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Pathophysiology of chronic inflammation, ethiopathogenesis, 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

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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)

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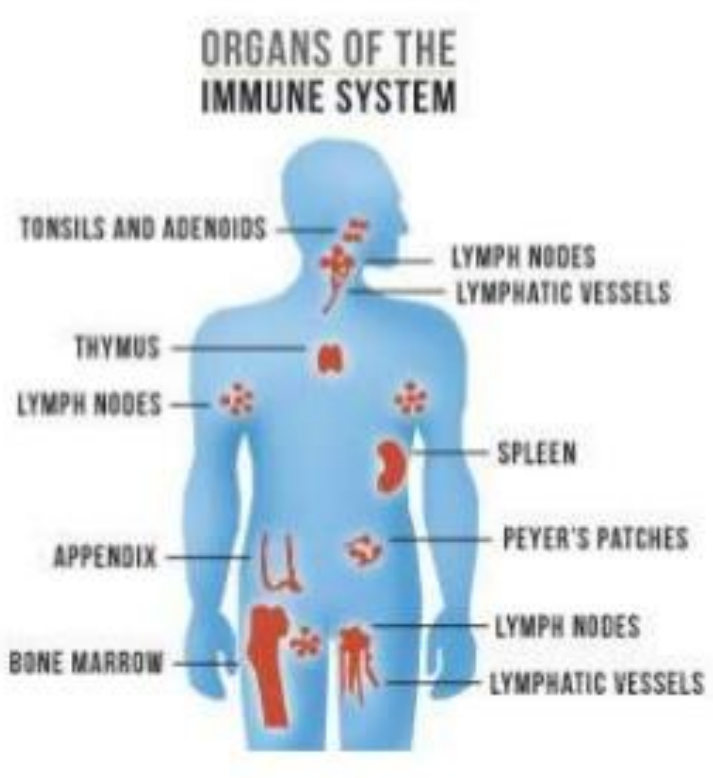
The components of the immune system

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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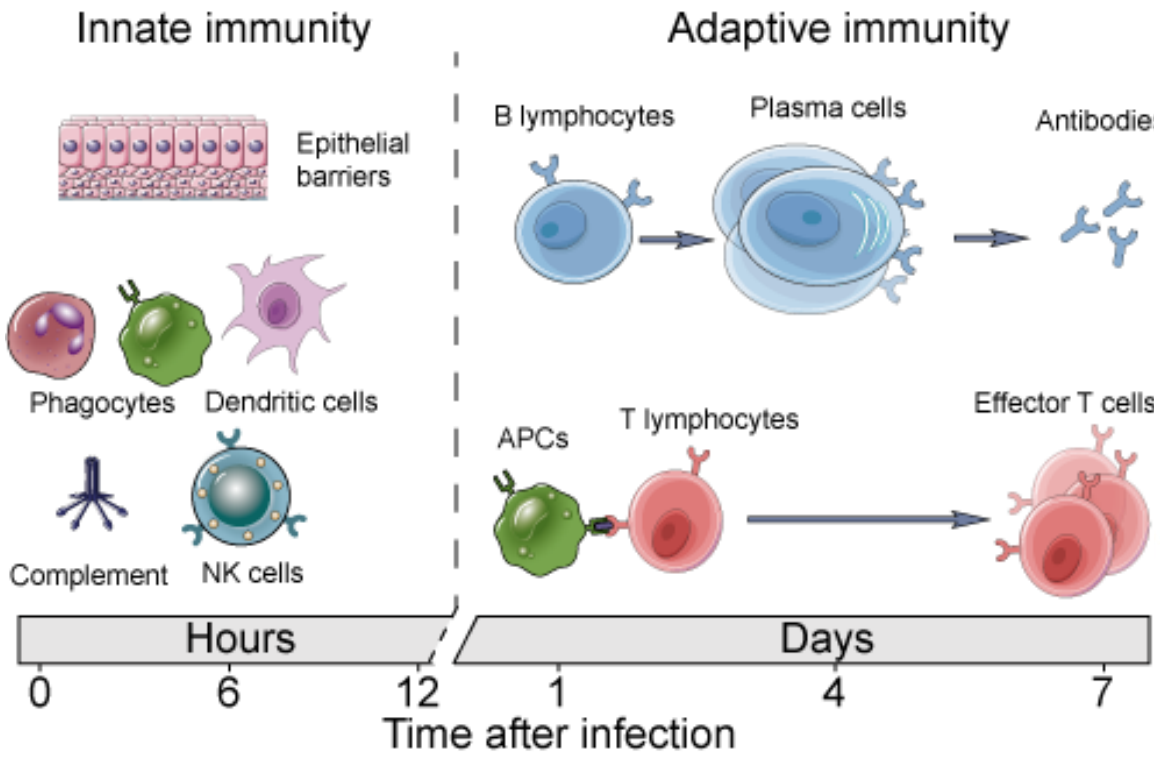
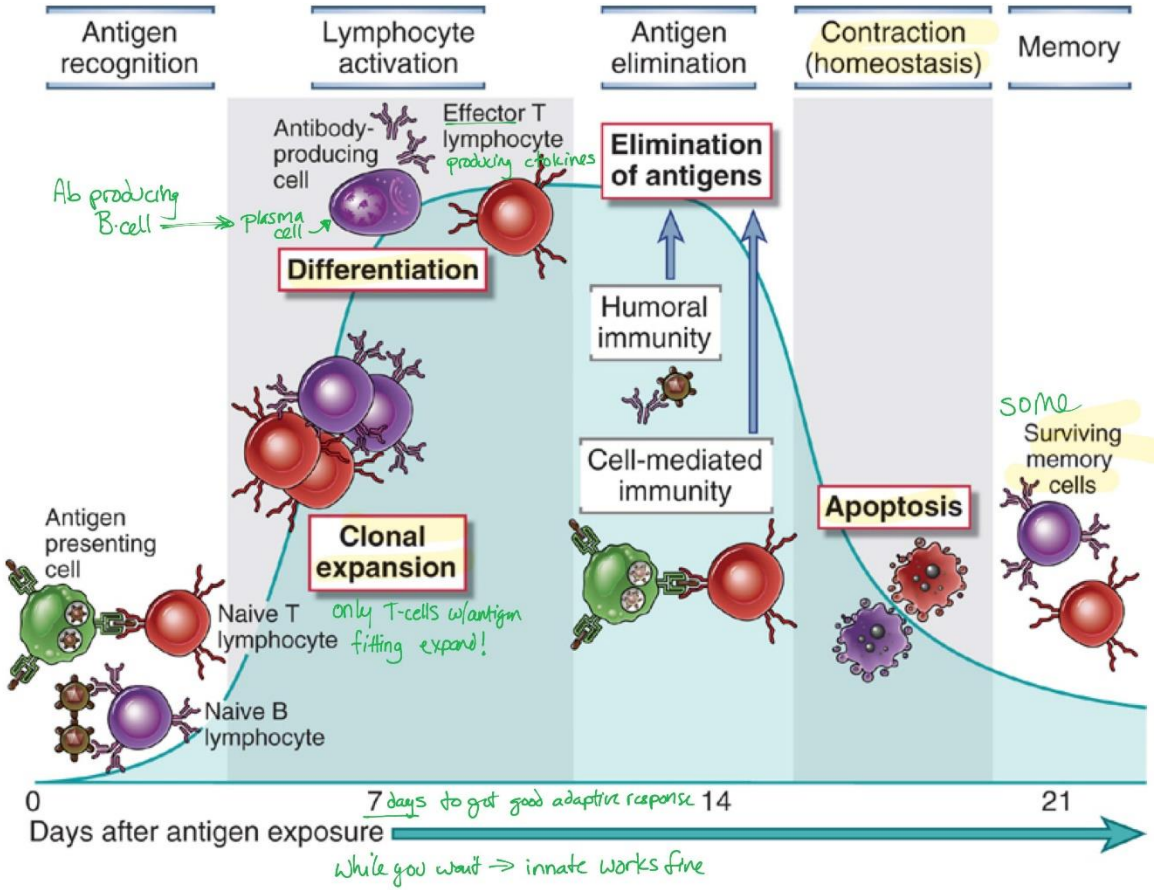
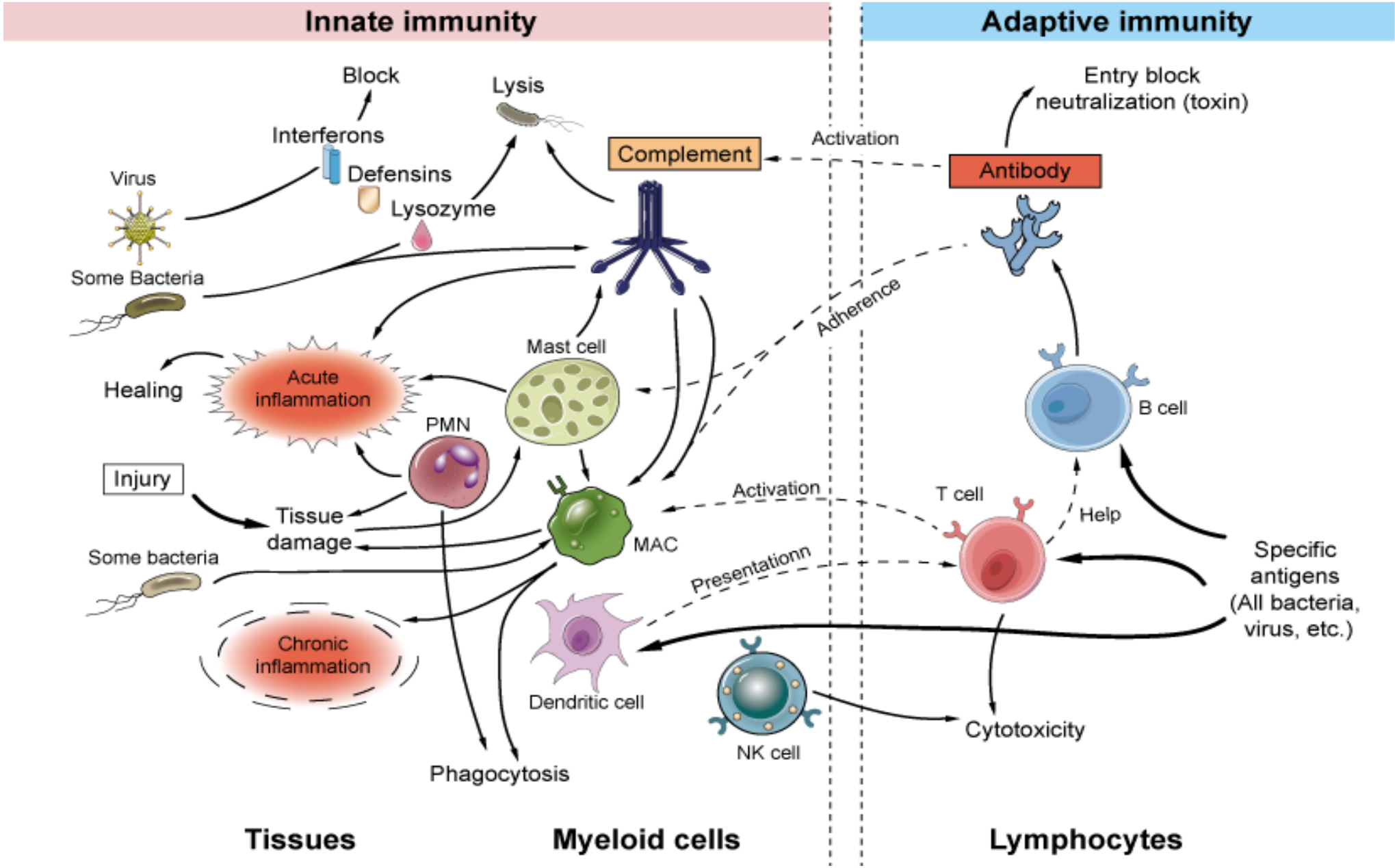
Timeline


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
Differentiation
Humoral immunity
Cell-mediated immunity
Clonal expansion
Apoptosis
Surviving memory cells
Antigen presenting cell
Naive T lymphocyte
Naive B lymphocyte
0
14
21
Days after antigen exposure


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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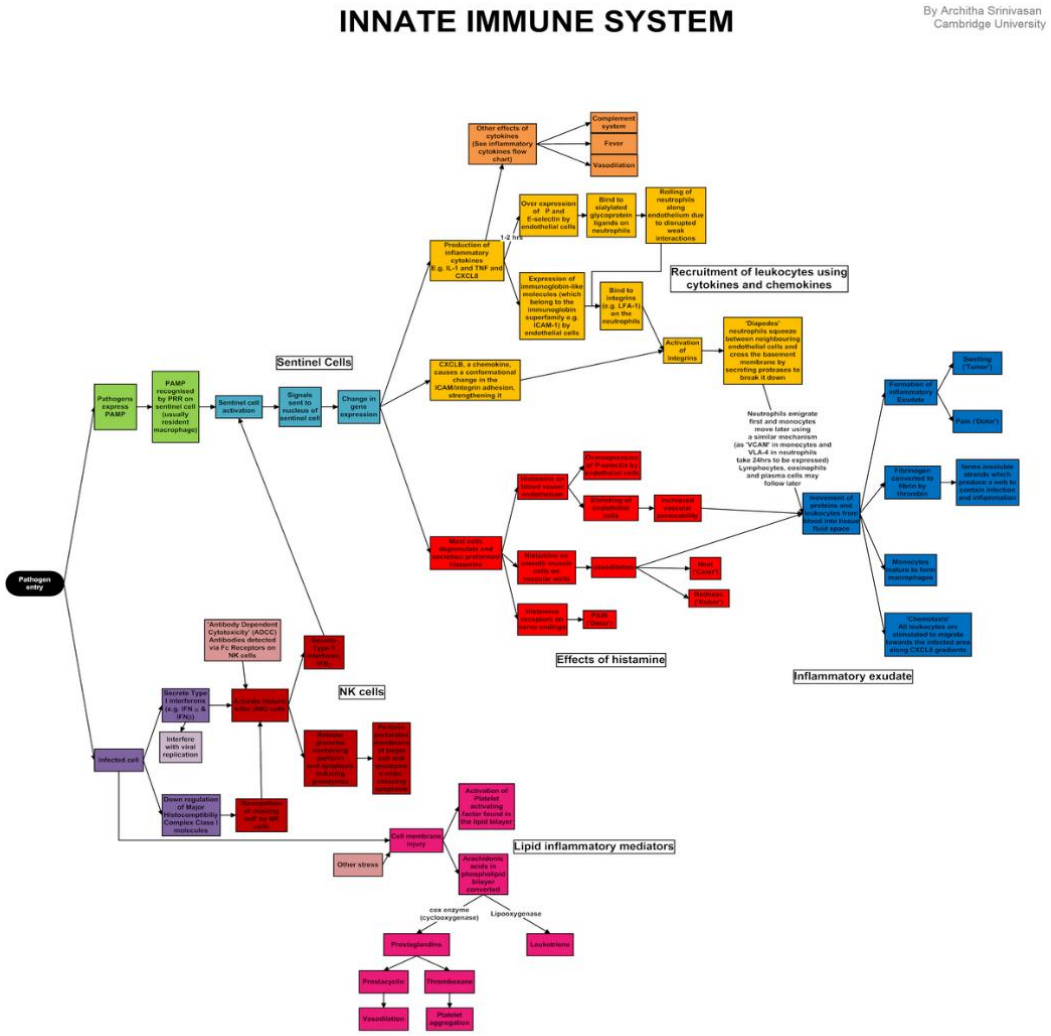
Innate immunity

- 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



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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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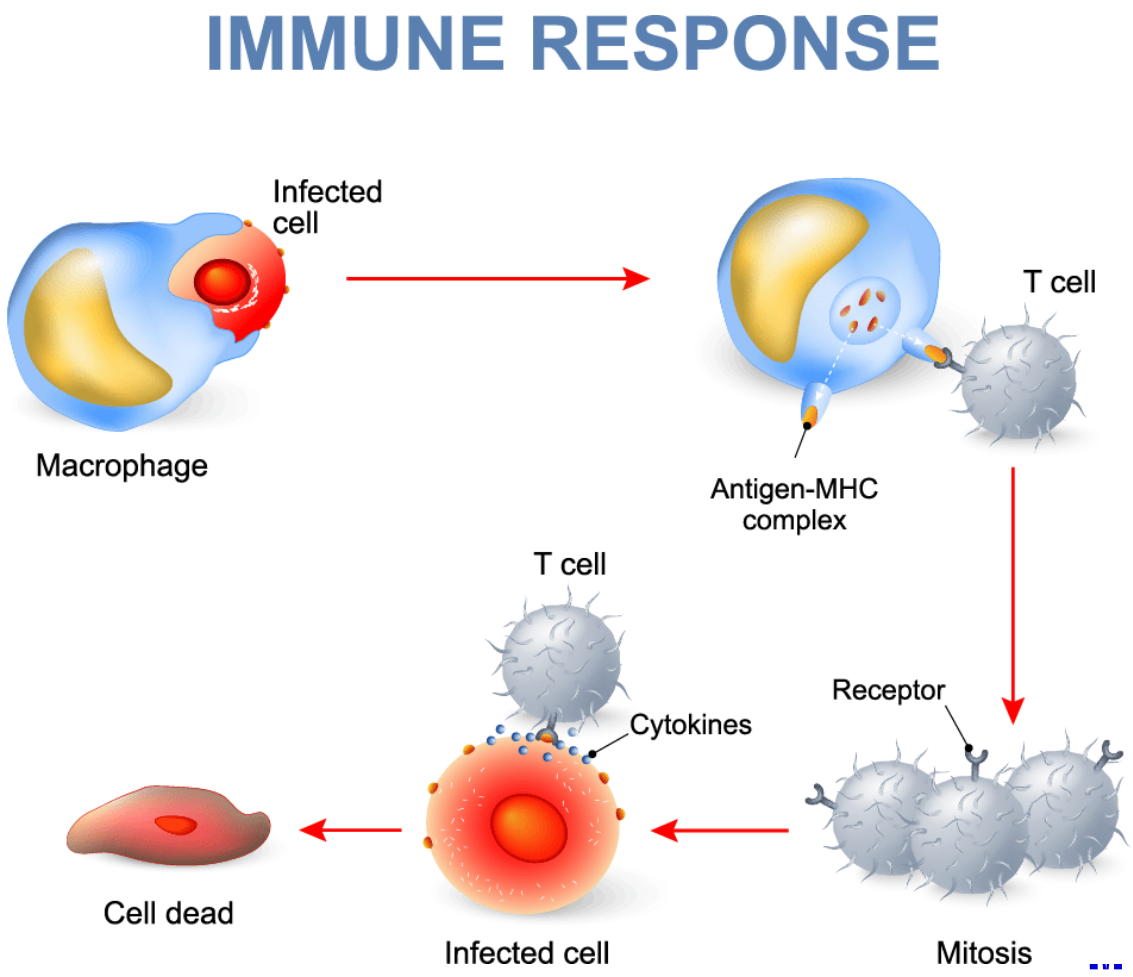
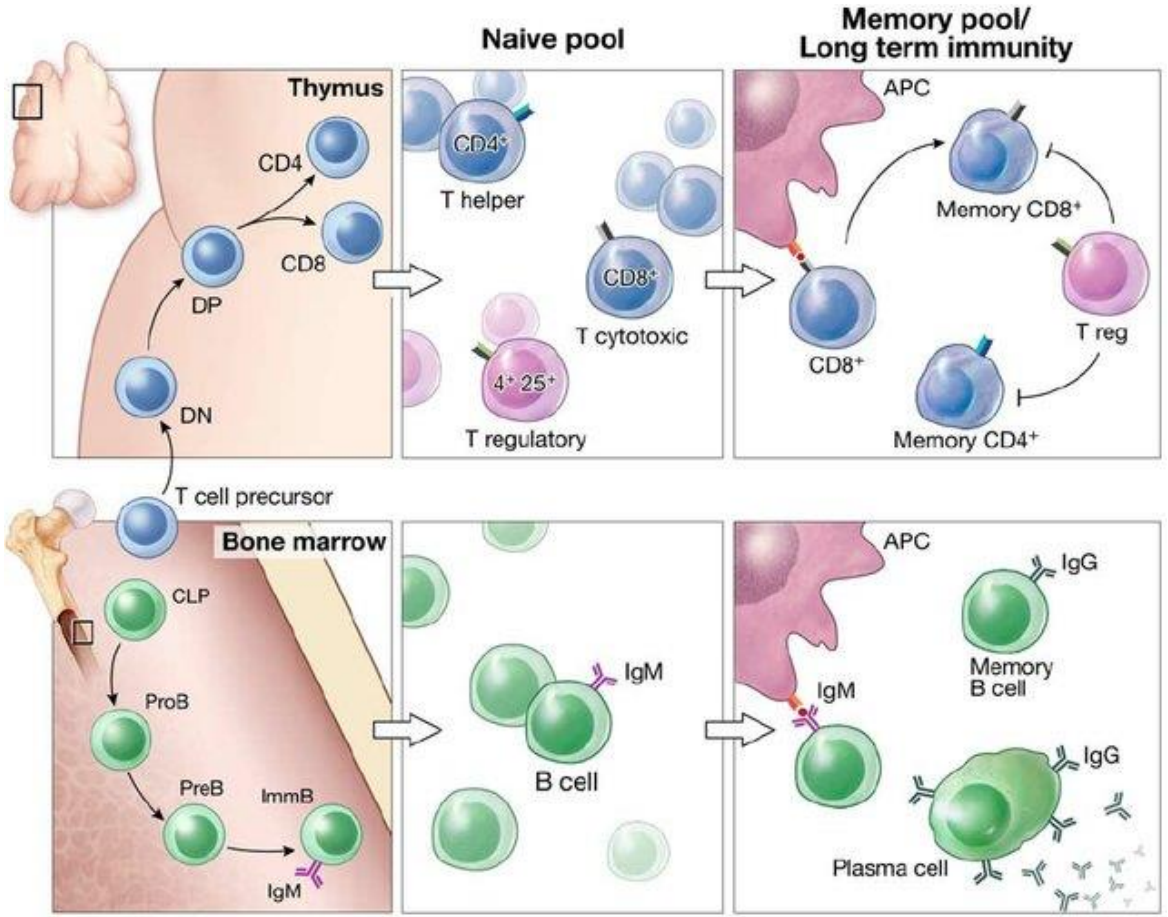
Adaptive immunity mechanisms

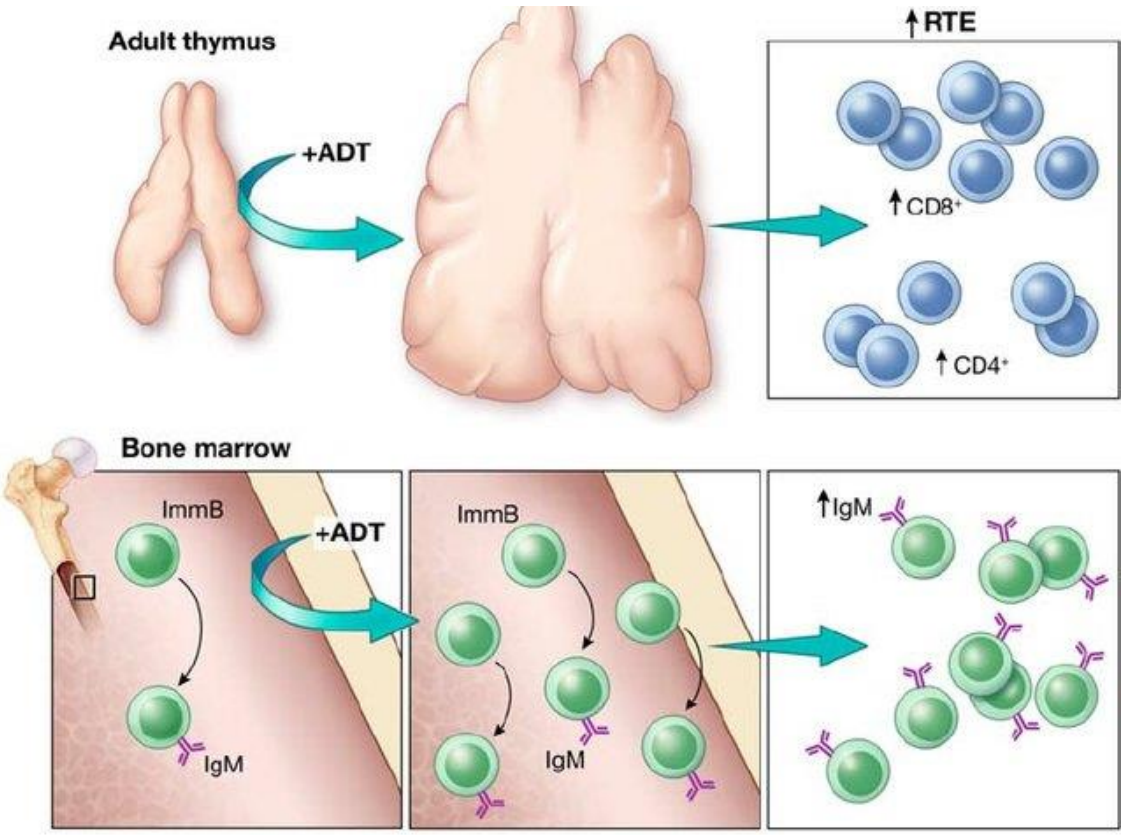
- **Cell-mediated immune response** (CMIR)
- T-lymphocytes
- Elimination of intracellular microbes that survive inside phagocytes or other infected cells

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



Adaptive immunity: mechanisms





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Inflammation

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.

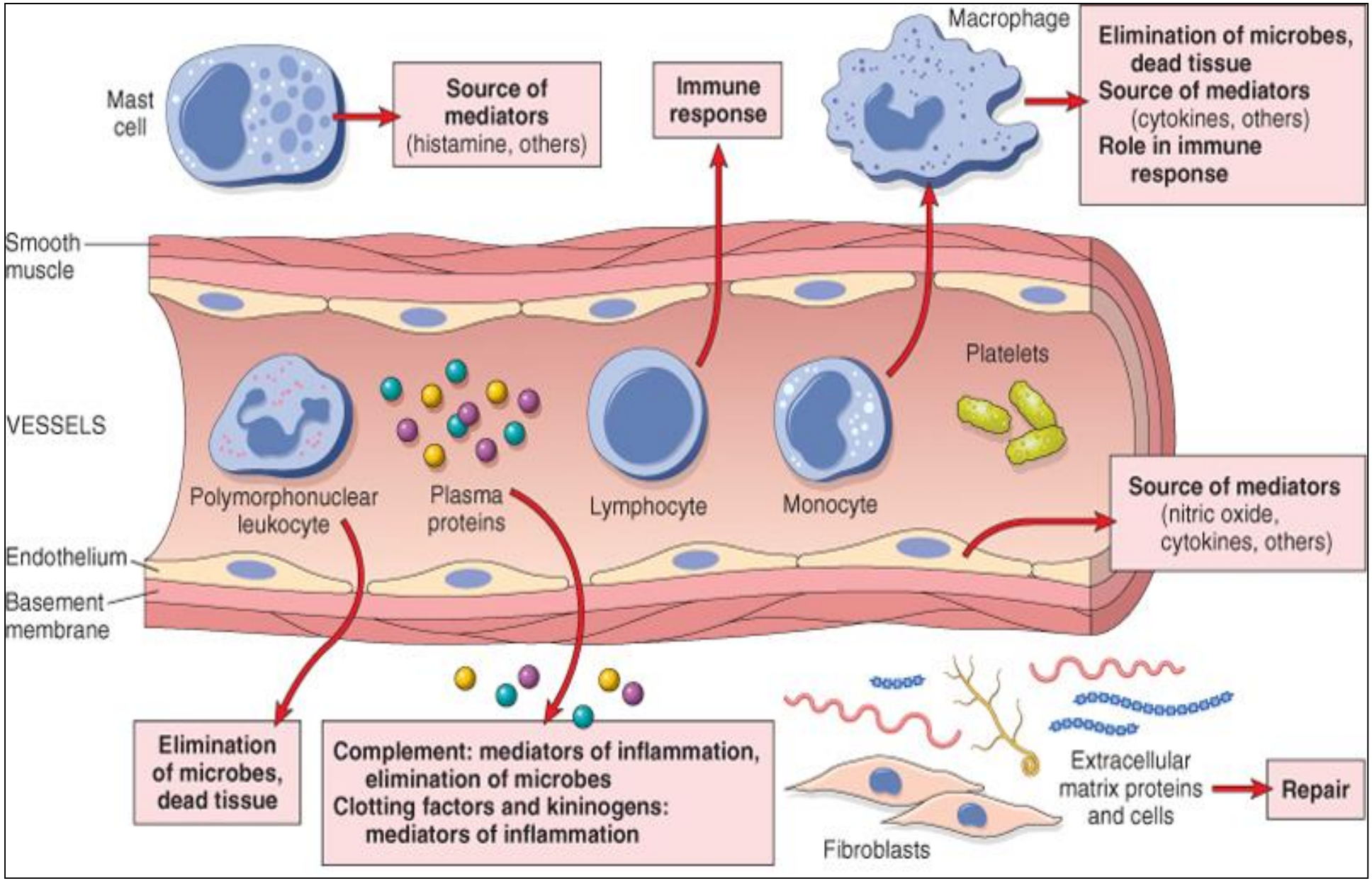
How to accomplishes protective mission?

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.

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

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

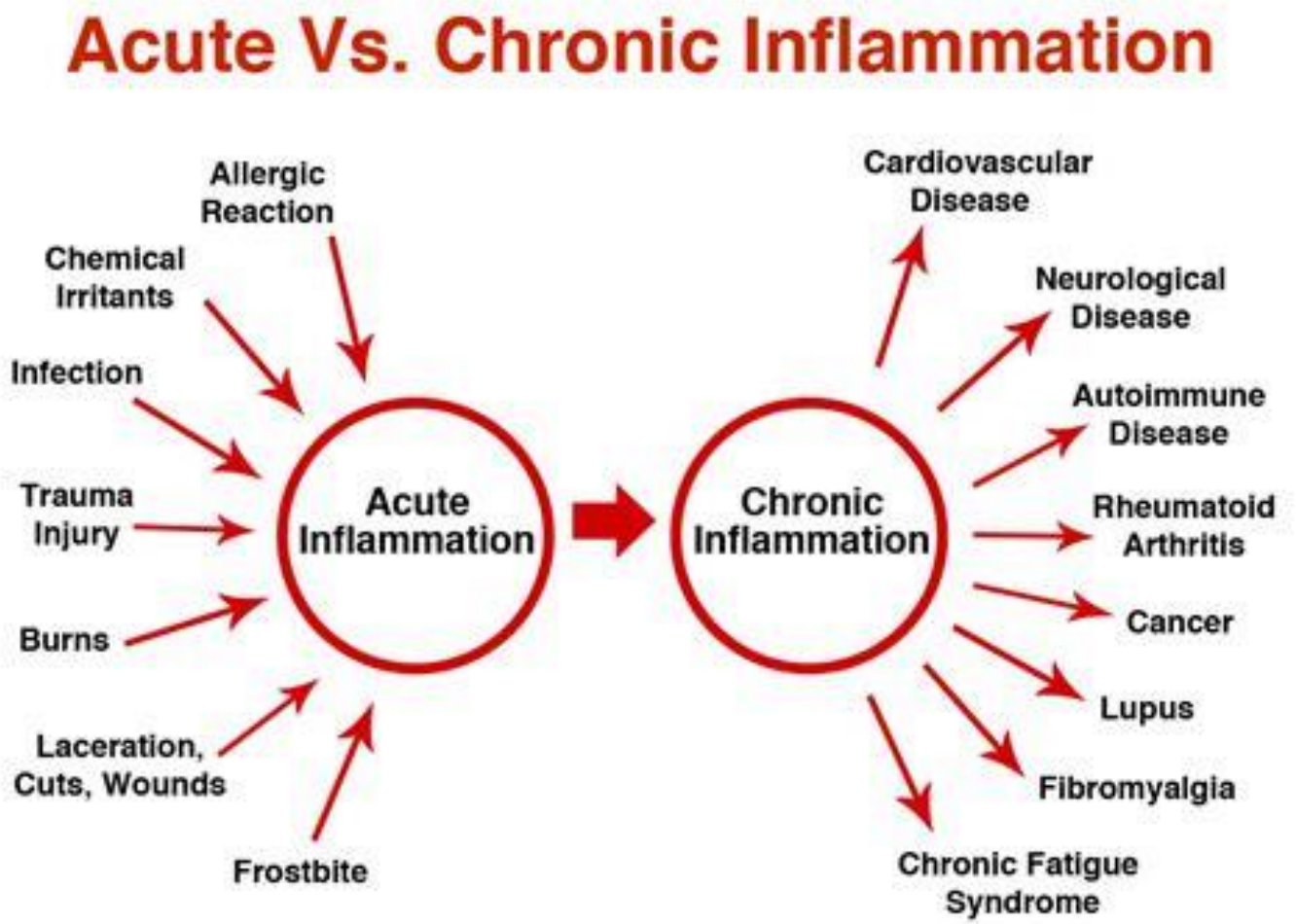
Acute inflammation

- 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.

Inflammation



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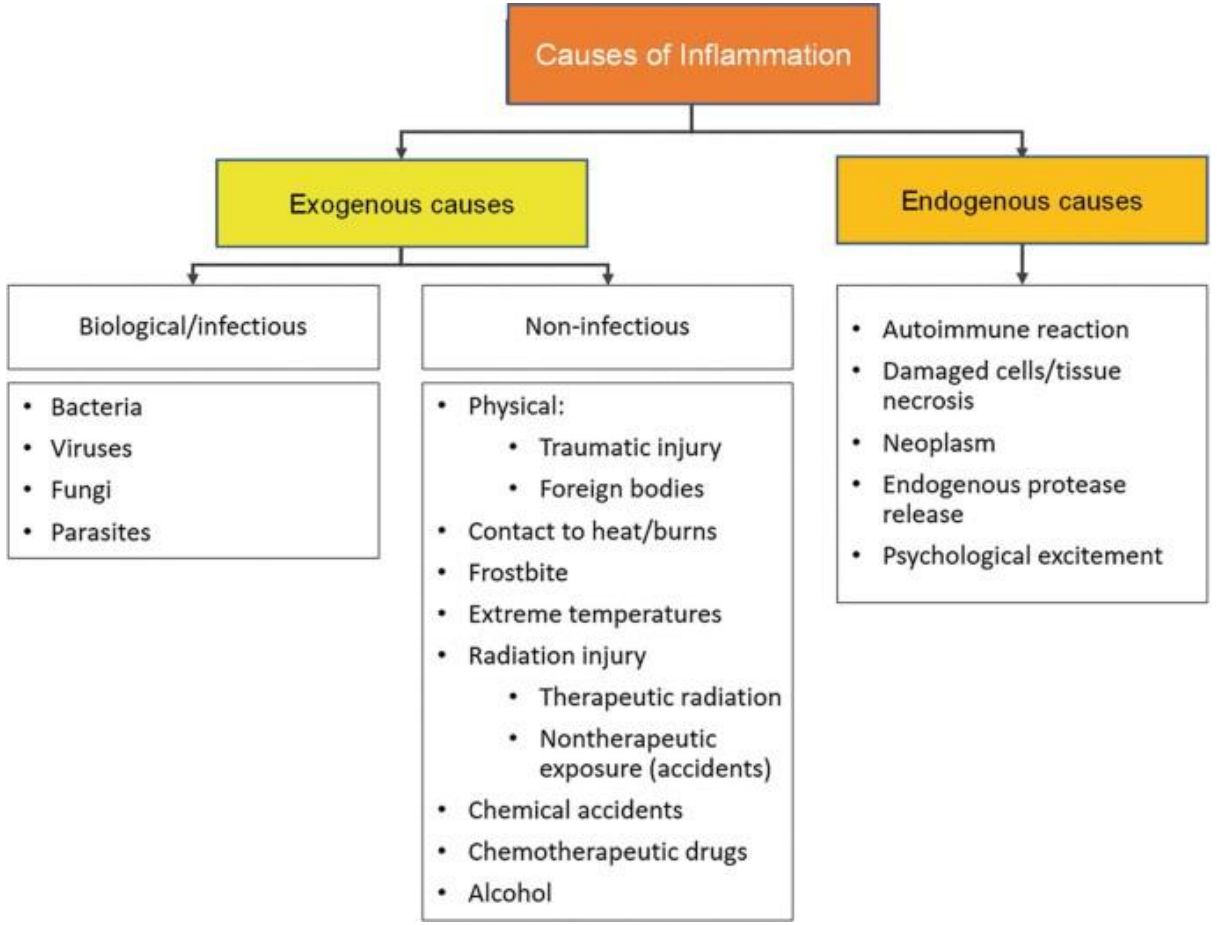
Chronic inflammation

- 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



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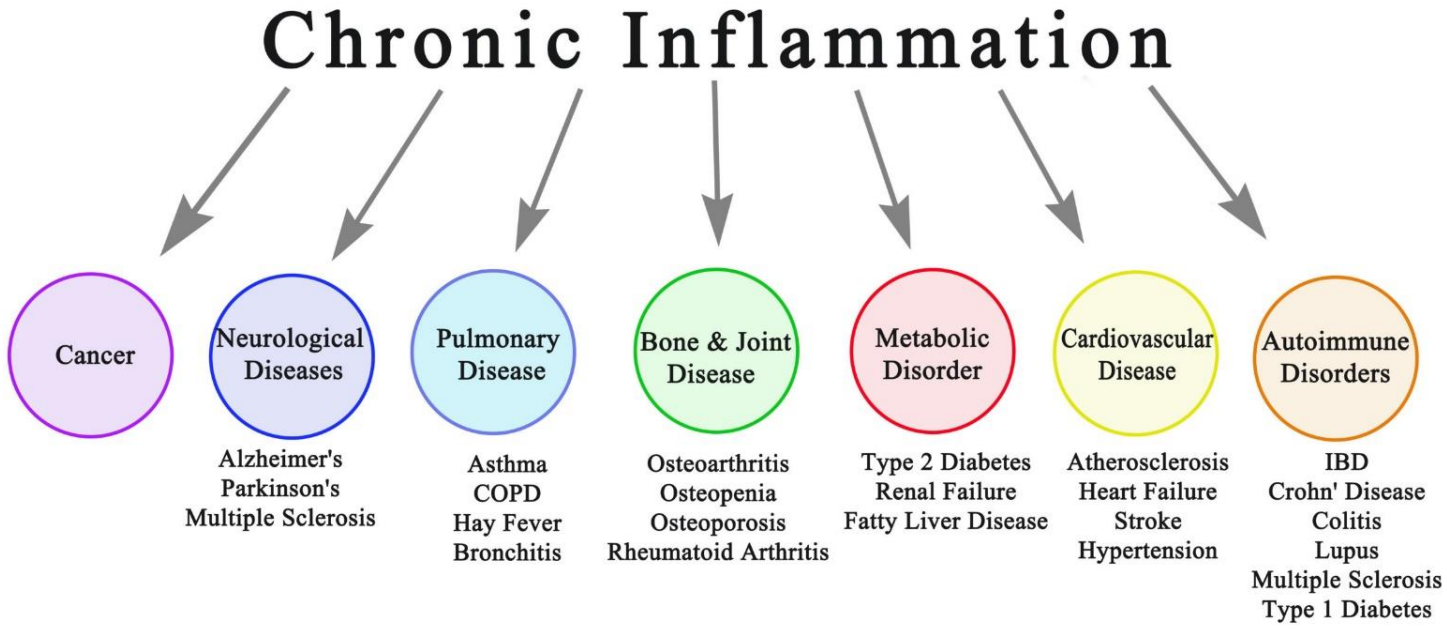
Can Inflammation cause considerable harm to the body?

They may induce harm
e.g. 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 :

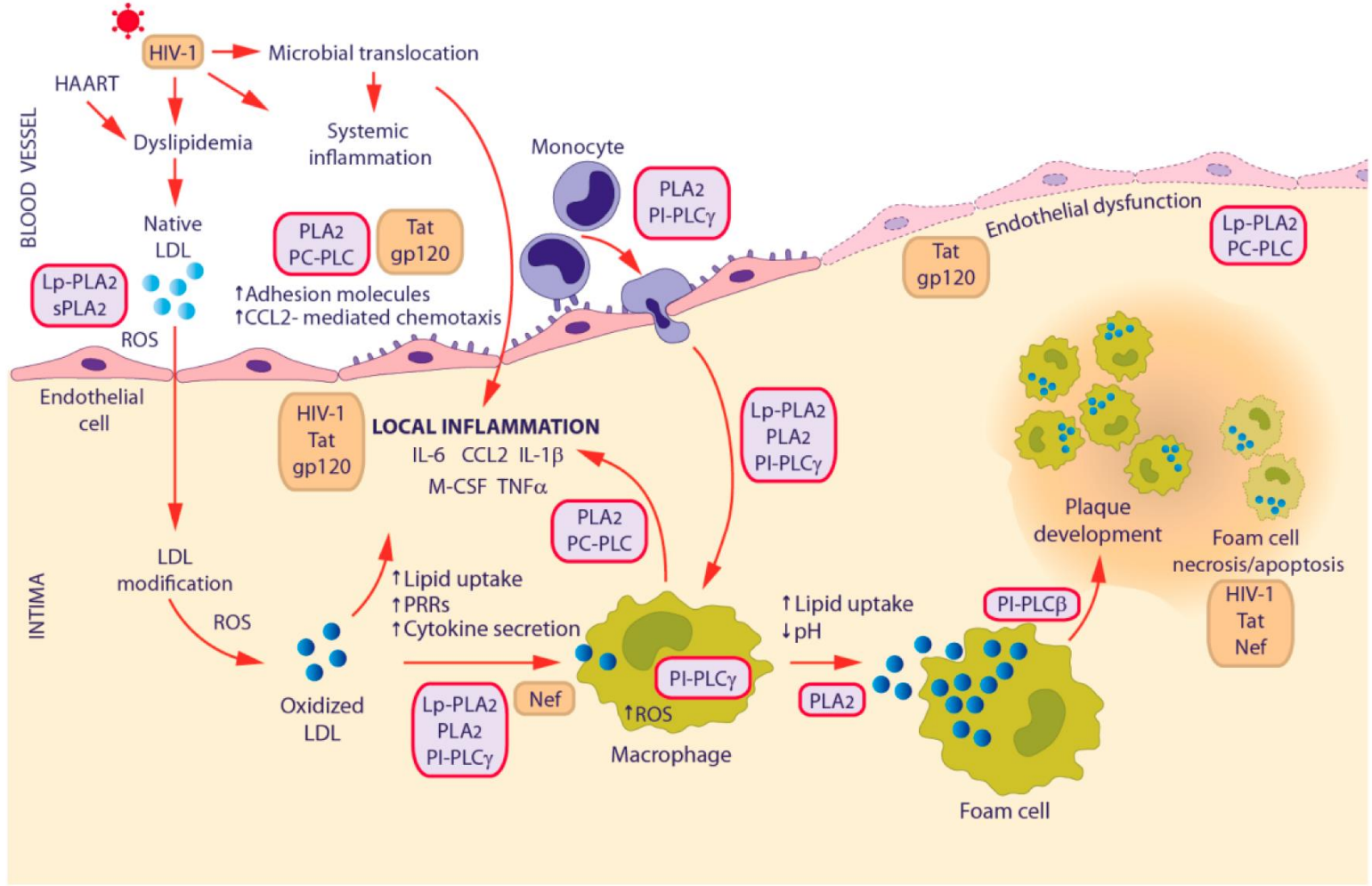
The fluid and proteins of plasma, circulating cells, blood vessels and connective tissue

- 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

The role of macrophages in chronic inflammation



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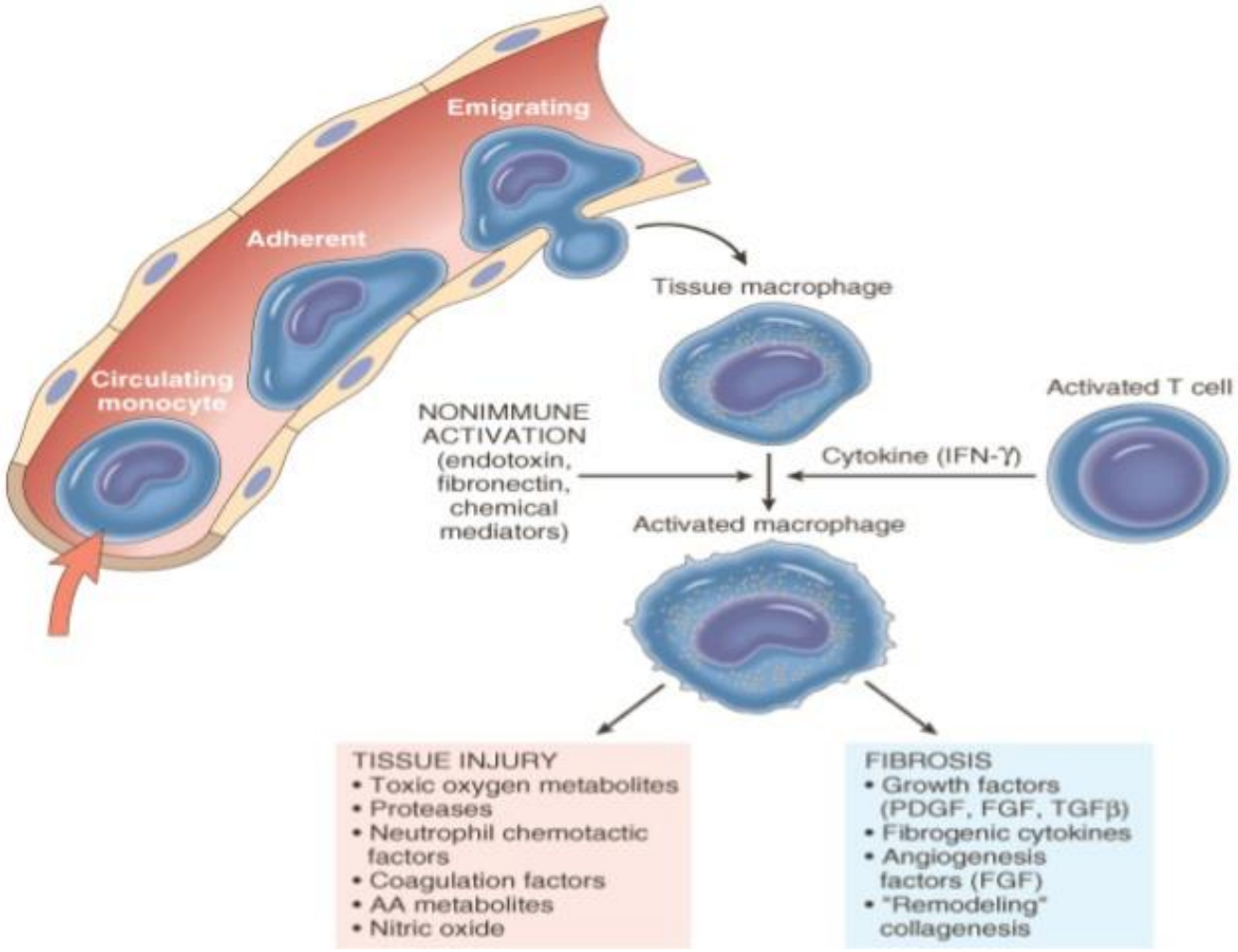
The role of macrophages in chronic inflammation and ECM remodelling

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.



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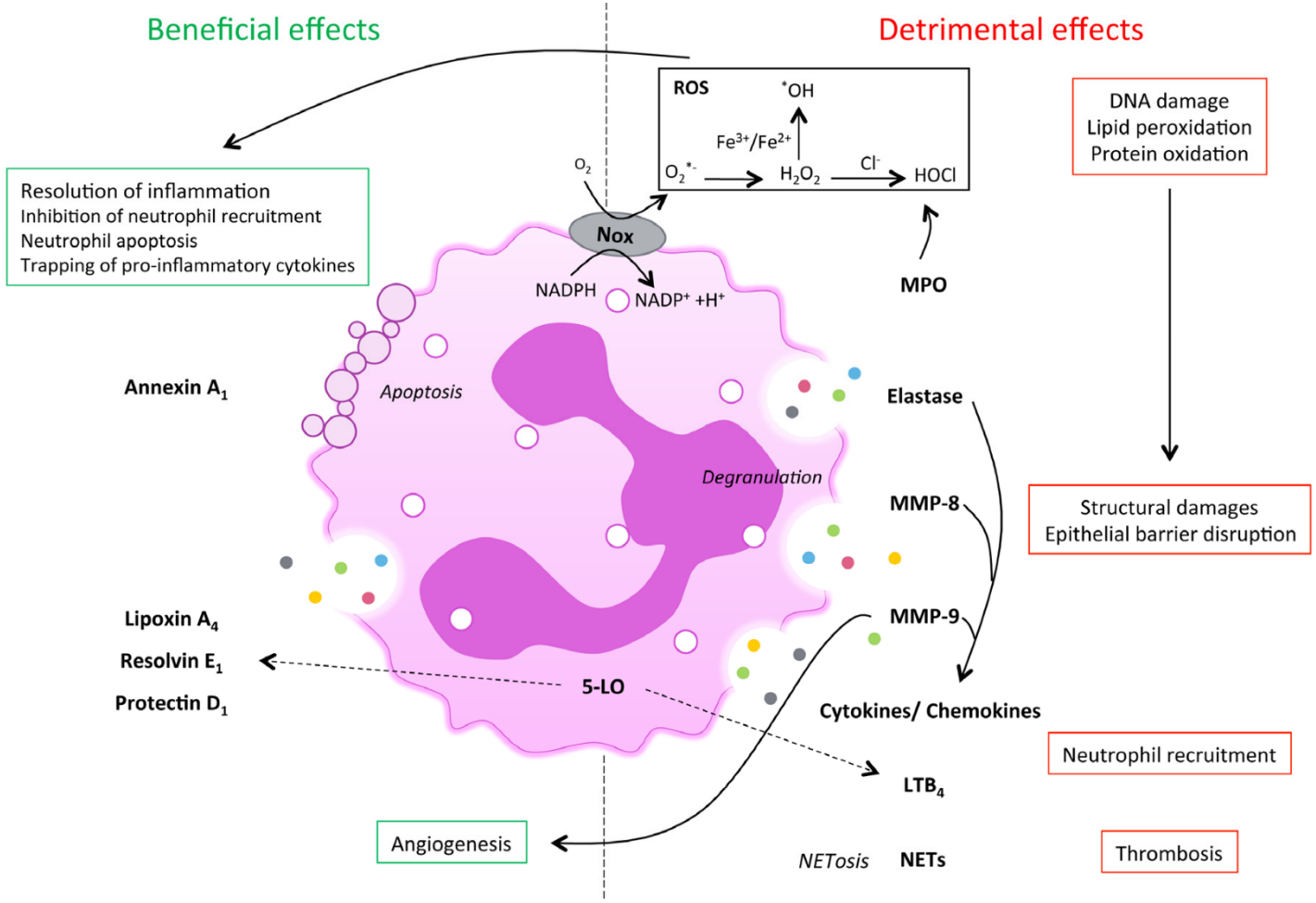
The role of neutrophils in chronic inflammation and ECM remodelling

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.

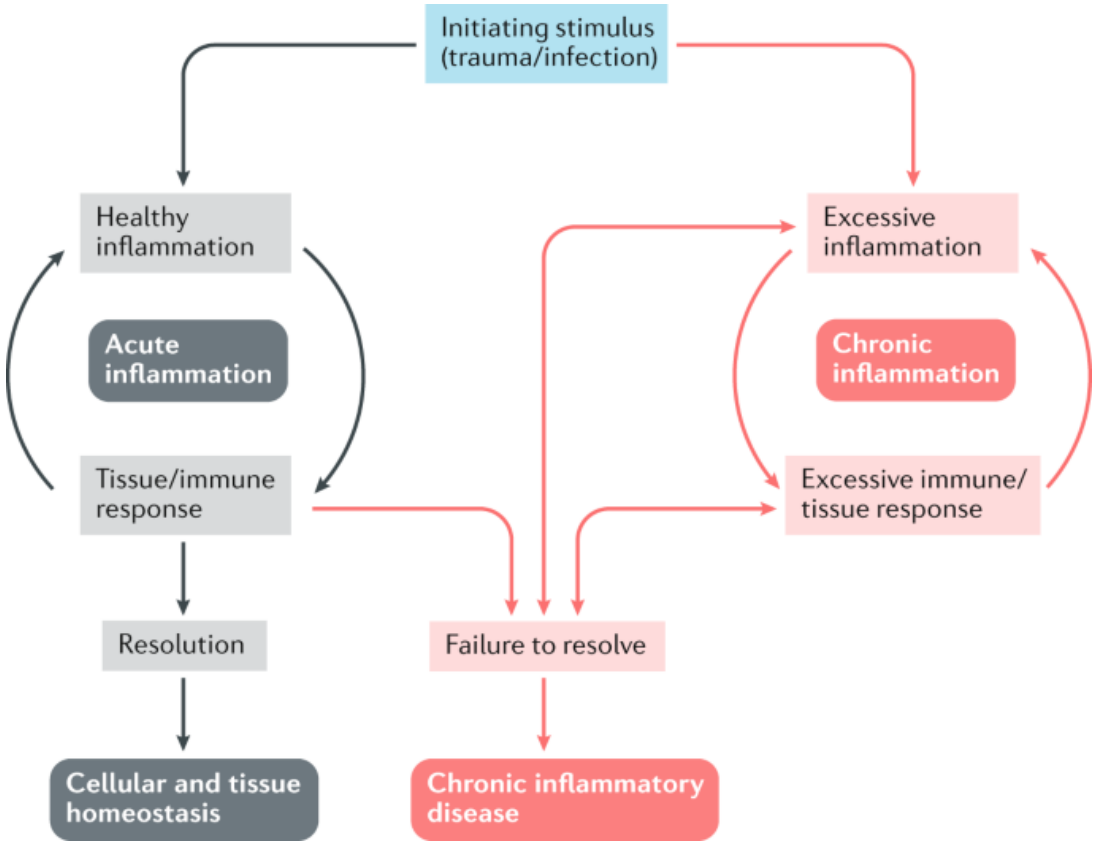


Inflammation

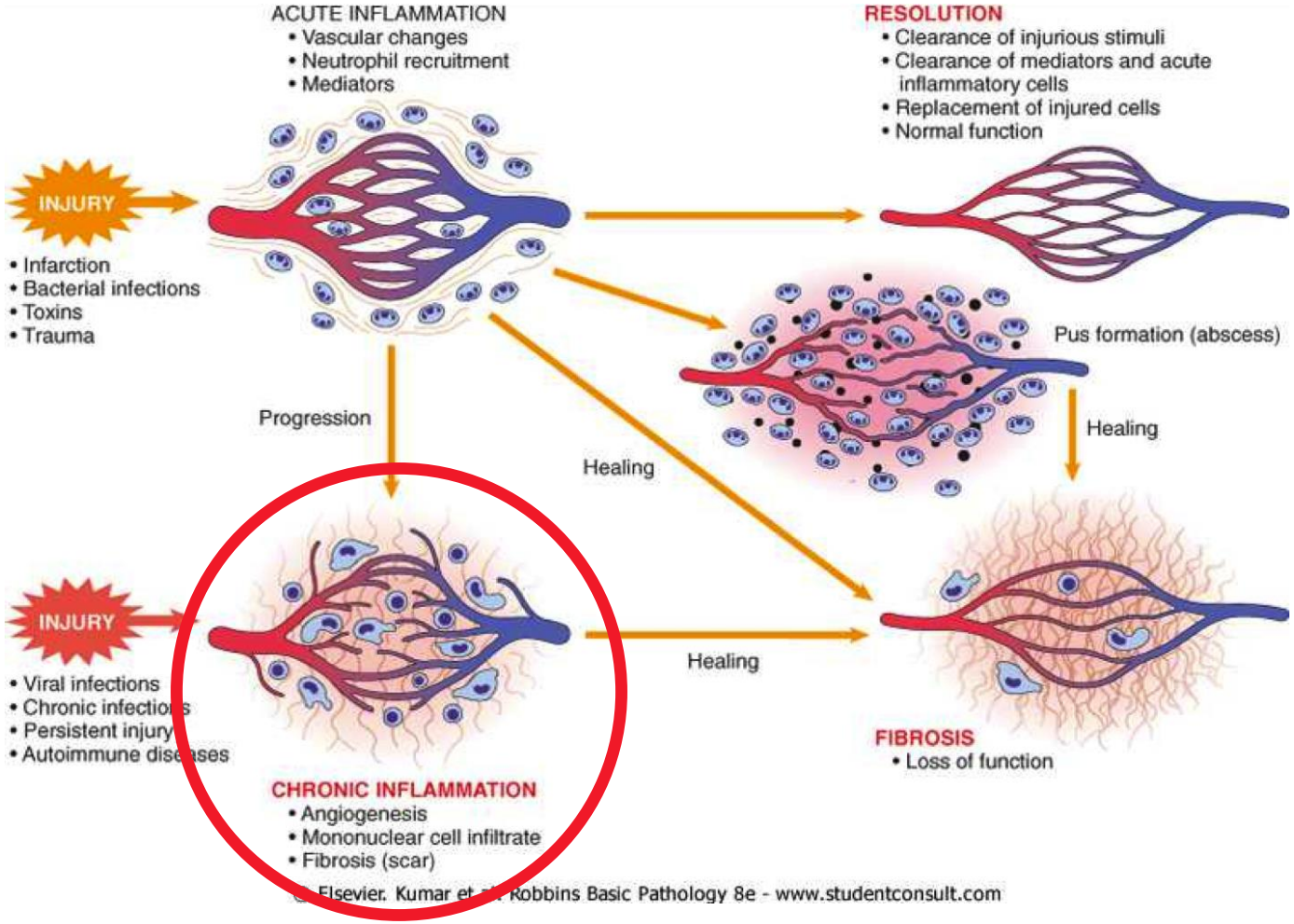
During repair, the injured tissue is replaced by :

- 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



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Low-grade inflammation

- This subclinical disorder has been recognized as a risk factor for a number of chronic diseases including cancer, cardiovascular (CVD) and neurodegenerative disease
- a 44% increased risk of all-cause mortality

- association of low-grade inflammation with mortality was higher in high-risk subjects, such as those with type 2 diabetes or a history of cardiovascular disease

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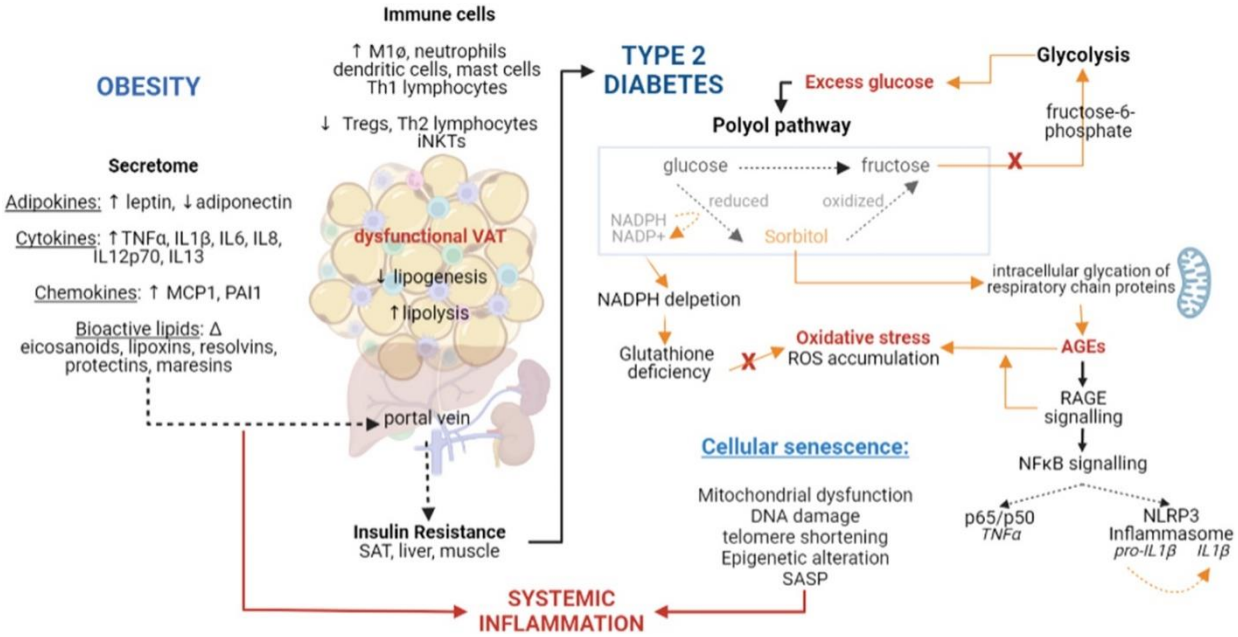
VAT dysfunction and DM2-associated pathological alterations

- dysregulated expansion and hypertrophy of VAT during obesity induce tissue hypoxia, alter the secretory profile of adipokines, cytokines/chemokines, bioactive lipids, and modify the distribution and quantity of immune cells within tissue
- hypergycaemia - imbalance in diabetes and overload of the polyol pathway results in NADPH depletion and the accumulation of sorbitol which in turn cause widespread glycation of respiratory chain proteins and triggers intracellular damage by inducing oxidative and endoplasmic reticulum stress through elevated production of cytosolic ROS

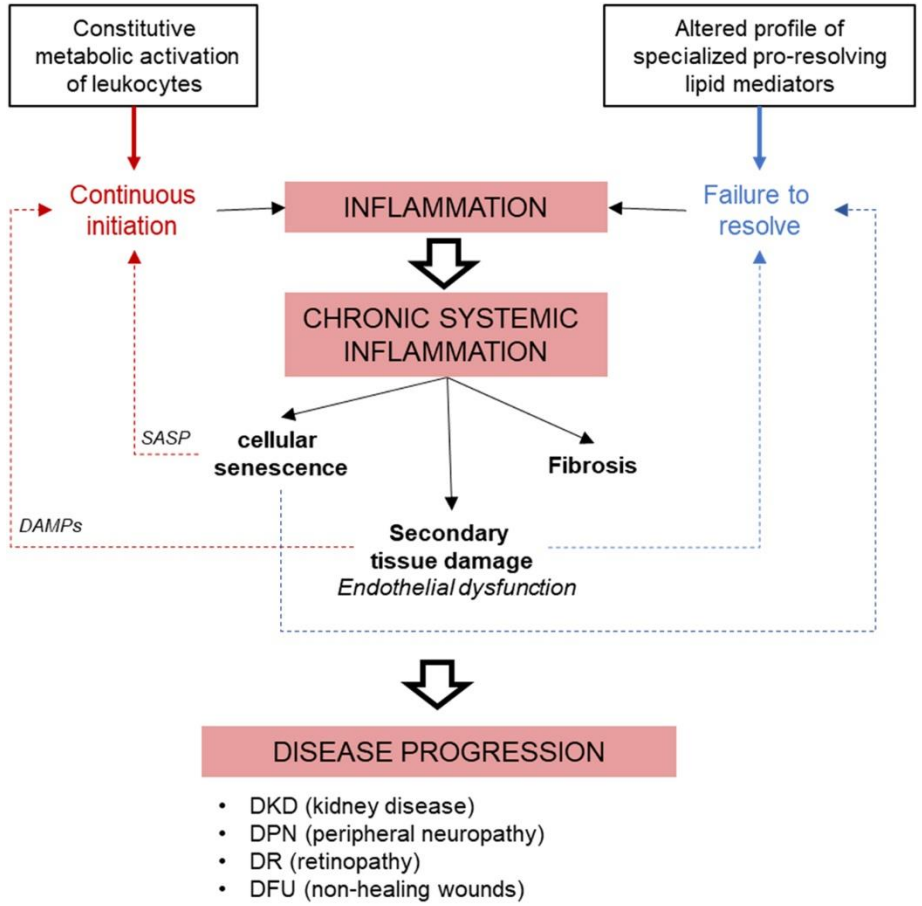


Journal of Endocrinology 257, 1, 2023

- dying adipocytes release toxic cargo including cell-free DNA
- hypoxia
- obesity-induced genotoxicity and related stress

Factors contributing to chronic inflammation in DM2

- dysfunctional adipose tissue, the aberrant metabolic activation of leukocytes, damage-associated molecular patterns (DAMPs) released from injured tissue and endothelium, and excessive cytokines released by senescent cells as part of the senescence-associated secretory phenotype (SASP).
- The failure of inflammation to resolve is associated with an altered profile of specialized pro-resolving lipid mediators (SPM), together with DAMPs derived from secondary tissue damage and the non-responsiveness of senescent immune cells to regulatory signals.



Journal of Endocrinology 257, 1, 2023

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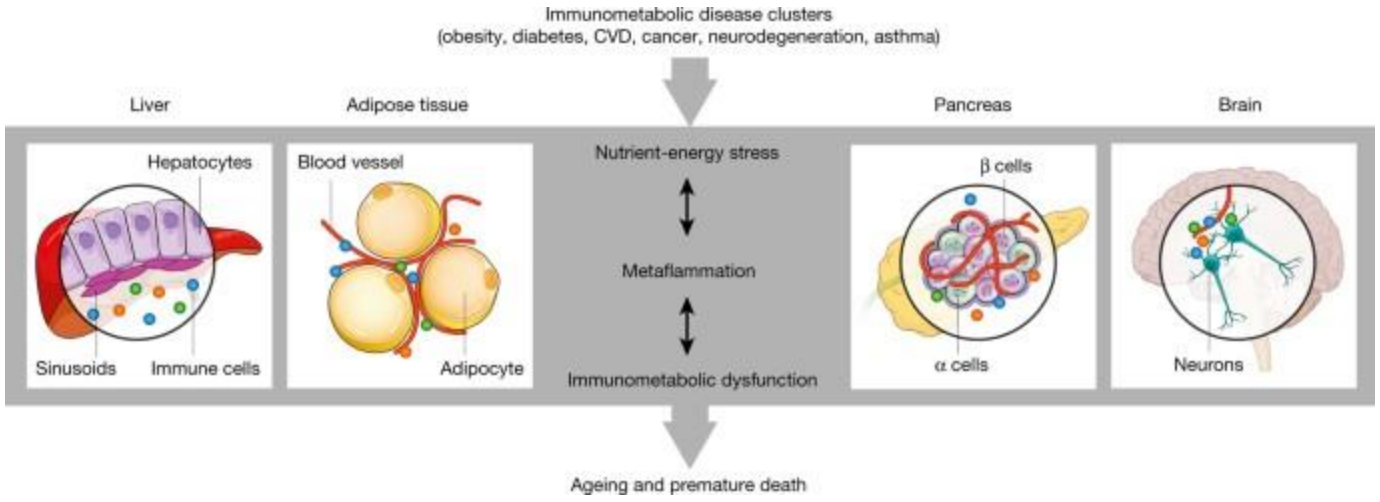
Metainflammation

- **Metabolic inflammation** (*metainflammation)* refers to chronic low-grade systemic inflammation fuelled by metabolic disturbances.
- The evolutionary advantages of a strong defense system are obvious in protecting against pathogens, and as a strong immune response is dependent on energy sources
- Except of adipose tissue, obesity-related influx of immune cells occurs in many other tissues such as the hypothalamus, liver, muscle, pancreatic islets and the gut



Nature volume 542, pages177–185 (2017)

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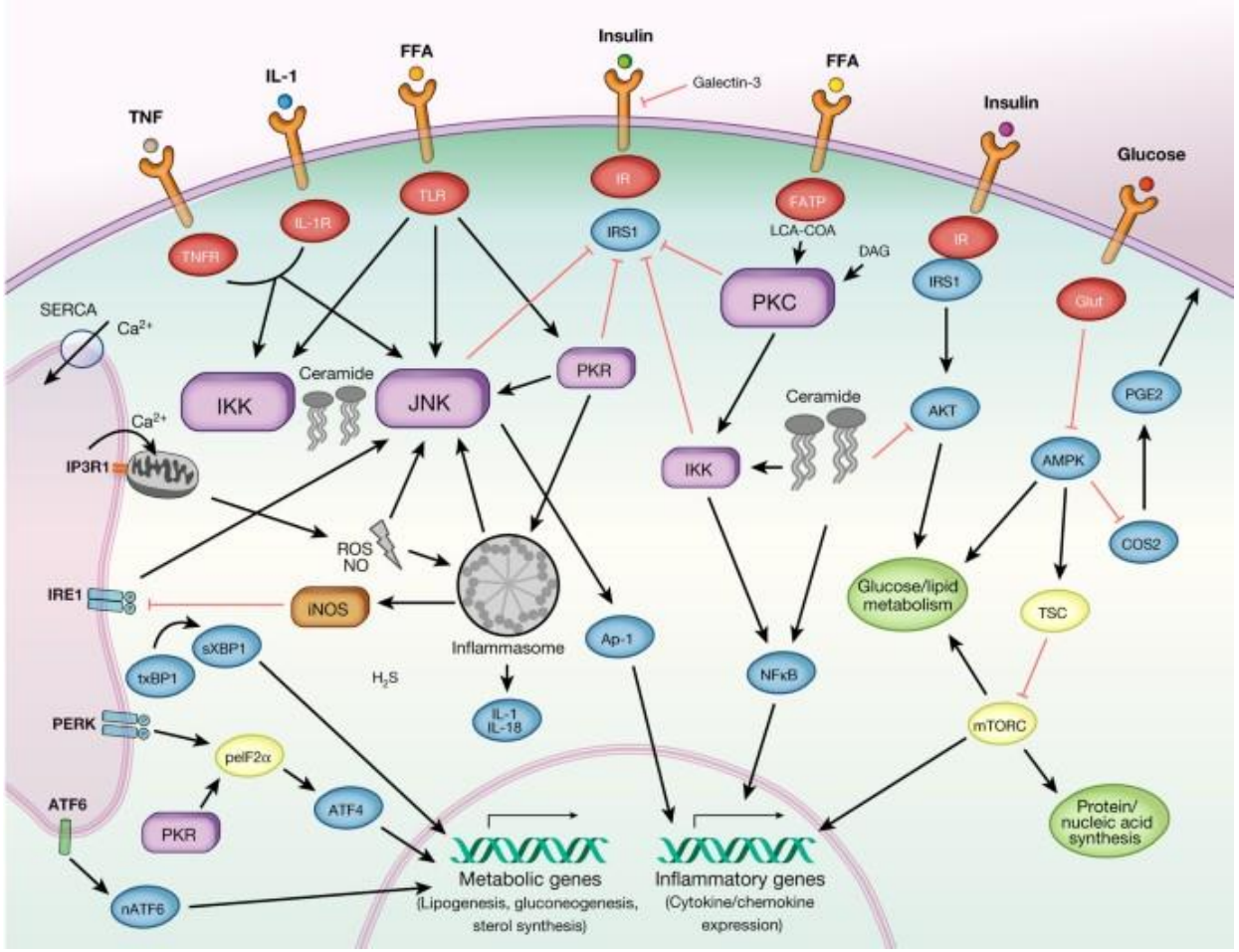
Integration of metabolic and inflammatory signalling

PKC (protein kinase C), JNK (c-Jun N-terminal kinase) and IKK (IkappaB kinase) can signal:

- a multitude of immune (both innate and adaptive responses, resolution of inflammation) and
- metabolic (insulin, glucagon or FGF21 action, fatty acid and cholesterol metabolism, appetite regulation, and so on) responses



Nature volume 542, pages177–185 (2017)

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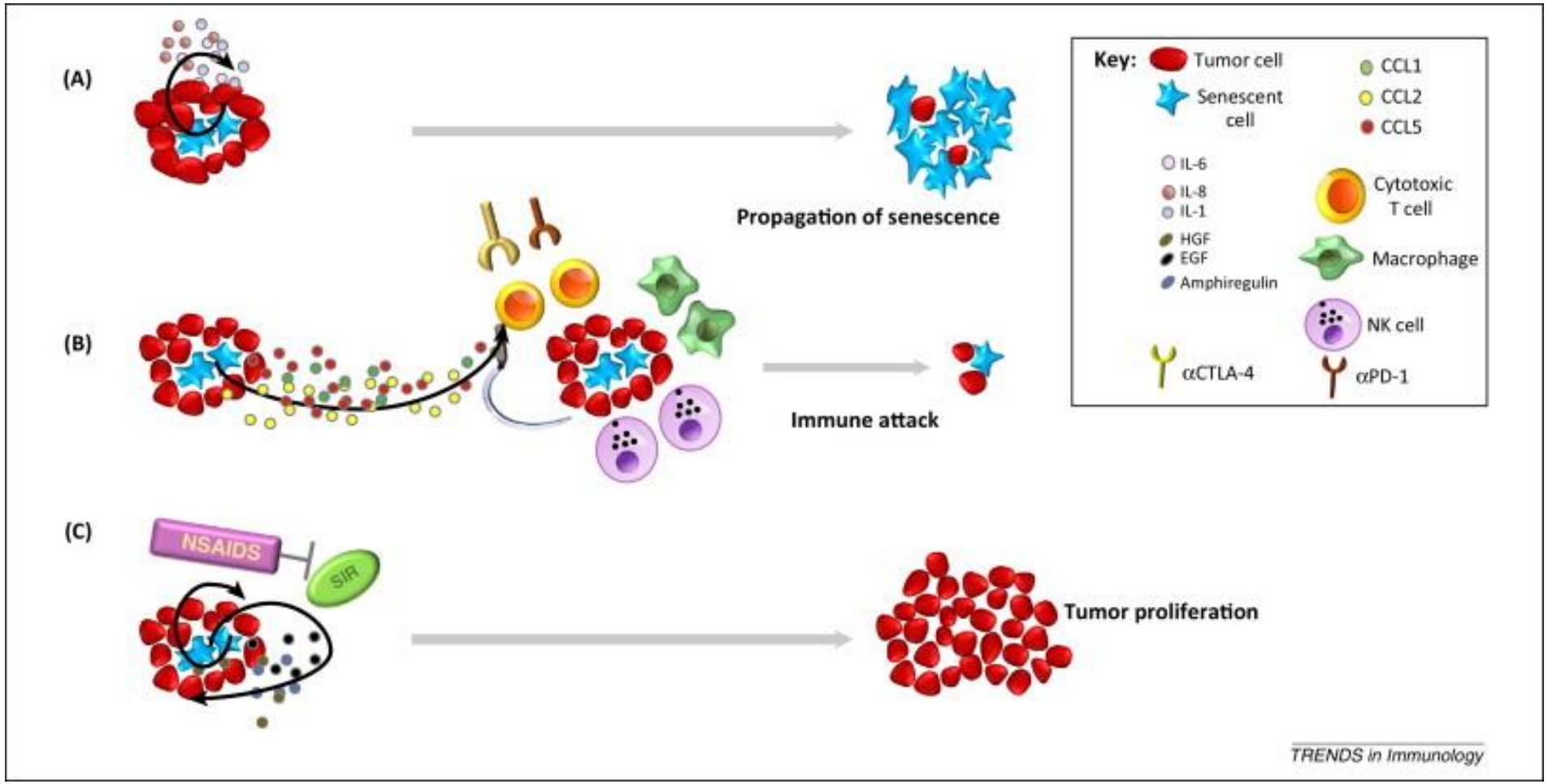
Age-dependent consequences



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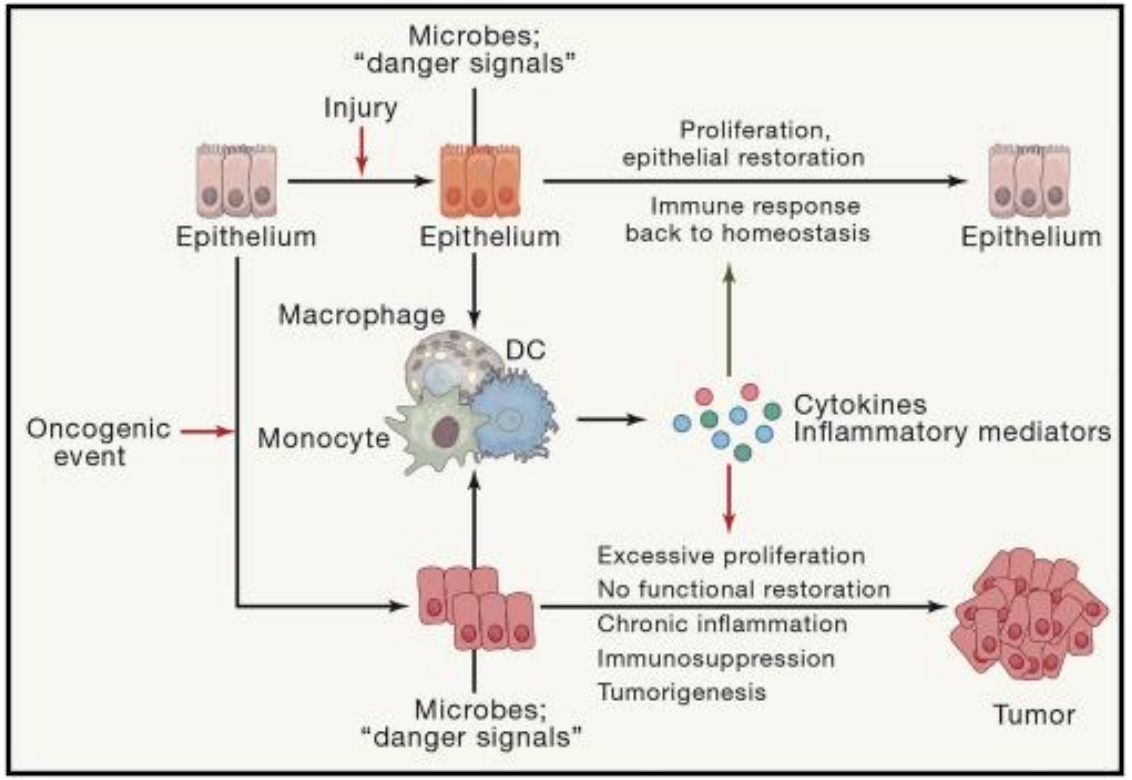
Tumor-initiating inflammation

- Around 15%–20% of all cancer cases are preceded by infection, chronic inflammation, or autoimmunity at the same tissue or organ site
- low-grade inflammation induced by obesity, hyperglycemia, and excessive lipid accumulation is generally of systemic nature and, as a result, can promote or increase risk of many different cancers, including liver, pancreatic, colon, breast, and other malignancies



Immunity, Volume 51, Issue 1, 16 July 2019

Macrophages and neutrophils are potent producers of reactive oxygen (ROS) and nitrogen (RNI) species, which induce mutations. Therefore, induction of inflammation can lead to increased mutagenesis, predisposing to accumulation of mutations in normal tissue.

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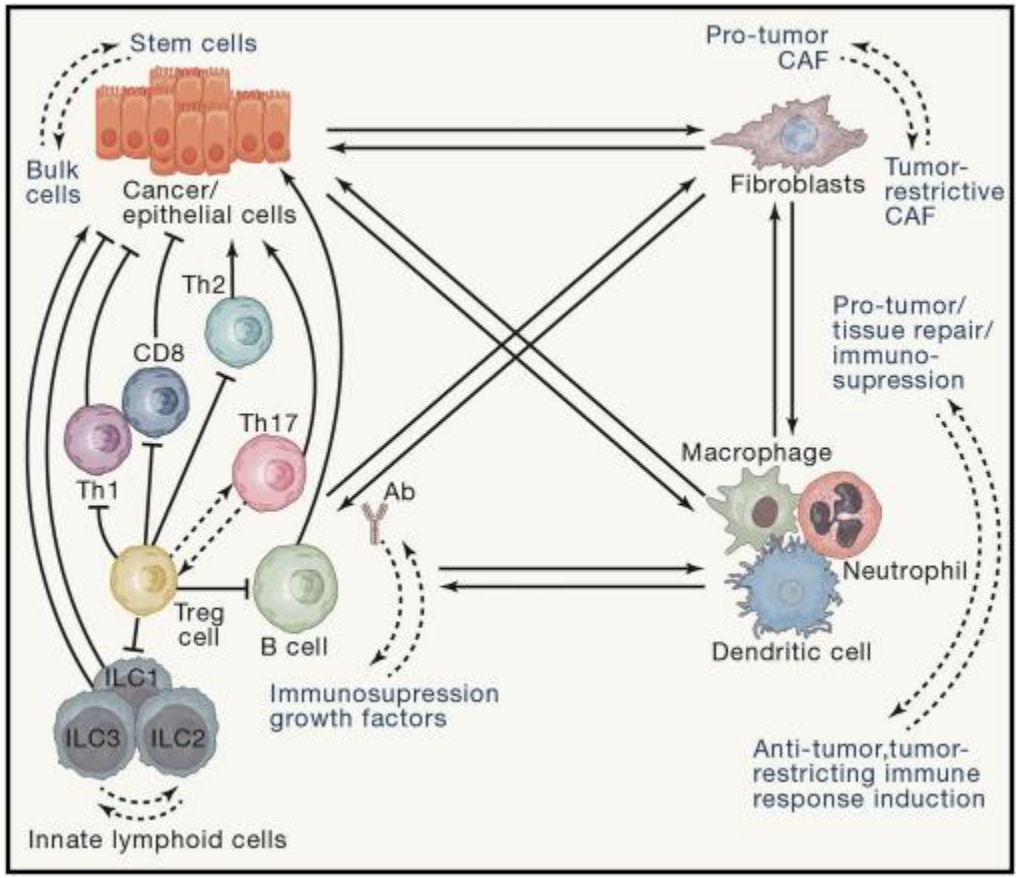
Tumor-associated inflammation

- cancers previously defined as “non-inflammatory” recruit immune cells and increase expression of inflammatory mediators to support tumor growth and re-shape the TME (tumor microenvironment) to their benefit, has led to the term “tumor-elicited (or -associated) inflammation” (TEI)
- An intricate reciprocal interplay between all cells (cancer, stromal, and immune) in the TME shapes polarization of immune cells activation states (for myeloid cells and lymphocyes) as well as of cancer-associated fibroblasts and states of differentiation of epithelial cells.



Immunity, Volume 51, Issue 1, 16 July 2019

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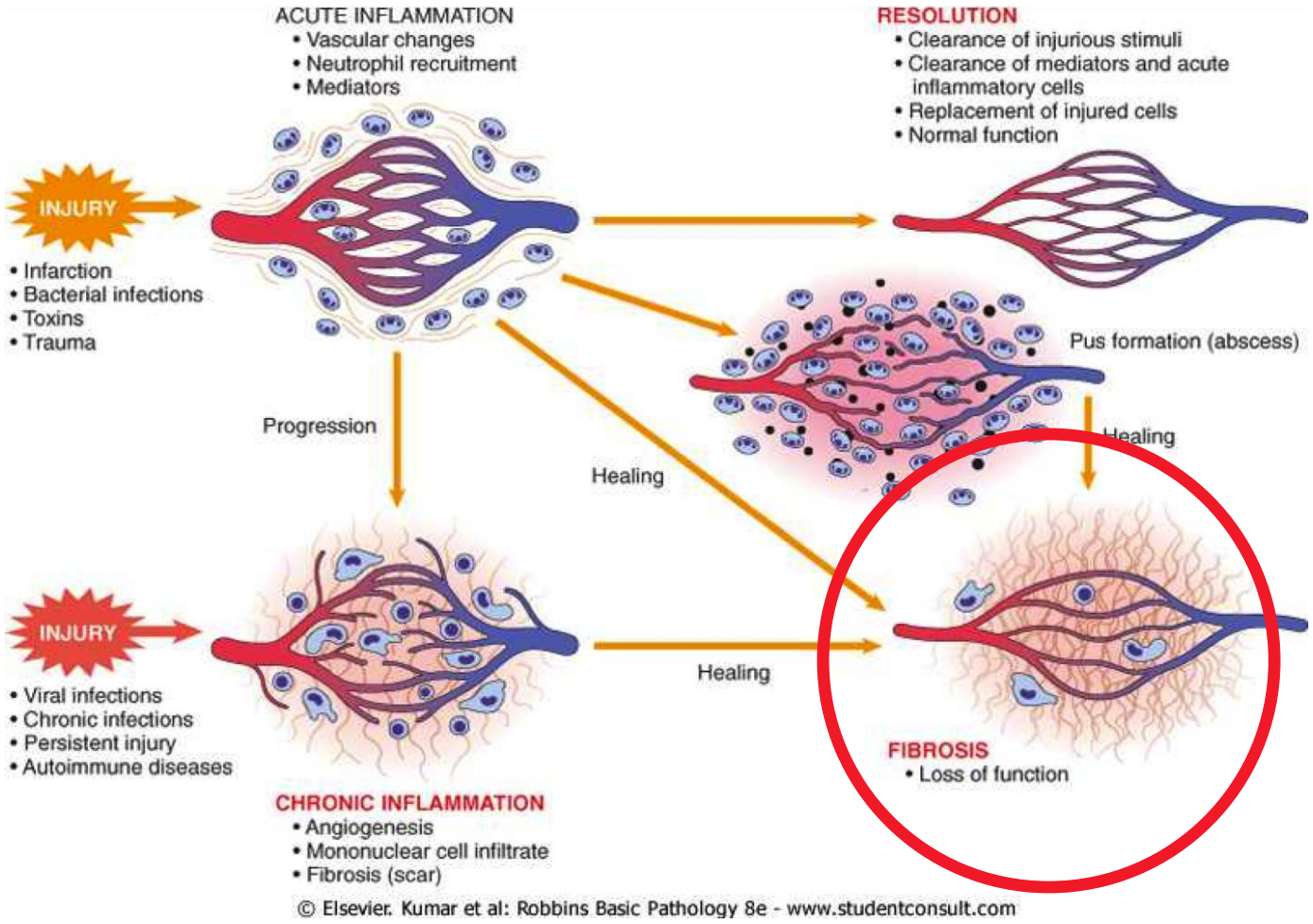
Fibrosis



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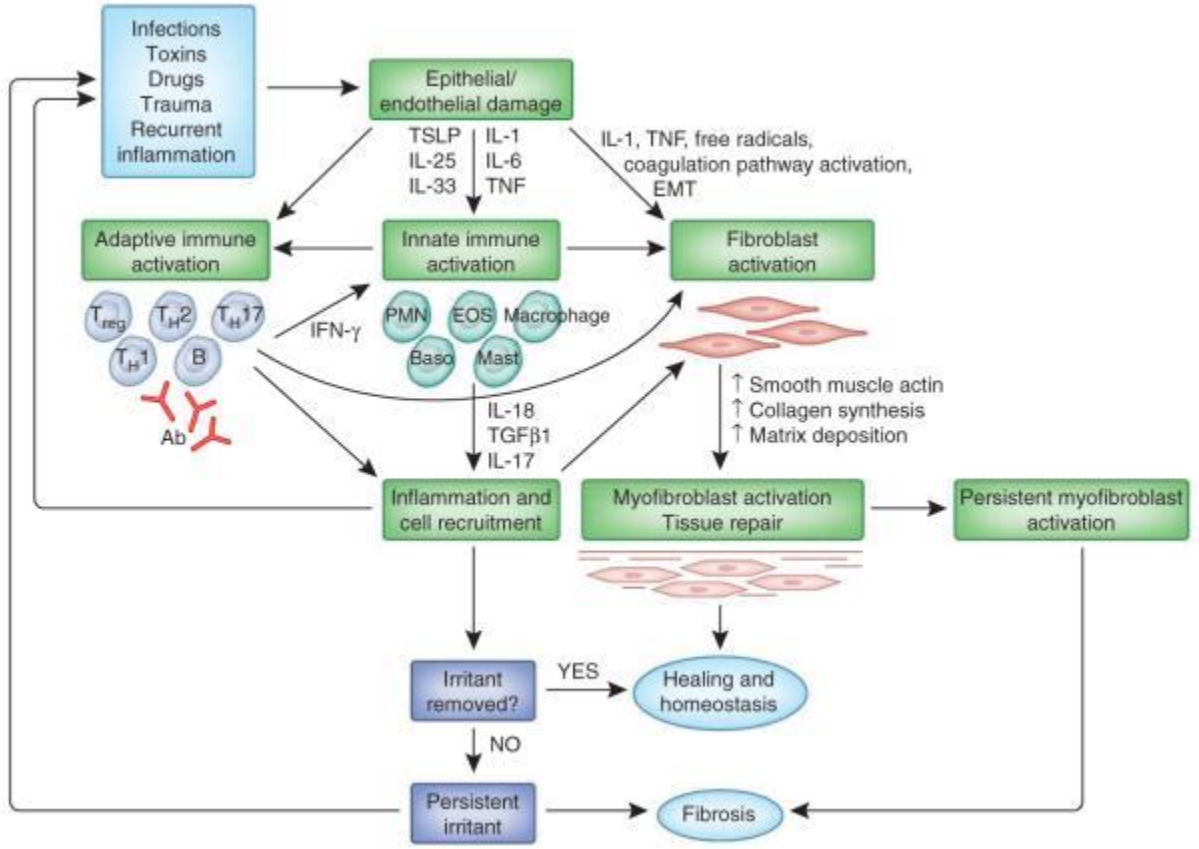
Fibrosis

– Failure to adequately contain or eliminate the inciting factors can exacerbate the inflammatory response and lead to a chronic wound-healing response, with continued tissue damage, repair and regeneration, ultimately resulting in fibrosis.



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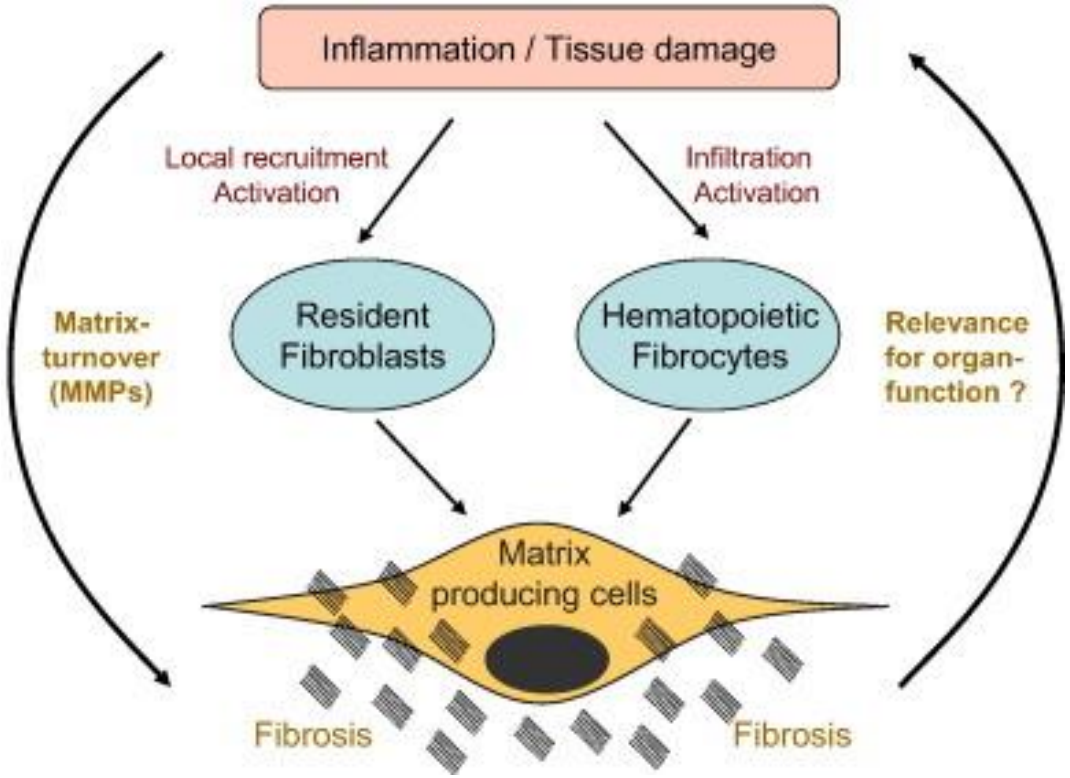
Fibrosis

- Fibrosis is characterized by the excessive extracellular matrix deposition due to dysregulated wound and connective tissue repair response. Multiple organs can develop fibrosis, including the liver, kidney, heart, and lung.
- 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,

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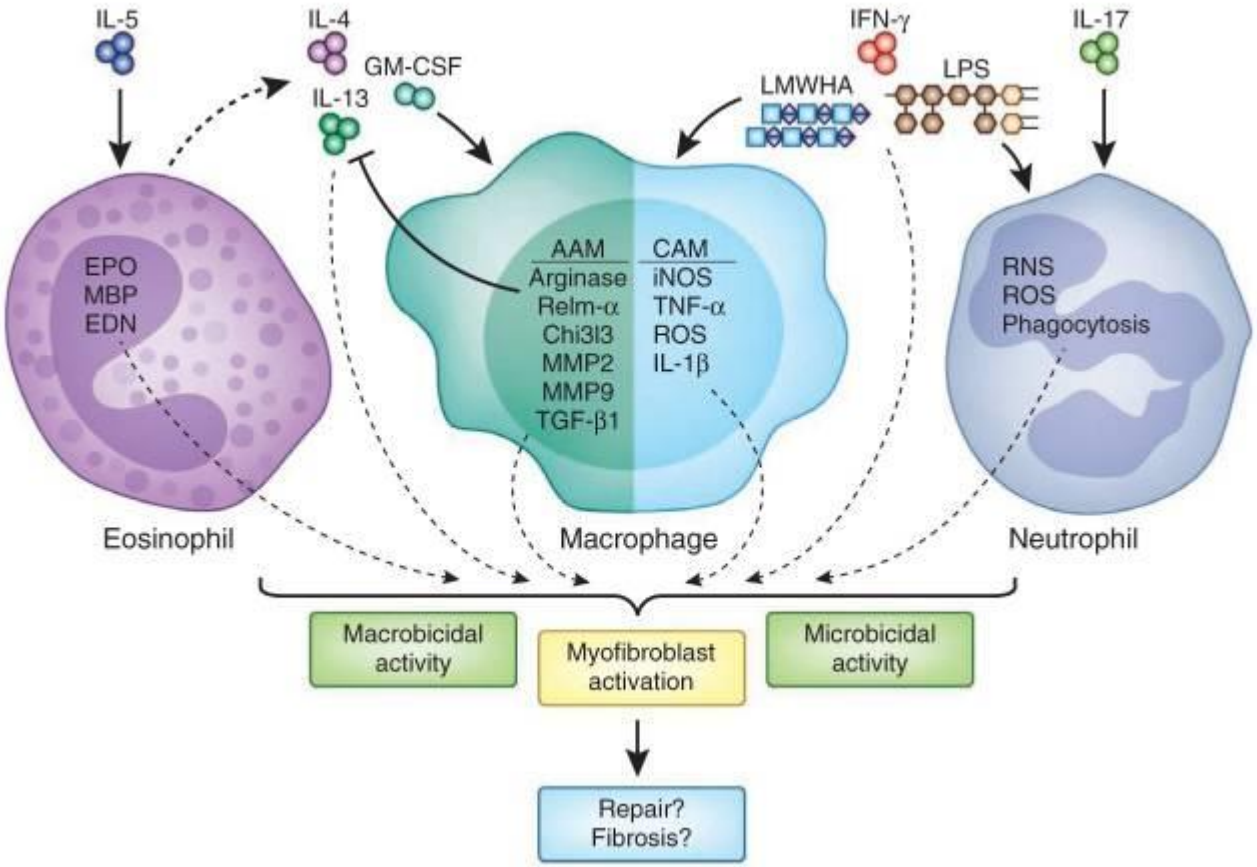
Major tissues affected by fibrosis and possible contributing factors

- *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 orgnanisms
- *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

J Pathol. 2008 Jan; 214(2): 199–210

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



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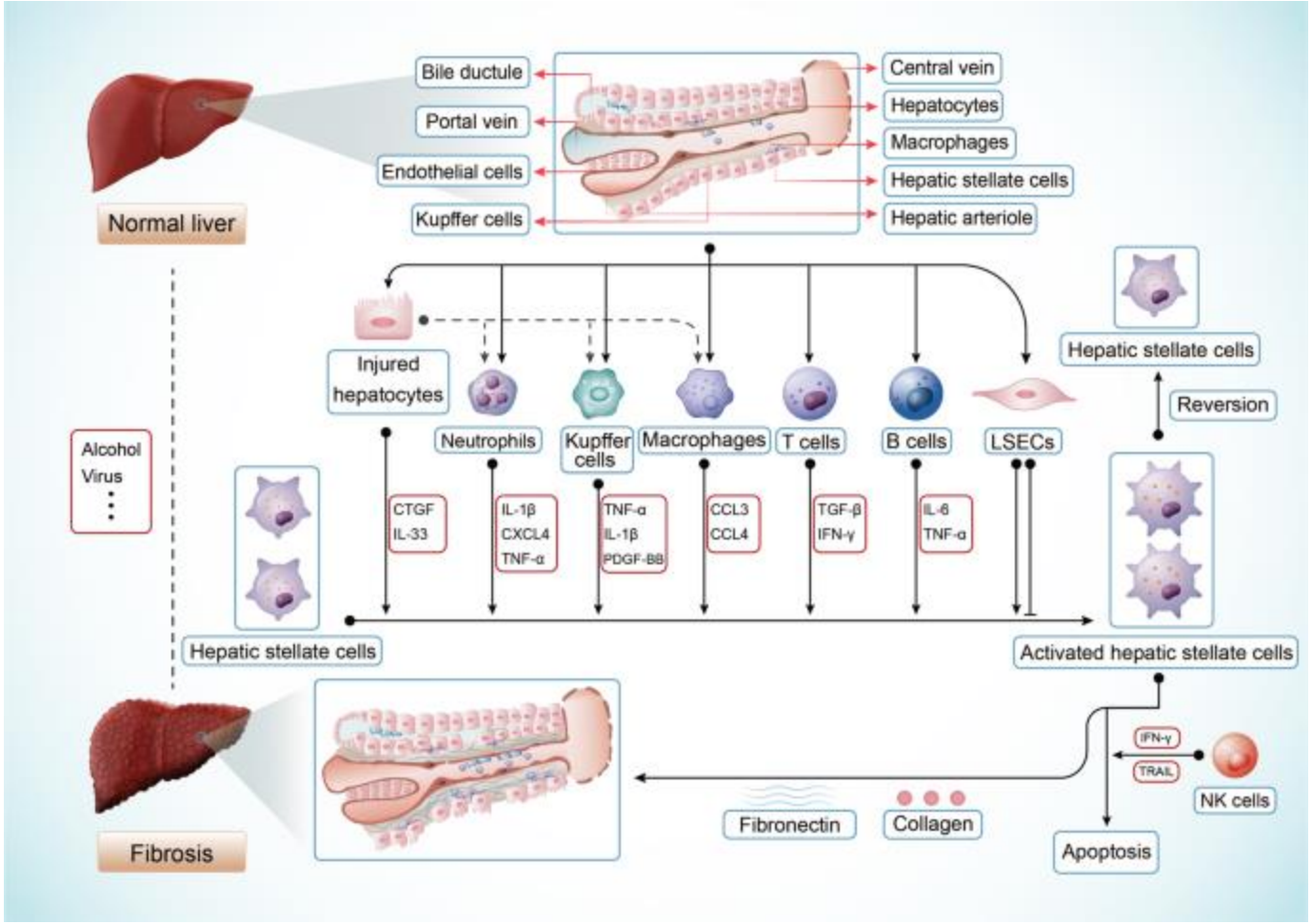
Liver fibrosis

Extracellular components from injured hepatocytes, Kupffer cells, macrophages, NK cells, T and B lymphocytes modulate HSCs activation via various cytokines. continuous HSCs activation, which promotes ECM accumulation and tissue structure remodeling, and then results in progressive liver fibrosis



Signal Transduction and Targeted Therapy volume 7, Article number: 206 (2022)

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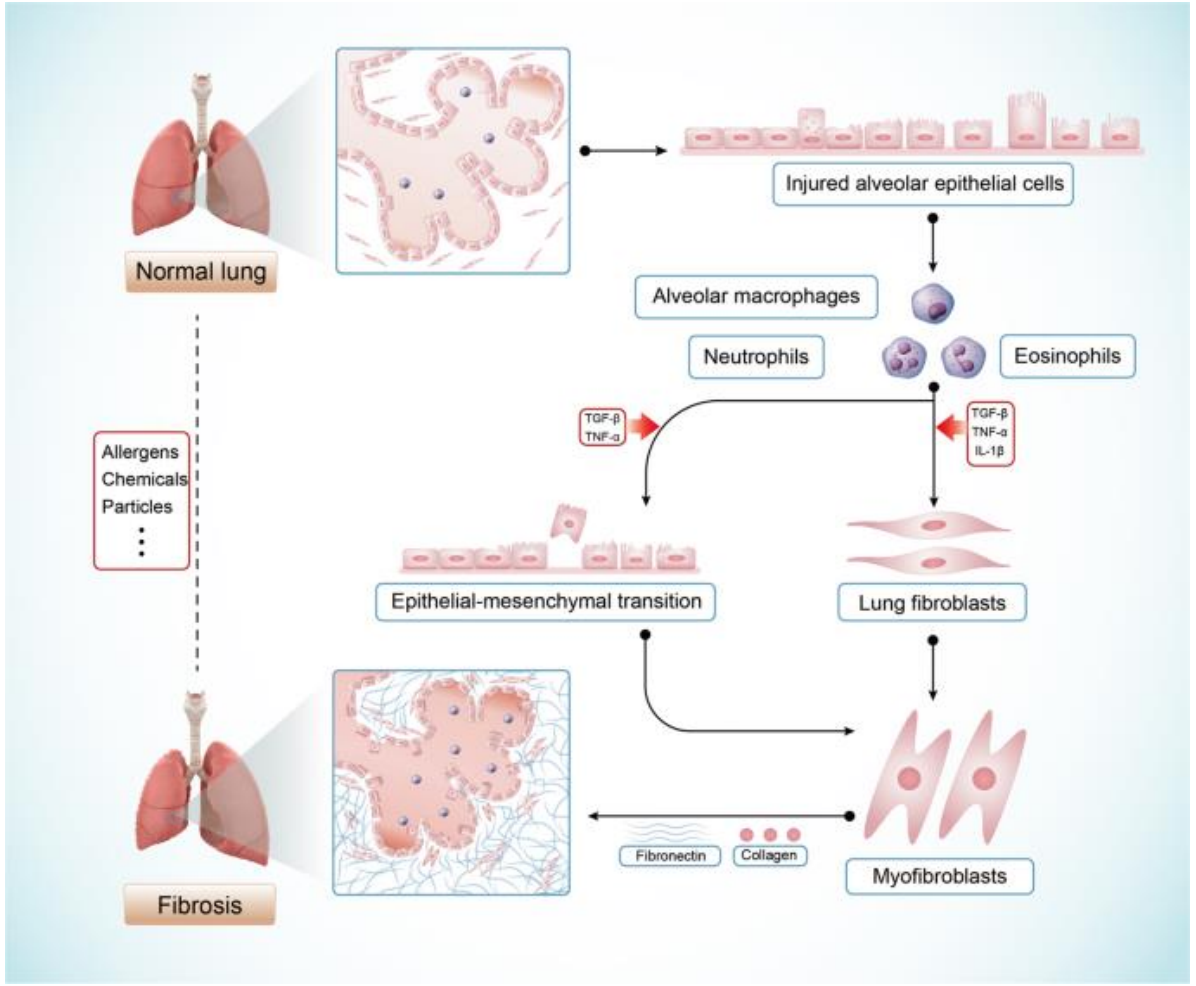
Lung fibrosis

Injured alveolar epithelial cells activate macrophages, neutrophils, and eosinophils, resulting in the secretion of cytokines, such as TGF-β, IL-1β, and TNF-α. These cytokines mediate the differentiation of fibroblasts into myofibroblasts and the epithelial-mesenchymal transition, which result in the ECM deposition at the injury site



Signal Transduction and Targeted Therapy volume 7, Article number: 206 (2022)

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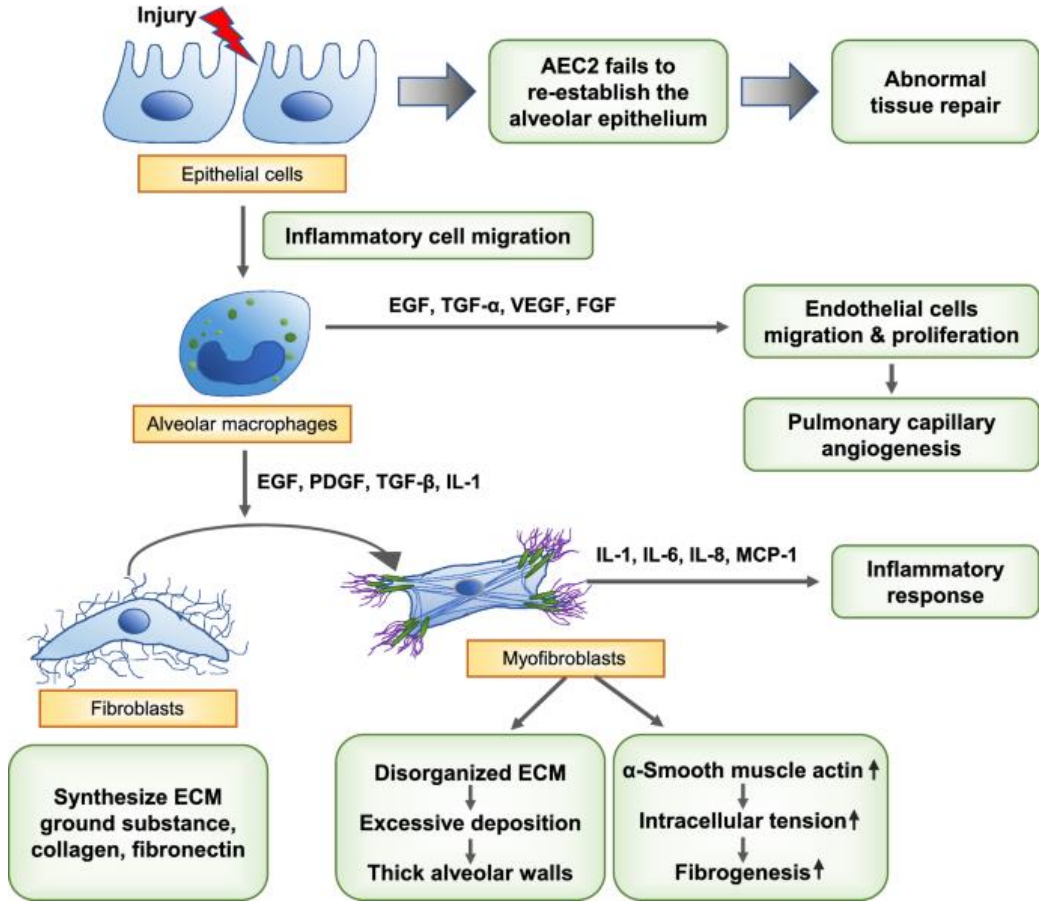
Summary of pulmonary fibrosis mechanisms

interstitial lung diseases, for example non-specific interstitial pneumonia, autoimmune-featured interstitial lung disease, and idiopathic pulmonary fibrosis, have a similar onset to COVID-19-induced pulmonary fibrosis



Arch. Pharm. Res. 44, 499–513 (2021)

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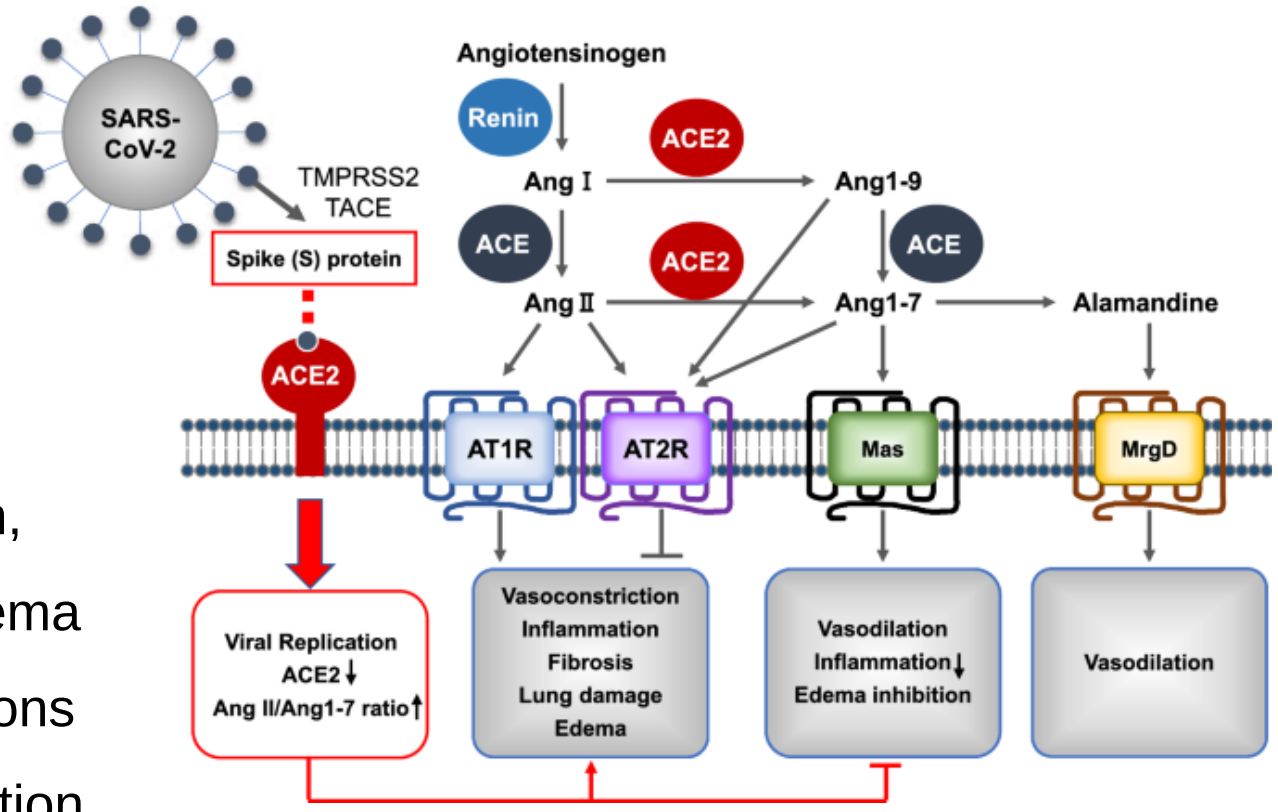
Covid-19 and pulmonary fibrosis - ratio Ang II:Ang 1–7

- RAAS helps to regulate inflammation and pulmonary diseases such as idiopathic pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease
- Through AT1R, Ang II performs biological functions such as promoting vasoconstriction, inflammation, fibrosis, lung damage, and edema
- Through the Mas receptors downstream actions of Ang 1–9 or Ang 1–7 contribute to vasodilation, inflammation reduction, and edema inhibition
- the major sources of ACE2 are alveolar type 2 pneumocytes

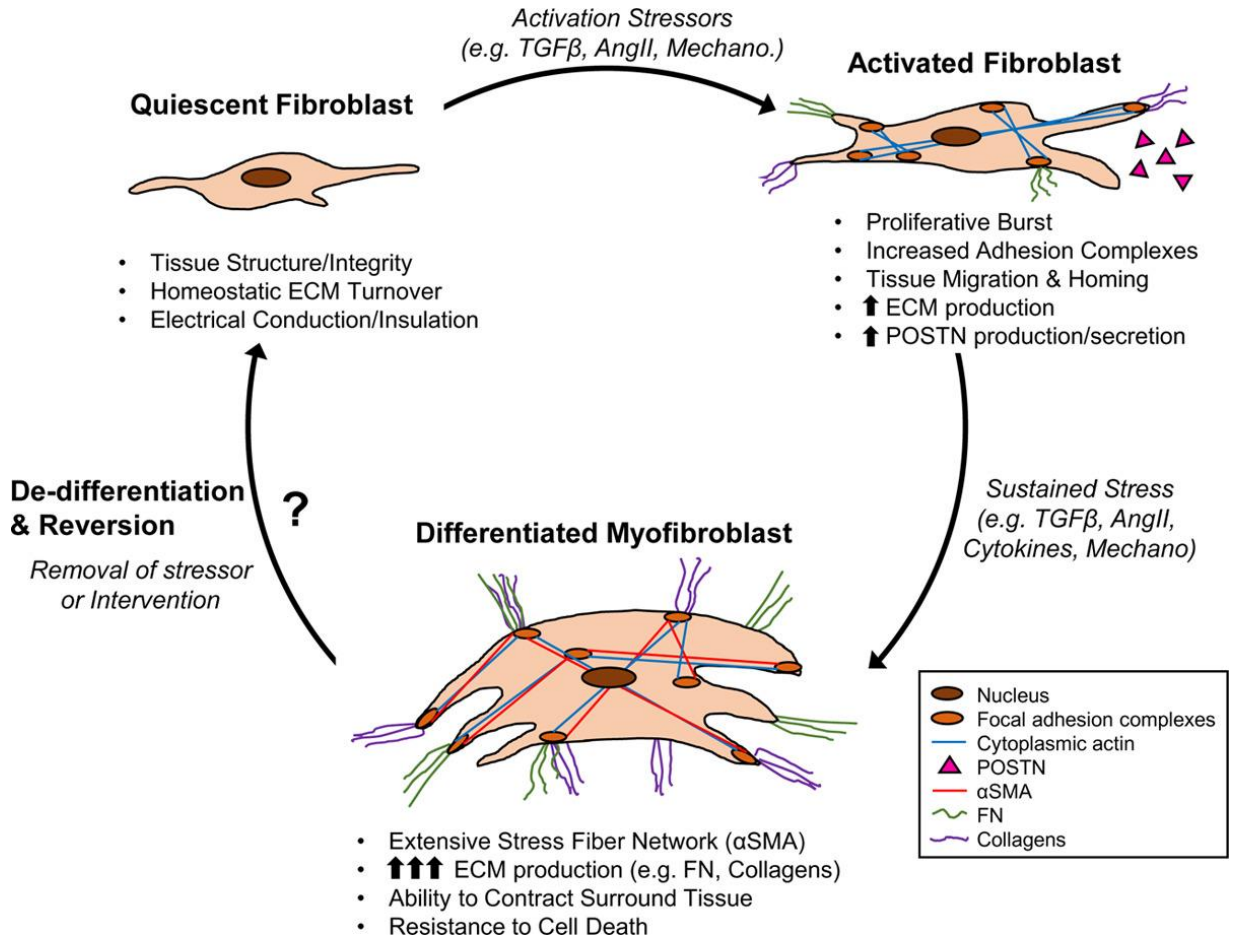


Arch. Pharm. Res. 44, 499–513 (2021)

MUNI MED

Cardiac Myofibroblast

- fibroblasts have been identified and characterized in the uninjured, infarcted, and pressure-overloaded myocardium in both animal models and human patients
- Upon increased mechanical tension and profibrotic mediators (eg, TGFβ, AngII), resident cardiac fibroblasts become activated, infiltrate and expand at the site of injury as well as begin to remodel the ECM.
- myofibroblasts are capable of de-differentiating upon removal of stress stimuli

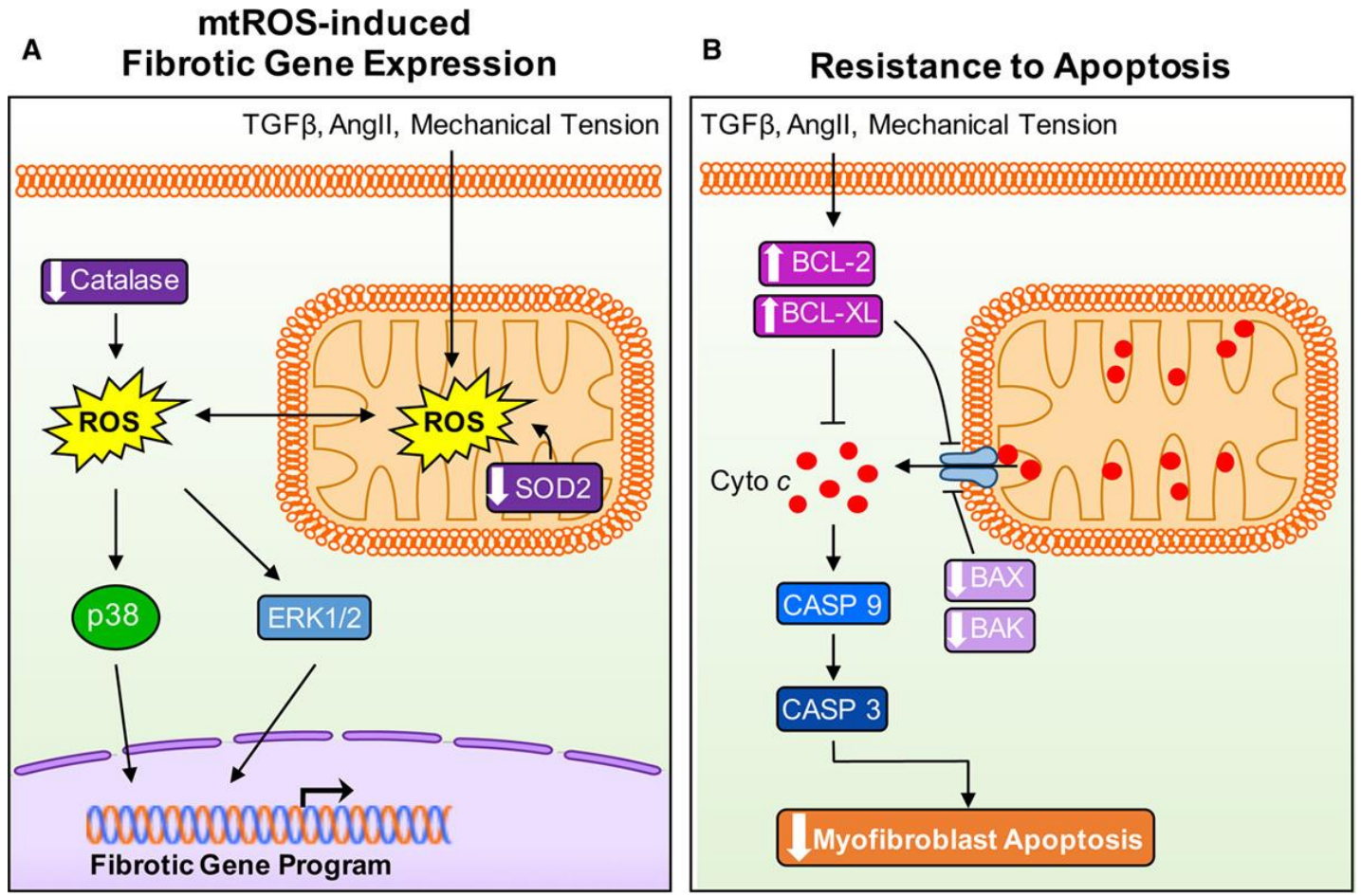


Circulation Research
Volume 127, Number 3, 2020

MUNI MED

Mitochondrial mechanisms of myofibroblast differentiation and persistence

- Myofibroblasts are resistant to cell death, resulting in persistence in the injured heart, eventually leading to maladaptive tissue remodeling.
- Mitochondrial cytochrome c (Cyto c) release is prevented through the upregulation of antiapoptotic factors

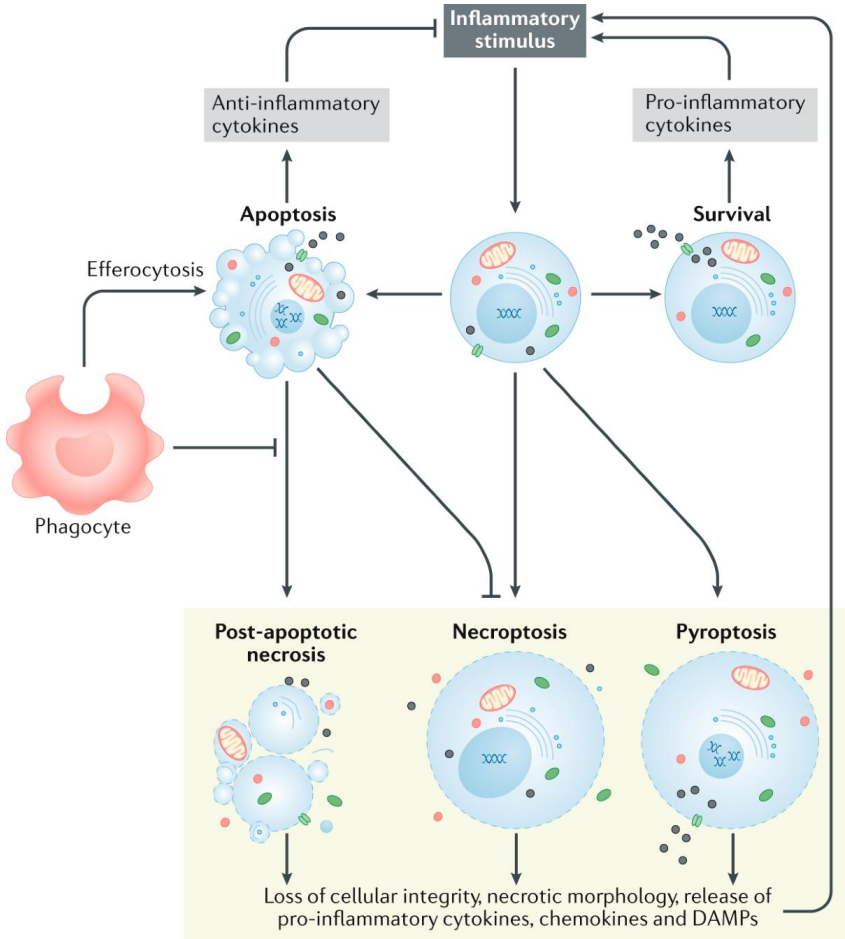


Circulation Research
Volume 127, Number 3, 2020

MED

Cell death in chronic inflammation

- Cell death can be both a 1) consequence and a 2) cause of inflammation, which can be difficult to distinguish in chronic diseases.
- Excessive or poorly regulated cell death is increasingly recognized as a contributor to chronic inflammation.

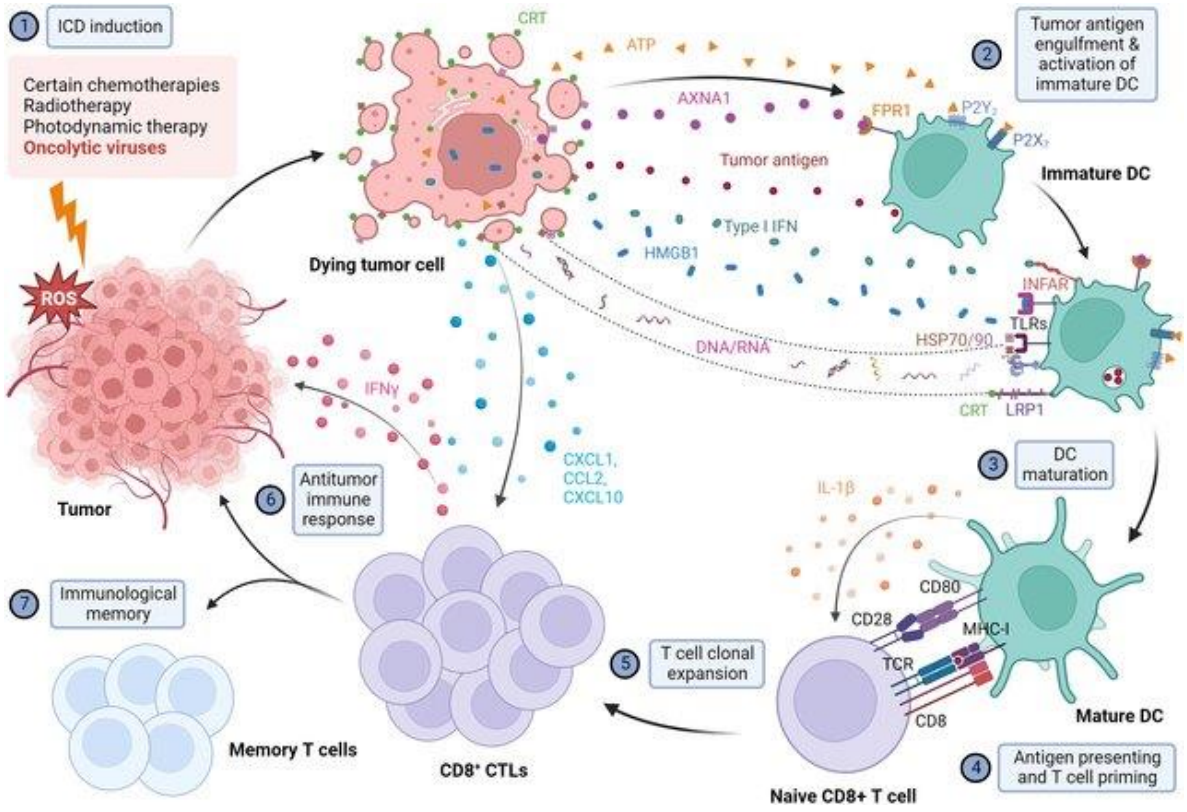


Nature Reviews Rheumatology volume 16, pages496–513 (2020)

MUNI MED

Immunogenic cell death

When exposed to different immunogenic cell death (ICD) inducers, including OVs, cancer cells are under extreme ER stress and undergo ICD. Dying cancer cells express various damage-associated molecular patterns (DAMPs), including the release of high mobility group box 1 (HMGB1) from the nucleus, translocation and cell surface exposure of calreticulin (ecto-CRT) and heat shock proteins HSP70/90, and extracellular secretion of ATP, Annexin A1 (AXNA1), cytokines, chemokines, and nucleic acids. Exposure to DAMPs serves as a "find me" signal which recruits immature DC to TME and induces the maturation of DC. Ecto-CRT provides a pro-phagocytic signal that promotes the phagocytosis of antigens by DC. In addition, HMGB1 and HSP70/90 assist in promoting the processing of phagocytic cargo by binding to toll-like receptors (TLRs), thereby escalating antigen engulfment, processing, and presentation to T cells to mediate tumor-specific immune response and protective immunological memory.



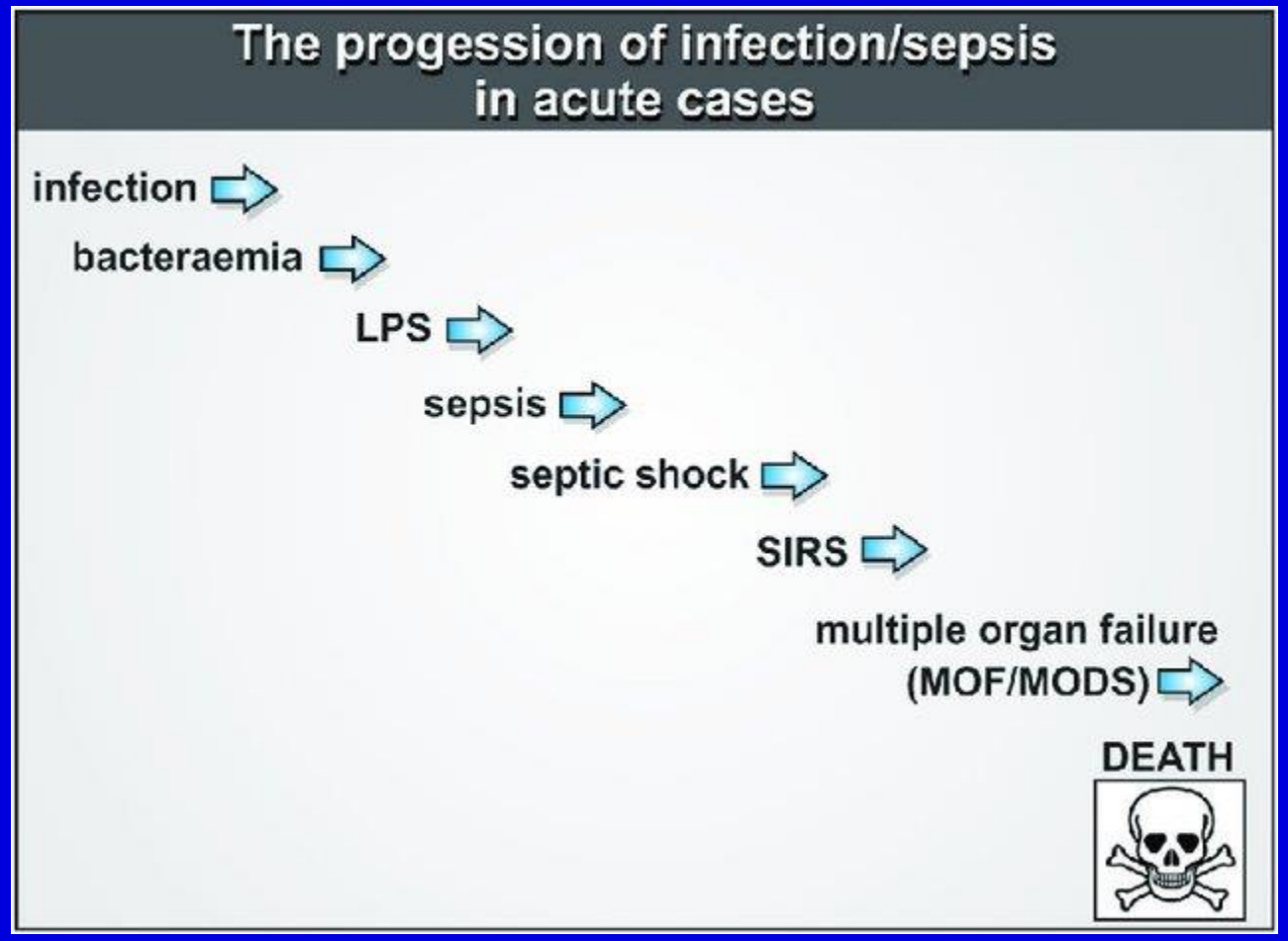
2023Frontiers in Immunology 13:1038226

MUNI MED

SIRS

Sepsis

MODS

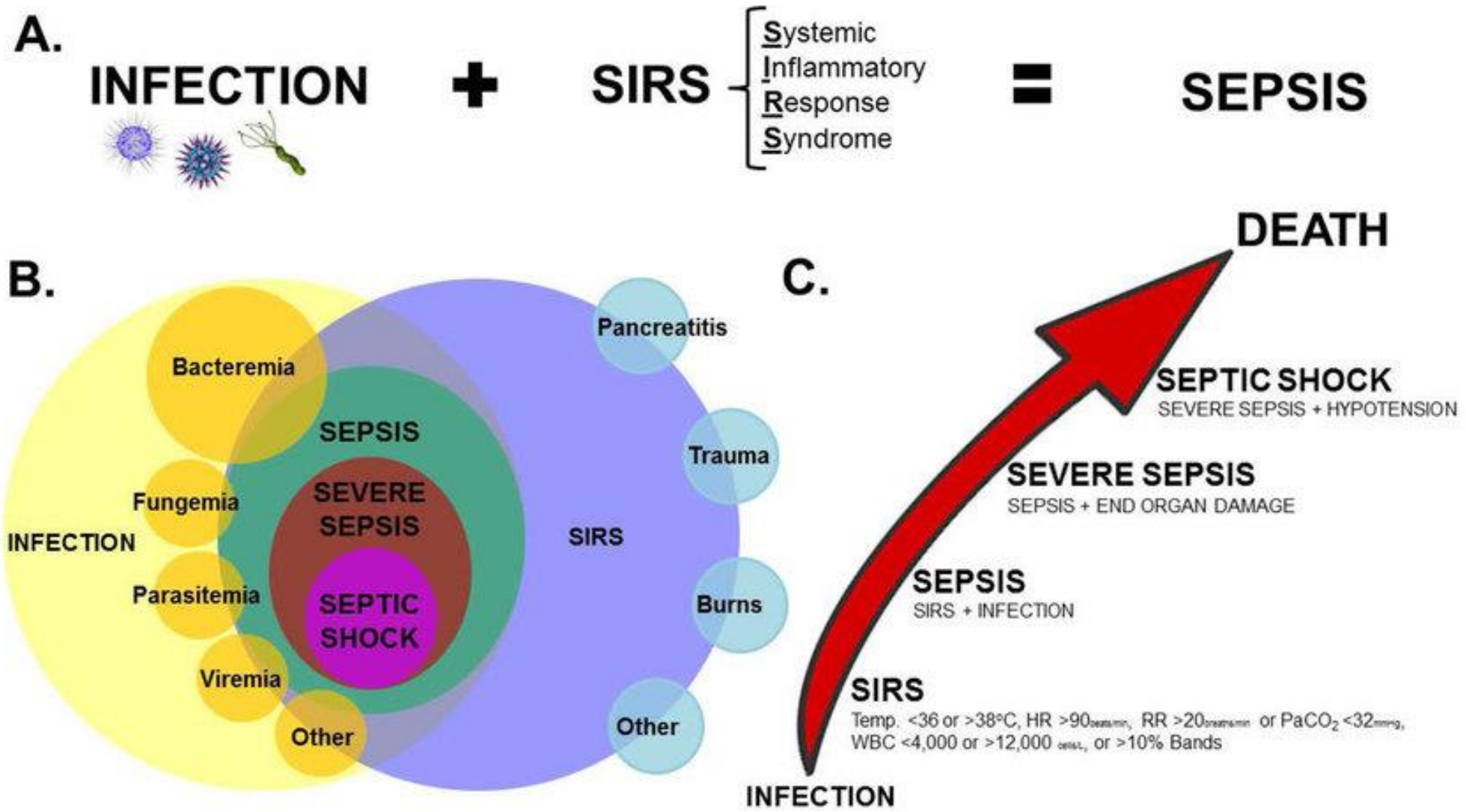


DOI: 10.1039/c5ib00158g

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

MUNI
MED


A.
INFECTION
SIRS
Systemic
Inflammatory
Response
Syndrome
SEPSIS
B.
Bacteremia
Fungemia
Parasitemia
Viremia
Other
INFECTION
SEPSIS
SEVERE SEPSIS
SEPTIC SHOCK
SIRS
Pancreatitis
Trauma
Burns
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

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 *Nonseptic SIRS*	INFECTIOUS INSULTS *Septic SIRS*
• Burns • Chemical aspiration • Heatstroke • Immune-mediated disease • Ischemic organ necrosis (eg, splenic torsion) • Neoplasia • Pancreatitis • Trauma	• Anaerobic bacteria • Fungi • Products of gram-negative bacteria • Products of gram-positive bacteria • Protozoa • Viruses

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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

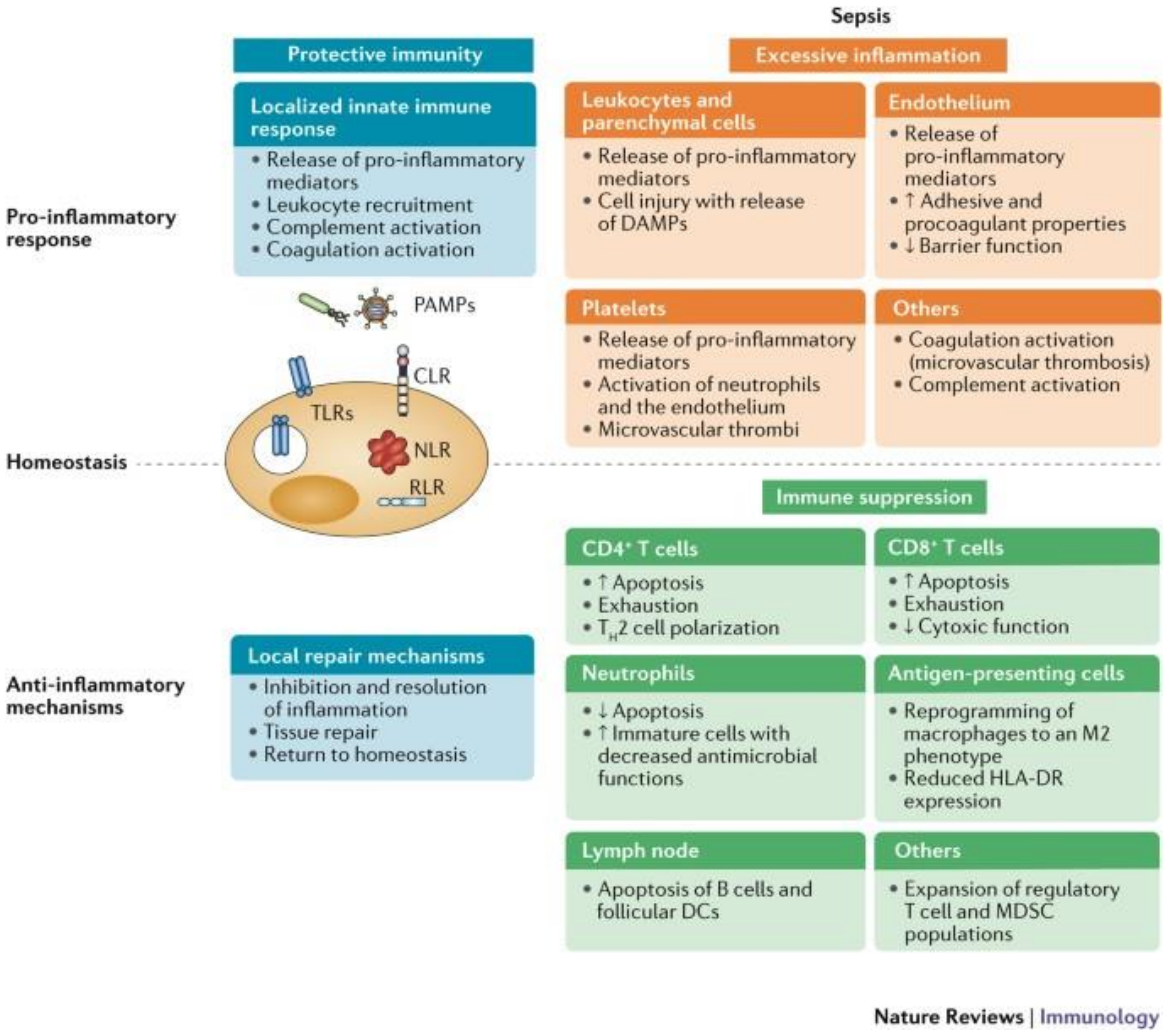
Primary SIRS
Secondary SIRS

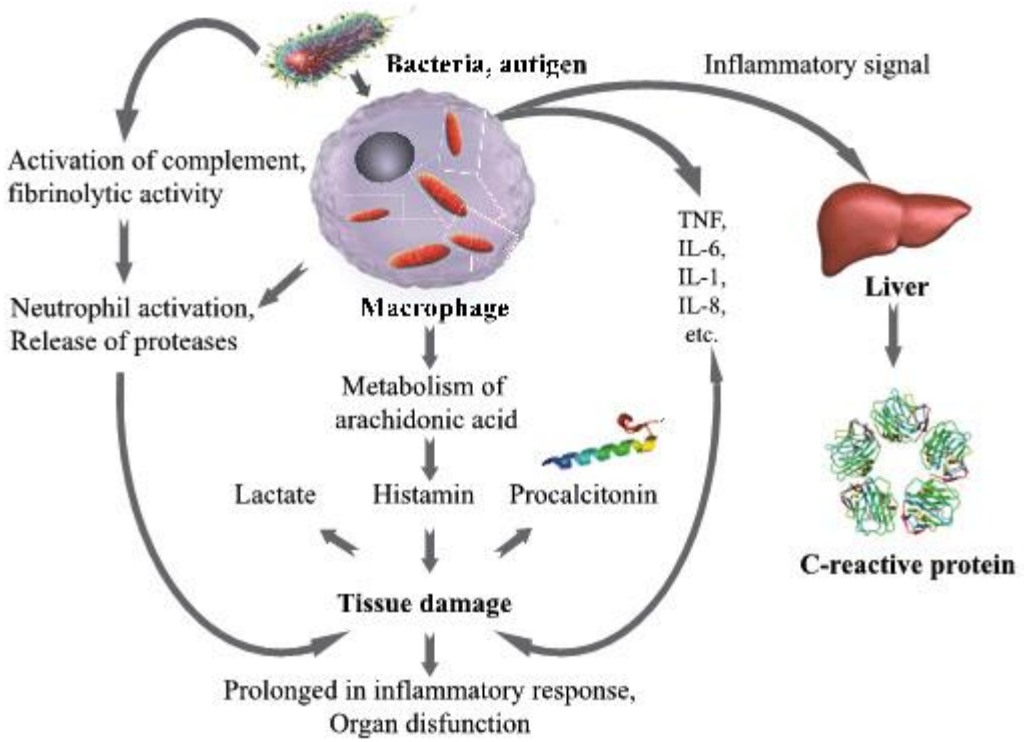
Distinctions Between SIRS & Sepsis

SIRS	Clinical manifestation of systemic inflammation, which results from either: • 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: • Arterial hypotension • Organ dysfunction • Hypoperfusion; abnormalities suggestive of hypoperfusion may include hyperlactatemia and oliguria
SEPTIC SHOCK	Despite adequate intravascular fluid resuscitation, sepsis-associated: • 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

MUNI MED





Nature Reviews Immunology volume 17, pages407–420 (2017)

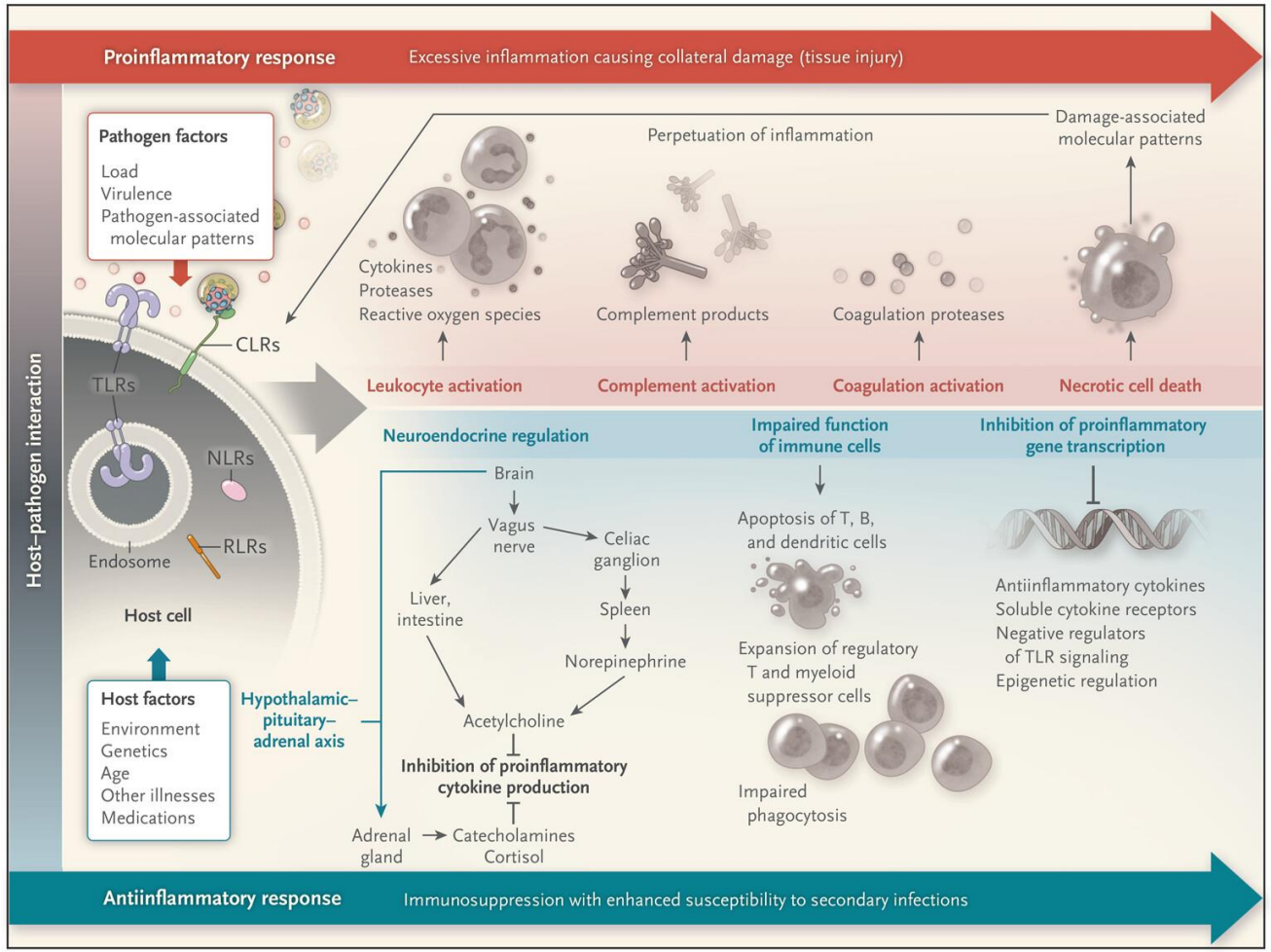
Host response to sepsis

characterized by both

- **proinflammatory** responses (top of panel, in red) and
- **antiinflammatory** immunosuppressive responses (bottom of panel, in blue).

The direction, extent, and duration of these reactions are determined by both host factors (e.g., genetic characteristics, age, coexisting illnesses, and medications) and pathogen factors (e.g., microbial load and virulence).

The consequence of exaggerated inflammation is collateral tissue damage and necrotic cell death, which results in the release of damage-associated molecular patterns that perpetuate inflammation at least in part by acting on the same pattern-recognition receptors that are triggered by pathogens.

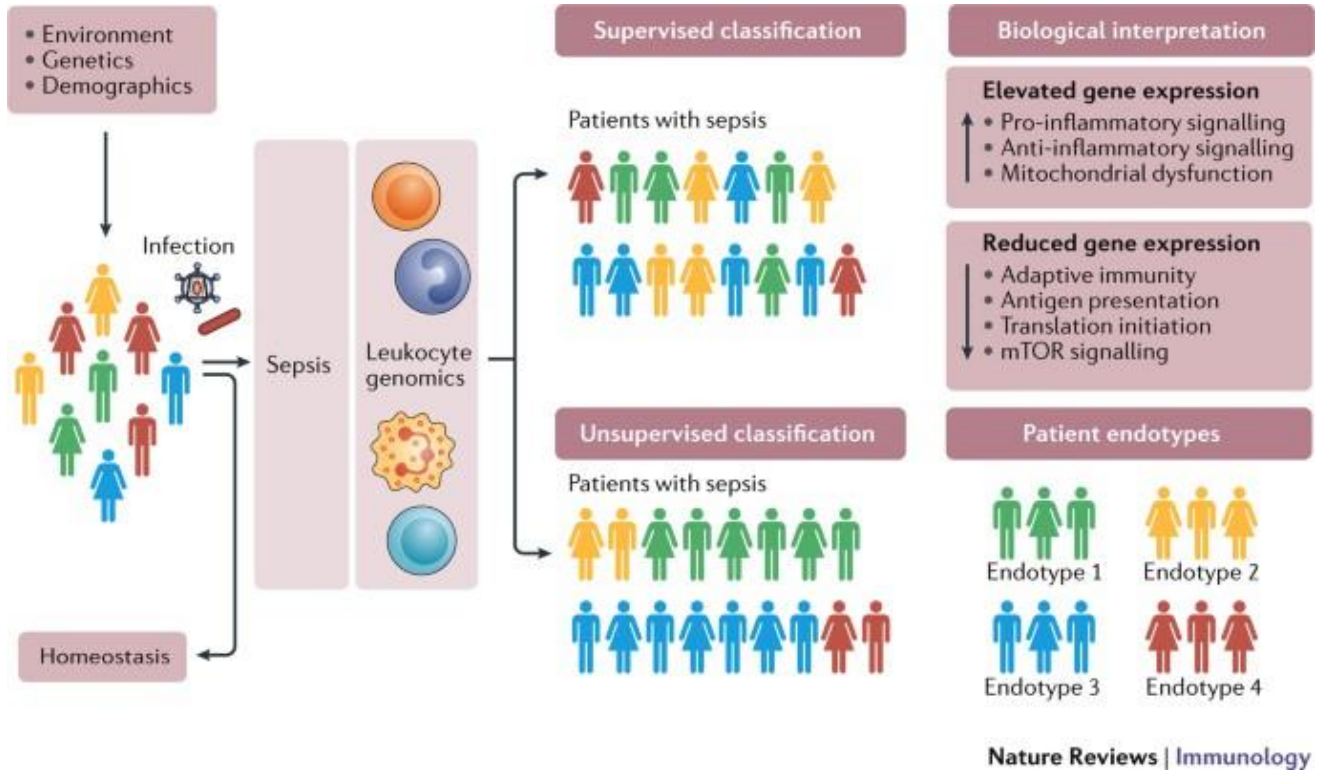


Nature Reviews Immunology volume 17, pages407–420 (2017)

Genomic background lymphocyte fce in sepsis

- leukocyte transcriptomes - expression of 70–80% of measured RNA transcripts in these cells is significantly altered compared control (healthy)
- identified patterns of gene expression that include the increased expression of genes involved in pro-inflammatory, anti-inflammatory and mitochondrial pathways, and the decreased expression of genes with functions in adaptive immunity, antigen presentation, translation initiation and mechanistic target of rapamycin (mTOR) signaling

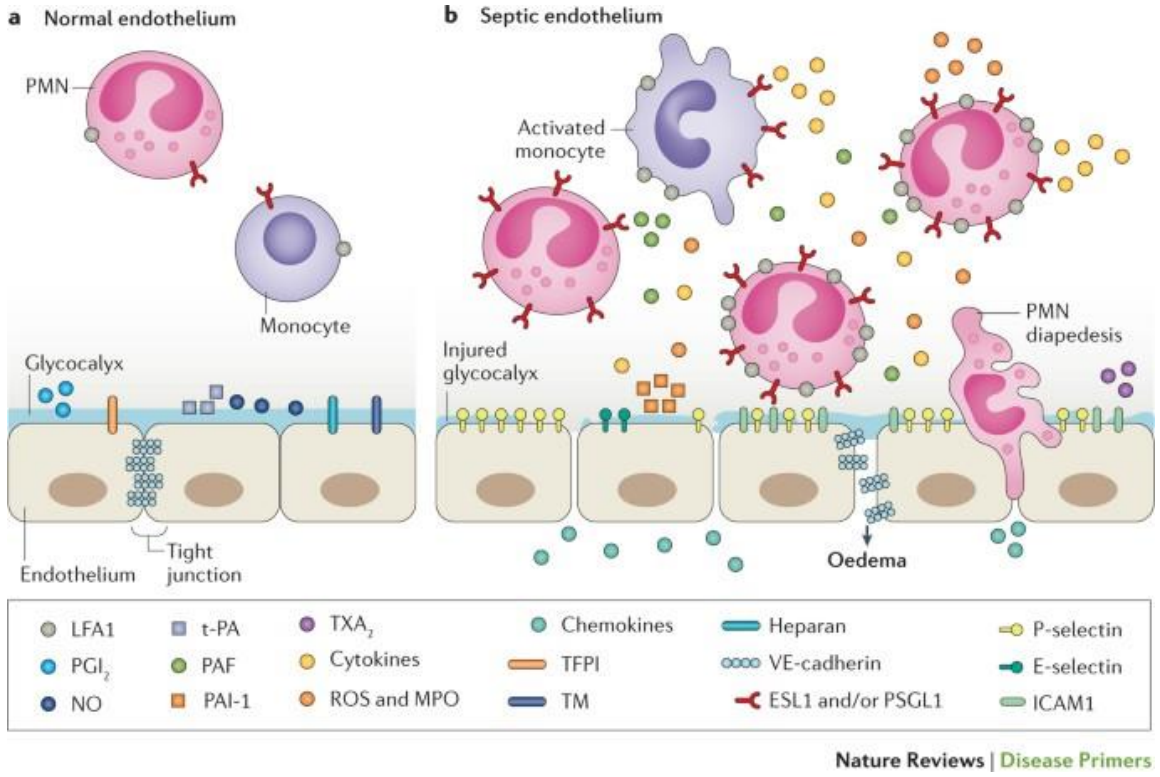
- a large proportion of the heterogeneity in the host response remains unexplained !!!

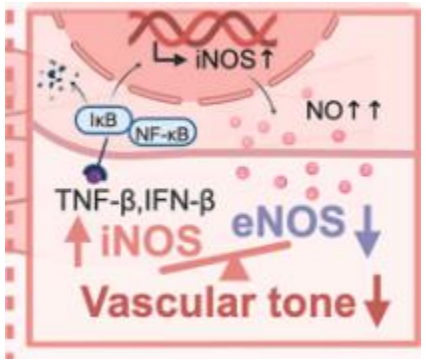


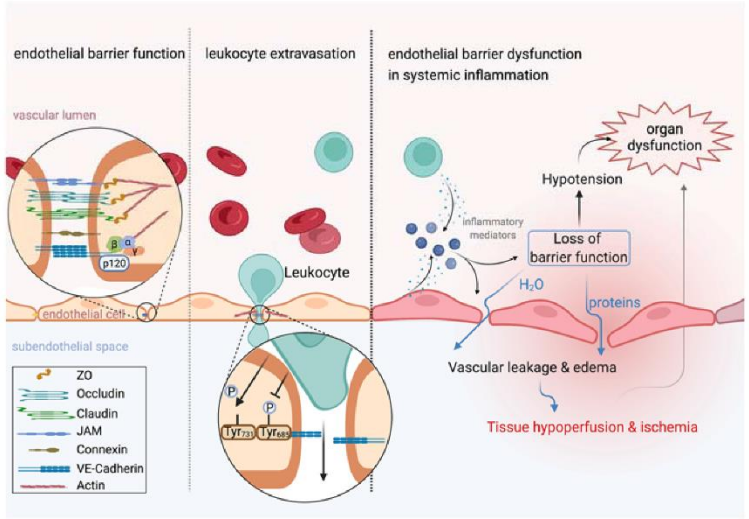
Endothelial barrier

- endothelial barrier dysfunction is a fundamental pathophysiological event that occurs early in sepsis and septic shock in particular

- Upregulation of the iNOS gene increased and the excessive NO production result in decreased vascular tone.



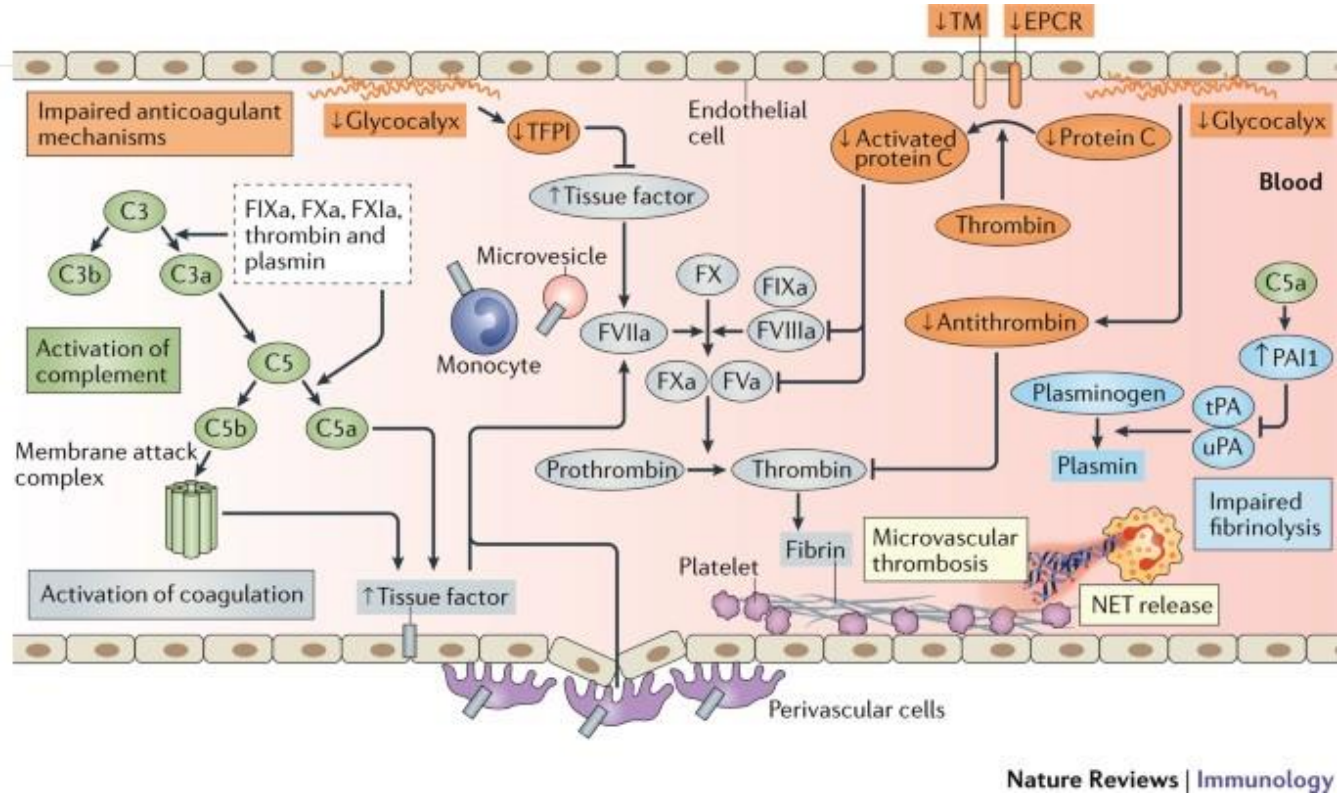




Sepsis and procoagulant state

Sepsis results in a net procoagulant state in the microvasculature via at least three mechanisms:

1) tissue factor-mediated thrombin generation (grey),
2) dysfunctional endogenous anticoagulant mechanisms (orange)
3) and impaired fibrin removal due to the suppression of the fibrinolytic system (blue) by increased levels of plasminogen activator inhibitor 1 (PAI1), which inhibits the activities of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).
4) Coagulation and fibrinolysis tightly interact with the complement system (green)
5) Fibroblasts, pericytes and epithelial cells express tissue factor during inflammation-induced vessel injury
6) Further facilitated by neutrophil extracellular traps (NETs) released from dying neutrophils.

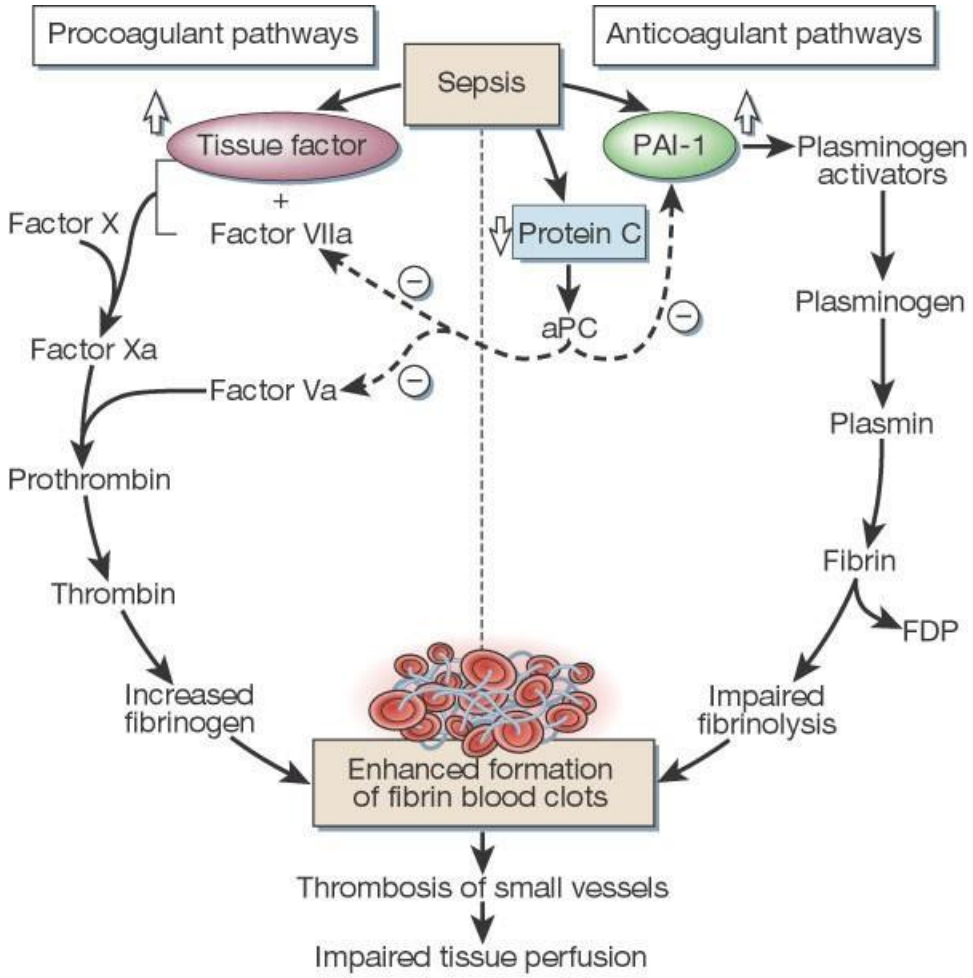


Nature Reviews Immunology volume 17, pages407–420 (2017)

Anticoagulant pathways and sepsis

The tendency towards thrombosis during sepsis is augmented by the concurrently compromised activity of the three main anticoagulant pathways:

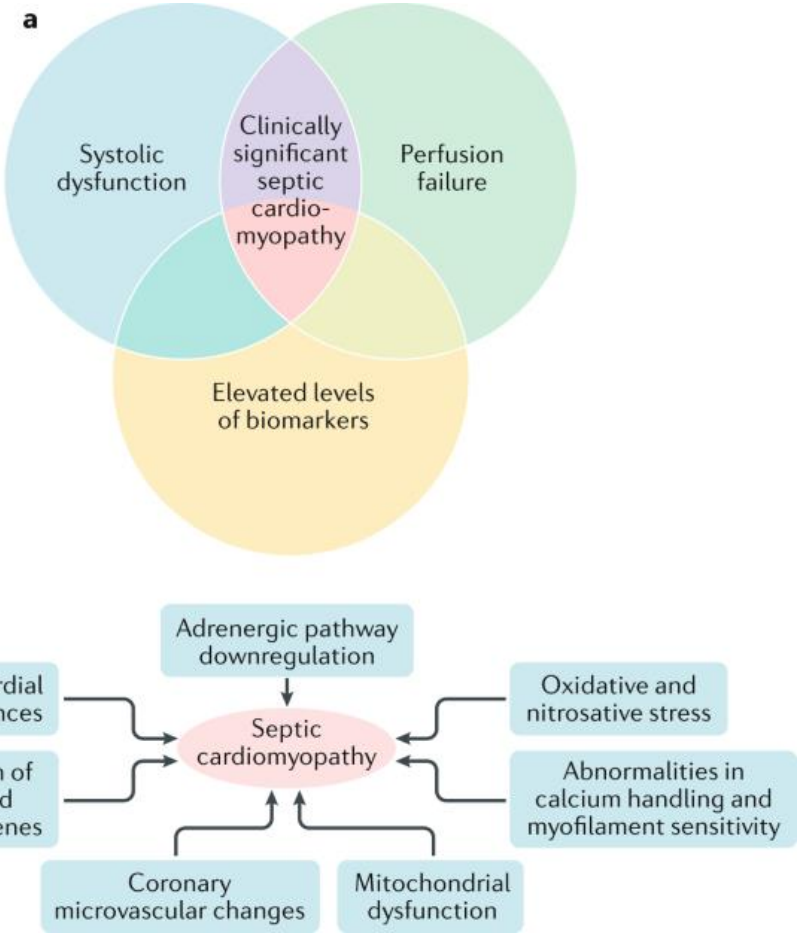
1) Antithrombin is the main inhibitor of thrombin and FXa, whereas
2) Tissue factor pathway inhibitor (TFPI) is the main inhibitor of the tissue factor–FVIIa complex. The anticoagulant properties of antithrombin and TFPI are supported by the glycocalyx, a glycoprotein–polysaccharide layer that covers the endothelium. During sepsis, the continuity of the endothelial glycocalyx is disturbed, which increases vascular permeability and impairs the function of antithrombin and TFPI.
3) Protein C system is impaired as a result of multiple factors, most notably the decreased synthesis of protein C by the liver, the increased consumption of protein C and the impaired activation of protein C as a result of diminished TM expression on endothelial cells.



Nature volume 420, pages885–891 (2002)

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).

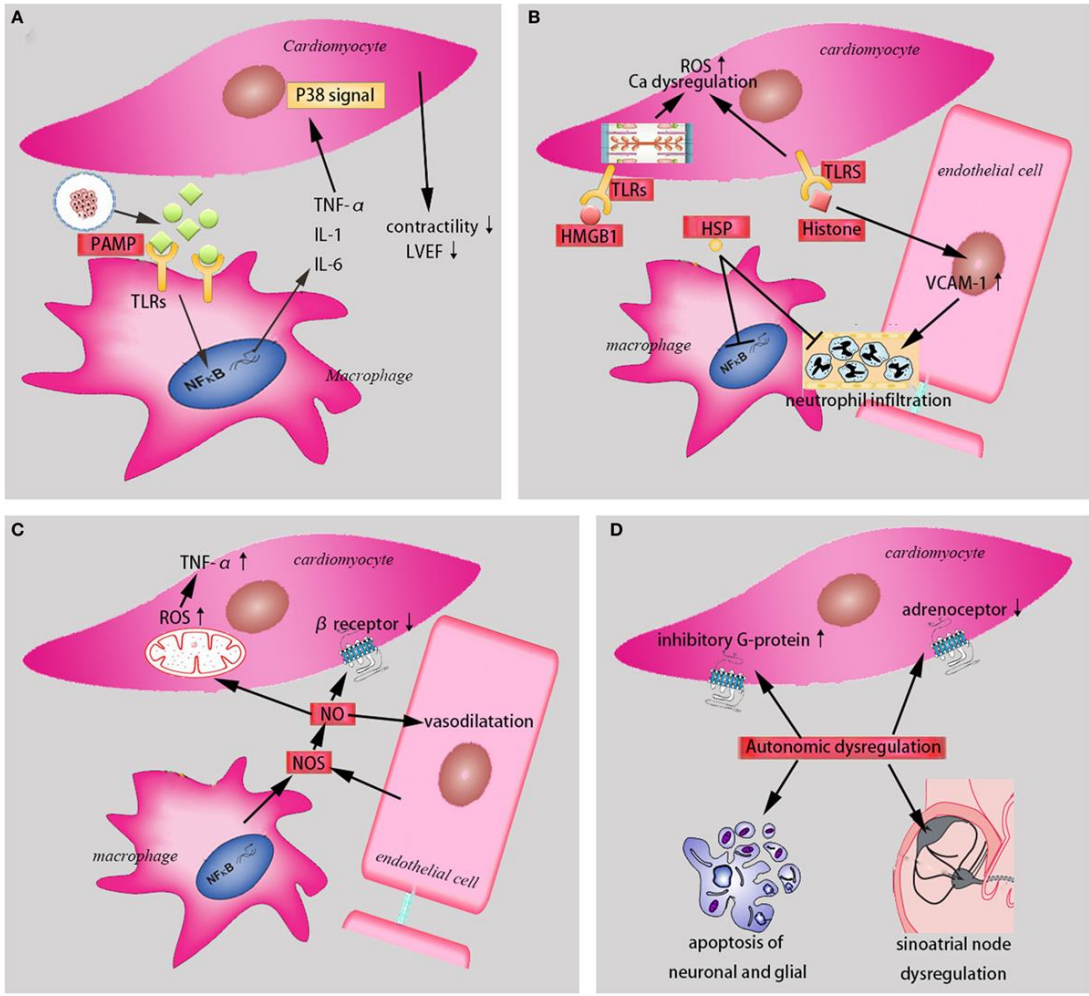
Patophysiology of SIC

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.

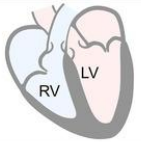
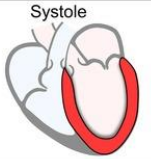
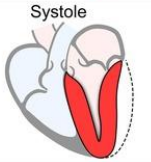
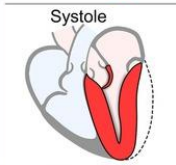
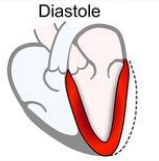
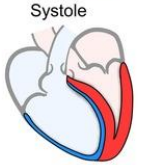
- interaction of a wide range of signalling pathways rather than any single individual factor



Front. Immunol., 24 August 2017

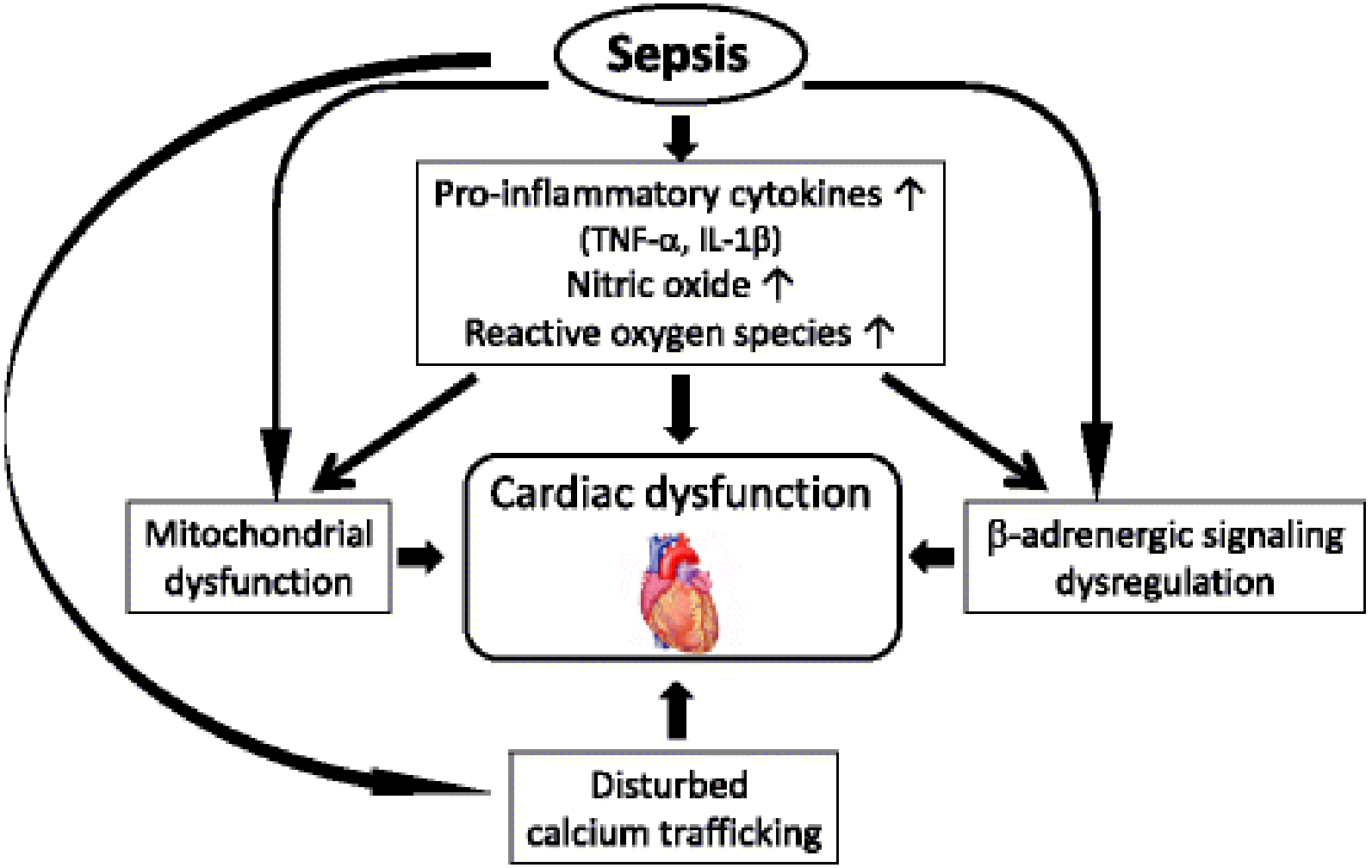
Mitochondrion

- 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	 • Reduced LV contractility and increased LVESV • EF may appear normal if low afterload (hypovolemia/low SVR) • LV dilation may occur	↓/-	↓
LV hyperdynamic function	 • Hyperdynamic contractility of LV • Pseudohypertrophy of the LV wall may be seen • If normal preload, CO is elevated • May indicate hypovolemia • Reduced LVESV	↑	↑/↓
	 Dynamic LVOT obstruction: • 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	 • Impaired relaxation of ventricle reduces filling leading to decreased CO • Reduced LVEDV	↓/-	↓
RV dysfunction	 • 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	↑/↓	↓

Front. Cardiovasc. Med., 14 July 2023

Sepsis and cradiac dysfunction - summary

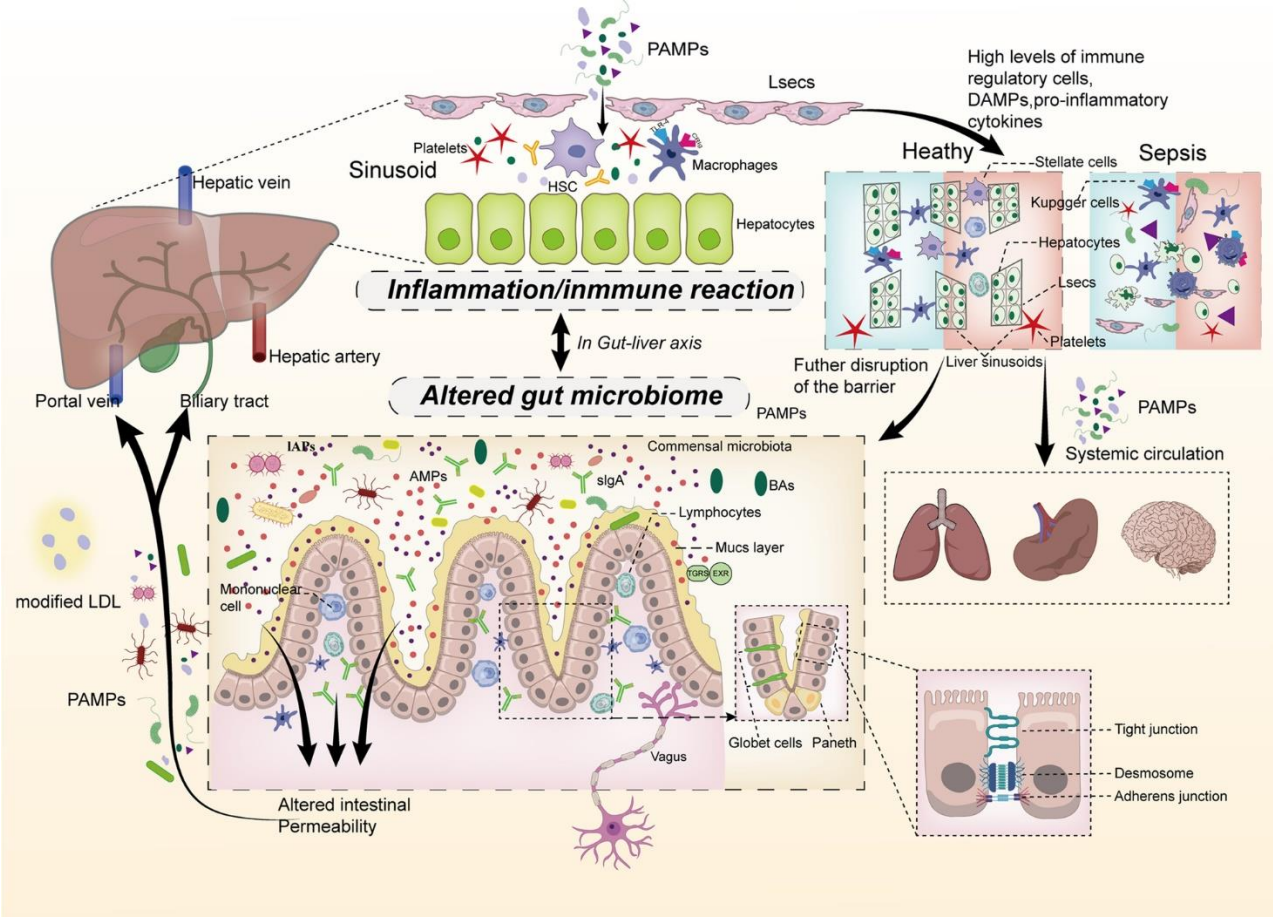


Suzuki, T., Suzuki, Y., Okuda, J. *et al. j intensive care* **5**, 22 (2017).

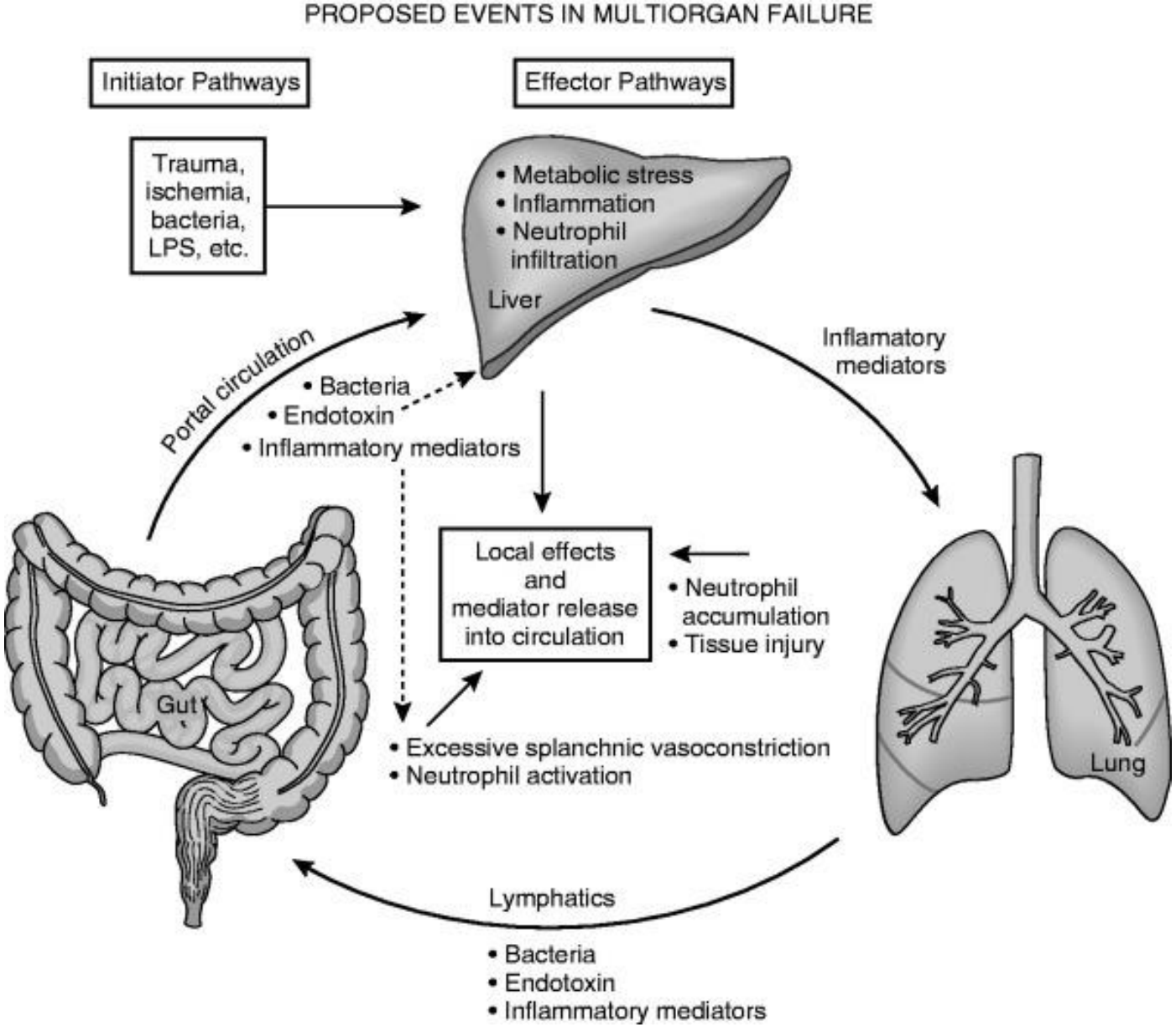
Multifactor Models - Gut

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).



Zhang, X., Liu, H., Hashimoto, K. *et al. Crit Care* **26**, 213 (2022).



LPS, Lipopolysaccharide.

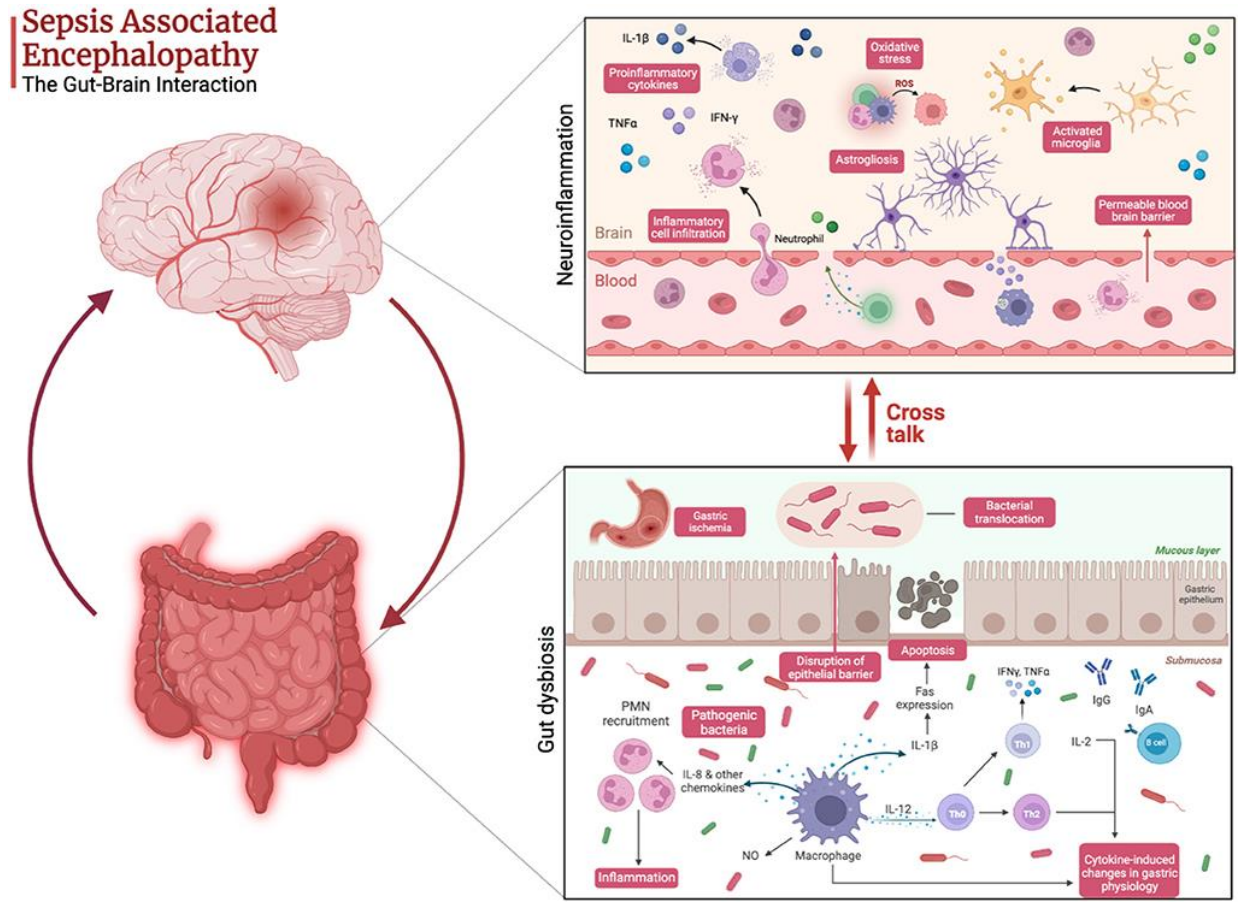
Gut-liver-lung axis in response to shock and hemorrhage *Martinez-Mier G, Toledo-Pereyra LH, Ward PA: J Trauma 51:408, 2001.*

Sepsis-associated encephalopathy

- SAE is defined as diffuse cerebral dysfunction occurring as a result of the systemic response to infection without clinical or laboratory evidence of brain infection or other etiologies of encephalopathy.

- manifests from mild delirium and altered speech to coma

- drivers of SAE include
  - systemic and central inflammation,
  - permeabilization of the blood brain barrier (BBB),
  - ischemia secondary to systemic vasodilation,
  - mitochondrial dysfunction,
  - concomitant metabolic derangements,
  - accumulation of toxic neuropeptides

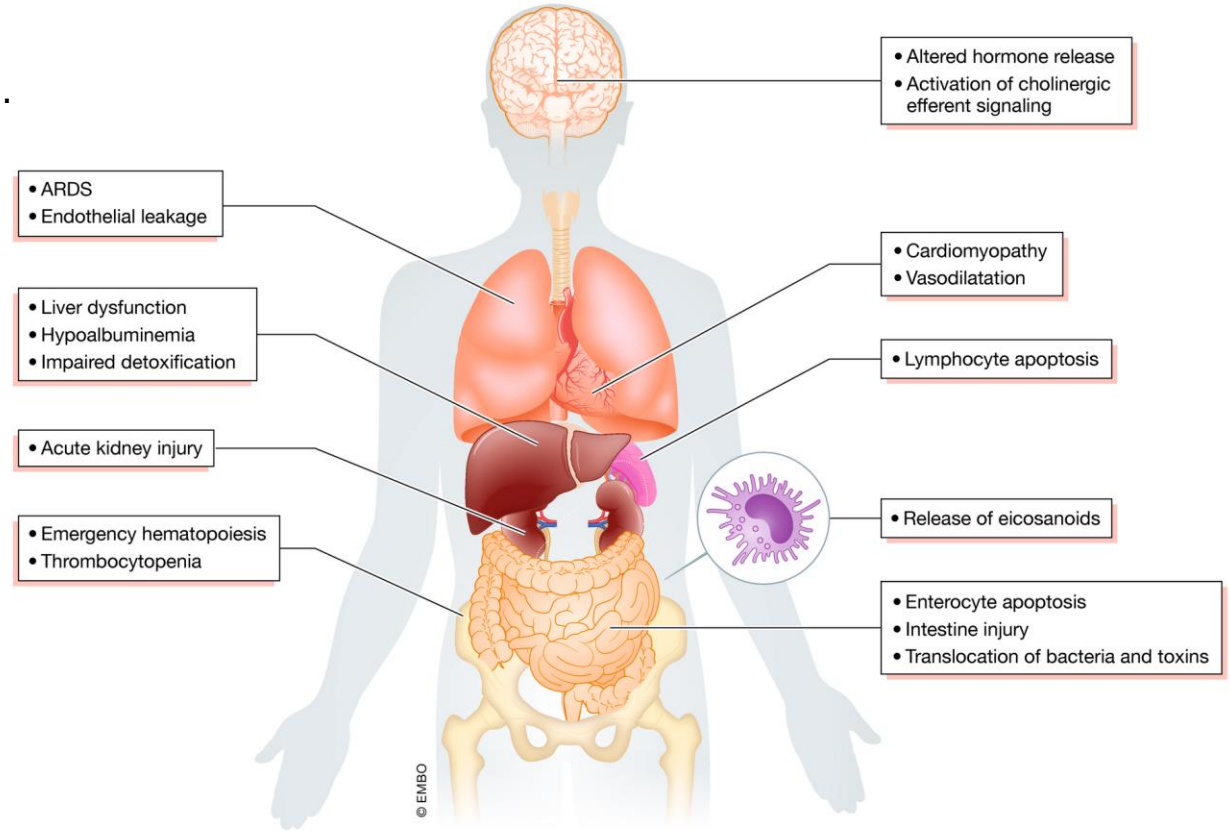


Front. Neurol., 29 September 2022

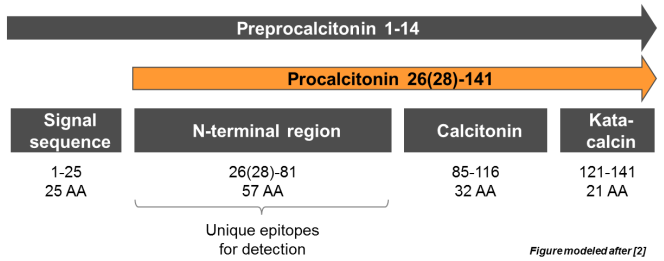
Summary of sepsis pathophysiology

Upon direct activation of immune and endothelial cells by the pathogen-associated molecular patterns, there is a massive release of inflammatory mediators which affect each body system.

- activates the central nervous system, which acts by cholinergic anti-inflammatory impulsion and altered neuroendocrine response to control the body response to infection and increase chances of survival.
- Cardiovascular dysfunction plays a central role in the pathogenesis of sepsis with the major role of vasoplegia, hypovolemia, microcirculation perturbations, and cardiomyopathy.
- Altered endothelium lead to the development of acute respiratory distress syndrome (ARDS).
- The direct action of cytokines and toxins, together with decreased blood flow, leads to acute kidney injury (AKI).
- Inflammatory response and ischemia alter gut permeability which enables entry of bacteria and their metabolites into the tissues.
- Both bacterial products and inflammatory mediators affect bone marrow progenitor cells enhancing the emergency myelopoiesis.

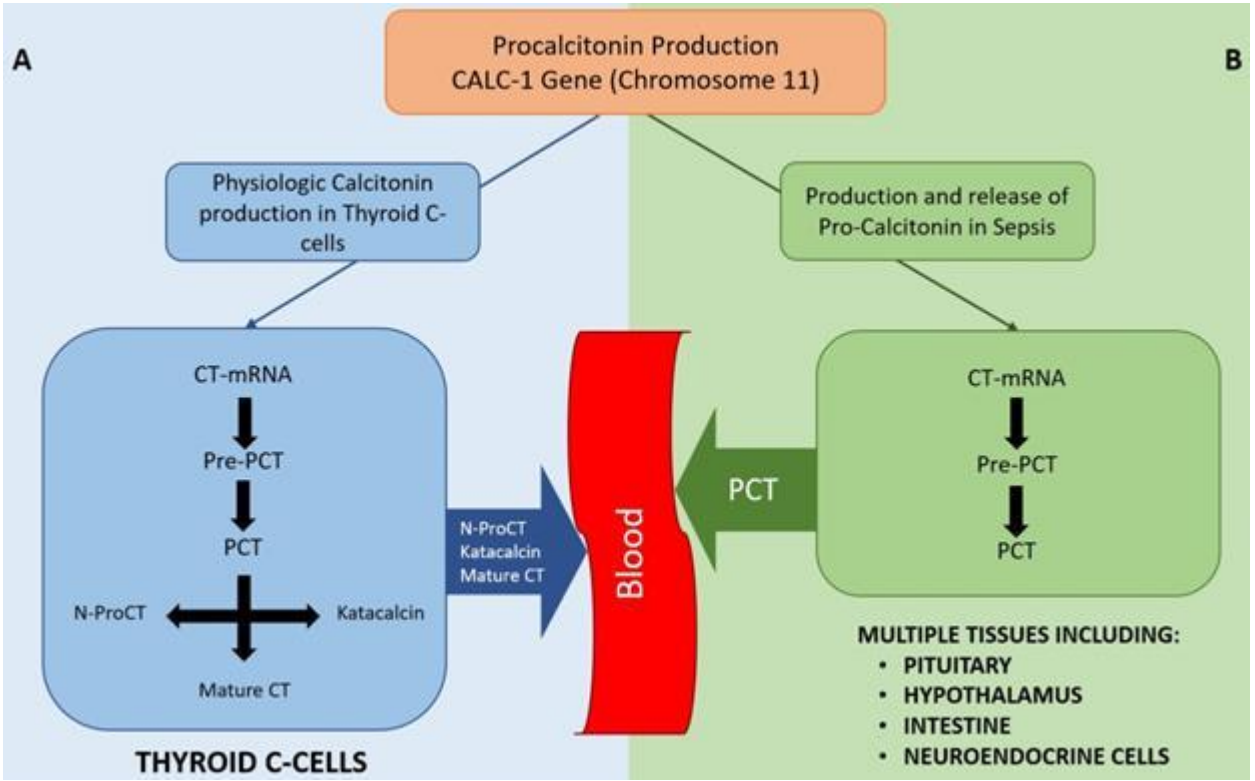


Procalcitonin: A promising tool or just another overhyped test?



- PCT is produced in the thyroid C-cells, broken down to form N-terminal PCT, C-terminal katacalcin and active calcitonin, and is not typically secreted into the bloodstream in normal physiological conditions

- multiple tissues can secrete PCT in sepsis, in the bloodstream PCT cannot be degraded



Int J Med Sci 2020; 17(3):332-337.

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°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or *Pa*co2 < 32 mmHg (or ventilator dependence)
- White blood cell count > 12 000 cells/mm3, < 4000 cells/mm3 or > 10% band forms

Mulitple 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

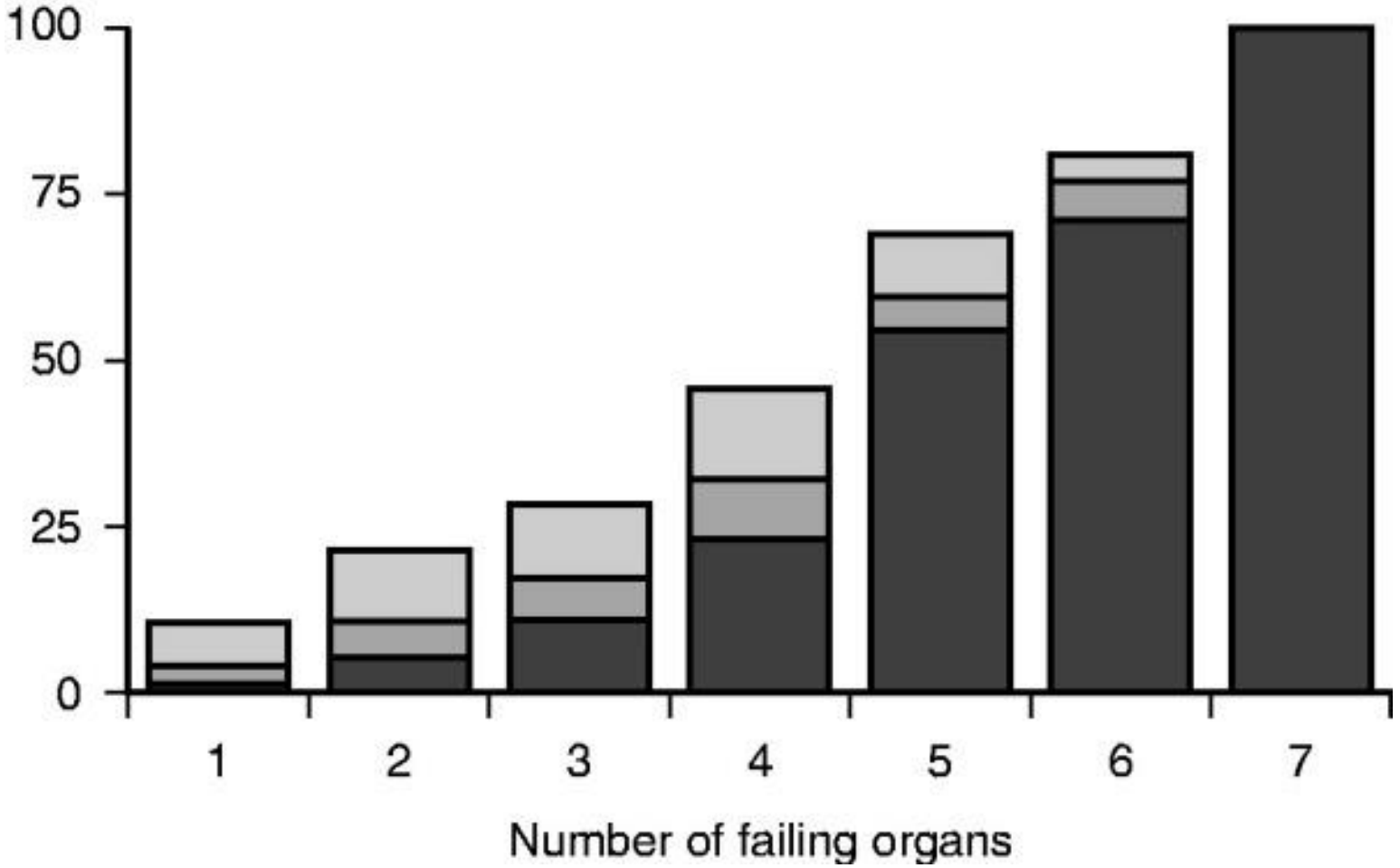
- Multiple Organ Dysfunction Syndrome “MODS”

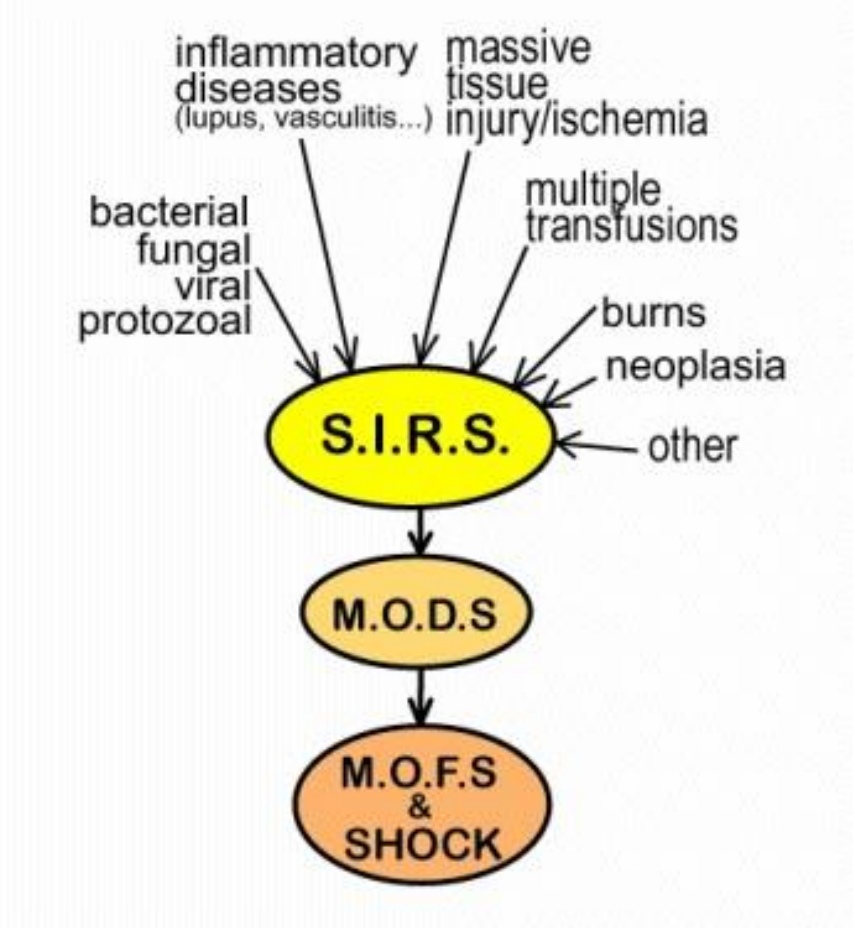
  1991 Consensus conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)

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





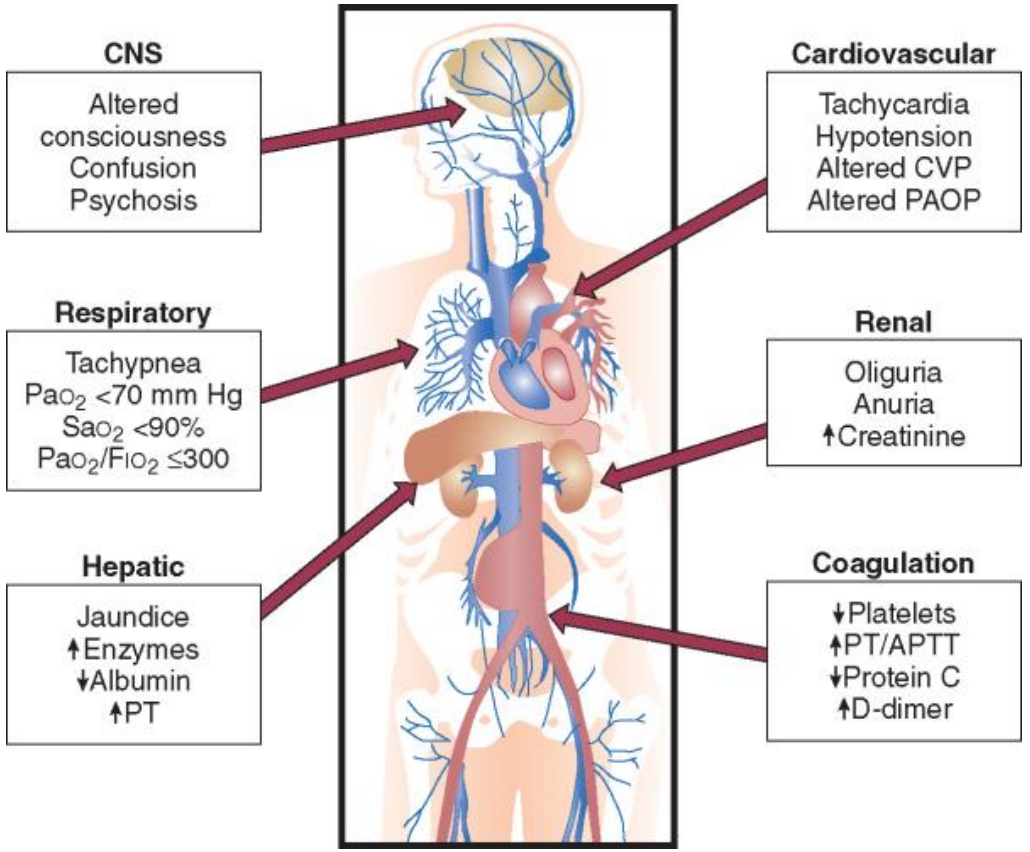
Mortality in intensive care unit *black*
Mortality to hospital discharge *black* + *dark grey*
Mortality to 1 year *black* + *dark grey* + *light grey.*

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
	PH ≤ 7.24 with PaCO2 ≤ 49 mm Hg
Respiratory	Respiratory rate ≤ 5/min or ≥ 49/min
	PaCO2 ≥ 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 ≤ 20,000/mm^3
	Hematocrit ≤ 20%
Neurologic	Glasgow coma score ≤ 6 (in the absence of sedation)

Abbreviations: CPAP, continuous positive airway pressure; OSF, organ system failure; PaCO2, arterial CO_2 tension.

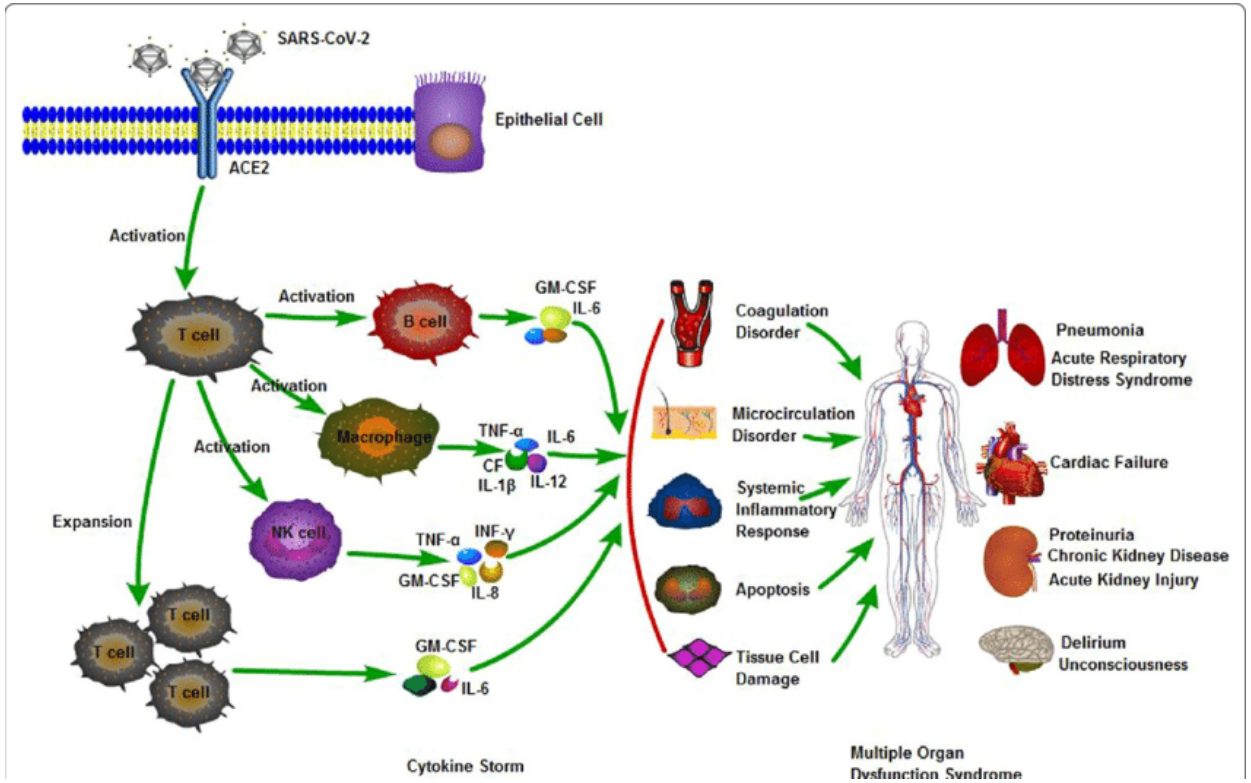
Definitions and grading of organ dysfunction (MODS score)

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

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

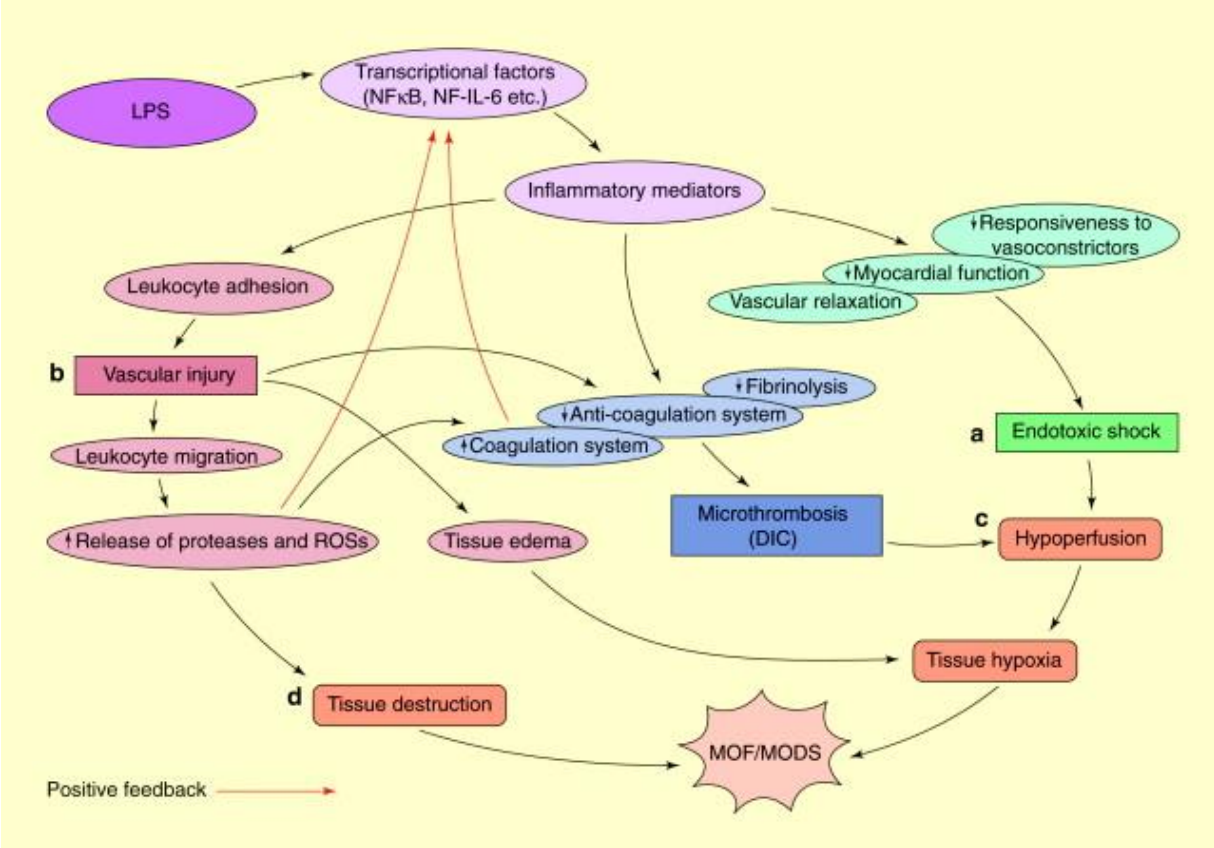
Potential Pathophysiologic Mechanisms Producing MODS

- 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

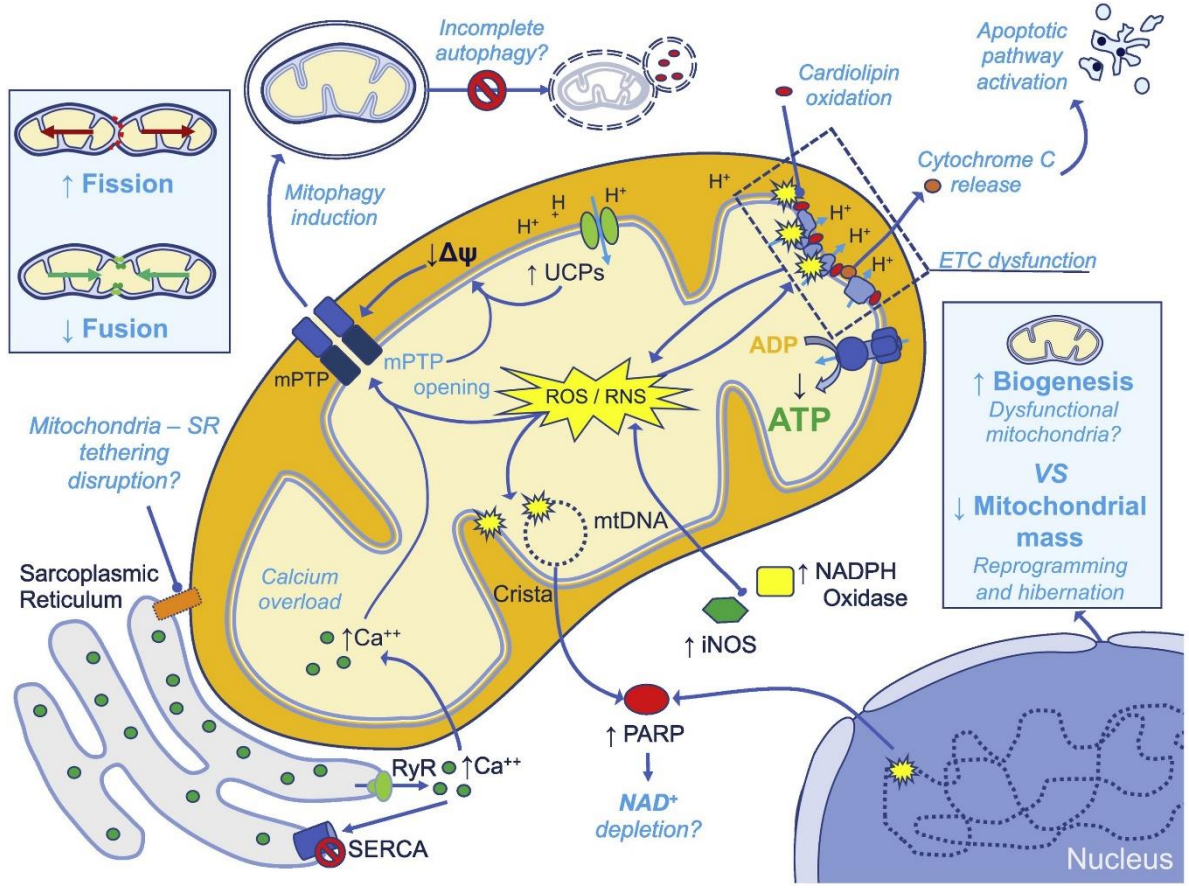
- MODS is caused by an overwhelming imbalance between systemic inflammatory response and counter regulation (anti-inflammatory) response.
- May be activated by a number of external and internal factors, including pro-inflammatory (e.g., infection, sepsis, shock, and trauma) and immunosuppression (e.g., 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

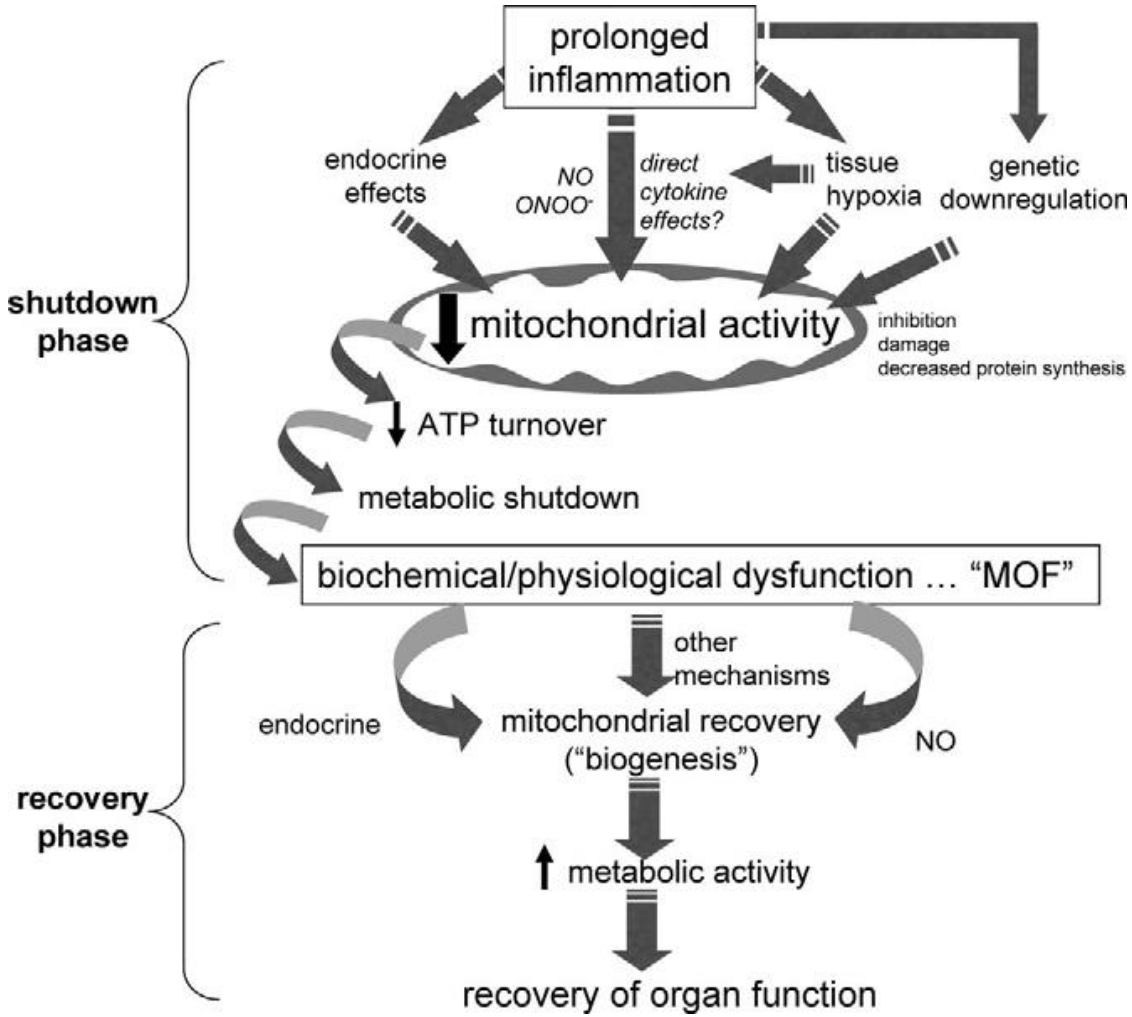
Bioenergetics Model

- 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



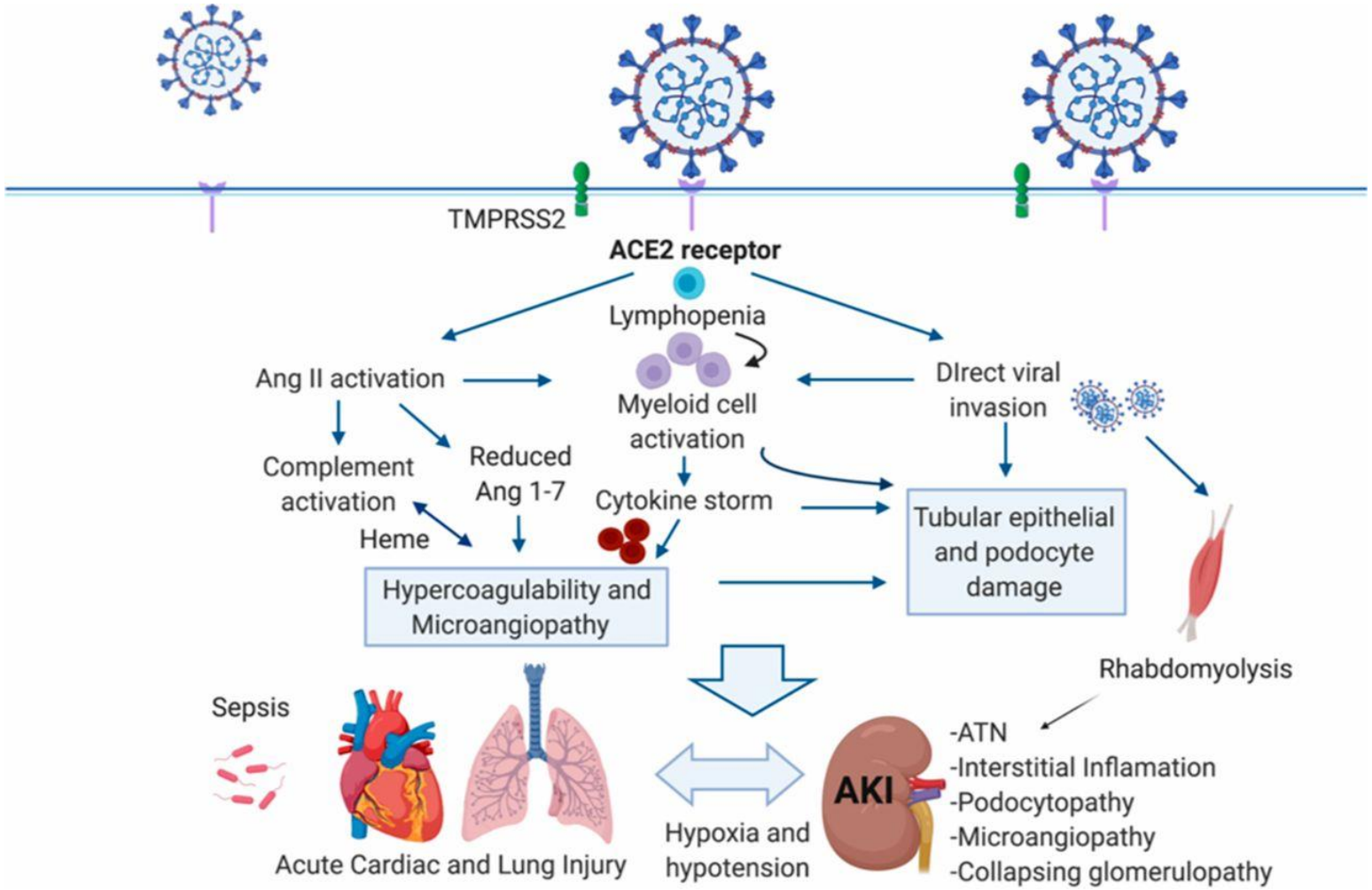
Giacomo Stanzani, et al. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, Volume 1865, Issue 4, 2019.

Progression of Bioenergetics Dysfunction



Mervyn Singer, Mitochondrial function in sepsis: Acute phase versus multiple organ failure (Crit Care Med 2007; 35)

Pathogenesis of Covid-19 disease



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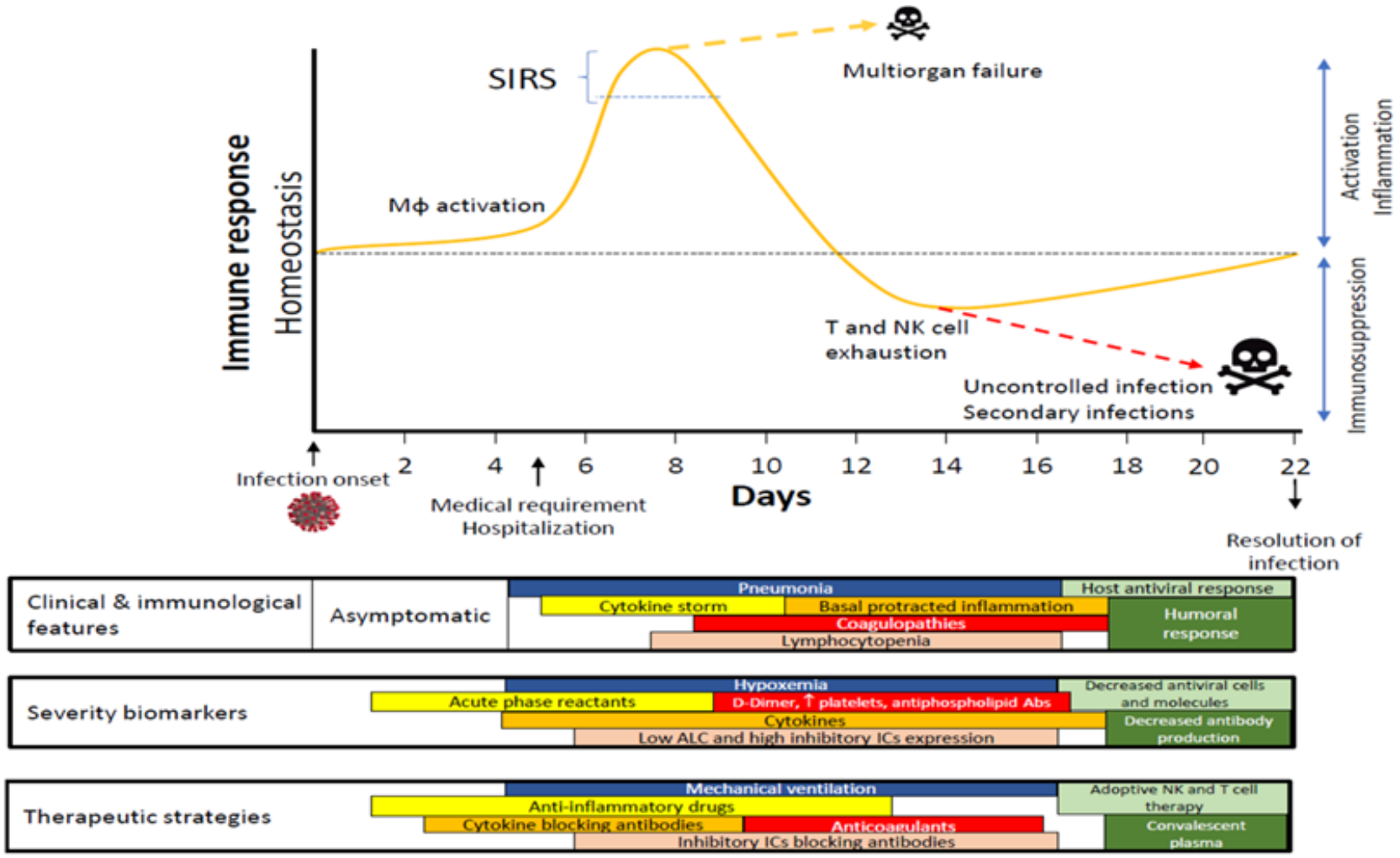
SIRS, MODS and Covid-19



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Shock

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 (→preload)
- R – systemic resistance (mostly arterioles) - afterload

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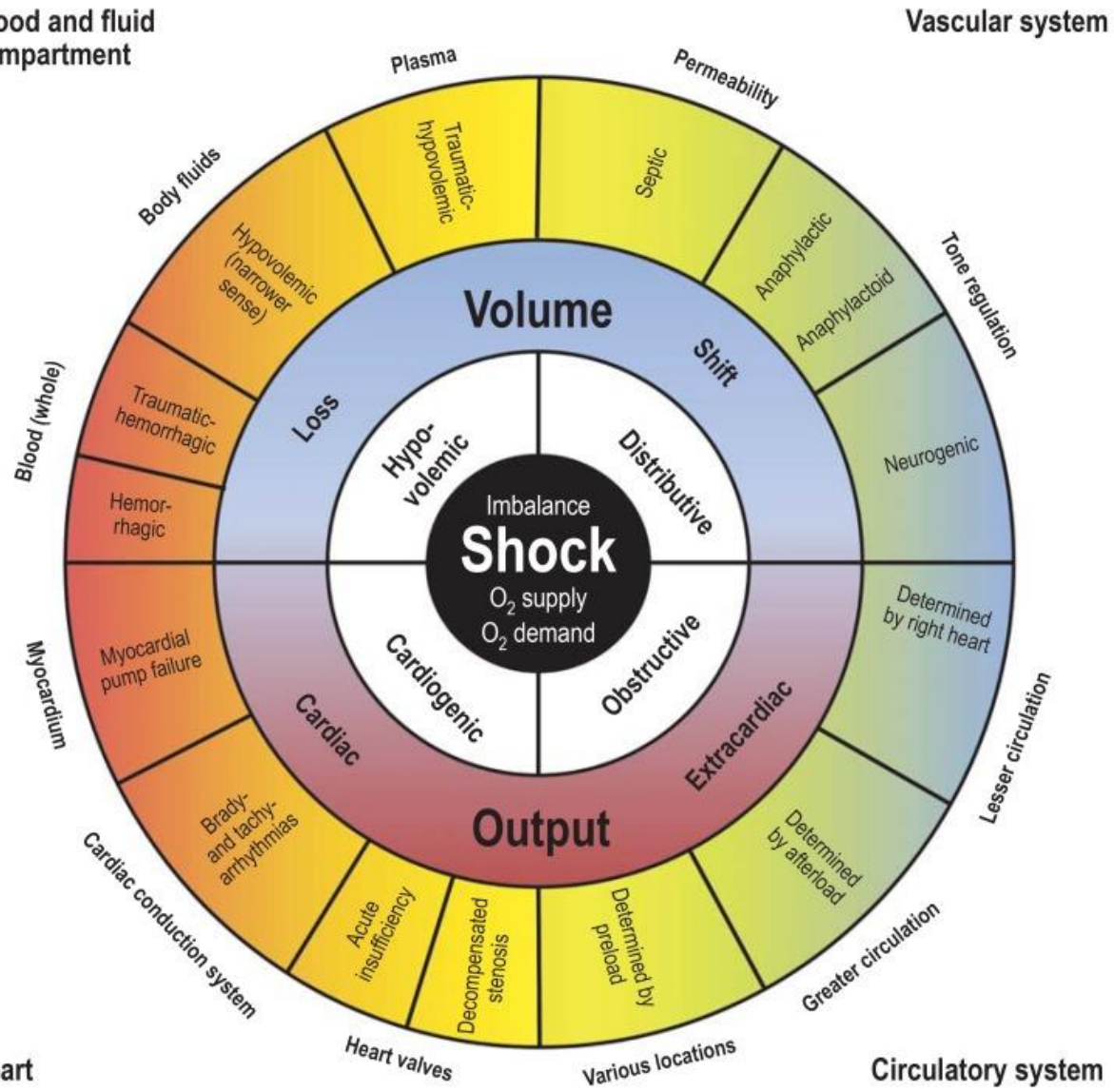
Shock categories

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



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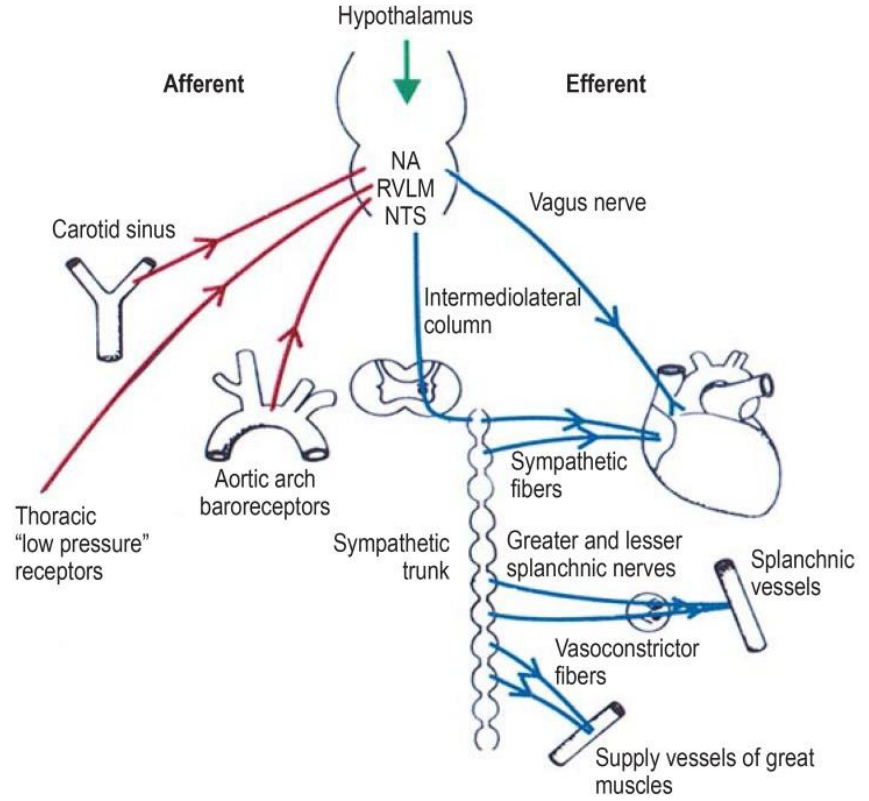
Neurogenic shock – special situation

- 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.

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Phases of shock

- Compensation of initiating cause
- Decompensation
- Refractory shock

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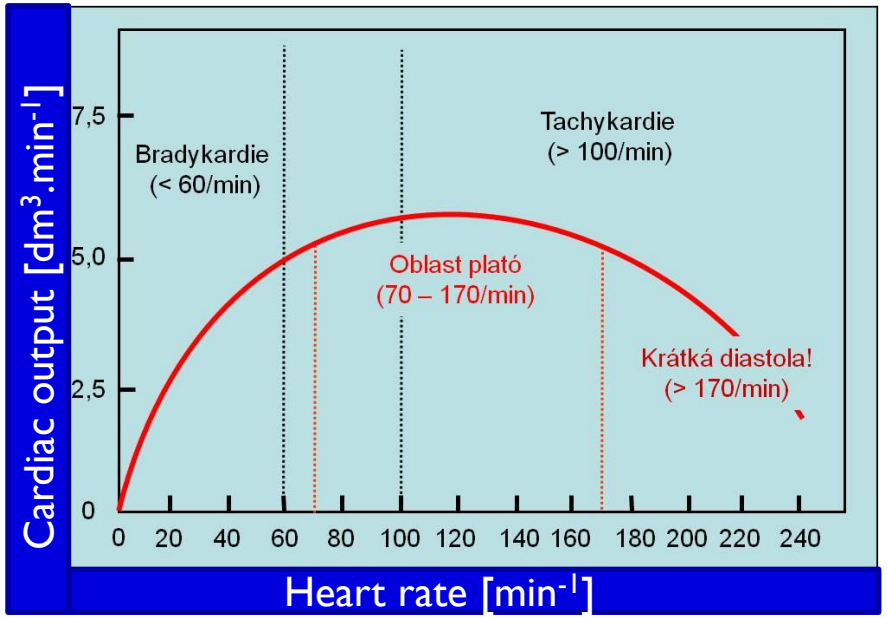
- In early shock, compensation occurs by modulation of cardiac output and vascular tone by the autonomic nervous system.
- Carotid baroreceptors respond to decreased blood pressure by triggering increased sympathetic signaling.
- This autonomic nervous system-mediated sympathetic response results in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

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



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Decompensated shock

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

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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 vasodilation 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 O_2 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 supression
- That leads into ↓brain perfusion

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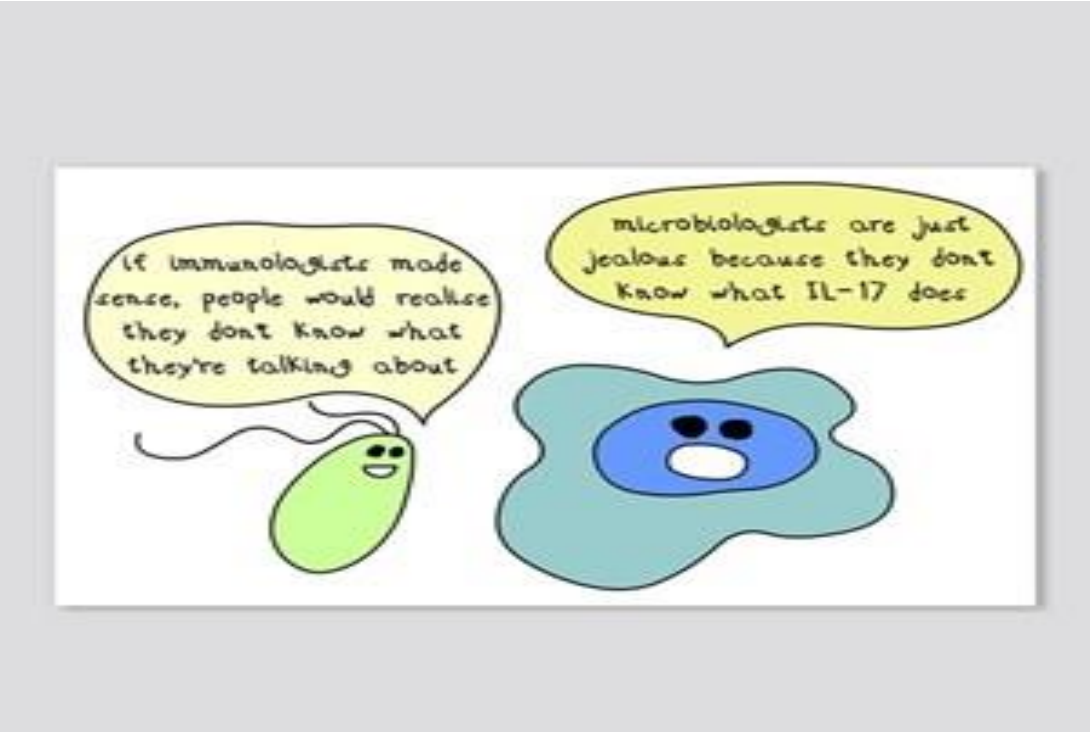
Thank you for you attention



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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.

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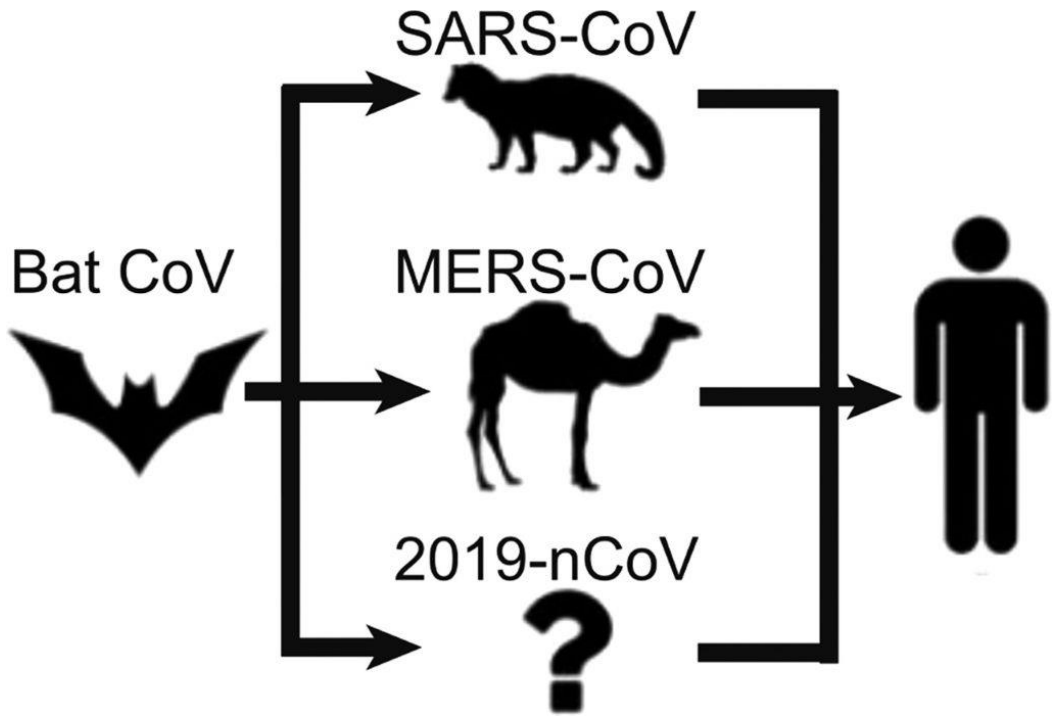
Human coronaviruses

- 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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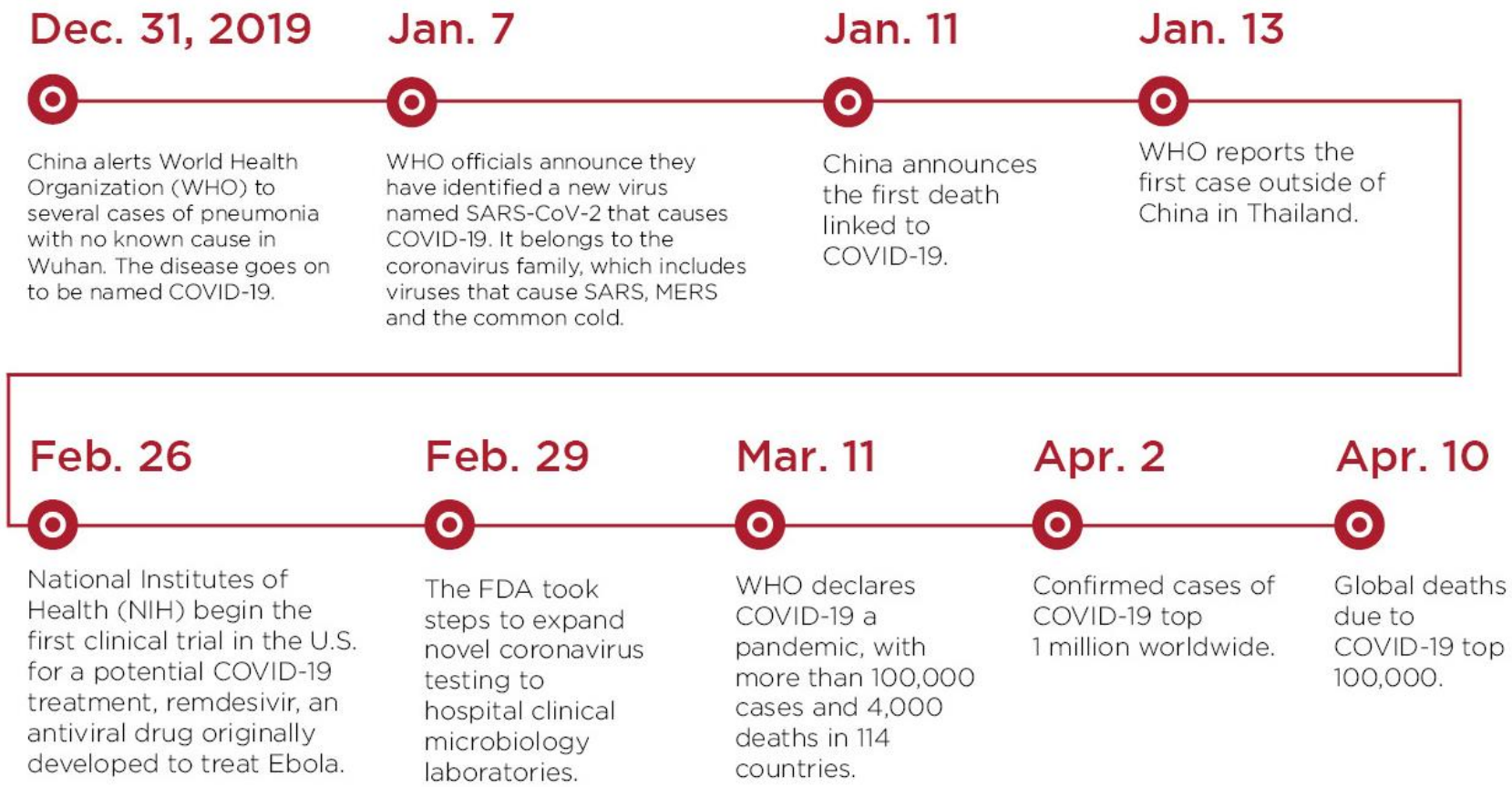
Covid-19 timeline



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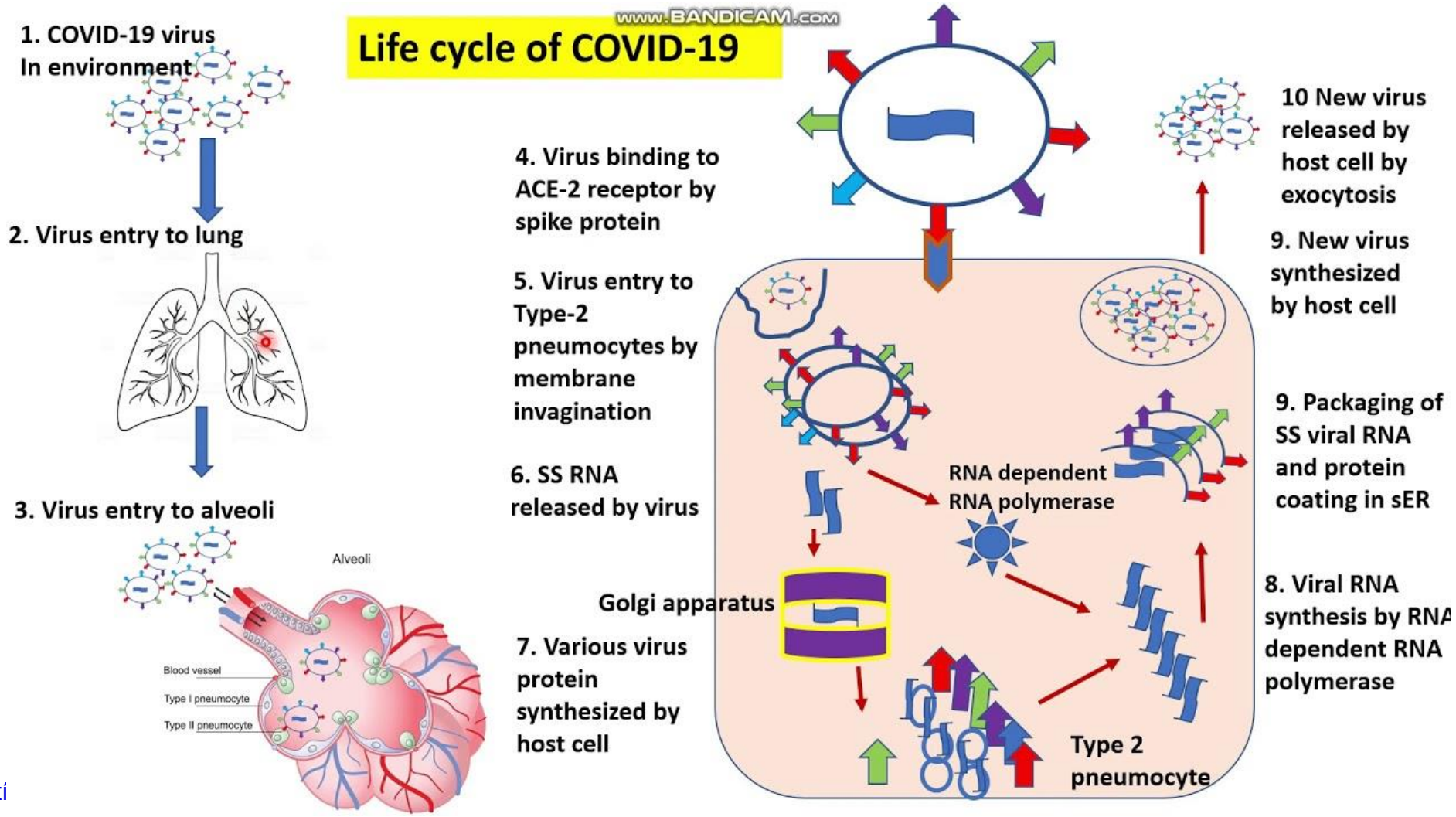
Pathogenesis of Covid-19 disease



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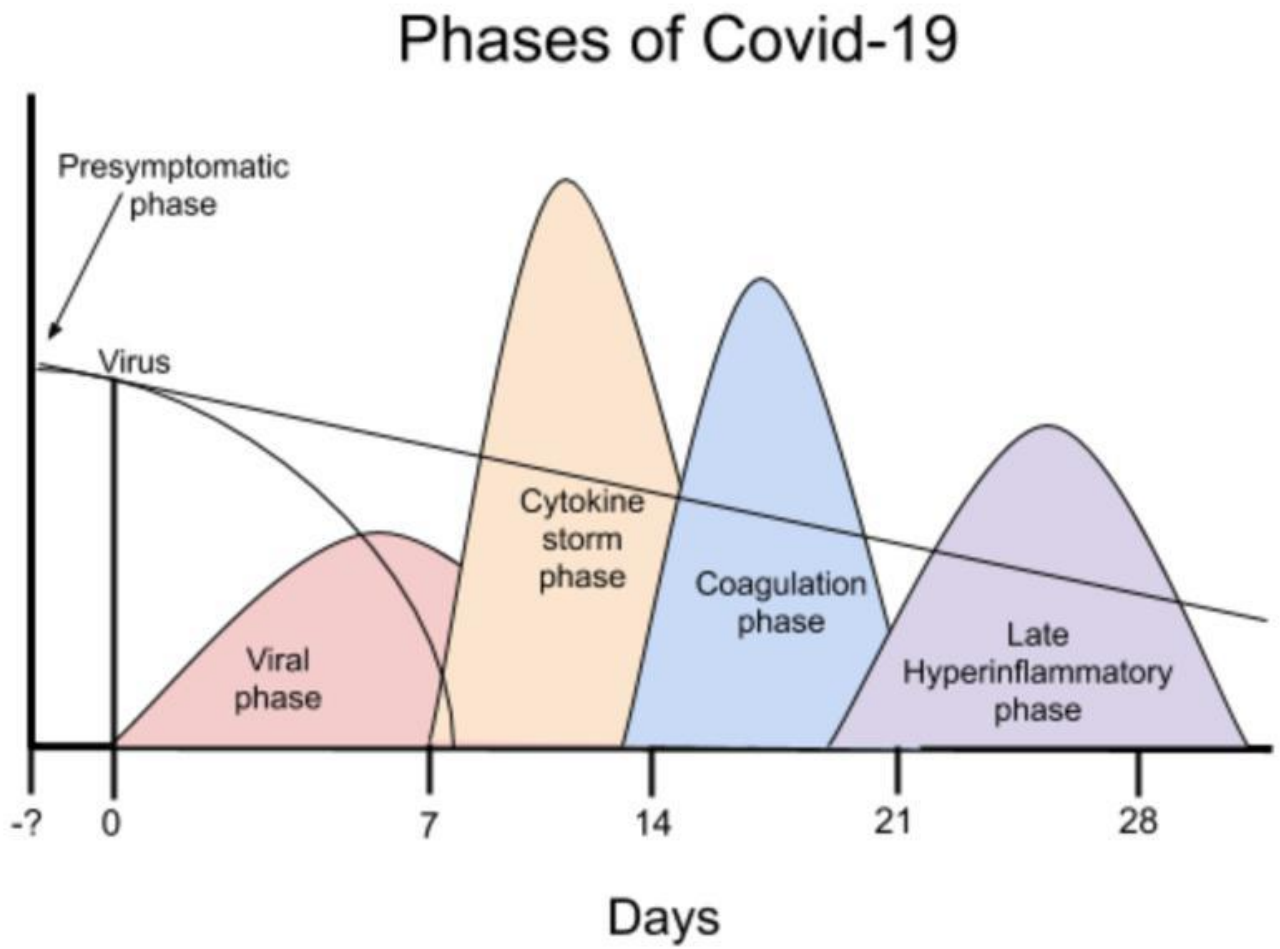
Pathogenesis of Covid-19 disease

- 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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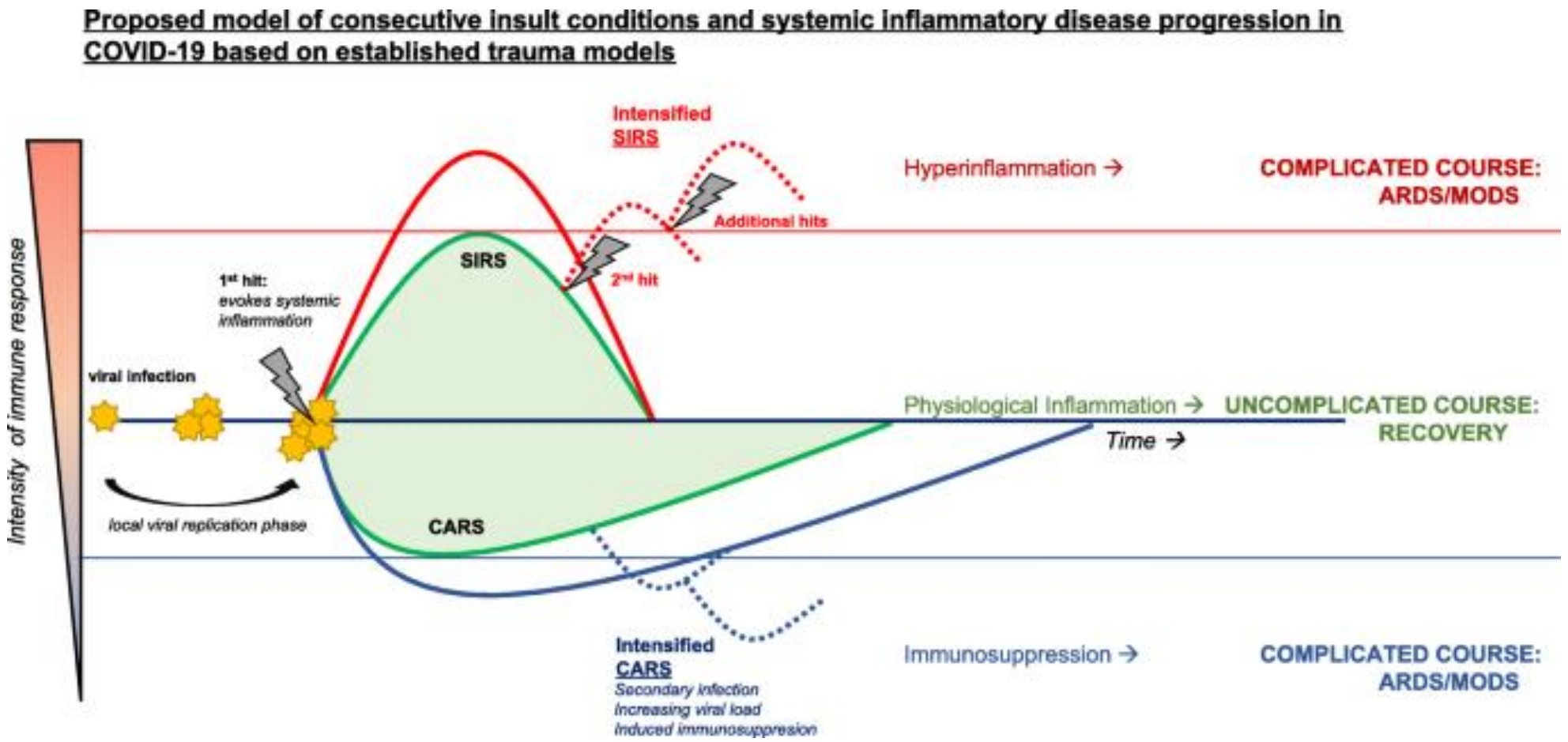
SIRS and Covid-19



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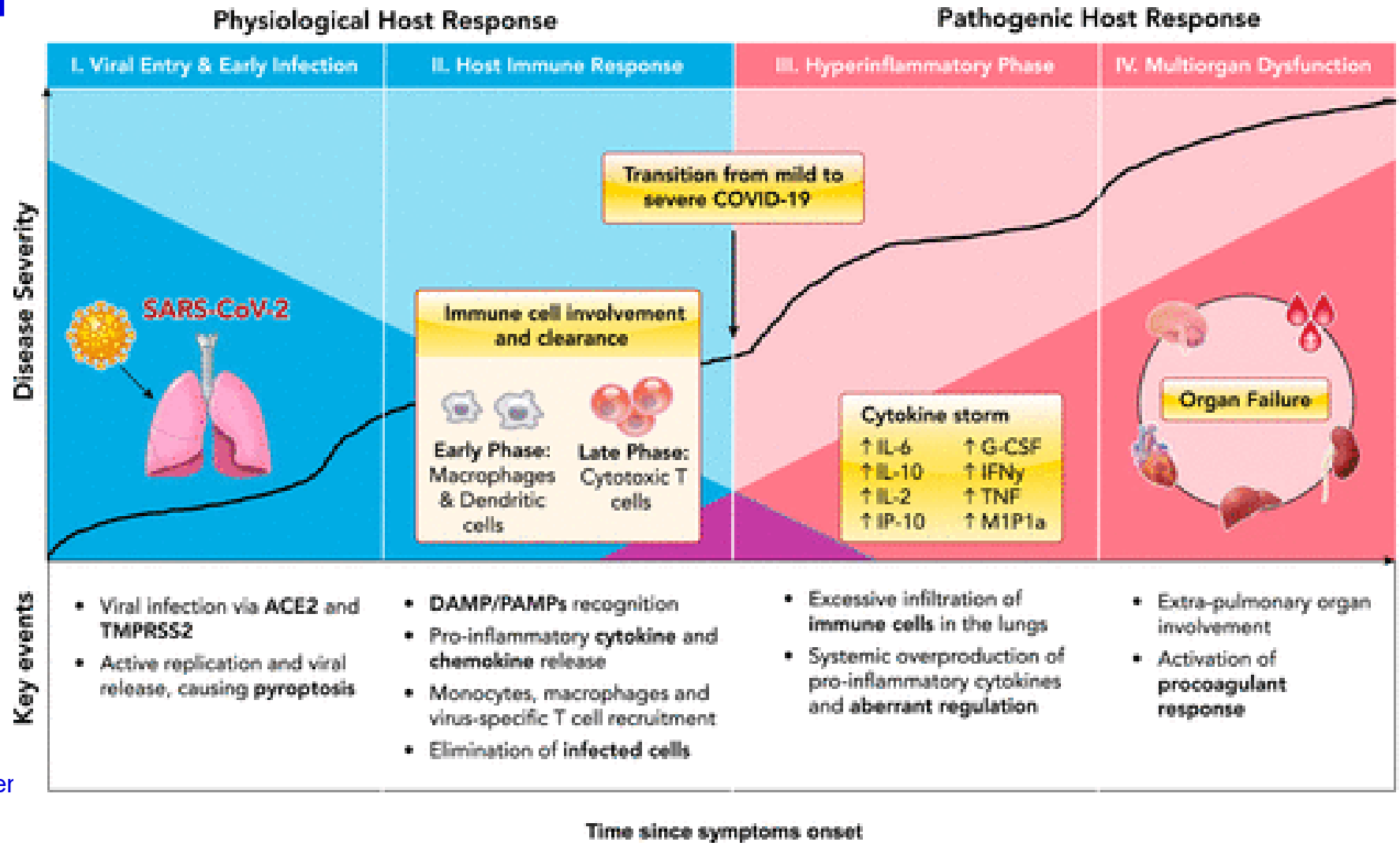
Pathogenesis of Covid-19 disease – key steps



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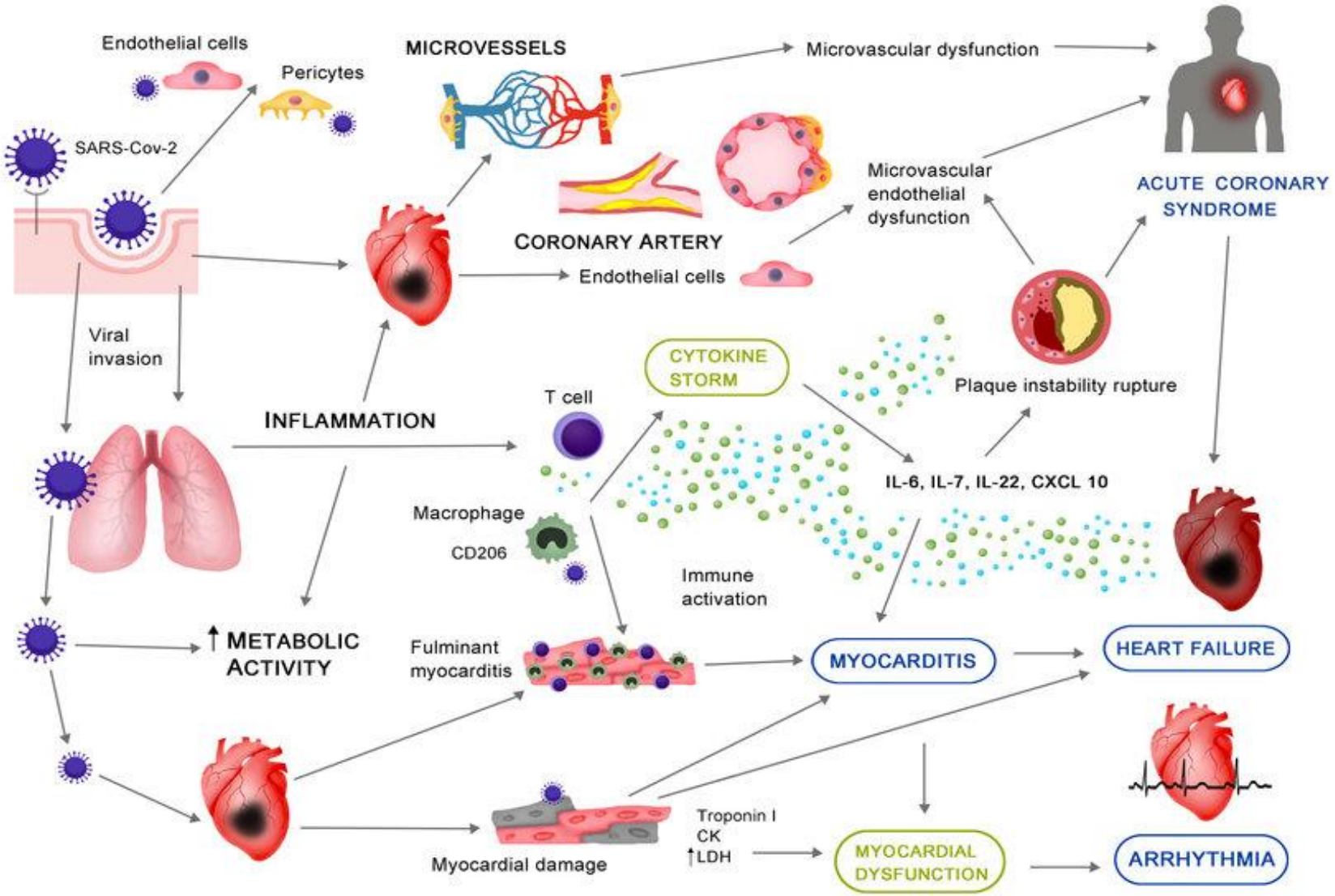
Endothelial cells
Pericytes
MICROVESSELS
Microvascular dysfunction
SARS-Cov-2
CORONARY ARTERY
Endothelial cells
Microvascular endothelial dysfunction
ACUTE CORONARY SYNDROME
Viral invasion
CYTOKINE STORM
Plaque instability rupture
INFLAMMATION
T cell
IL-6, IL-7, IL-22, CXCL 10
Macrophage
CD206
Immune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

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