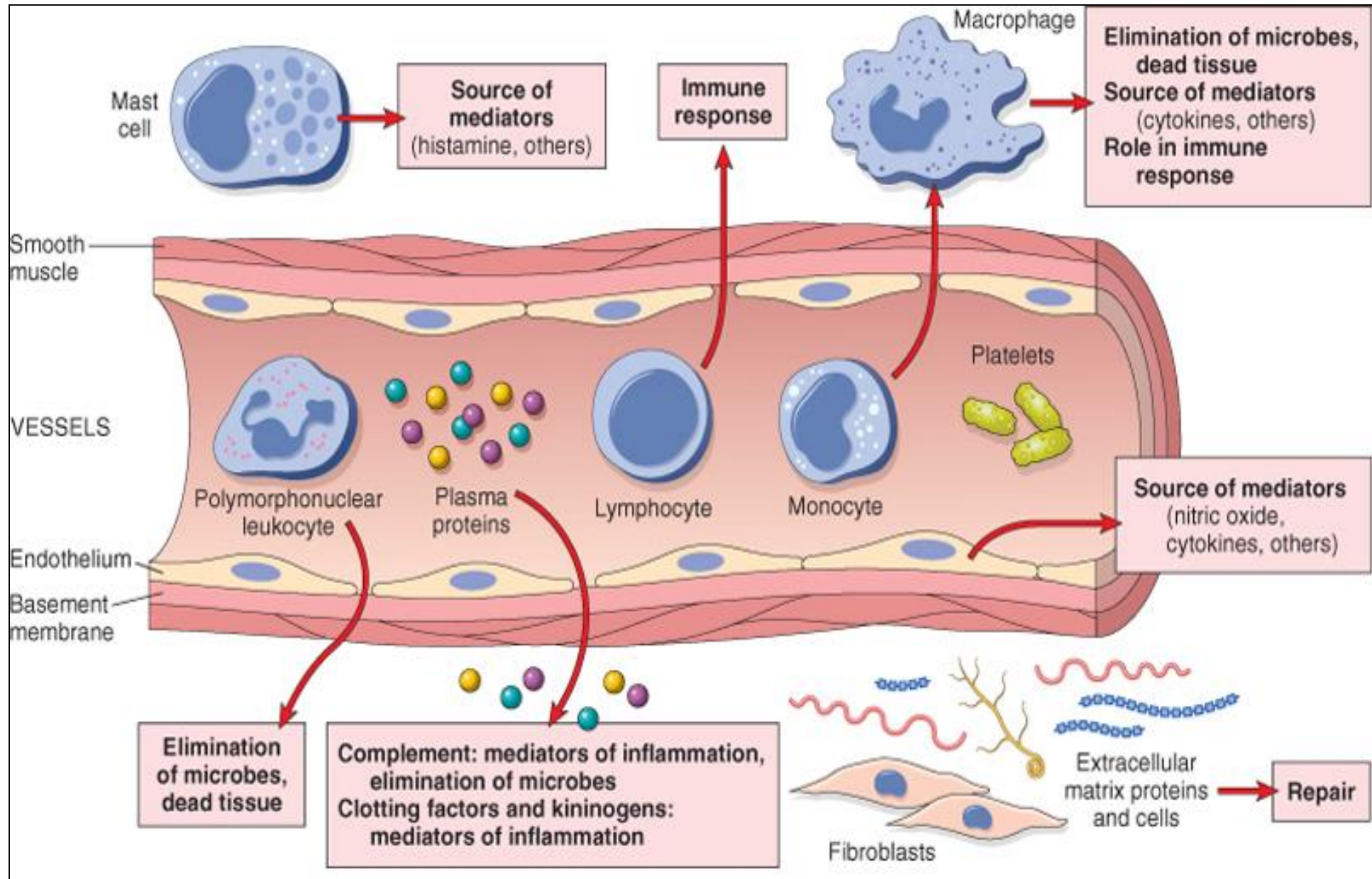
How to accomplish protective mission?

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.

Cells and molecules that play important roles in inflammation

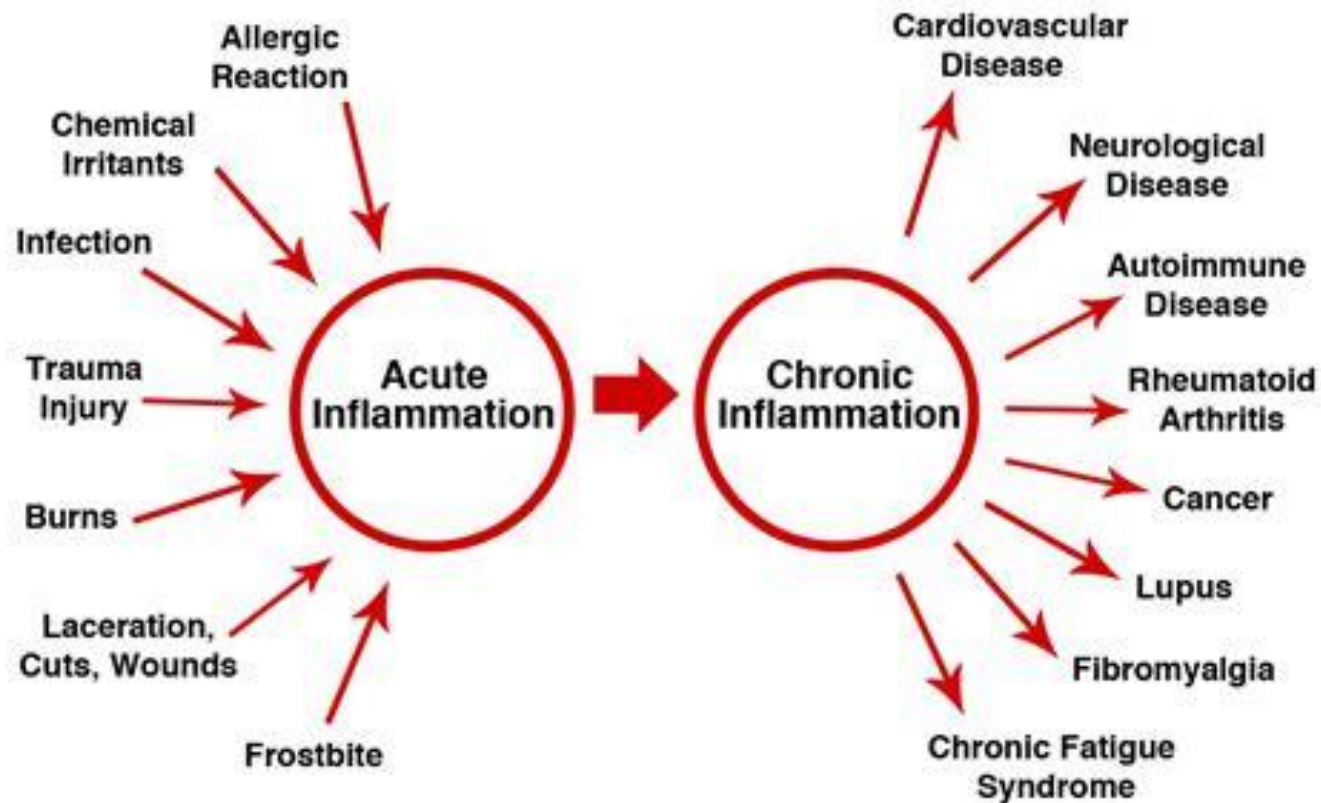


Steps of the inflammatory response

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

Inflammation

Acute Vs. Chronic 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.

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

Can Inflammation cause considerable harm to the body?

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

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

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

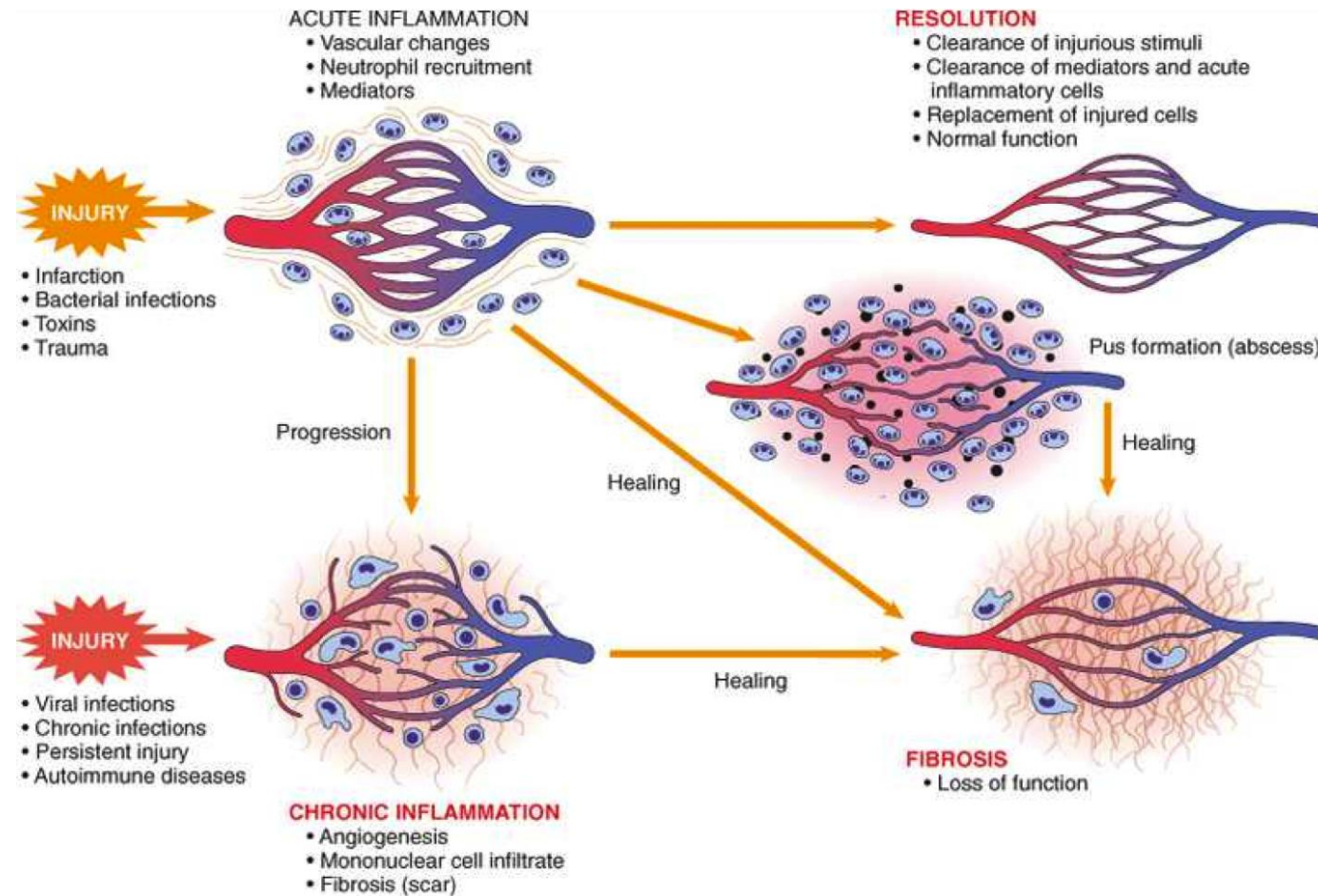
Inflammation

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

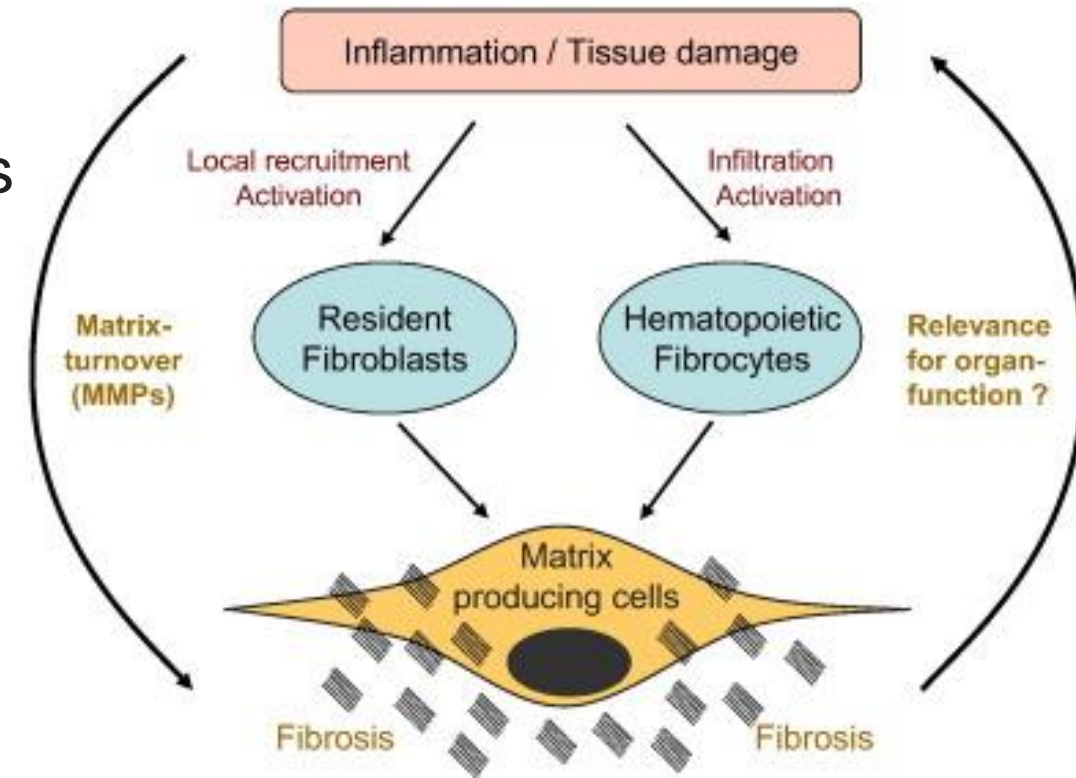
Morphological features of chronic inflammation



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

Fibrosis

- Fibrosis is defined by the overgrowth, hardening, and/or scarring of various tissues and is attributed to excess deposition of extracellular matrix components including collagen.
- Fibrosis is the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults, radiation, and tissue injury.



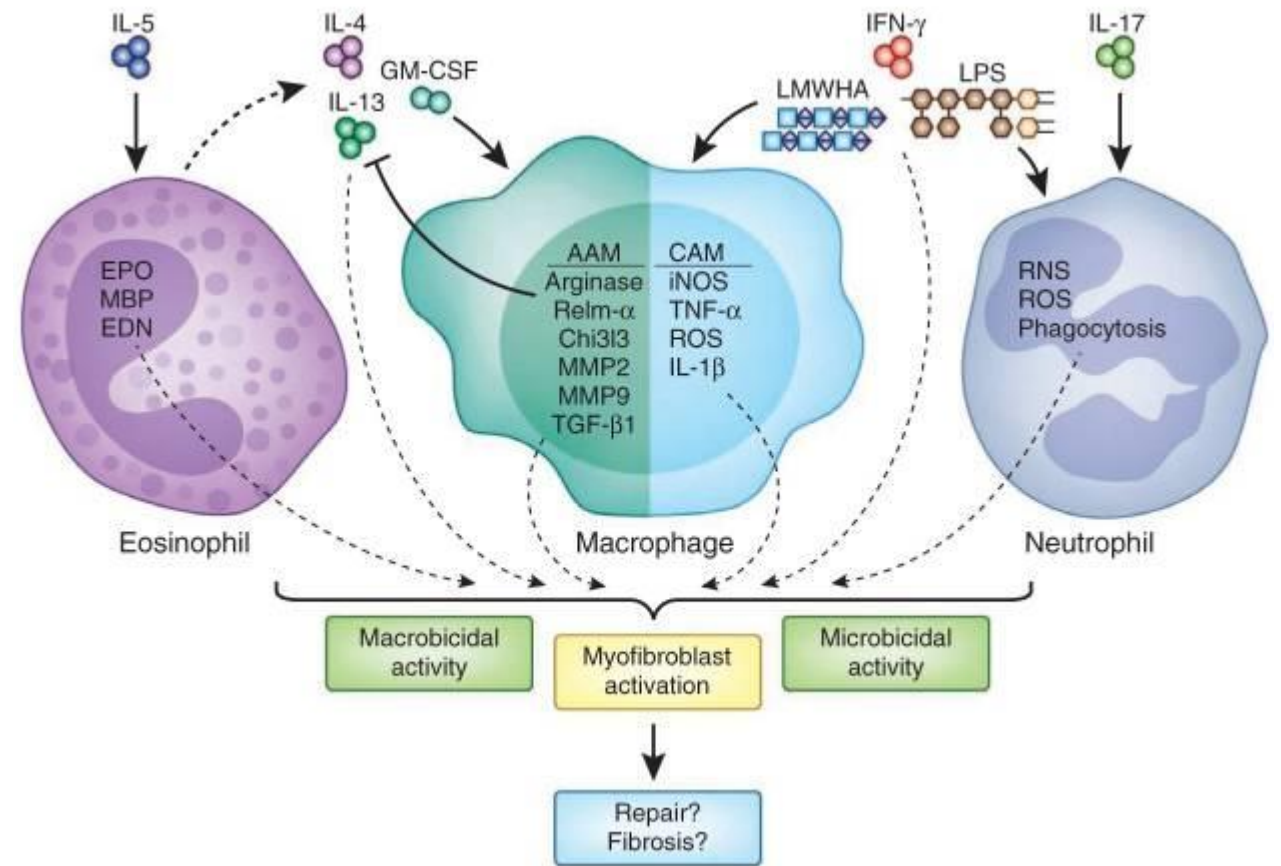
Matthias Mack, Matrix Biology, Volumes 68–69, 2018,

Major tissues affected by fibrosis and possible contributing factors

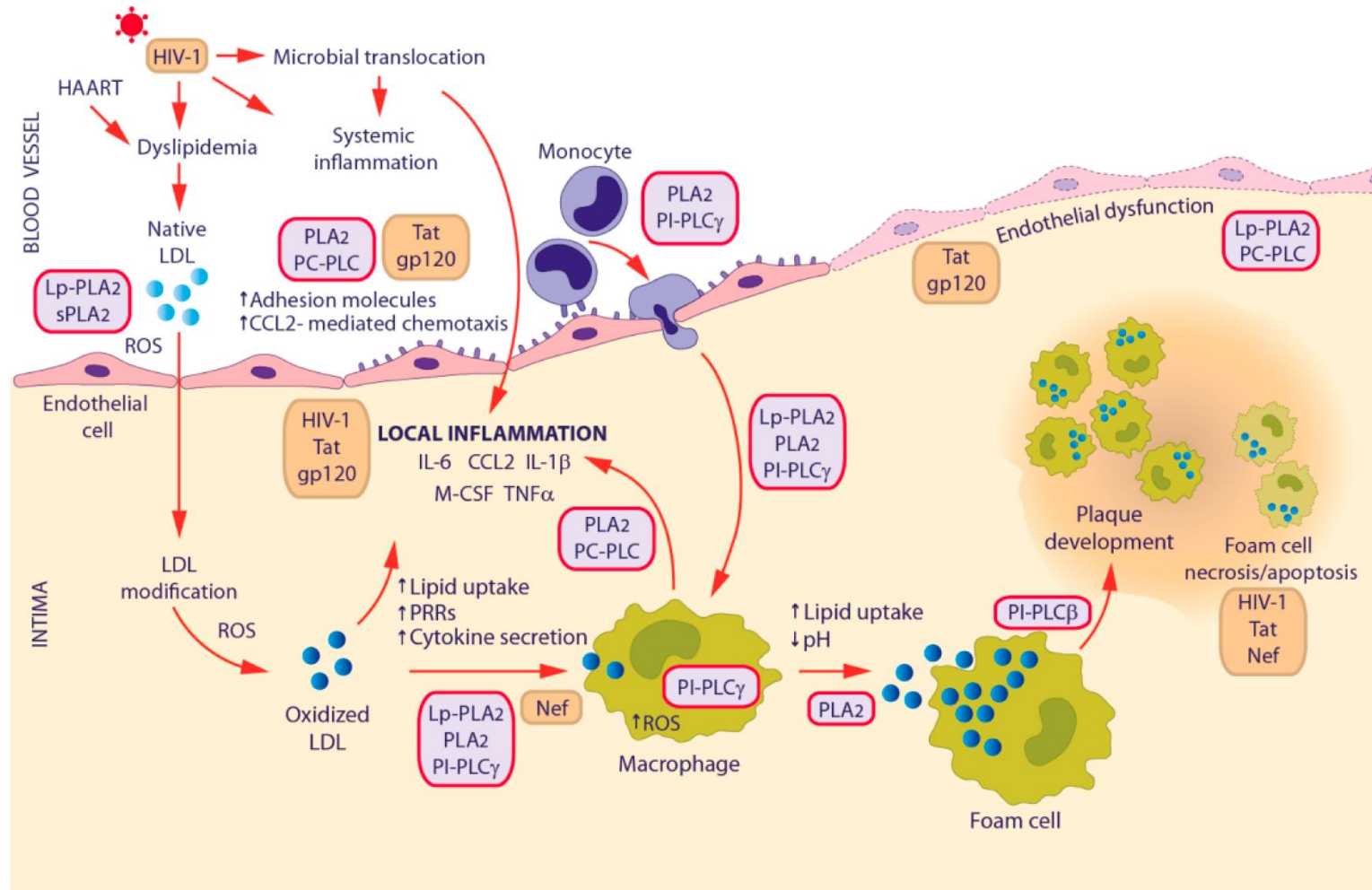
- *Liver*—Viral hepatitis, schistosomiasis, and alcoholism are leading causes of cirrhosis worldwide.
- *Lung*—The interstitial lung diseases (ILDs) include a diverse set of disorders in which pulmonary inflammation and fibrosis are the final common pathological manifestations. There are more than 150 different causes of ILDs, including sarcoidosis, silicosis, drug reactions and infections, as well as collagen vascular diseases, such as rheumatoid arthritis and systemic sclerosis (scleroderma). Idiopathic pulmonary fibrosis, the most common type of ILD, has no known cause
- *Kidney disease*—Diabetes damages and scars the kidneys, which can lead to a progressive loss of function. Untreated hypertension can contribute
- *Heart and vascular disease*—Following a heart attack, scar tissue can impair the ability of the heart to pump blood. Hypertension, atherosclerosis and restenosis also contribute
- *Eye*—Macular degeneration, retinal and vitreal retinopathy can lead to blindness
- *Skin*—Including keloids and hypertrophic scars. Systemic sclerosis and scleroderma, burns and genetic factors may also contribute
- *Pancreas*—Poorly understood but possible autoimmune/hereditary causes
- *Intestine*—Crohn's disease/inflammatory bowel disease. Pathogenic organisms
- *Brain*—Alzheimer's disease, AIDS
- *Bone marrow*—Cancer and ageing
- *Multi-organ fibrosis*—(a) Due to surgical complications; scar tissue can form between internal organs, causing contracture, pain and, in some cases, infertility; (b) chemotherapeutic drug-induced fibrosis; (c) radiation-induced fibrosis as a result of cancer therapy/accidental exposure; (d) mechanical injuries

Innate immune cells in fibrosis

- Dysregulated innate and adaptive immune responses are major contributors to fibrosis.
- However, cell-intrinsic modifications in fibroblasts and other structural cells can also contribute to fibrosis

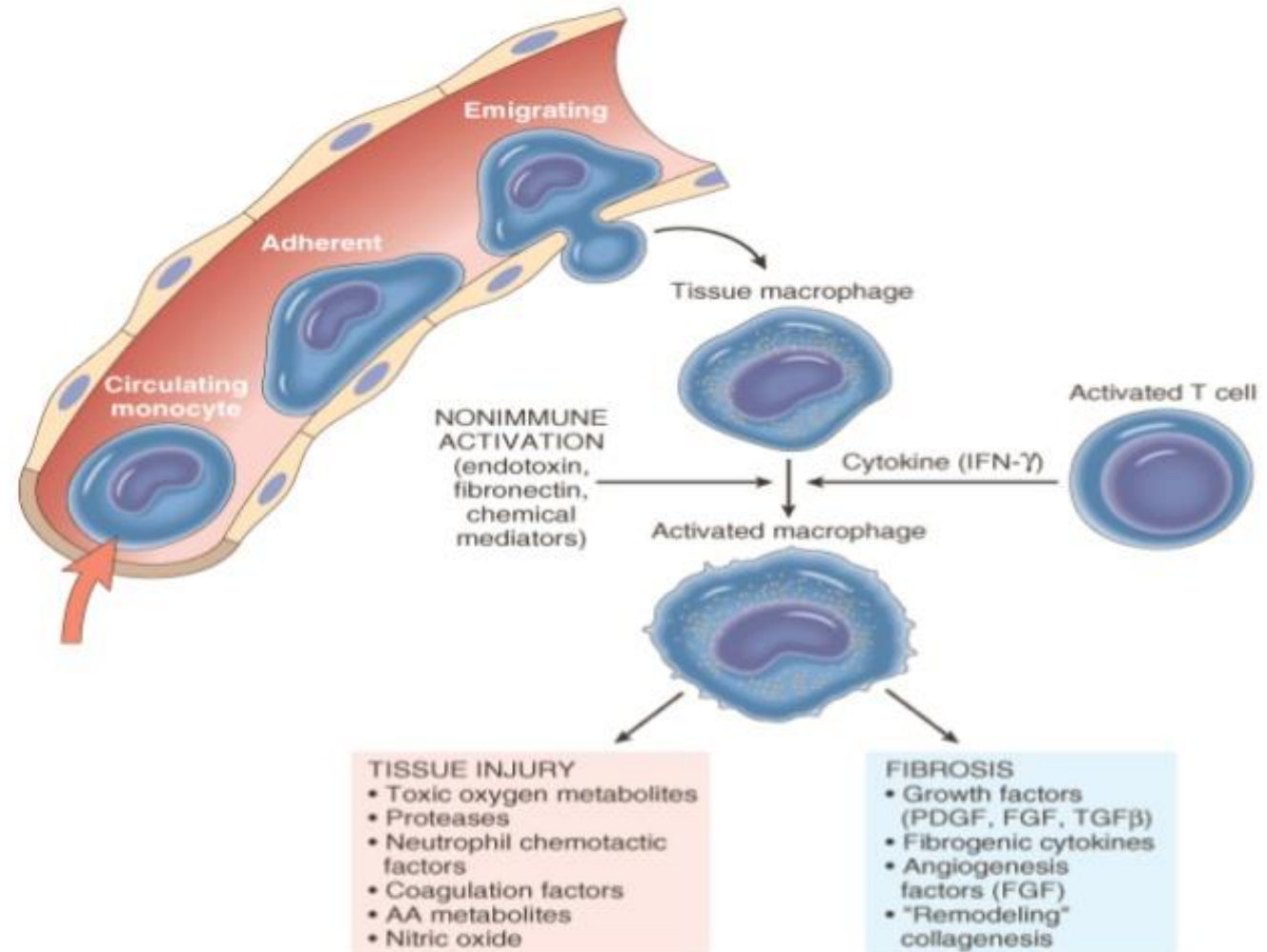


The role of macrophages in chronic inflammation



The role of macrophages in chronic inflammation and ECM remodelling

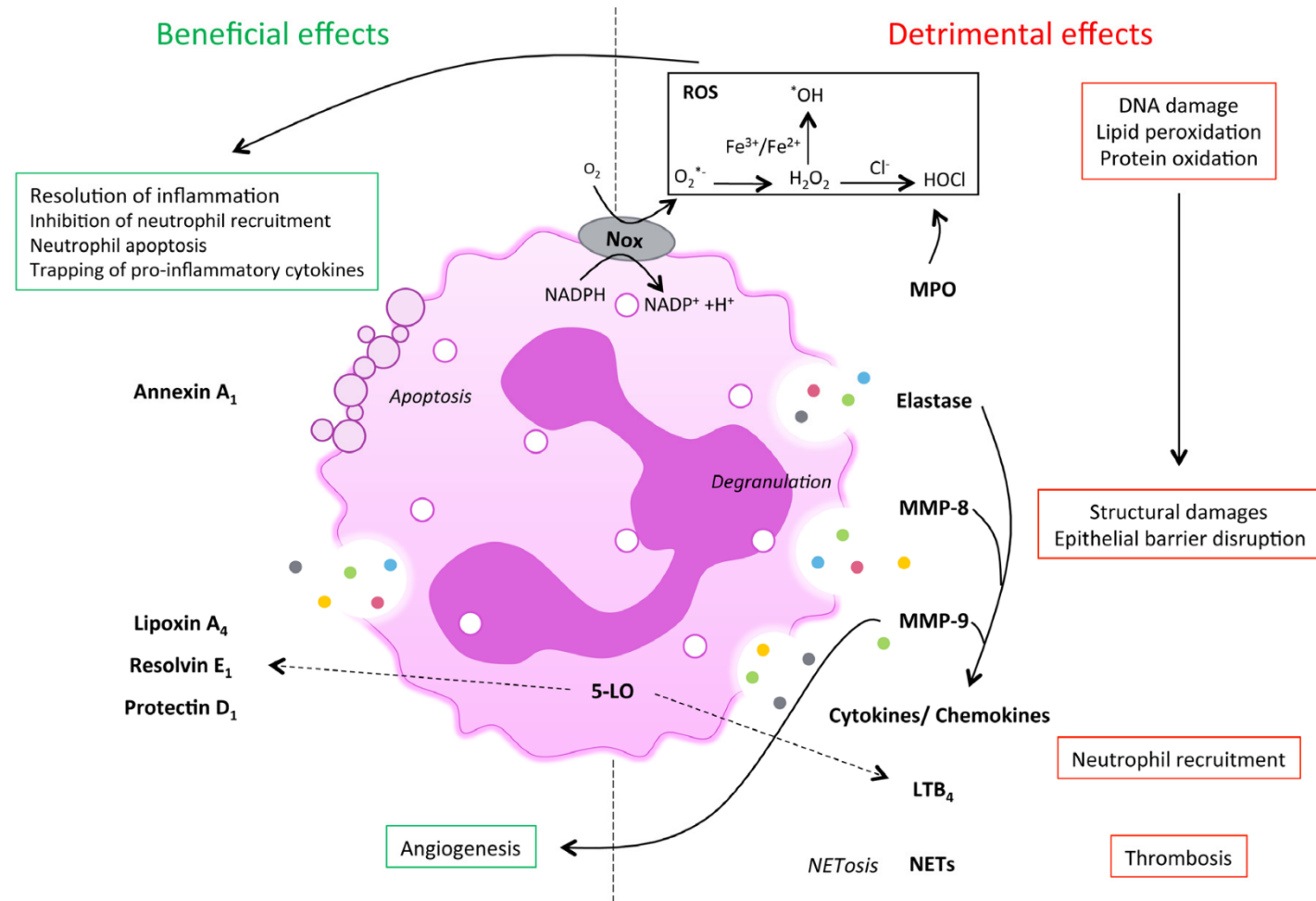
Macrophages play a pivotal role in secretion of ECM components and in ECM remodelling. They are major sources of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) and are the primary cells involved in the phagocytosis of cellular debris and infectious agents.



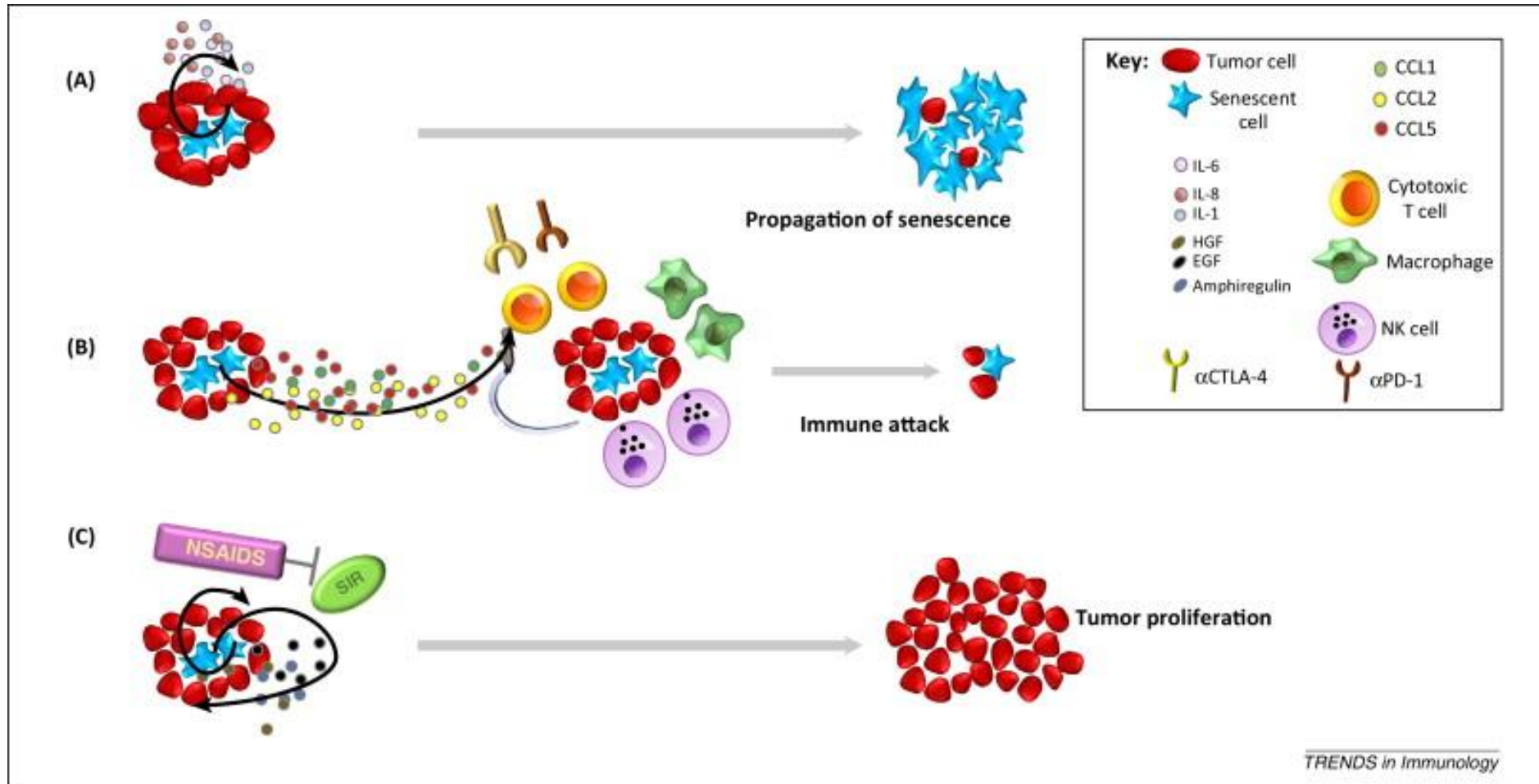
The role of neutrophils in chronic inflammation and ECM remodelling

Activated neutrophils have recently been found to form neutrophil extracellular traps (NETs) that are involved in immune responses to pathogens.

NETs are composed of chromatin and granular proteins, including nuclear DNA, histones, MMP-9, myeloperoxidase (MPO), neutrophil elastase (NE), and cathepsin G.

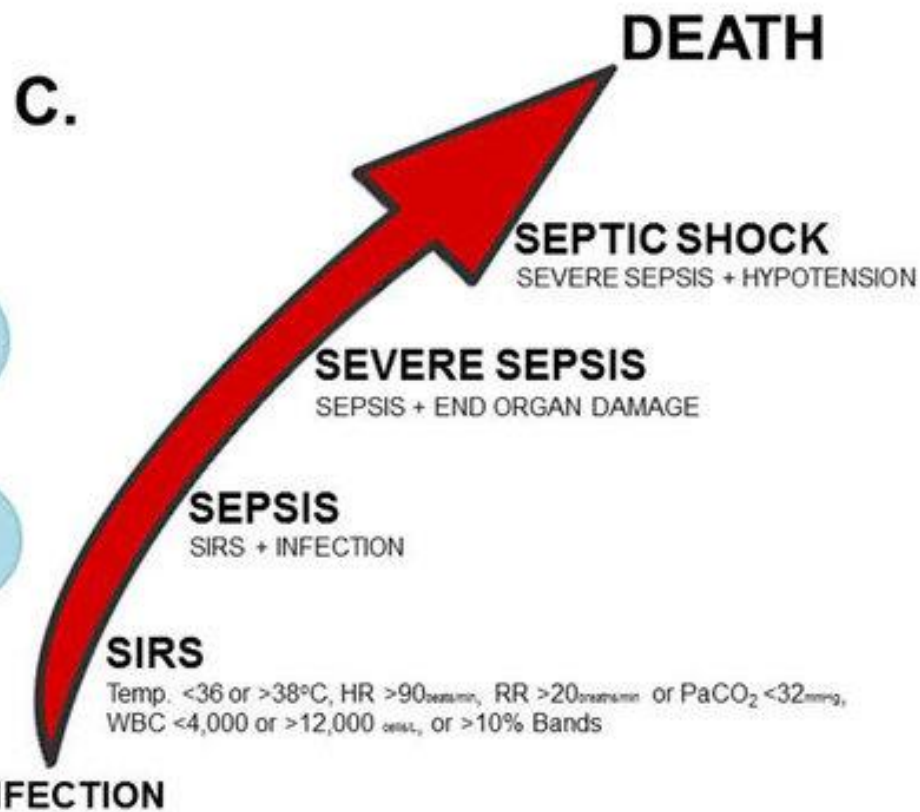
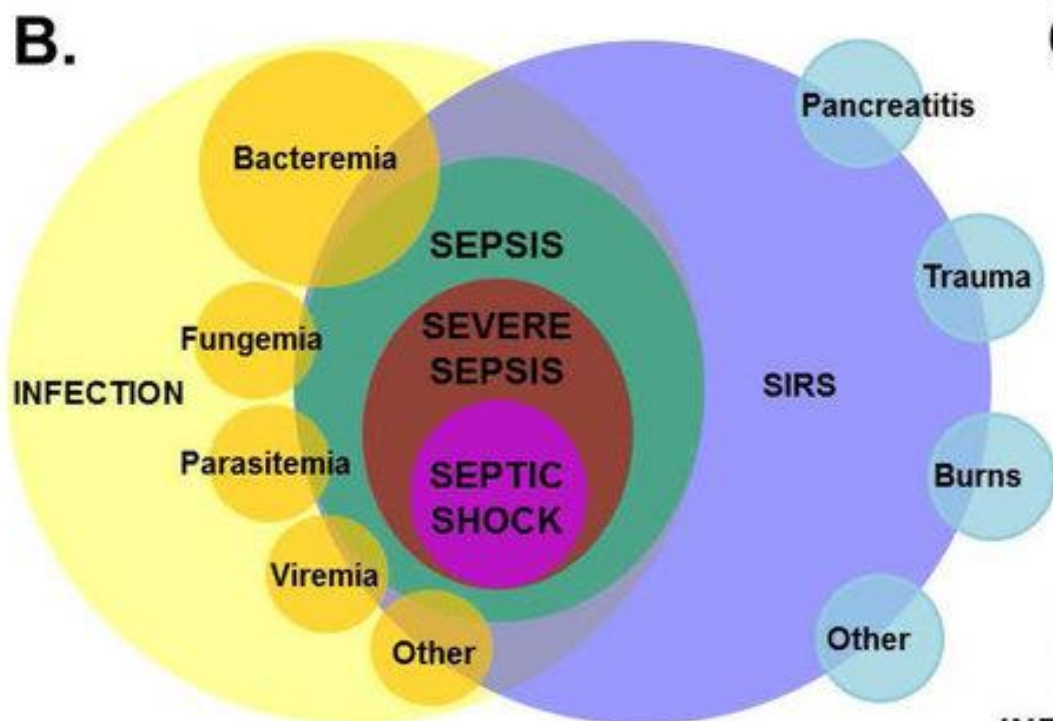
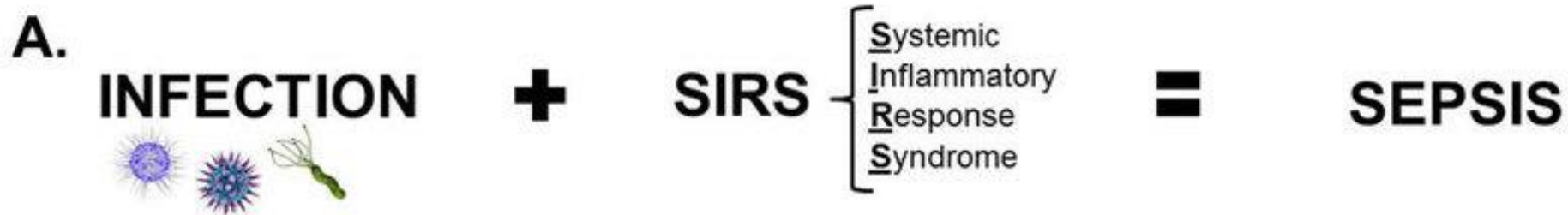


Age-dependent consequences



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



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) non-septic SIRS - after severe trauma, hypoxemia, burns, poisoning, incompatible transfusion

Examples of Inciting Factors of SIRS

STERILE INFLAMMATORY DISEASES <i>Nonseptic SIRS</i>	INFECTIOUS INSULTS <i>Septic SIRS</i>
<ul style="list-style-type: none">• Burns• Chemical aspiration• Heatstroke• Immune-mediated disease• Ischemic organ necrosis (eg, splenic torsion)• Neoplasia• Pancreatitis• Trauma	<ul style="list-style-type: none">• Anaerobic bacteria• Fungi• Products of gram-negative bacteria• Products of gram-positive bacteria• Protozoa• Viruses

Sepsis

- 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

Distinctions Between SIRS & Sepsis

SIRS	Clinical manifestation of systemic inflammation, which results from either: <ul style="list-style-type: none">• Infectious insult (septic SIRS)• Noninfectious insult (nonseptic SIRS)
SEPSIS	Clinical manifestation of SIRS, secondary to an underlying pathogenic organism
SEVERE SEPSIS	Sepsis—with associated SIRS—with 1 or more of the following: <ul style="list-style-type: none">• Arterial hypotension• Organ dysfunction• Hypoperfusion; abnormalities suggestive of hypoperfusion may include hyperlactatemia and oliguria
SEPTIC SHOCK	Despite adequate intravascular fluid resuscitation, sepsis-associated: <ul style="list-style-type: none">• Acute circulatory failure• Persistent arterial hypotension
MODS	Physiologic derangements of at least 2 major organ systems associated with SIRS (see Table 4)

MODS = multiple organ dysfunction syndrome

Definition of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS)

Systemic inflammatory response syndrome

- The systemic inflammatory response to a variety of severe clinical insults is manifest by two or more of the following conditions:
- Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $P_{\text{aco}2} < 32$ mmHg (or ventilator dependence)
- White blood cell count $> 12\,000$ cells/mm³, < 4000 cells/mm³ or $> 10\%$ band forms

Multiple organ dysfunction syndrome

The presence of altered function involving at least two or more organ systems in an acutely ill patient such that homeostasis cannot be maintained without intervention

Definitions

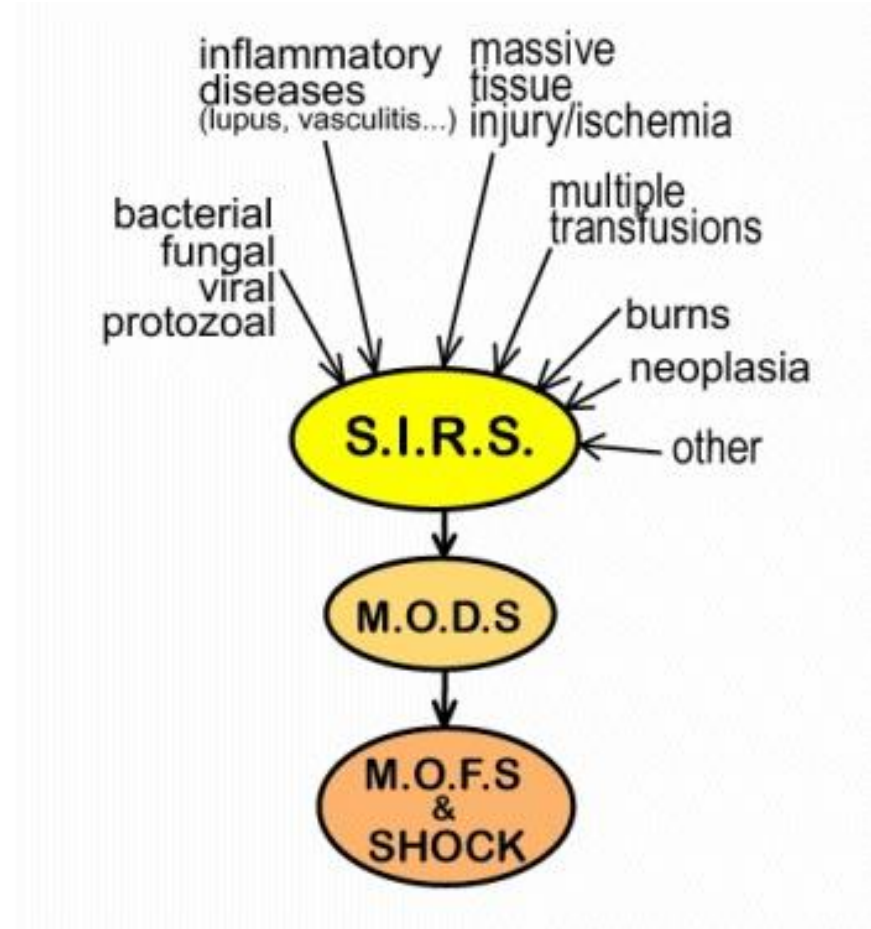
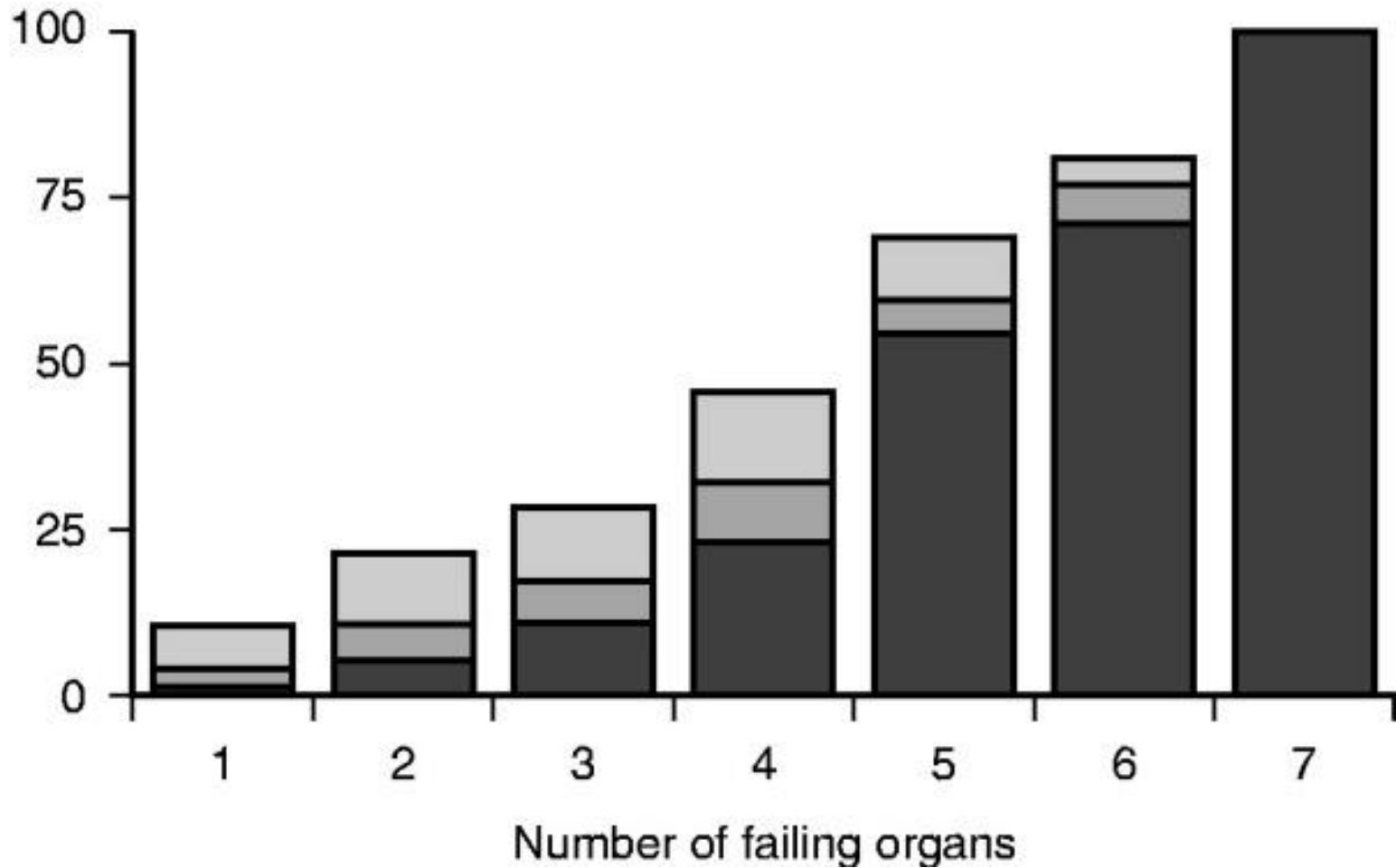
- Multiple Organ Dysfunction Syndrome “MODS”

1991 Consensus conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)

Dysfunction replaced failure to accentuate the reversible nature of the condition

- Underlying concept

Sepsis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), and MODS are closely related phenomena



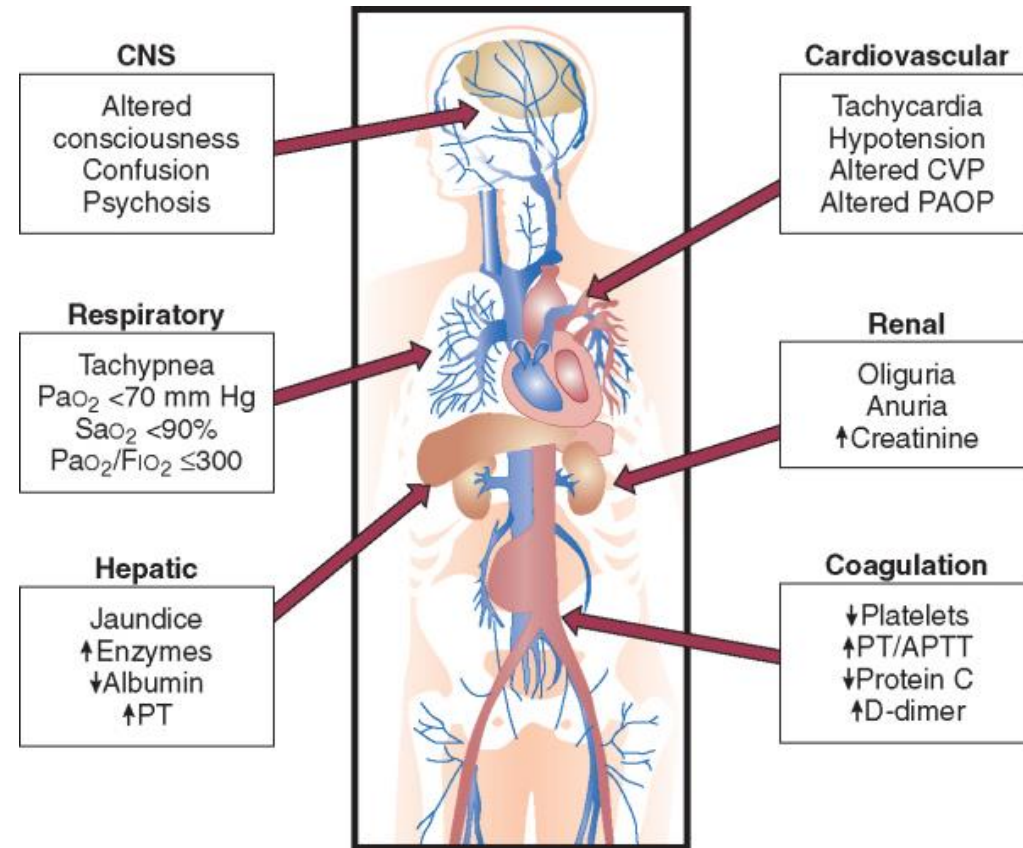
Mortality in intensive care unit *black*
 Mortality to hospital discharge *black + dark grey*
 Mortality to 1 year *black + dark grey + light grey.*

Mayr VD et al Causes of death and determinants of outcome in critically ill patients Crit Care 10:R154, 2006.

Definitions

Most organ failure assessment systems assign values to six organ systems

- Respiratory
- Cardiovascular
- Renal
- Hematology
- Hepatic
- Central nervous system



Pathogenesis of multiple organ dysfunction Crit Care Clin
2000;16:337-352

Multiple System Organ Failure Score

Organ failure	Criteria
Cardiovascular	Heart rate ≥ 54 /min
	Mean arterial pressure ≤ 49 mm Hg or systolic blood pressure < 60 mm Hg
	Ventricular tachycardia or fibrillation
Respiratory	PH ≤ 7.24 with PaCO ₂ ≤ 49 mm Hg
	Respiratory rate ≤ 5 /min or ≥ 49 /min
	PaCO ₂ ≥ 50 mm Hg
	Alveolar to arterial oxygen tension gradient ≥ 350 mm Hg
	Dependent on ventilator or CPAP on second day of OSF
Renal	Urine output ≤ 479 mL/24 hours or ≤ 159 mL/8 hours
	Blood urea nitrogen ≥ 100 mg/dL
	Creatinine ≥ 3.5 mg/dL
Hematologic	White blood cell count ≤ 1000 /mm ³
	Platelets $\leq 20,000$ /mm ³
	Hematocrit $\leq 20\%$
Neurologic	Glasgow coma score ≤ 6 (in the absence of sedation)

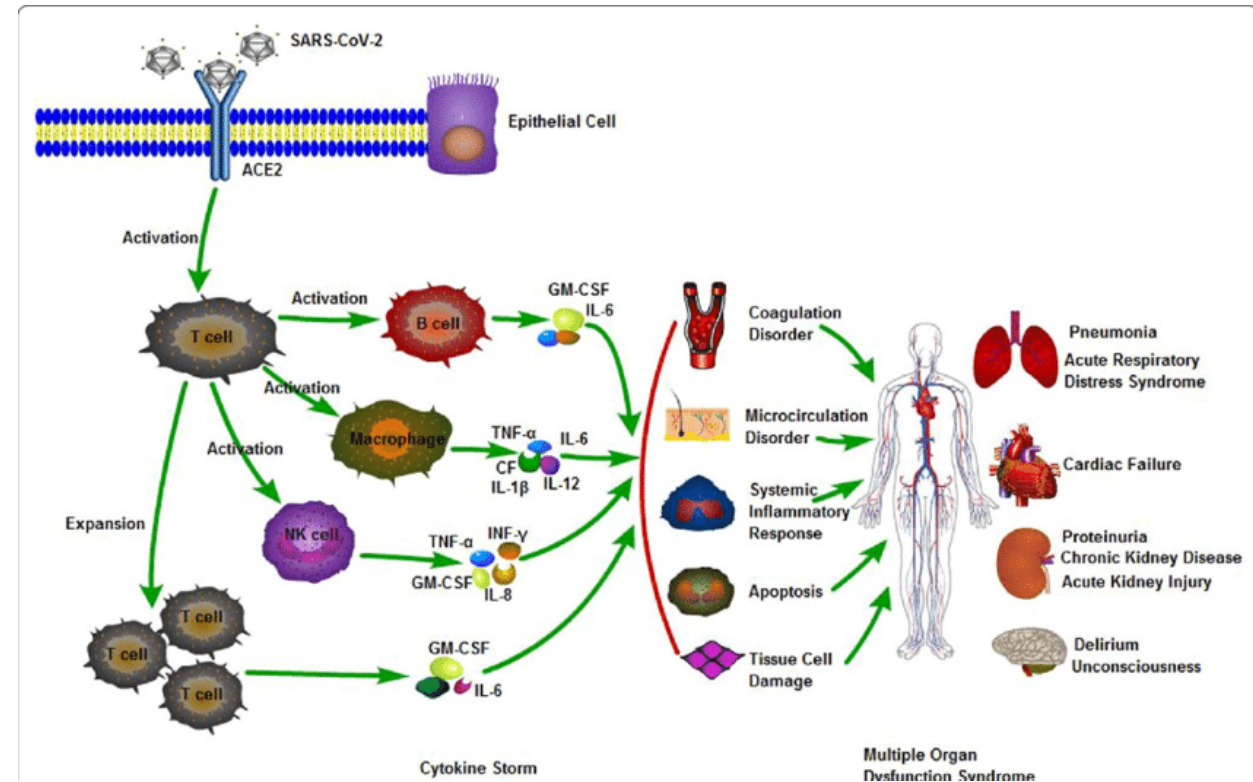
42 *Abbreviations:* CPAP, continuous positive airway pressure; OSF, organ system failure; PaCO₂, arterial CO₂ tension.

Definitions and grading of organ dysfunction (MODS score)

Function	No organ dysfunction/failure	Organ dysfunction	Organ failure
Pulmonary	PaO ₂ /FiO ₂ ratio ≥ 300	PaO ₂ /FiO ₂ ratio ≥ 250	PaO ₂ /FiO ₂ ratio <250
Renal	Creatinine ≤ 2.0 mg/dl	Creatinine >2.0 mg/dl; doubling of creatinine in patients with previous compensated renal failure	Continuous veno-venous haemofiltration
Hepatic	Bilirubin <2 mg/dl; ASAT/ALAT within normal range	Bilirubin 2 to 5 mg/dl; ASAT/ALAT ≤ three times normal value	Bilirubin >5 mg/dl; ASAT/ALAT > three times normal value
Haematologic	Thrombocytes within normal range; normal coagulation	Thrombocyte decrease ≥ 25%; abnormal PT/aPTT with and without bleeding	Haemorrhagic diathesis; massive transfusion five blood products per hour or > 10 blood products per 24 hours
Cardiovascular	Normal blood pressure; no vasoactive drugs except dopamine ≤ 5 µg/kg per minute	Fluid resuscitation > 50% of normal need and/or dopamine >5 µg/kg per minute, dobutamine <10 µg/kg per minute, phenylephrine	Dobutamine >10 µg/kg per minute, AVP, epinephrine, norepinephrine, combination of catecholamines, IABP, VAD
Gastrointestinal	Normal gastrointestinal function, no bleeding	Ileus >7 days or bleeding requiring ≤ six blood products per 24 hours	Massive bleeding requiring > six blood products per 24 hours
Central nervous system	GCS ≥ 12	GCS 9–11	GCS ≤ 8

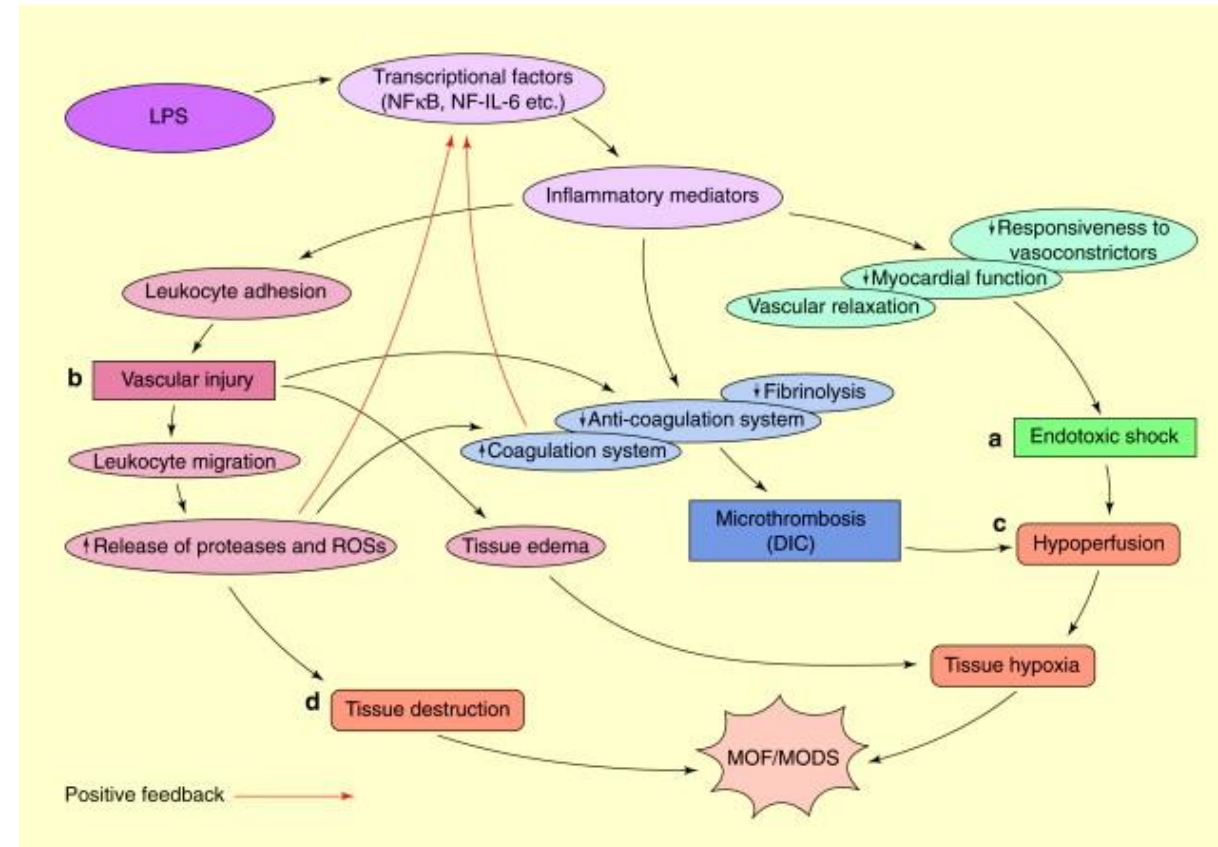
Potential Pathophysiologic Mechanisms Producing MODS

- Circulating immune/inflammatory mediators
- Primary cellular injury
- Mitochondrial Injury/ down-regulation
- Inadequate tissue/organ perfusion
 - Hypoperfusion
 - Ischemia/reperfusion
 - Microaggregation and/or DIC
- Diffuse endothelial cell injury
- Circulating humoral factors
- Protein calorie malnutrition
- Bacterial-toxin translocation
- Adverse effect of directed treatment or medication



Inflammatory Model

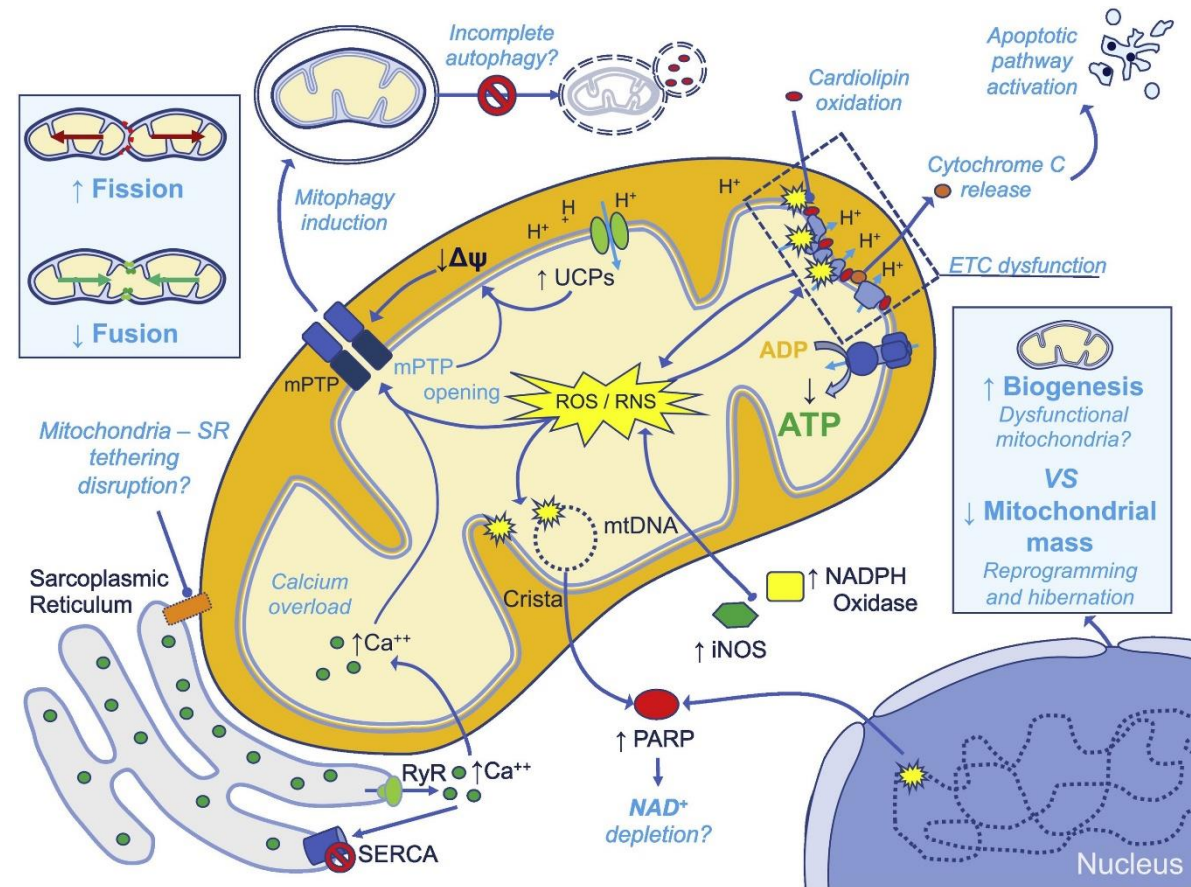
- MODS is caused by an overwhelming imbalance between systemic inflammatory response and counter regulation (anti-inflammatory) response.
- May be activated by a number of external and internal factors, including pro-inflammatory (e.g., infection, sepsis, shock, and trauma) and immunosuppression (e.g., Blood transfusion, infection, and steroids).
- The imbalance in favor of inflammatory response causes loss of the host's ability to localize the inflammation to initial inciting factor, leading to systemic inflammation and tissue damage.



Karima et. al, The molecular pathogenesis of endotoxic shock and organ failure Mol Med Today 1 March 1999, 123-132

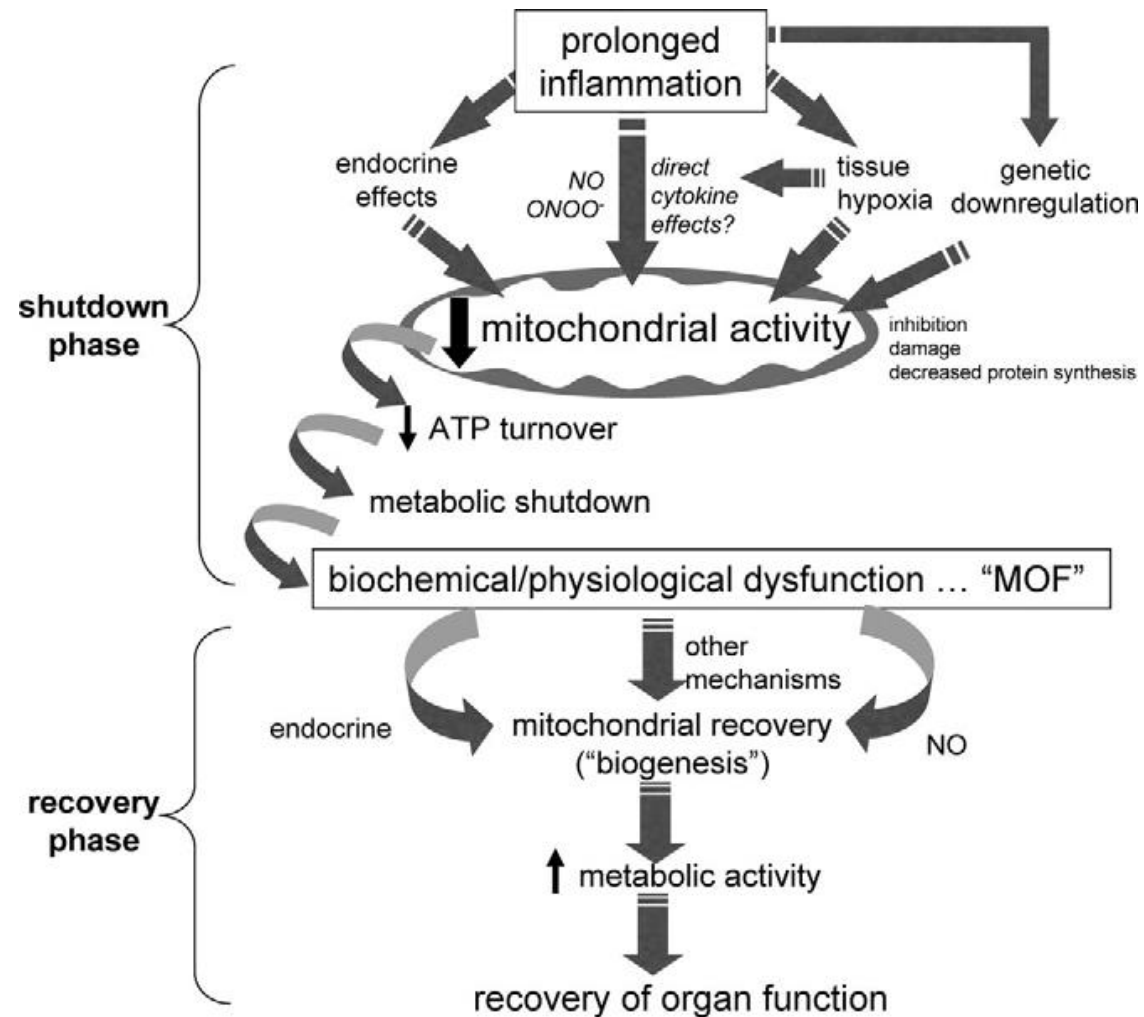
Bioenergetics Model

- Multiple organ dysfunction - result of the dysregulation of mitochondria
- Mitochondrial activity is down-regulated as a **protective reflex** to inciting factors
- Failure to recover mitochondrial function results in **self perpetuating cycle** of cell damage furthering **shutdown of mitochondria**
- Findings imply a metabolic shutdown rather than structural damage as a key pathophysiological mechanism



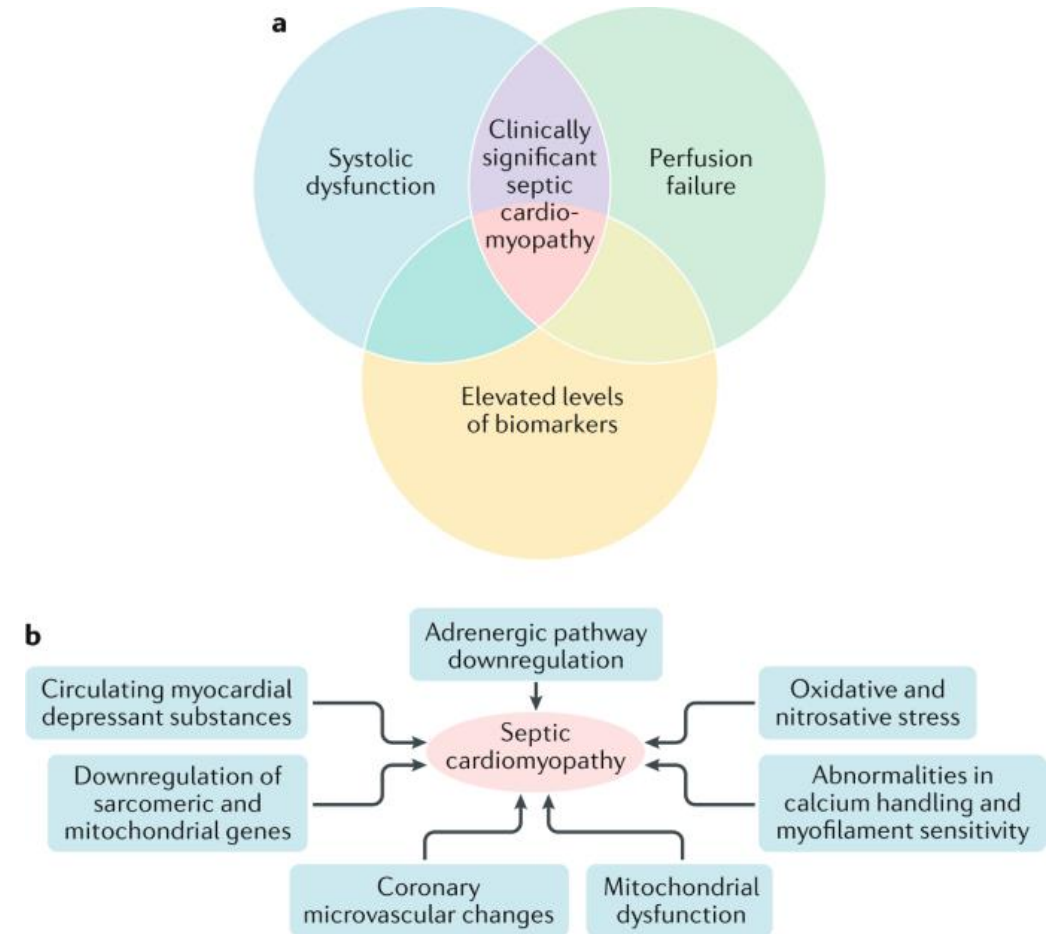
Giacomo Stanzani, et al. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, Volume 1865, Issue 4, 2019.

Progression of Bioenergetics Dysfunction



Sepsis-induced cardiomyopathy (SIC)

- cardiovascular abnormalities during sepsis - recognised for over 50 years
- an intrinsic and reversible systolic and diastolic dysfunction of both the left and right sides of the heart induced by sepsis
- potential reversibility observed in numerous studies
- Both macroscopic and microscopic findings of myocarditis have been noted at post-mortem while evidence of non-ischemic cardiac injury compatible with inflammation or tissue acidosis was observed

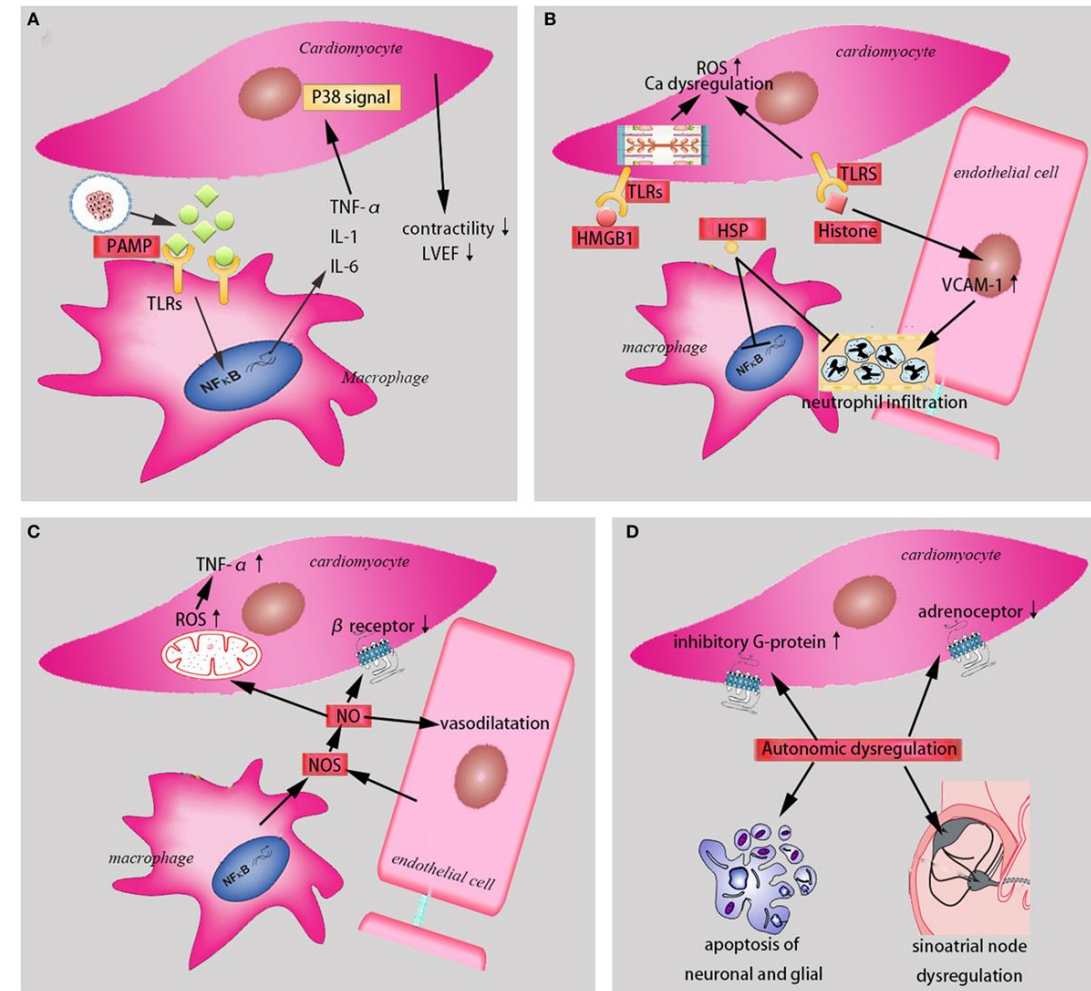


Hollenberg, S.M., Singer, M. *Nat Rev Cardiol* **18**, 424–434 (2021).

Patophysiology of SIC

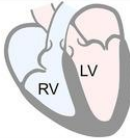

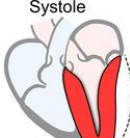
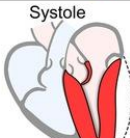
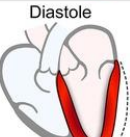
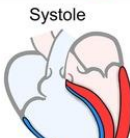
Numerous circulating factors contribute

- include both pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) and host-produced danger-associated molecular patterns (DAMPs)
- These endogenous danger signals include cytokines, heat-shock proteins, high-mobility group box 1, histones, activated complement components, and mitochondrial DNA.
- interaction of a wide range of signalling pathways rather than any single individual factor

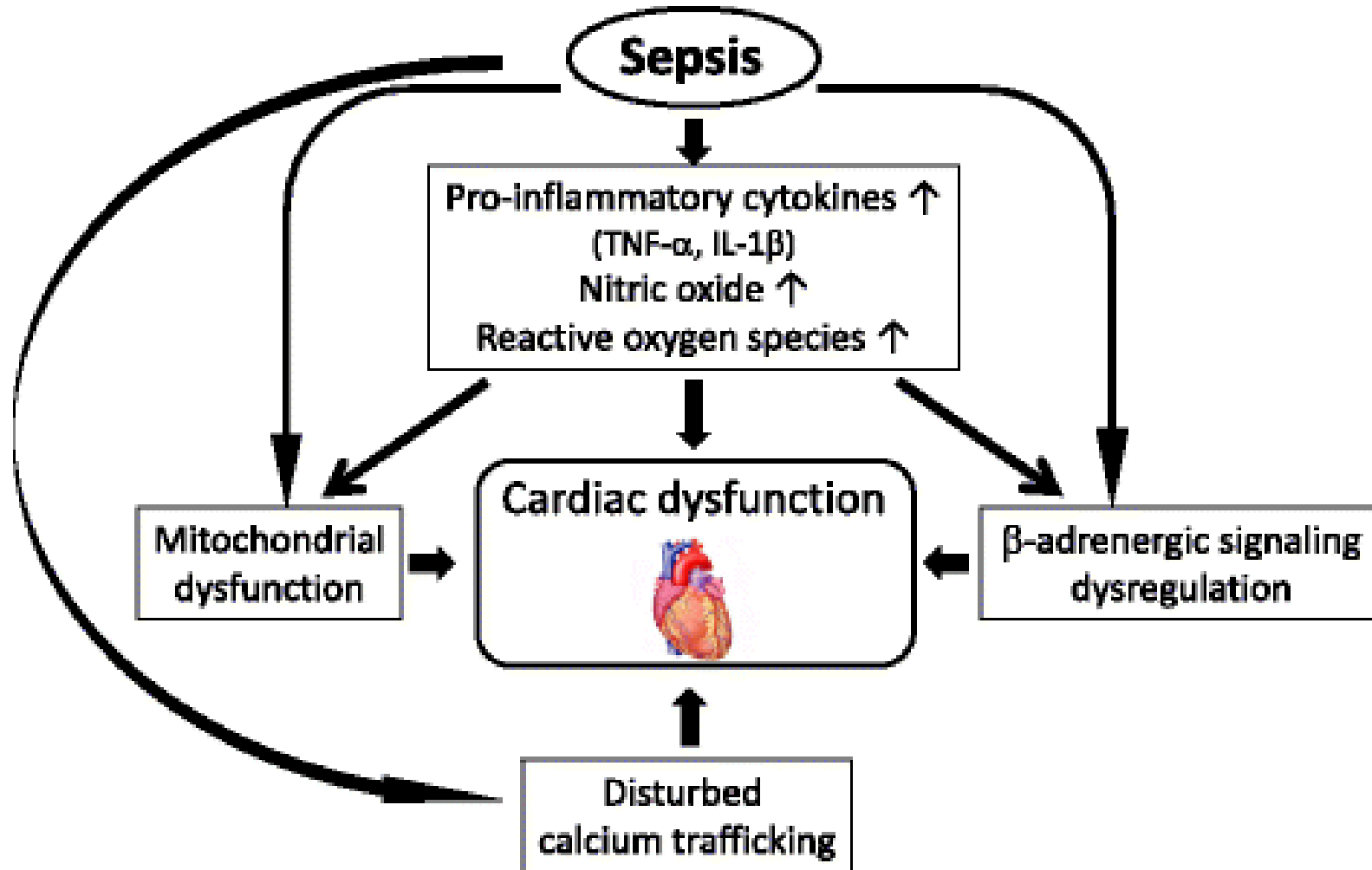


Mitochondrion

- Besides their role in ATP production, mitochondria also play an essential role in numerous other cell functions
 - calcium homeostasis,
 - hormone metabolism,
 - thermoregulation,
 - reactive oxygen and nitrogen species production,
 - cell signalling,
 - key regulators of apoptosis and cell death.
- Mitochondrial dysfunction and bioenergetic failure** are thus increasingly recognized as **central to the pathophysiology** of numerous cardiovascular diseases.
- These findings suggest a key role for both a cellular bioenergetic deficit, and more specifically mitochondrial dysfunction, and a metabolic shutdown, in the pathogenesis of sepsis-induced organ failure.

Function	Pathophysiology	EF	CO
Normal systolic function			
LV systolic dysfunction	Systole  <ul style="list-style-type: none"> Reduced LV contractility and increased LVESV EF may appear normal if low afterload (hypovolemia/low SVR) LV dilation may occur 	↓/-	↓
LV hyperdynamic function	Systole  <ul style="list-style-type: none"> Hyperdynamic contractility of LV Pseudohypertrophy of the LV wall may be seen If normal preload, CO is elevated May indicate hypovolemia Reduced LVESV 	↑	↑/↓
	Systole  <p>Dynamic LVOT obstruction:</p> <ul style="list-style-type: none"> Anterior movement of mitral valve against interventricular septum due to high flow obstructs outflow from LV Can lead to severely reduced CO 	↑	↓
LV diastolic dysfunction	Diastole  <ul style="list-style-type: none"> Impaired relaxation of ventricle reduces filling leading to decreased CO Reduced LVEDV 	↓/-	↓
RV dysfunction	Systole  <ul style="list-style-type: none"> Reduced contractility of RV, increased RV ESV Due to ventricular interdependence, RV dilation reduces LV filling Reduced LVEDV and reduced CO May occur concomitantly with LV systolic or diastolic dysfunction 	↑/↓	↓

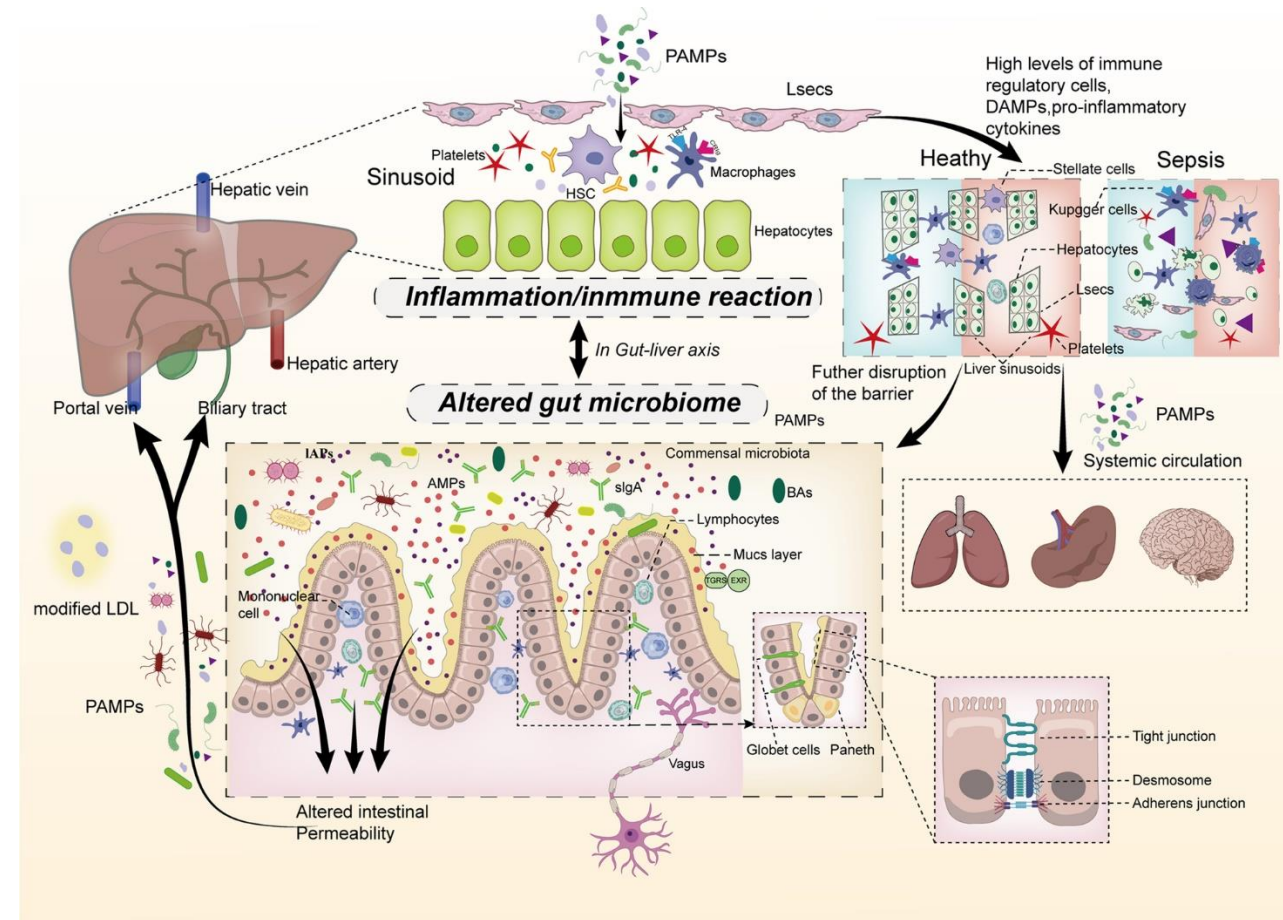
Sepsis and cardiac dysfunction - summary



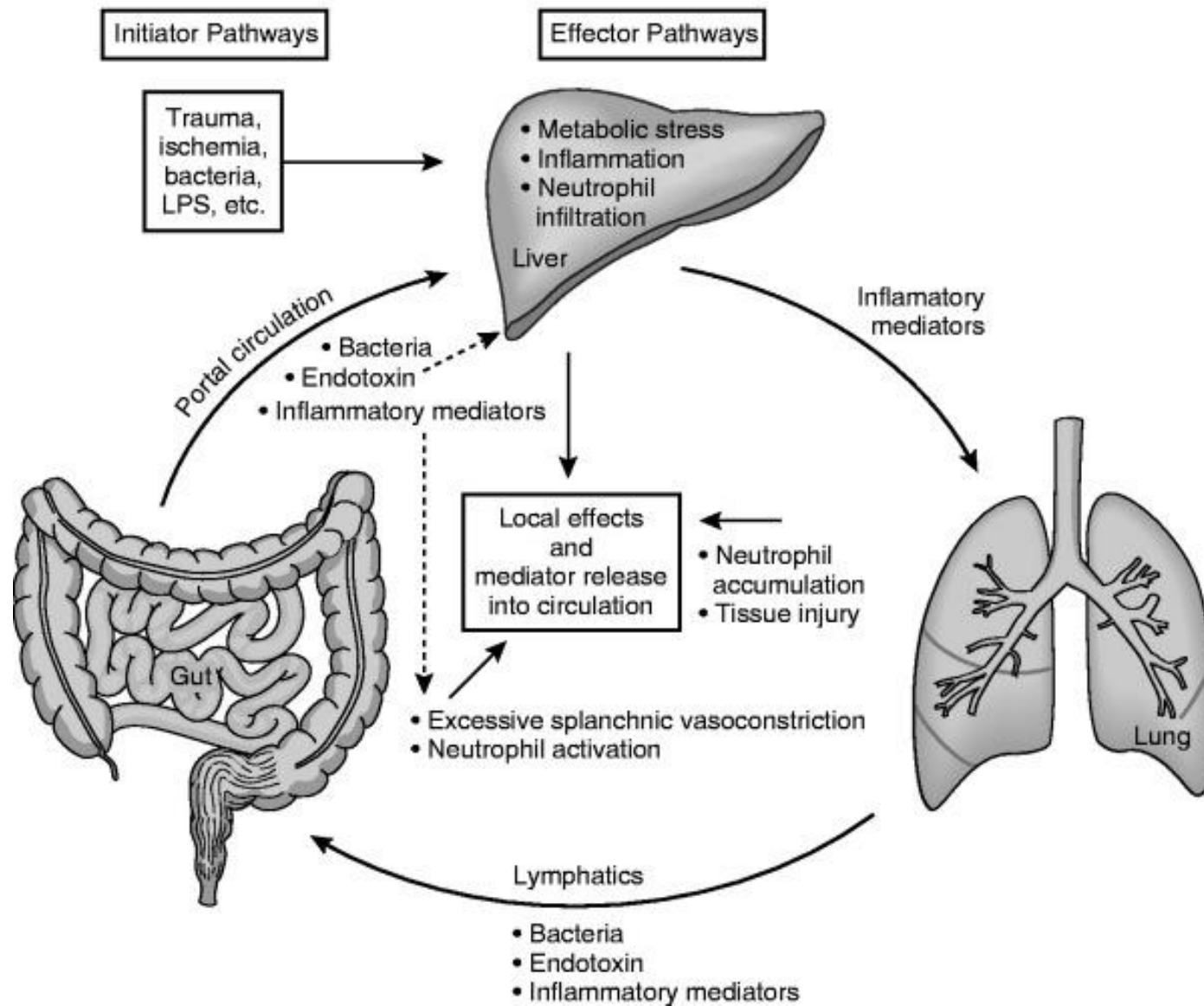
Multifactor Models - Gut

Gut-liver-lung axis

- Initiation of the inflammatory state can occur in any of these organs following trauma or shock.
- The gut can leak inflammatory mediators into the portal circulation, causing a response in the liver.
- Inflammatory mediators then travel in the hepatic vein to the inferior vena cava and to the lungs.
- The lungs may become injured and release inflammatory substances themselves, which travel systemically to distant organs (including the gut).



PROPOSED EVENTS IN MULTIORGAN FAILURE

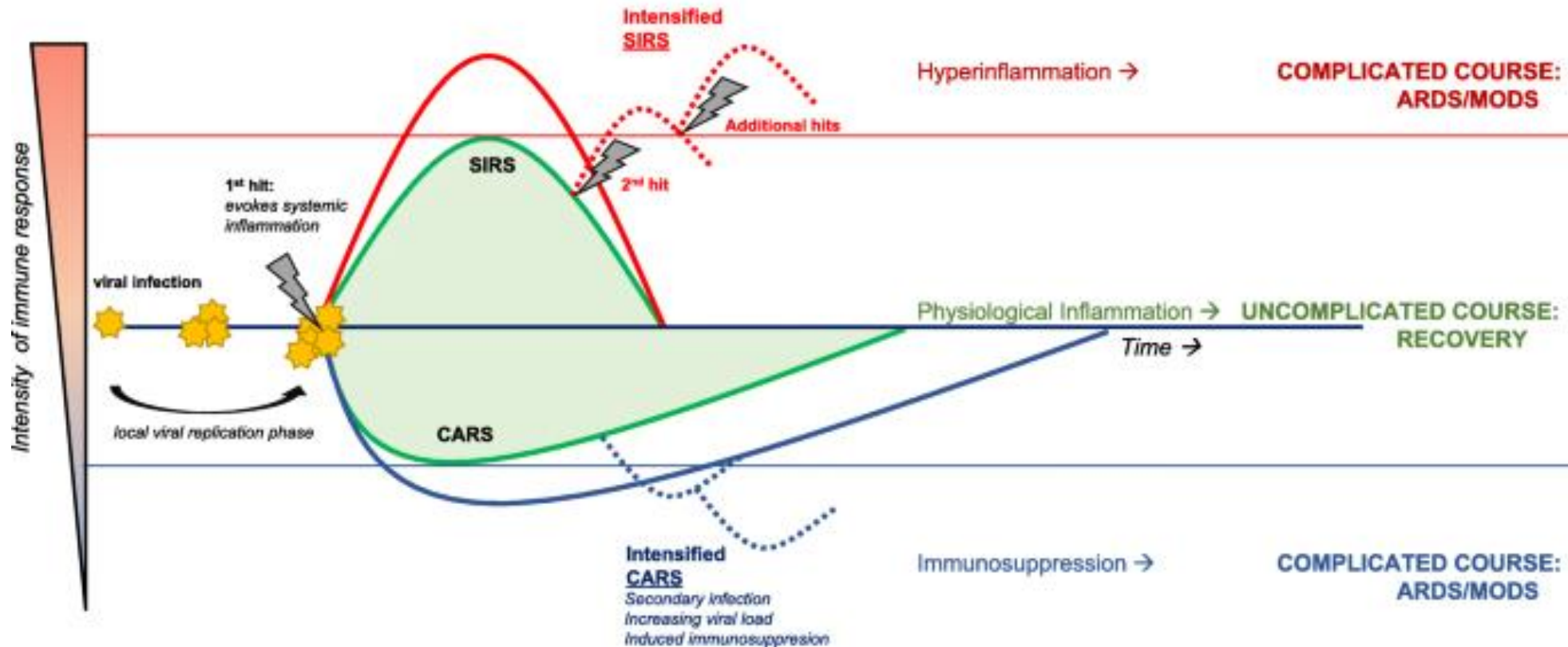


LPS, Lipopolysaccharide.

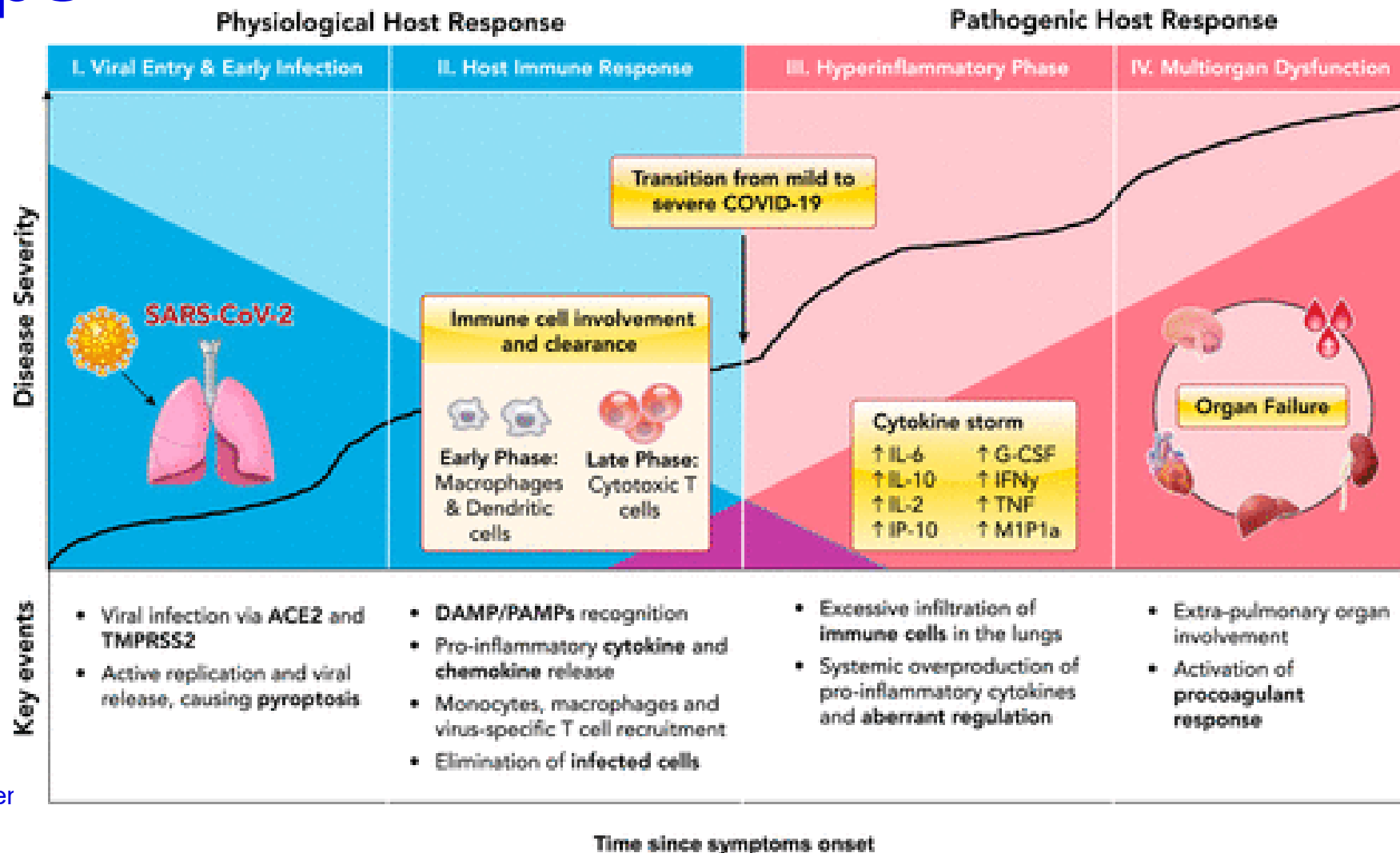
Gut-liver-lung axis in response to shock and hemorrhage *Martinez-Mier G, Toledo-Pereyra LH, Ward PA: J Trauma 51:408, 2001.*

SIRS and Covid-19

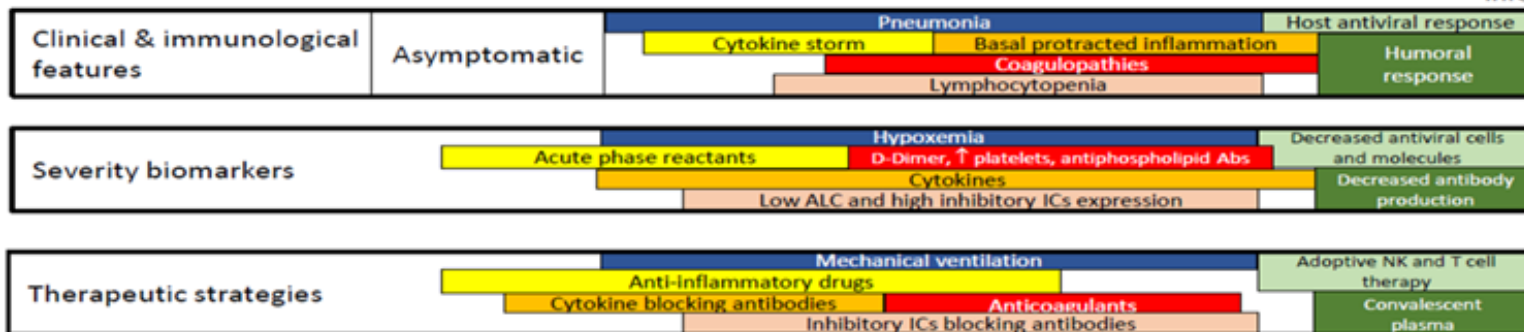
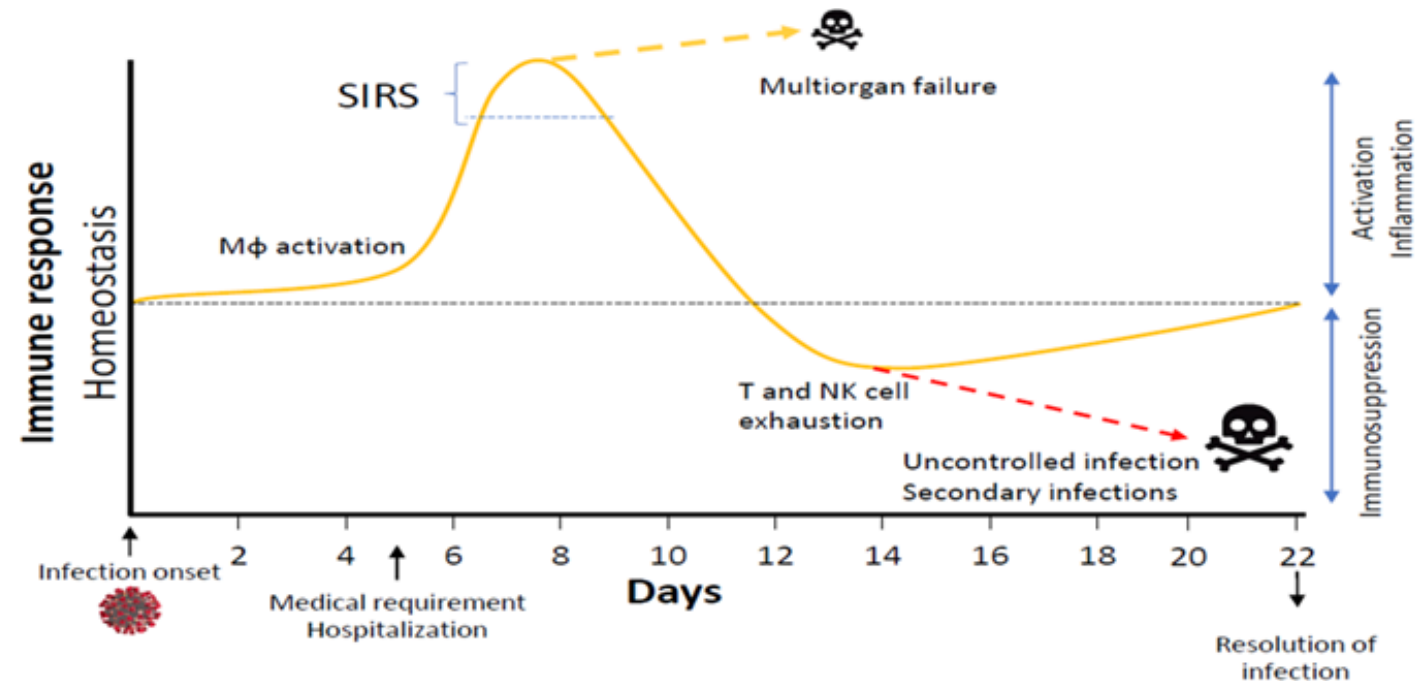
Proposed model of consecutive insult conditions and systemic inflammatory disease progression in COVID-19 based on established trauma models

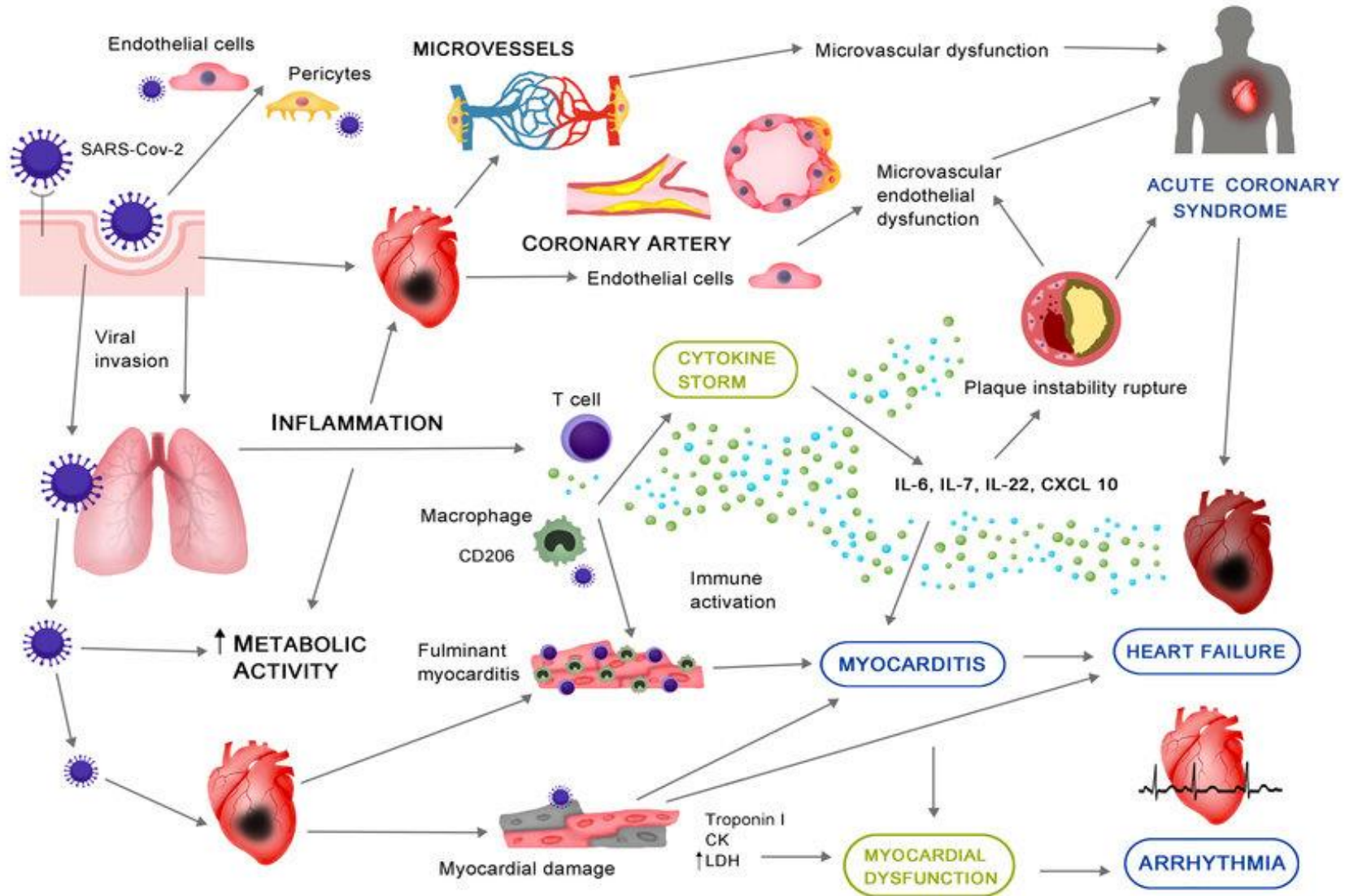


Pathogenesis of Covid-19 disease – key steps



SIRS, MODS and Covid-19





Shock - definition

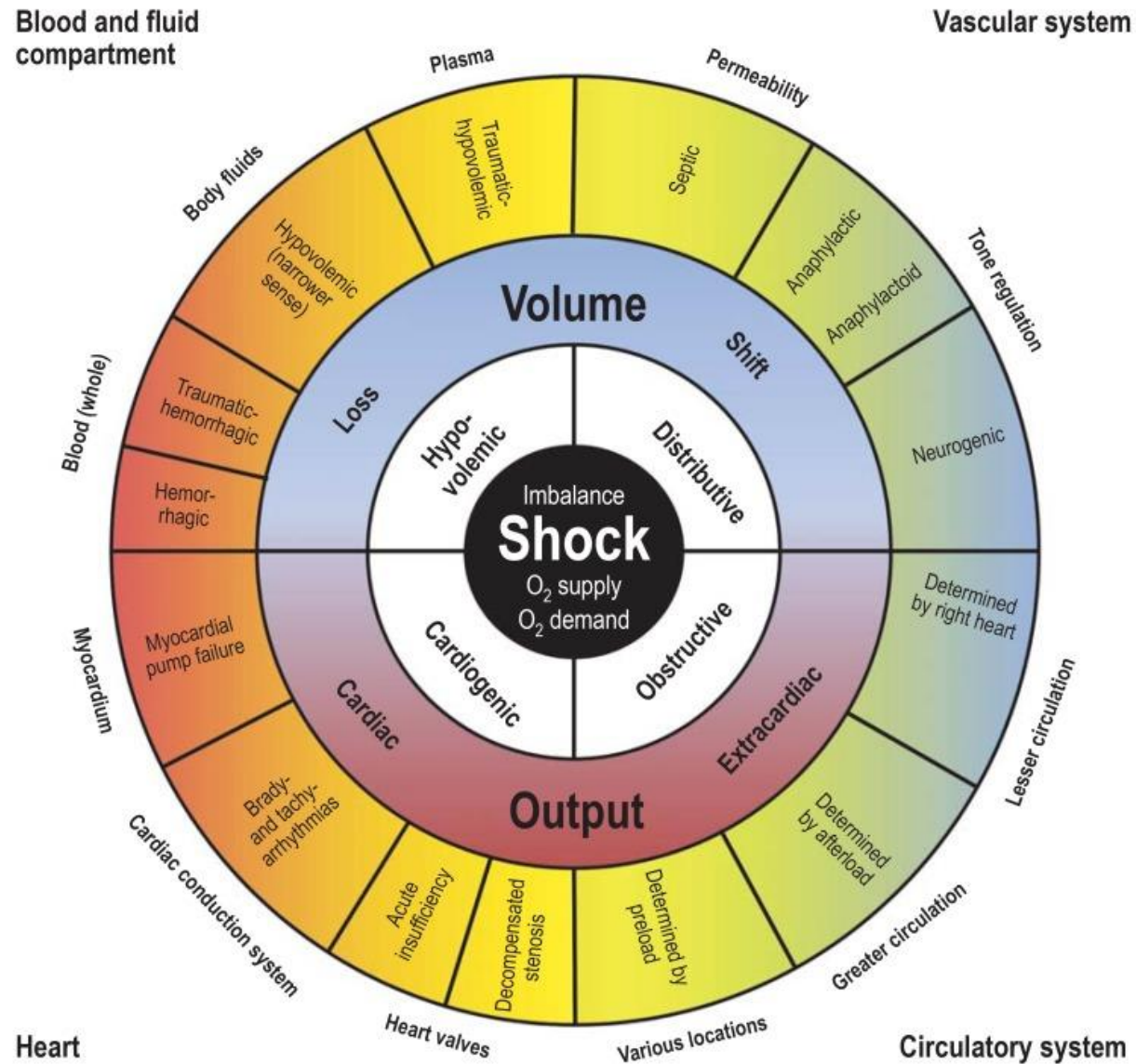
- Severe tissue hypoperfusion resulting in low supply of oxygen to the organs
- Systemic hypotension (of various causes) is present
- $P = Q \times R$
- $Q \sim CO = SV \times f$
- CO depends on
 - a) cardiac function
 - b) venous return (\rightarrow preload)
- R – systemic resistance (mostly arterioles) - afterload

- In early shock, compensation occurs by modulation of cardiac output and vascular tone by the autonomic nervous system.¹ Carotid baroreceptors respond to decreased blood pressure by triggering increased sympathetic signaling. This autonomic nervous system-mediated sympathetic response results in an increase in contractility and heart rate, thereby increasing cardiac output.

Shock categories

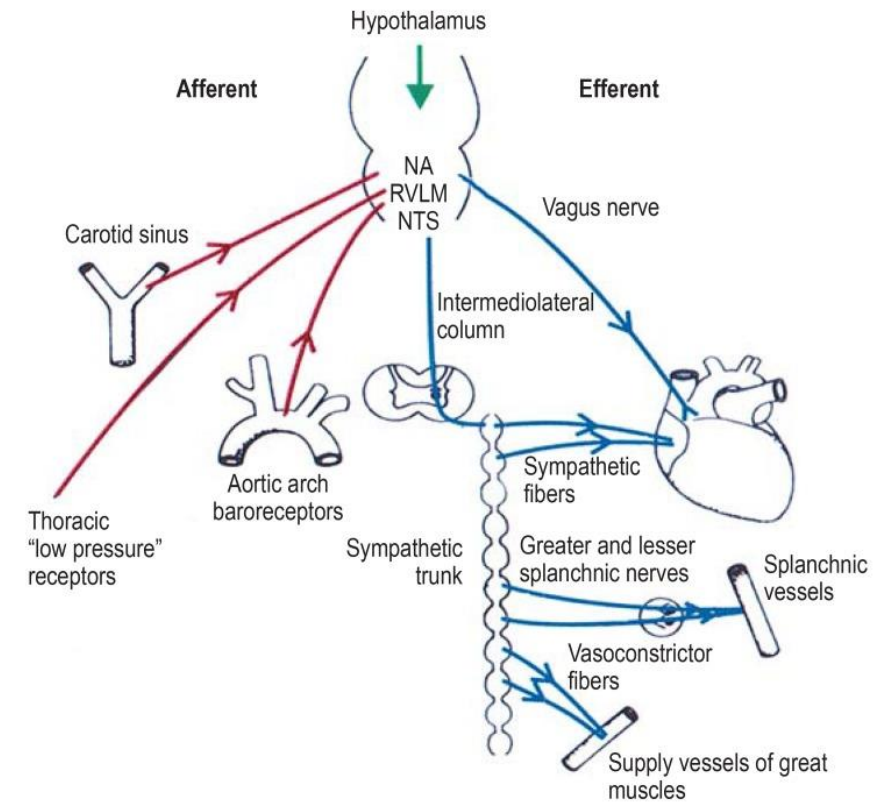
Category	Hemodynamics	Causes
Hypovolemic	↓ preload ↑ SVR ↓ CO	Hemorrhage, GI losses, third spacing, burns
Distributive	↓ preload ↓ SVR ↑/↓ CO	Sepsis, anaphylaxis, neurogenic shock, pancreatitis
Cardiogenic	↑ preload ↑ SVR ↓ CO	Myocardial infarction, symptomatic bradycardia, valvular disease, heart blocks, end-stage heart failure
Obstructive	↓ preload ↑ SVR ↓ CO	Pulmonary embolism, tension pneumothorax, pericardial tamponade

Shock



Neurogenic shock – special situation

- state of imbalance between sympathetic and parasympathetic regulation of cardiac action and vascular smooth muscle. The dominant signs are profound vasodilation with relative hypovolemia while blood volume remains unchanged, at least initially.
- Direct injury to the centers for circulatory regulation due to compression (brainstem trauma), ischemia (e.g., basilar artery thrombosis), or the influence of drugs
- Altered afferents to the circulatory center in the medulla oblongata due to fear, stress, or pain or dysregulated vagal reflexes
- Interruption of the descending connection from the bulbar regulatory centers to the spinal cord, especially in patients who have sustained trauma above the middle of the thoracic spine (paraplegia).



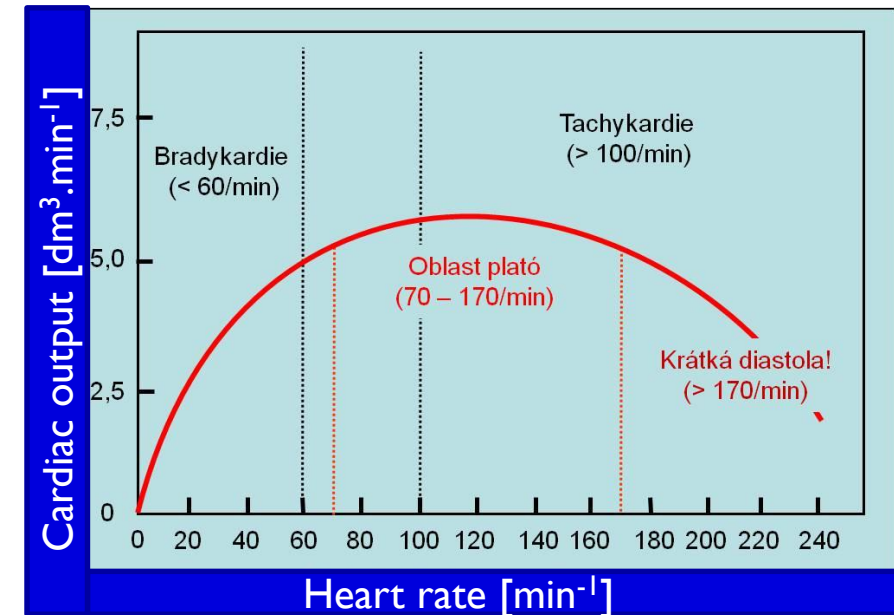
[Dtsch Arztebl Int.](#) 2018 Nov; 115(45): 757–768.

Phases of shock

- Compensation of initiating cause
- Decompensation
- Refractory shock

Compensatory mechanisms and their limits

- Activation of sympathetic nervous system (tens of seconds)
- Activation of RAAS (cca 1 hour)
- Vasoconstriction (if possible) – but it leads into lower blood supply
- Vasodilatation in some tissues (esp. myocardium)
- Positively inotropic effect of SNS (if possible) – but at cost of higher metabolic requirements of the heart
- Increased heart rate – but CO decreases in high HR (>150 bpm)
- Keeping circulating volume by lower diuresis – but at cost of acute renal failure
- Shift to anaerobic metabolism – but at cost of ↓ ATP a ↑ lactate (acidosis)
- Increased respiratory rate (but shallow breathing results in ↑ relative deadspace)
- Shift of saturation curve of hemoglobin to right (↑2,3-DPG)
- Hyperglycemia – but there is decreased utilization of Glc in the periphery



Decompensated shock

- ↓ BP
- ↓ diuresis
- Brain hypoperfusion – involvement of mental functions
- Acrocyanosis
- Tachypnea
- “Golden hour“

Refractory shock

1) Vasodilatation ↔ hypoperfusion

- Endothelial cells contain two isoforms of nitric oxid synthase – constitutive (eNOS) and inducible (iNOS)
- In lasting hypoxia of endothelial cells there is increased iNOS activity (primarily physiological mechanism)
- ↑NO increases vasodilatation and hypoperfusion
- Lactate acidosis → hypotension (lactate – prognostic factor)

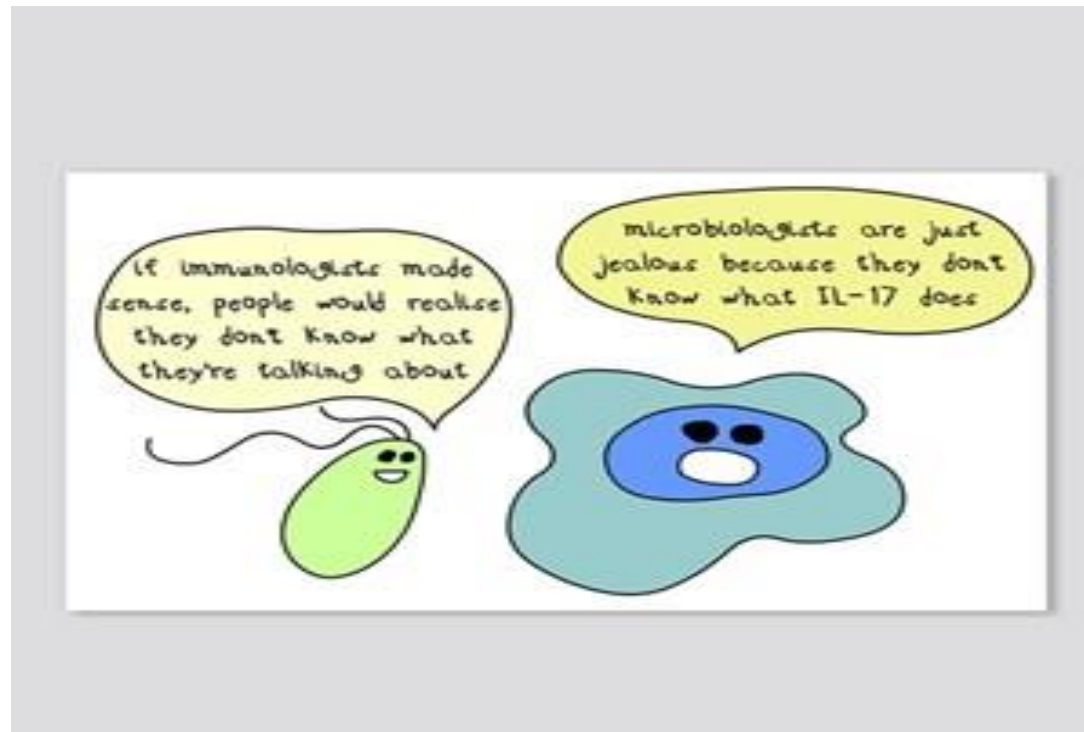
2) Myocardial hypoxia ↔ lower contractility

- Lower myocardial perfusion leads into ↓CO, which further reduces coronary flow
- Myocardium does not benefit from the shift of Hb saturation curve – efficiency of O₂ extraction is already at its maximum

3) Brain hypoperfusion ↔ ↓SNS activity

- Lower perfusion of vasomotor centre leads first into SNS hyperactivity, which is then followed by its suppression
- That leads into ↓brain perfusion

Thank you for you attention



Pathogenesis of Covid-19 disease

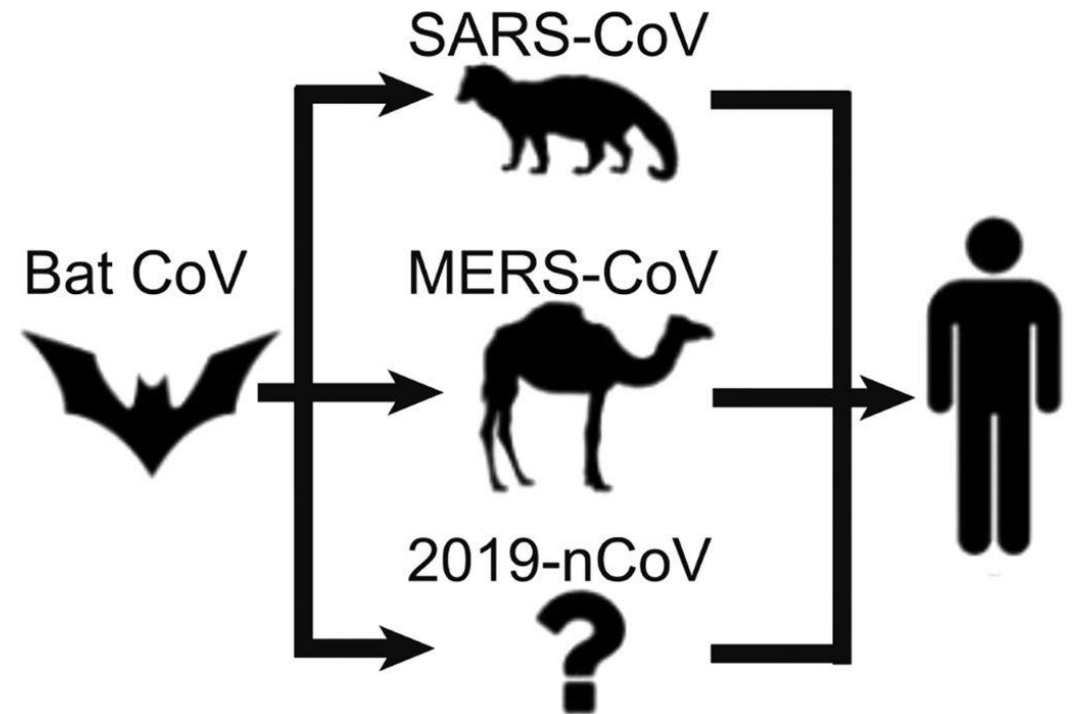
- Coronaviruses belong to the Coronaviridae family in the Nidovirales order
- Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus
- Coronaviruses are enveloped viruses, minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a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

Covid-19

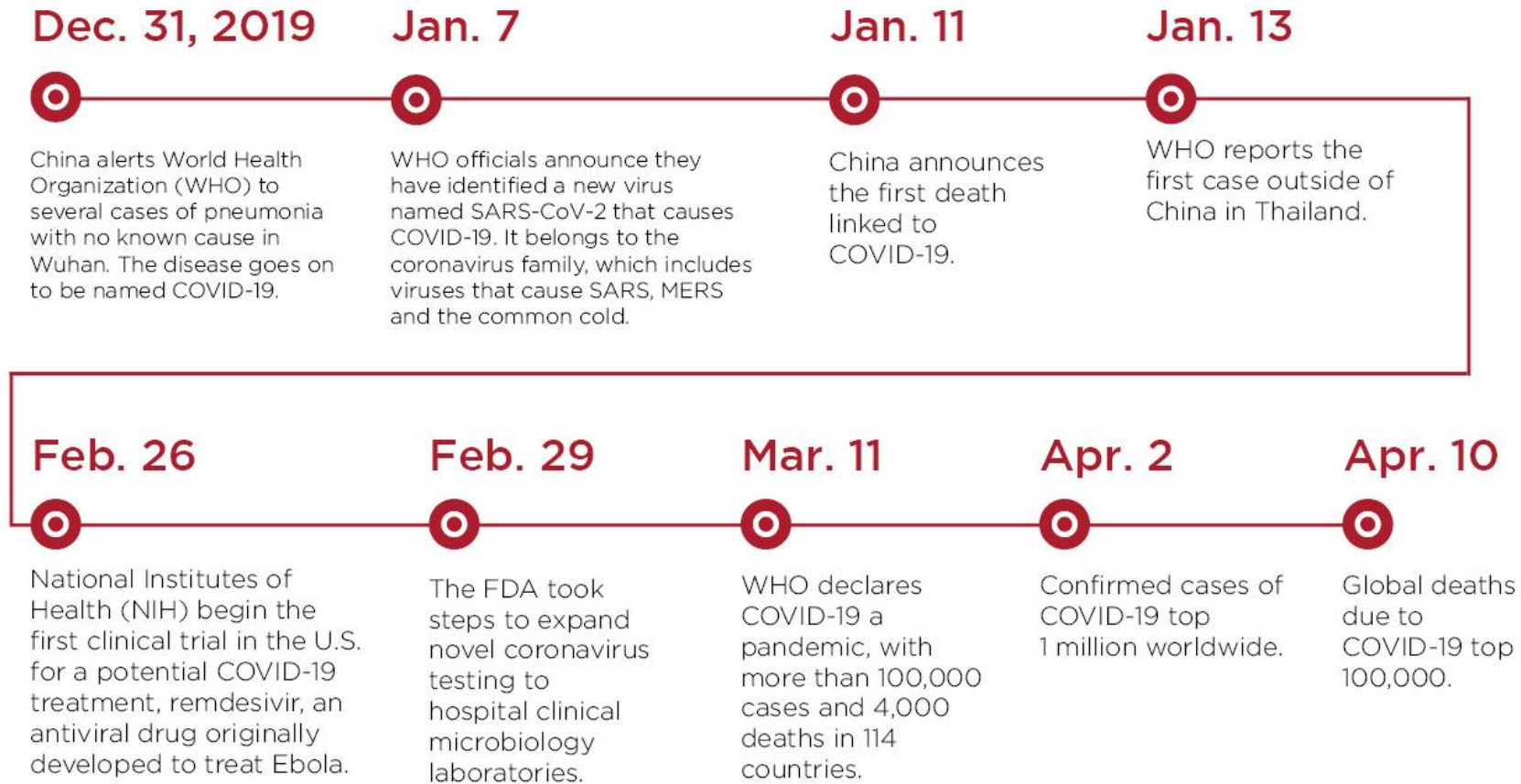
- The virus that causes COVID-19 is known as SARS-CoV-2
It appears to have first emerged in Wuhan, China, in late 2019.
- The outbreak has since spread across China to other countries around the world. By the end of January, the new coronavirus had been declared a public health emergency of international 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.



Covid-19 timeline



Pathogenesis of Covid-19 disease

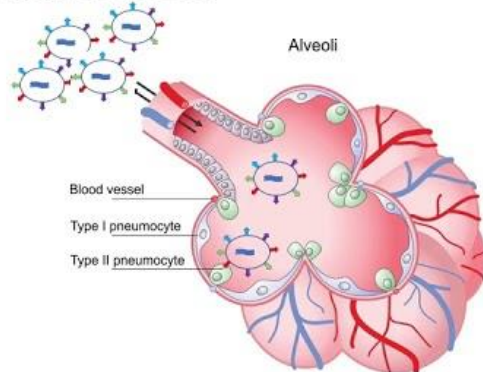
1. COVID-19 virus
In environment



2. Virus entry to lung



3. Virus entry to alveoli



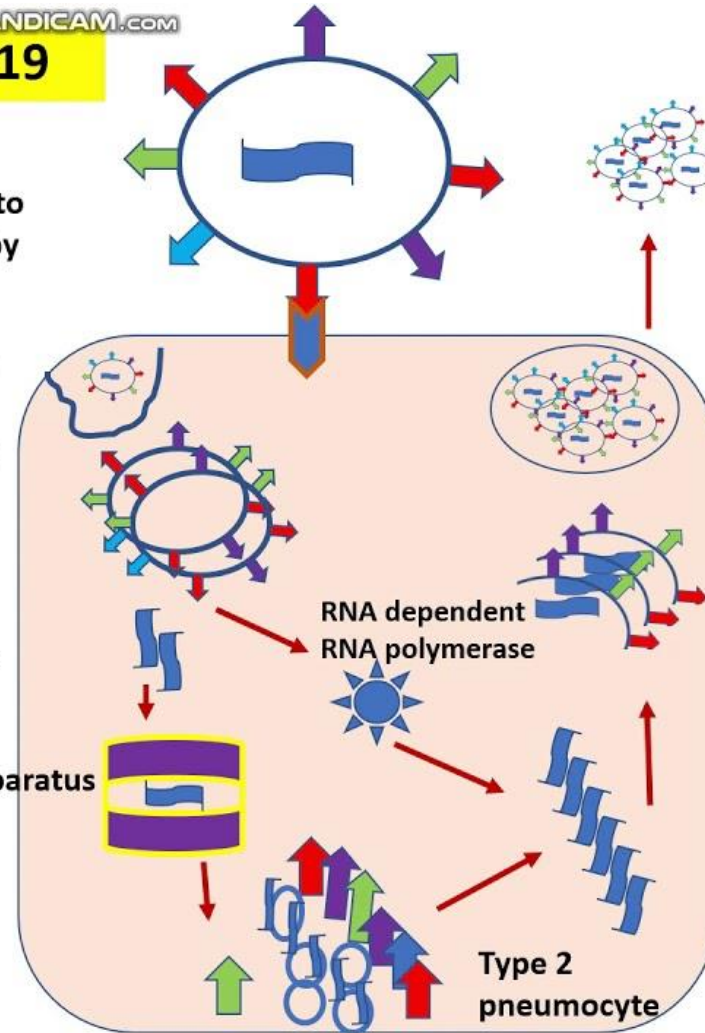
Life cycle of COVID-19

4. Virus binding to
ACE-2 receptor by
spike protein

5. Virus entry to
Type-2
pneumocytes by
membrane
invagination

6. SS RNA
released by virus

7. Various virus
protein
synthesized by
host cell



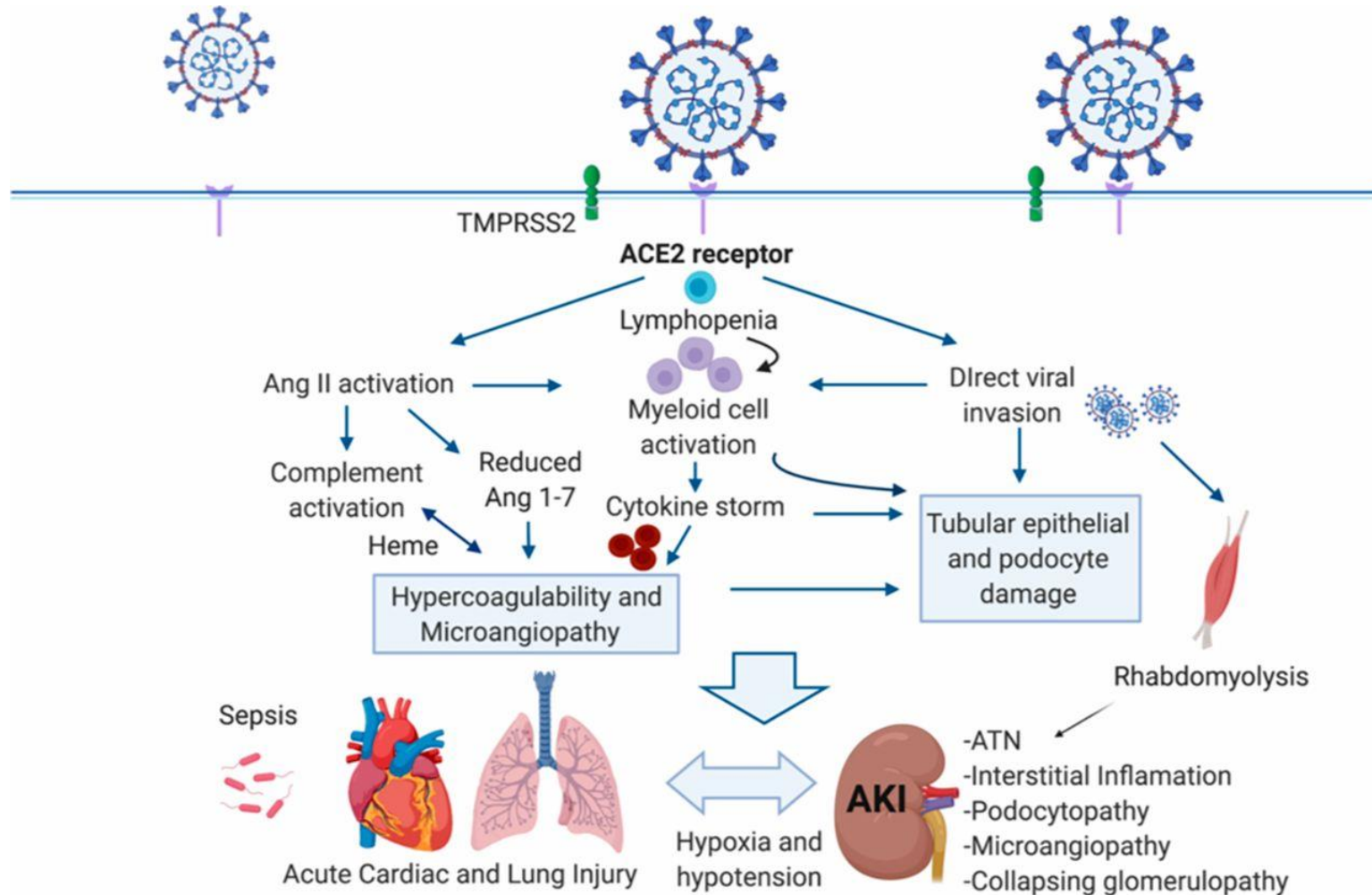
10 New virus
released by
host cell by
exocytosis

9. New virus
synthesized
by host cell

9. Packaging of
SS viral RNA
and protein
coating in sER

8. Viral RNA
synthesis by RNA
dependent RNA
polymerase

Pathogenesis of Covid-19 disease



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

