MASARYKOVA UNIVERZITA

Přednášky
Zubní lékařství
Embryolog
Patofyziologie II- jaro 2023

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Patofyziologie sepse, septický šok

ZLE – jaro 2023

History

- Over the past 30 years, attempts to treat the “cytokine storm” of sepsis have universally failed to improve outcomes. In addition, no single biological response modifier has been approved by the FDA for treating sepsis. However, the “Surviving Sepsis Campaign” initiated in 2002 promotes earlier recognition of sepsis and implementation of best practices that, as now recognized, results in lower in-hospital mortality for patients with sepsis . Unfortunately, similar to trauma, improved early survival has led to a new patient phenotype described as chronic critical illness (CCI). The definition of CCI includes ICU length of stay (LOS) greater than or equal to 14 days with evidence of persistent organ dysfunction. According to this definition, approximately 40% of sepsis patients progress to CCI .

Sepsis

- is a severe illness caused by an aberrant host response to infections, and it is associated with acute organ failure and a high mortality risk. Although there has been a global improvement in clinical outcomes as a result of improved treatment practices resulting from the dissemination and implementation of the Surviving Sepsis Campaign guidelines over the preceding decades, mortality rates remain unacceptably high, ranging from 25 to 30 percent for sepsis and 40 to 50 percent in cases of septic shock, with country-specific variations. Moreover, many sepsis survivors have long-term physical and cognitive impairments as well as higher death rates than the general population.

Zhang T, Yu-Jing L, Ma T. Role of regulation of PD-1 and PD-L1 expression in sepsis. Front Immunol. 2023 Mar 9;14:1029438

Sepsis

- is characterized by dysregulation and overactivation of host-protective innate immunity
- Host immune responses to pathogens depend on the magnitude of the physiologic insult. Highly virulent pathogens and host immune impairment may potentiate the host's vulnerability to sepsis.
- Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. An overactivated or a dysregulated innate immune response to infection can result in tissue damage, cellular compromise, and molecular dysregulation that lead to organ dysfunction and failure.

Front Immunol. 2018; 9: 595.

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„THE SYSTEMIC inflammatory response syndrome“ (SIRS)

- Klinická manifestace nespecifického zánětu, významná příčina morbidity a mortality a vedoucí příčina smrti na jednotkách intenzivní péče.
- SIRS může být iniciován mnoha příčinami, včetně infekce, závažnost kolísat až k život ohrožujícímu stavu.

Závažné poškození nebo infekce

- Závažné poškození nebo infekce začínají tím, že jsou rozpoznány alarminy, které se primárně skládají z mikrobiálních produktů a poškozené tkáně.
- Vrozený imunitní systém na základě vrozených rekogničních receptorů (PRRs – „pattern recognition receptors“) rozpoznává cizí antigeny a poškozené buňky. PRRs jsou exprimovány na mnoha buněčných liniích (myeloidní, endoteliální a epiteliální).
- PRRs detekují konzervované mikrobiální komponenty zvané „pathogen-associated molecular patterns (PAMPs)“, stejně jako hostitelské molekuly derivované z poškozených buněk, známě jako „damage-associated molecular patterns (DAMPs)“.

Front Immunol. 2018; 9: 595.

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PRRs

- PRRs zahrnují Toll-like receptory (TLRs), C-type lectin receptory (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic-acid-inducible gene-I (RIG-I)-like receptors (RLRs) a receptor pro získané produkty glykaces (RAGE).
- Velký počet, diverzita a redundance se uplatňují v rámci optimalizace imunitní odpovědi.

Front Immunol. 2018; 9: 595.

PRRs

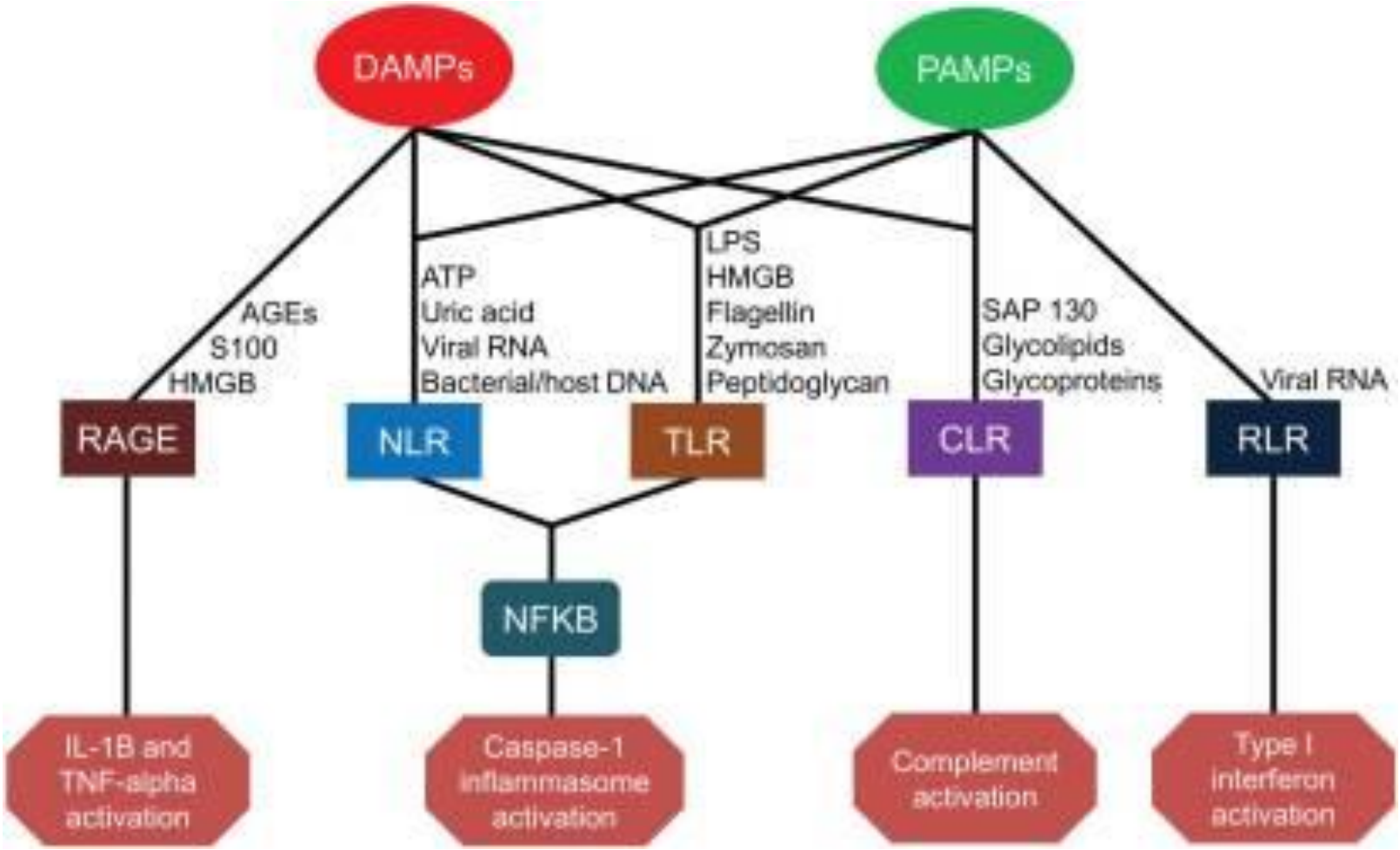
- Na základě rozpoznání hostitelských PAMPs nebo DAMPs PRRs iniciují komplexní soubor signálních událostí , které indukují hostitelskou obranyschopnou odpověď. Jedná se o povolávání a fosforylaci intracelulárních intermediálních látek, což vede částečně k aktivaci genů okamžité odpovědi.

Front Immunol. 2018; 9: 595.

PRRs

- PRRs aktivace a následná signalizace vede k nespecifickým i pro patogen specifickým buněčným odpovědím, které mají zajistit eliminaci stresorů nebo prevenci jejich uplatnění. Těmito stresory jsou mikrobiální infekce nebo tkáňové poškození.
- Suprese mikrobiální replikace, invaze Mb do tkání a diseminace z místa infekce zahrnují mnoho buněk vrozeného imunitního systému: neutrofily (PMNs), monocyty/makrofágy (Mφ), dendritické buňky (DCs), natural killer (NK) buňky a innate lymphoid cells (ILCs) . Tyto buňky hrají klíčovou roli v časné zánětlivé odpovědi.

Front Immunol. 2018; 9: 595.



Pattern-recognition receptor pathways for damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). AGEs, advanced glycosylation end products; HMGB, high-mobility group box; ATP, adenosine triphosphate; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; LPS, lipopolysaccharide; RAGE, receptor for advanced glycation end products; NLR, nucleotide-binding oligomerization domain-like receptors; TLR, toll-like receptors; CLR, C-type lectin receptors; RLR, retinoic-acid-inducible gene-I-like receptors; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor.

Toll-like receptory (TLRs)

- Zatím u člověka známo 13 různých TLRs.
- Některé exprimovány na plasmatické mebráně buněk (TLRs 1, 2, 4, 5, 6) jako konstantní součást lokálního prostředí
- Jiné jsou v endosomálních kompartmentech (TLRs 3, 7, 8, 9, 11, 12, 13), kde vnímají signály nebezpečí pro hostitele, mikrobiální proteiny a nukleové kyseliny.

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TLRs

- TLRs na plasmatických mebránách detekují vnější mikrobiální komponenty a cirkulující signály poškození, jako jsou lipopolysacharidy (LPS), fosfolipidy, zymosan, flagellin, peptidoglycan, S100A8/9 a „endogenous high-mobility group box (HMGB)“ nukleární proteiny z buněk poškozených distresem.
- Cytoplasmatické TLRs detekují virové nebo mikrobiální nukleové kyseliny a mitochondriální nukleové kyseliny asociované se poškozením buňky.
- TLRs hrají centrální roli v iniciaci vrozené imunitní odpovědi ve spolupráci s jinými PRRs prostřednictvím různých i přesahujících se „pathways“.

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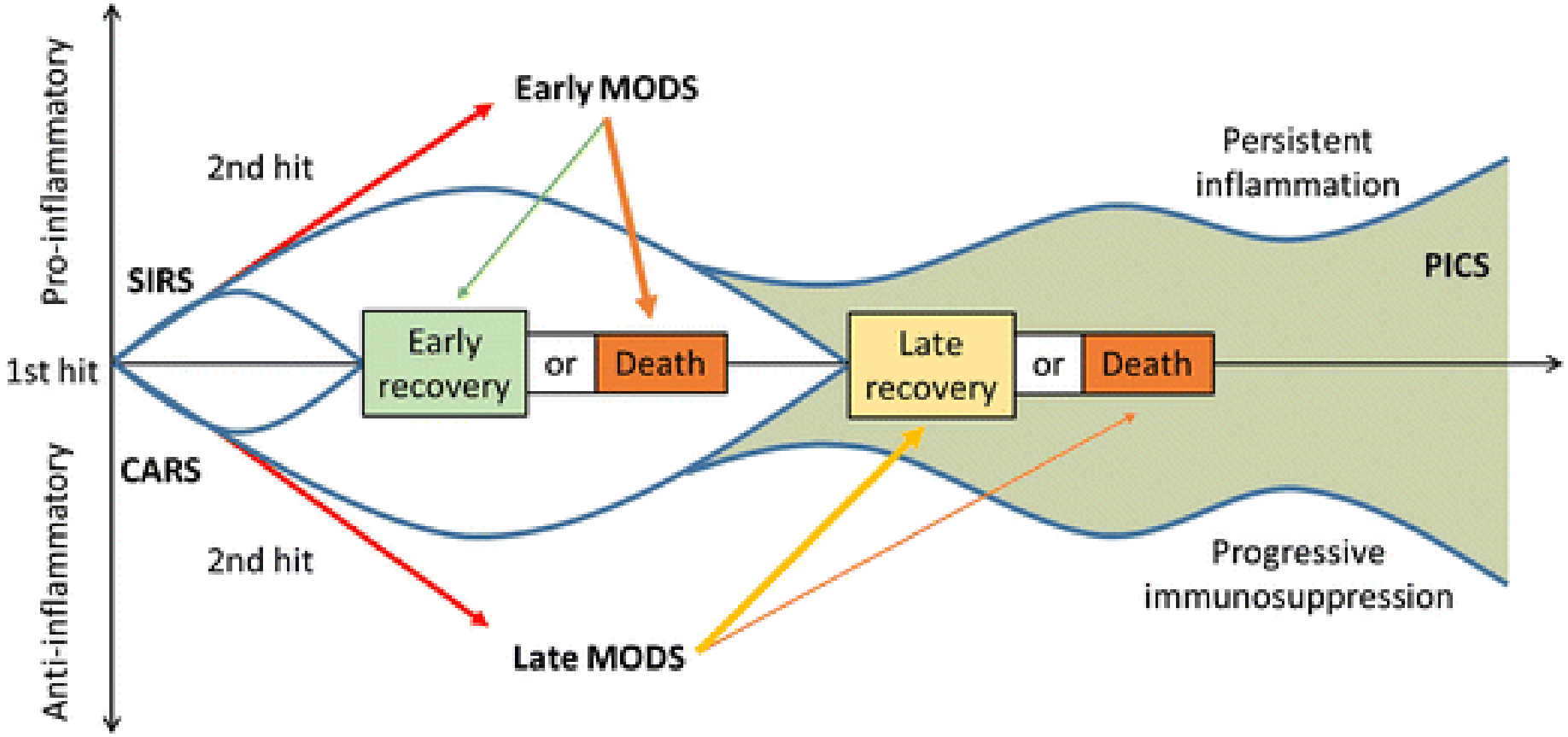
Zánět a získaná imunita

- Tradičně se vrozená imunitní odpověď definovala jako rychlá a nespecifická, bez schopnosti propisovat zkušenost do imunologické paměti. Dnes už víme, že některé buňky vrozené imunity jsou epigeneticky reprogramovány („imprinted“) minulými zkušenostmi. Tyto „trénované“ buňky vrozené imunity vykazují změněné prozánětlivé odpovědi při následném kontaktu s patogenem. Tato vlastnost se klasicky přisuzovala antigenně specifickým paměťovým T a B lymfocytům. Během opakovaně vyvolané odpovědi paměťové B a T lymfocyty rychle odpovídají proliferací s produkcí efektorových cytokinů a prováděním dalších efektorových funkcí. Často přehlíženou efektorovou funkcí paměťových CD4 a CD8 T lymfocytů je podpora prozánětlivého prostředí v místě infekce, která odráží primární zkušenost. Tato zánětlivá odpověď podmíněná pamětí spolu se sekundárními funkcemi efektorových T-lymfocytů má za následek lepší kontrolu a rychlejší řešení infekce i tkáňového poškození, které je s touto infekcí spojeno.



SIRS (Systemic Inflammatory Response Syndrome) is based on the presence of two out of four criteria: fever (> 38.0 °C) or hypothermia (< 36.0 °C), tachycardia (> 90 beats/min), tachypnea (> 20 breaths/min), leukocytosis (> 12 × 10^9/L), or leucopenia (< 4 × 10^9/L)
CARS (compensatory anti-inflammatory response) occurs with SIRS. CARS is regarded as a delayed response to SIRS, but some authors argue that it occurs at the same time SIRS begins. CARS is clinically expressed as hypothermia, leukopenia, and failure to clear infection
MODS (multiple organ dysfunction syndrome) is defined as the failure of two or more organ systems in the acutely ill patient
PICS (persistent inflammation-immunosuppression catabolism syndrome). PICS is proposed as a diagnosis for patients who have a prolonged stay in the ICU (intensive care units) with manageable organ dysfunctions, with protein catabolism, poor nutritional status, poor wound healing, immunosuppression, and recurrent infections. They also typically develop decubitus ulcers and tend to suffer from increased levels of pain, dyspnea, fatigue, and delirium.

Inflammation **volume 41**, pages1115–1127 (2018)

PICS

- We believe that individuals who experience a morbid post-ICU hospital course are developing a new syndrome, termed the persistent inflammation, immunosuppression, and catabolism syndrome (PICS).
- Emerging evidence indicates that the pathogenesis of PICS involves chronic low-grade inflammation, suppressed host protective immunity, and loss of lean tissue.

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PICS -criteria

• ICU stay ≥ 10 days
- Persistent inflammation
- C-reactive protein concentration > 150 µg/dl
- Retinol binding protein concentrations < 10 µg/dl
• Immunosuppression
- Total lymphocyte count < 800/mm3
• Catabolic state
- Serum albumin concentrations < 3.0 g/dl
- Creatinine height index < 80%
- Weight loss > 10% or BMI < 18 during the current hospitalization

Inflammation **volume 41**, pages1115–1127 (2018)

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Severe injury or infection

- Severe injury or infection leading to CCI and PICS begins with the recognition of alarmins, primarily consisting of microbial products and damaged tissue.
- The innate immune system relies on germ line-encoded pattern-recognition receptors (PRRs) to sense components of foreign pathogens and damaged cells to mount host-protective responses.

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Severe injury or infection

- These PRRs are expressed on a variety of host cells, including cells of myeloid, endothelial, and epithelial lineages. These PRRs detect conserved microbial components called pathogen-associated molecular patterns (PAMPs) as well as host molecules derived from damaged cells, known as damage-associated molecular patterns (DAMPs).

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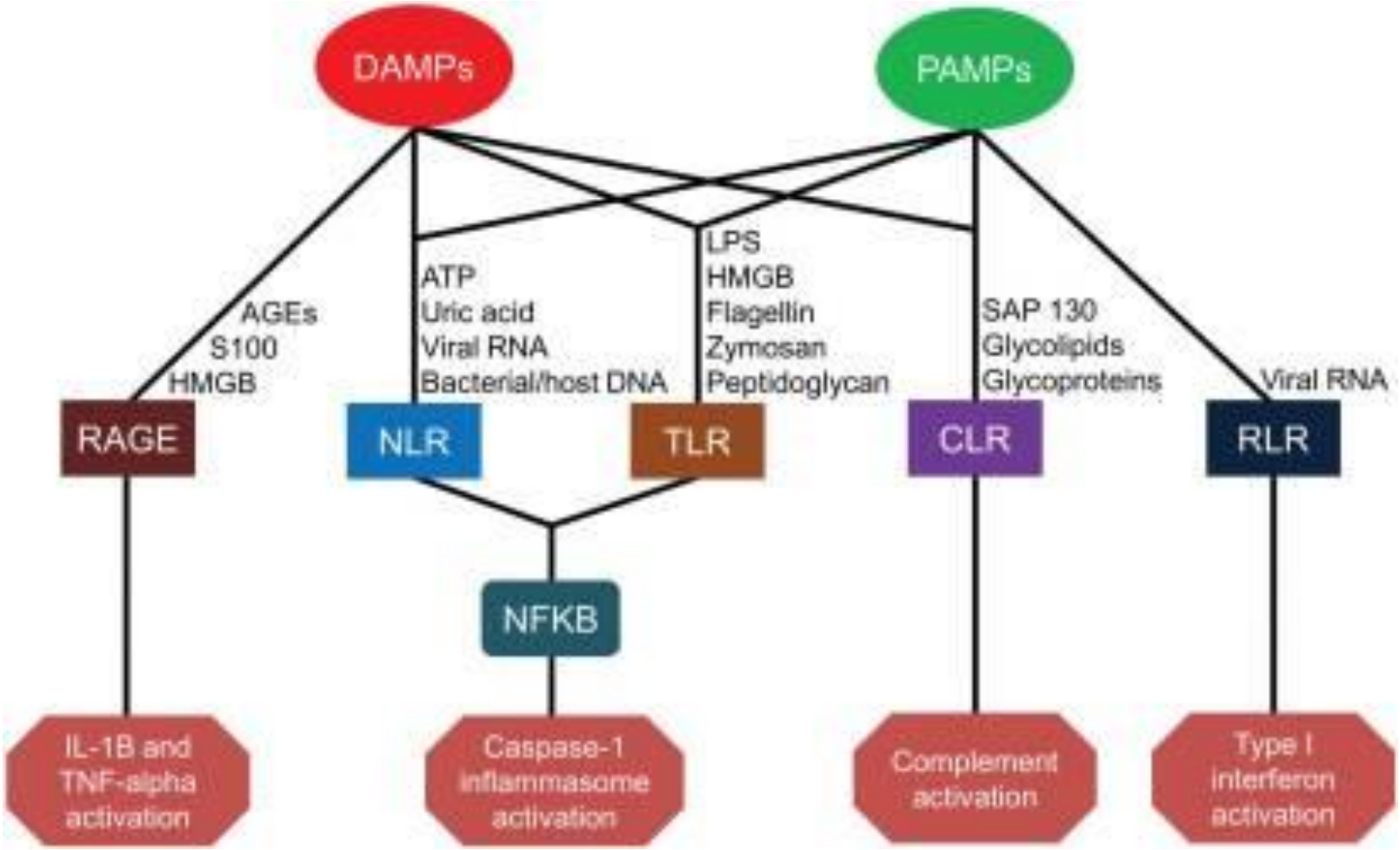

Pattern-recognition receptor pathways for damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). AGEs, advanced glycosylation end products; HMGB, high-mobility group box; ATP, adenosine triphosphate; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; LPS, lipopolysaccharide; RAGE, receptor for advanced glycation end products; NLR, nucleotide-binding oligomerization domain-like receptors; TLR, toll-like receptors; CLR, C-type lectin receptors; RLR, retinoic-acid-inducible gene-I-like receptors; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor.

Type of infection

- Most of the sepsis patients had bacterial infections.
- Patients with viral infection commonly, but not always, have considerably lower serum pre-CT values. This probably is related to the lower incidence of associated severe systemic inflammation in viral infection.

Neutrophil Priming and NETs in Sepsis

- PMNs exist in three states: resting, primed and activated. PMNs shift from a resting state in the circulation to an activated state at the site of infection *via* several priming stimuli, including cytokines, LPS, and C5a.
- During sepsis, excessive priming of PMNs can cause excessive production of ROS, which are released into the nearby environment, resulting in tissue damage.

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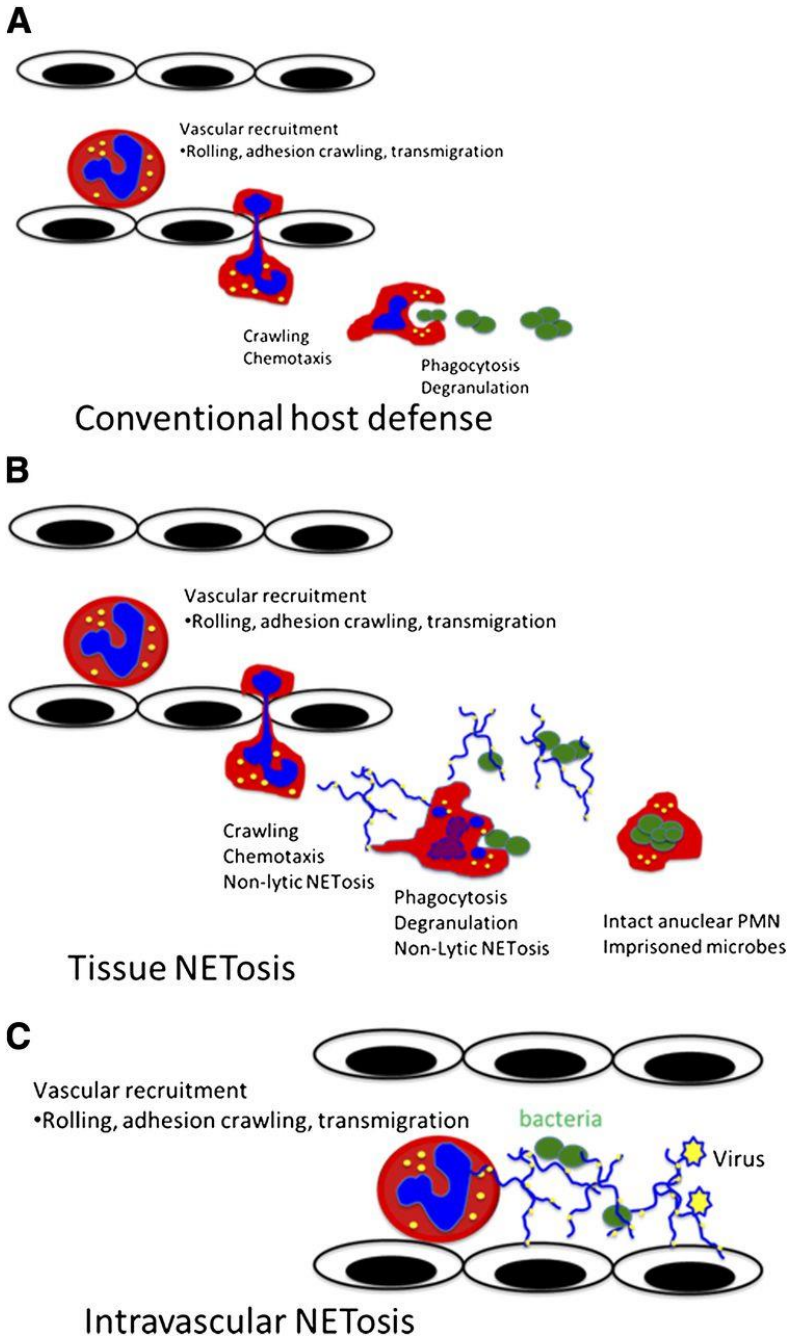
Neutrophil Priming and NETs in Sepsis

- Priming of the neutrophil respiratory burst is believed to be involved in the pathophysiology of the acute respiratory distress syndrome. In addition, NETs can harm the host during sepsis. Although NET formation can help eradicate a wide range of pathogens in the early phase of the infection, the generation of excessive amounts of NETs, as well as impairment of their degradation by extracellular DNAases within the bloodstream, can damage tissues and endothelia . This can induce diffuse thrombosis and lead to DIC and acute organ injury. Also, extracellular histones released by excessively accumulated NETs are cytotoxic to endothelial and epithelial cells.

NETosis

- Stimulated PMNs could release extracellular nucleic acids decorated with histones and granular proteins capable of entrapping exogenous bacteria.
- Suicidal vs. vital NETosis



Vital NETosis allows PMNs to maintain conventional host defensive functions.

(A) Conventional neutrophil host response incudes the recruitment cascade, emigration, chemotaxis, phagocytosis, and microbial killing.

(B) Vital NETosis aids in containing local infections, such as gram-positive cellulitis, by allowing PMNs to rapidly release NETs and continue to chemotax and phagocytose live bacteria. Additionally, the live NET-releasing PMNs are able to maintain their membrane integrity, thereby imprisoning the captured bacteria.

(C) Intravascular NET release optimizes the capture of both bacteria and viruses within the blood stream. Intravascular NETosis may also contribute to immunothrombosis.

Blood. 2013 Oct 17;122(16):2784-94

Coagulation in Sepsis

- Although the activation of the coagulation cascade is protective in reducing the dissemination of invading pathogens through fibrin deposition, overactivation of coagulation and subsequent microthrombus formation may lead to disseminated intravascular coagulation (DIC) which can reduce microcirculation and oxygen delivery to tissues . This can result in multiple organ failure. The prevalence of DIC in severe sepsis has been reported to be as high as 47% . During sepsis-induced activation of coagulation, the function of anticoagulant pathways such as antithrombin, activated protein C, and TF pathway inhibitor (TFPI) can be impaired. These impairments lead to increased fibrin formation and insufficient fibrinolysis, which results in microvascular thrombus.

Front Immunol. 2018; 9: 595.

Platelets

Platelet activation within the sites of bacterial infection also provides a first line of defense against pathogenic microbial agents . Although activated platelets can have bactericidal activity through platelet secretion, platelets contribute more to bactericidal activity by forming platelet-bound bacteria bundles, which boost the activity of professional phagocytes such as PMNs and Mφs . TLRs and the complement system seem to contribute to coagulation and thrombosis.

Front Immunol. 2018; 9: 595.

Complement Activation in Sepsis

- The complement system is activated during sepsis, resulting in increased levels of C3a, C4a, and C5a in plasma. Excessive amounts of these anaphylatoxins can lead to adverse systemic consequences through several mechanisms, including, but not limited to, hemodynamic instability and impaired oxygen delivery.
- In the complement system, C5a is the most powerful inflammatory mediator, and the C5a–C5aR interaction can induce various biological responses. In acute sepsis, C5a plays a central role in the production of both inflammatory and anti-ILCs. In addition, the excessive generation of C5a results in the aggravation of the cardiovascular system as well as paralysis of crucial neutrophil functions, such as chemotaxis, respiratory burst, and phagocytosis. Moreover, C5a regulates the host reaction to sepsis.

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MDSCs in Sepsis

- Myeloid-derived suppressor cell expansion is thought to be primarily mediated by the Janus kinase protein family leading to the activation of transcription 3 (STAT3). Activation is a second step dependent primarily on NF-κB activation through the MyD88 pathway. Several inflammatory mediators, such as IL-6, G-CSF, GM-CSF, and VEGF, are involved in the latter pathway .
- Following activation, MDSCs produce multiple mediators such as ROS, inducible nitric oxide synthase, arginase-1, TGF-β, and IL-10 that suppress T-effector and NK cell proliferation and activation, preferentially induce Th2 polarization.

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Microbiom during sepsis

- In sepsis, several changes occur in gut physiology and immunity, including loss of gut motility, increased bowel wall permeability, and apoptosis of intestinal epithelium due to extrinsic factors (e.g., antibiotics, opiates, and parental and enteral nutrition) and intrinsic factors (e.g., inflammation and increased bowel wall permeability).
- These changes may result in the alternation of the microbiota composition, overgrowth of pathogenic microbes, and loss of commensal organisms .
- In patients with the systemic inflammatory response syndrome, there is a loss of diversity in gut microbiota, which is associated with an increased incidence of bacteremia and an increased mortality.

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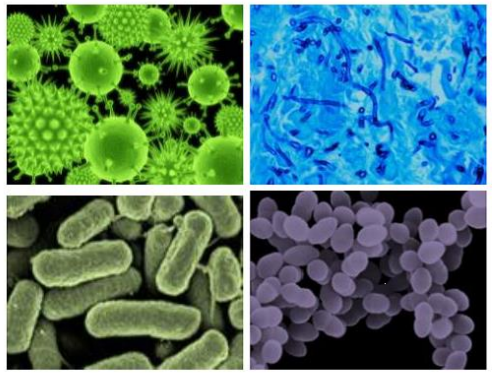
Inflammatory Mechanisms in Sepsis



Infection: Viral, Fungal, Bacterial, Parasitic

Tissue Injury

Trauma, Burn, Pancreatitis, Surgery

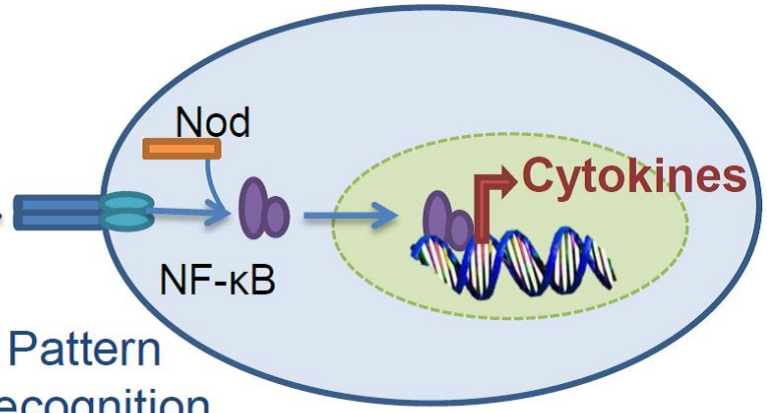
Pathogen-associated Molecular Pattern (PAMPs)

PAMPS

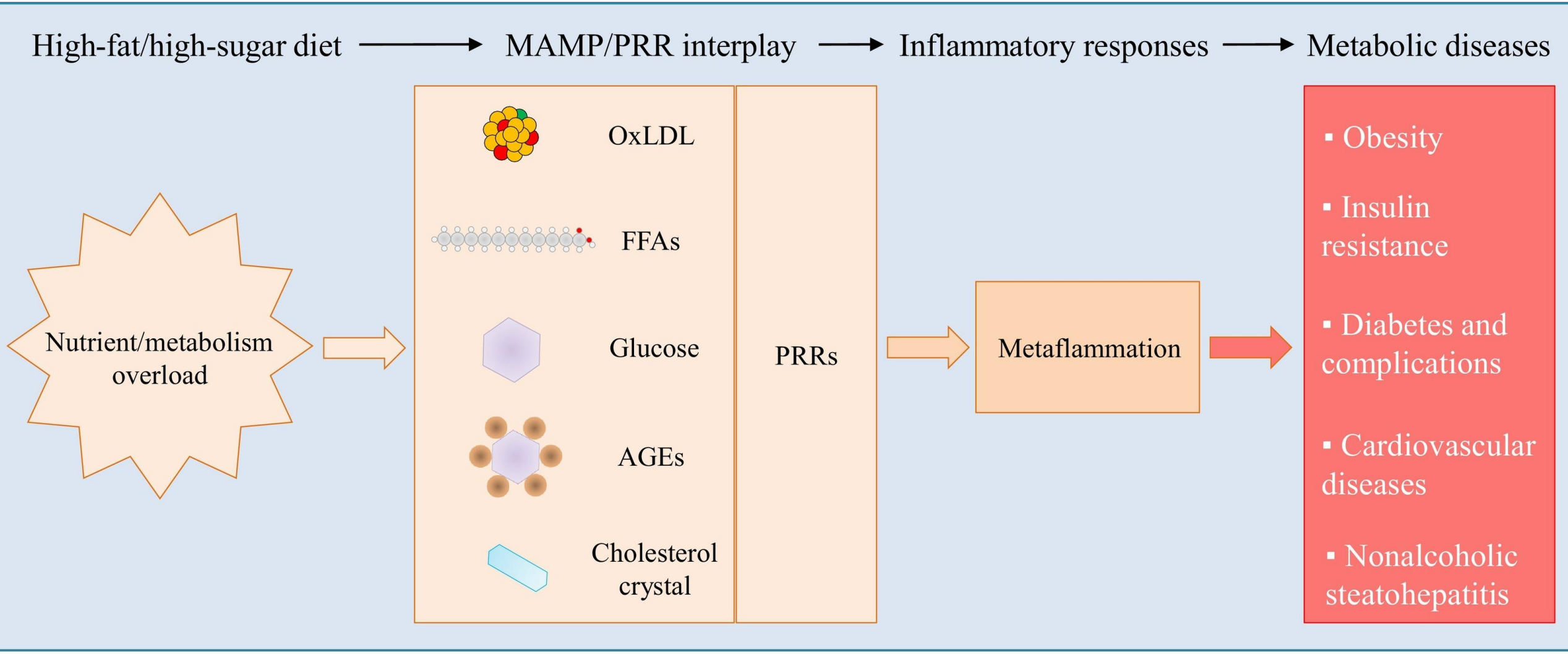
DAMPS

Damage-associated Molecular Pattern (DAMPs)

Pattern Recognition Receptors (PRRs)



Inflammatory Cascade
"Cytokine Storm"
Tissue/Organ Damage



Schematic Diagram of the Role of MAMPs in Metabolic Diseases.

Trends in Endocrinology & Metabolism

Upon the overload of nutrients and their metabolites, levels of MAMPs, such as OxLDLs, FFAs, glucose, AGEs, and cholesterol crystals, are significantly increased. These MAMPs are sensed by PRRs, leading to the initiation of metaflammation that is associated with the pathogenesis and development of various metabolic diseases. Abbreviations: AGEs, advanced glycation end products; FFAs, free fatty acids; MAMPs, metabolism-associated molecular patterns; OxLDL, oxidized low-density lipoproteins; PRR, pattern recognition receptor.

Wang X, Wang Y, Antony V, Sun H, Liang G. Metabolism-Associated Molecular Patterns (MAMPs). Trends Endocrinol Metab. 2020 Oct;31(10):712-724

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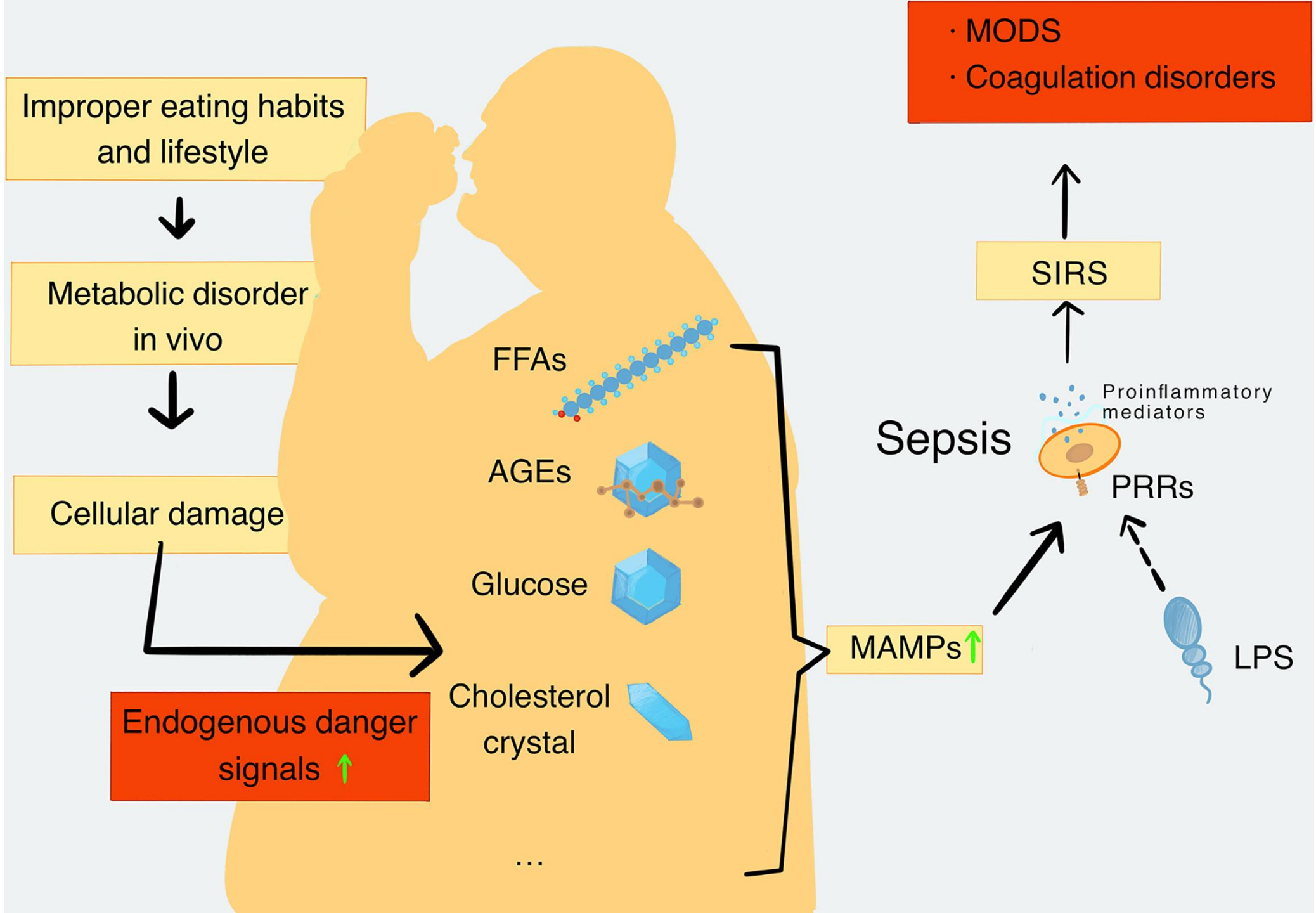
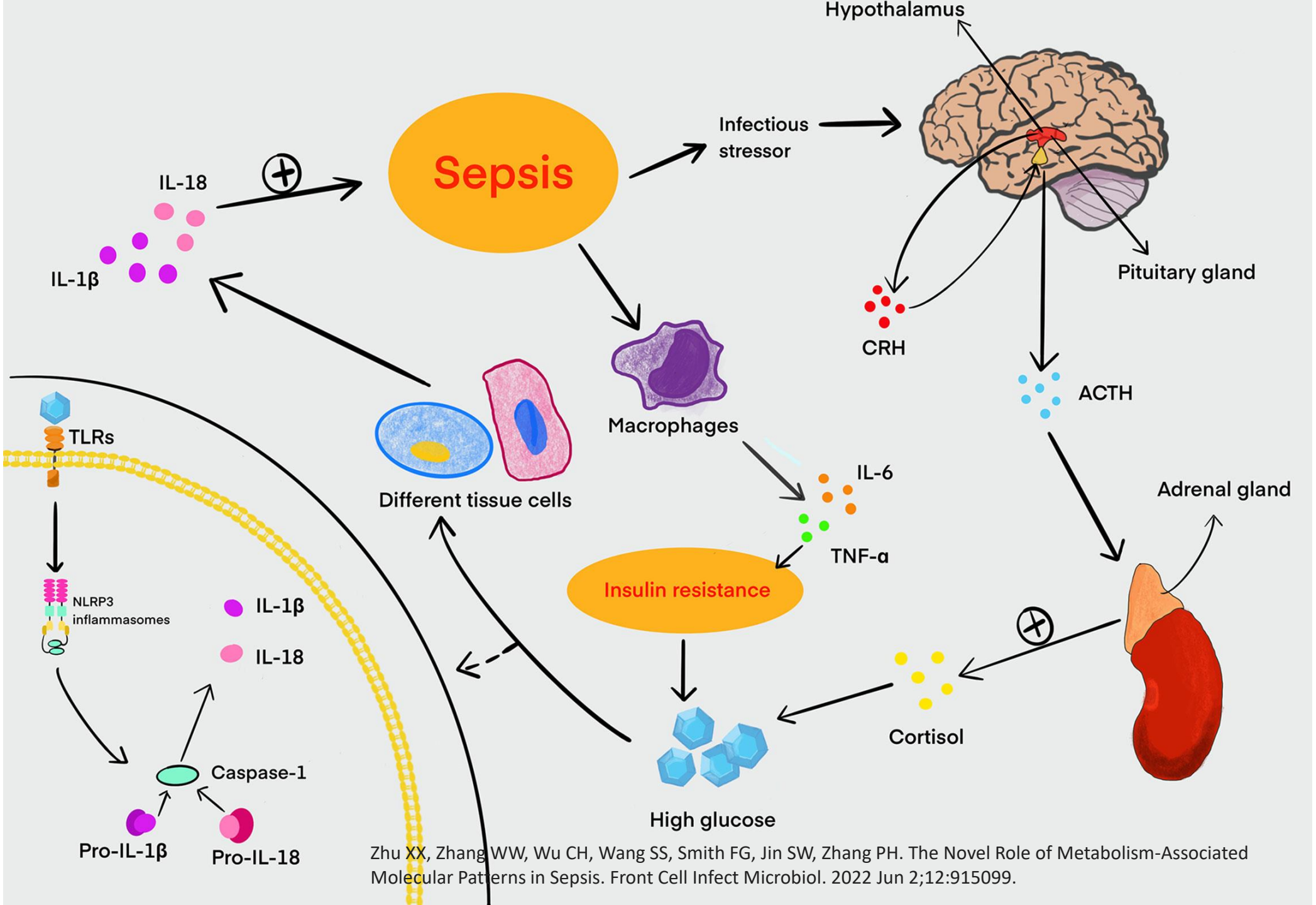

Improper eating habits and lifestyle
Metabolic disorder in vivo
Cellular damage
Endogenous danger signals ↑
FFAs
AGEs
Glucose
Cholesterol crystal
...
MAMPs ↑
· MODS
· Coagulation disorders
SIRS
Sepsis
Proinflammatory mediators
PRRs
LPS

To the previous figure: The production and types of MAMPs and their role in sepsis

- When the metabolic balance is broken, the metabolic disorders will lead to a decrease in repair ability of the body. Meanwhile, metabolic disorders can cause extensive cell damage in the body tissues. Cell damage leads to increased levels of endogenous danger signaling molecules (DAMPs), including FFAs, AGEs, glucose, cholesterol crystal, and mtDNA, which are closely related to metabolic disorders and are defined as MAMPs. MAMPs can be recognized by PRRs and activate proinflammatory signaling pathways to promote the release of proinflammatory mediators. In addition, pathogenic substances such as LPS can also be recognized by PRRs and further activate the proinflammatory signaling pathway to cause the formation and deterioration of sepsis. Sepsis further enhances catabolism and increases MAMPs' levels in turn. With the development of SIRS, the inflammatory process becomes uncontrollable, and the organ function and coagulation function become abnormal. Finally, these disorders cause the formation of MODS.
- MAMPs, metabolism-associated molecular patterns; FFAs, free fatty acids; AGEs, advanced glycation end products; mtDNA, mitochondrial DNA; PRRs, pattern recognition receptors; SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndromes.



Zhu XX, Zhang WW, Wu CH, Wang SS, Smith FG, Jin SW, Zhang PH. The Novel Role of Metabolism-Associated Molecular Patterns in Sepsis. Front Cell Infect Microbiol. 2022 Jun 2;12:915099.

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To the previous figure: Relationship between high glucose (HG) and sepsis

- Sepsis can stimulate the hypothalamus to increase the secretion and release of CRH. Meanwhile, CRH promotes the synthesis and release of ACTH from the pituitary gland, and ACTH in turn stimulates the adrenal cortex to secrete cortisol, which can lead to an increase in blood glucose. Sepsis can also stimulate macrophages to secrete large amounts of IL-6, TNF-α, and other proinflammatory mediators. These proinflammatory mediators can disrupt the signaling of the insulin transduction pathway, and it is a major cause of insulin resistance in the host. Insulin resistance can further exacerbate HG in turning. Glucose is recognized by TLRs in a variety of tissue cells and activates NLRP3 inflammasomes that can cleave pro-caspase-1 into activated caspase-1 to induce inflammation. Activated caspase-1 processes pro-IL-1β and pro-IL-18 to form mature IL-1β and IL-18, promoting the development of inflammation in sepsis.

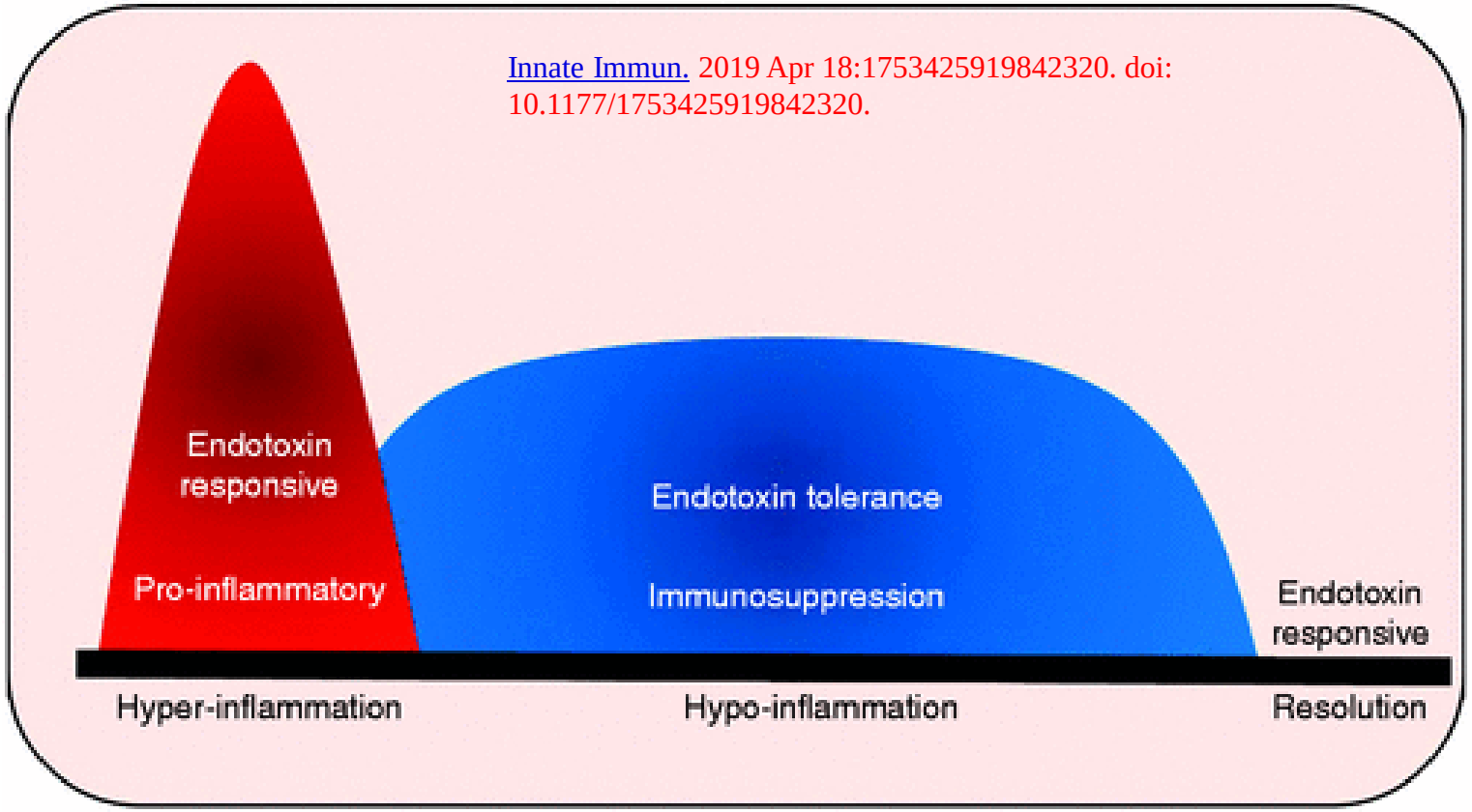
HG, high glucose; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; IL, interleukin; TNF, tumor necrosis factor; TLRs, Toll-like receptors.

Zhu XX, Zhang WW, Wu CH, Wang SS, Smith FG, Jin SW, Zhang PH. The Novel Role of Metabolism-Associated Molecular Patterns in Sepsis. Front Cell Infect Microbiol. 2022 Jun 2;12:915099.

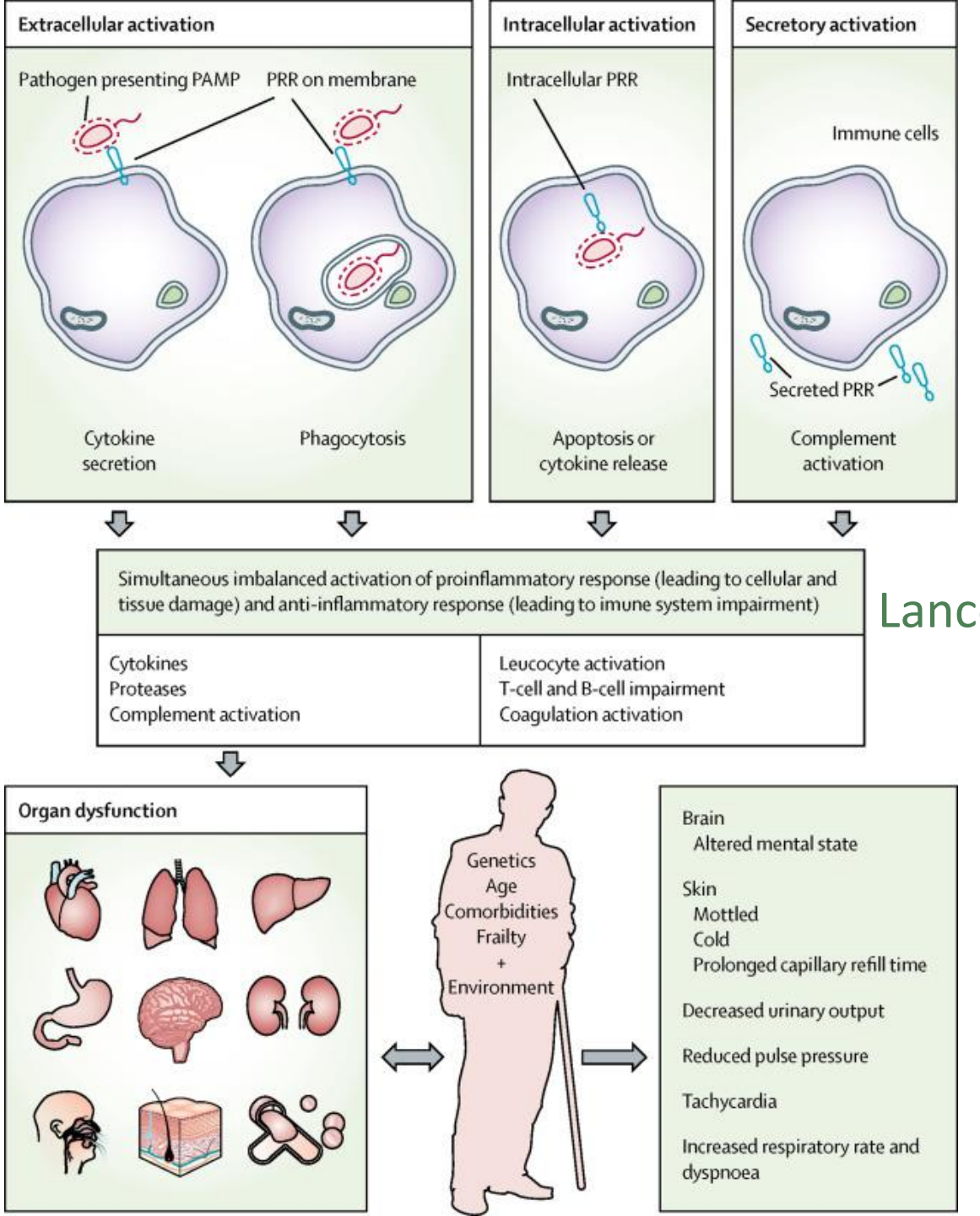
Sepsis

- Sepsis-3 defines sepsis as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
- The host "resists" invading pathogen by mounting a systemic inflammatory response in innate immune cells such as macrophages and monocytes that produce pro-inflammatory cytokines, chemokines, and coagulation cascade within minutes. Further fuel to the fire of pro-inflammatory response is added by the activated pro-coagulant factors such as thrombin, Factor X, tissue factor via PAR1 signaling.
- However, hyperinflammation cannot be sustained, as it also attacks the host tissue and organs indiscriminately. The hyperactive immune cells transition to a deactivation/tolerance state also known as a "hypoinflammatory" and immunosuppressive phenotype. This phase is characterized by increased anti-inflammatory cytokine expression and decreased pro-inflammatory mediators biomarked by endotoxin tolerance.

Innate Immun. 2019 Apr 18:1753425919842320.
doi: 10.1177/1753425919842320.



Immune response in sepsis: immune response in sepsis transitions from hyperinflammatory to a hypoinflammatory phase followed by resolution. Hyperinflammatory phase of immune cell activation is characterized by endotoxin responsive state with cytokine storm is cytotoxic to immune and other organ cells. Hypoinflammatory phase is characterized by endotoxin tolerance and immunosuppression. Hyper- and hypoinflammatory phases are associated with profound departure from homeostasis. Restoration of homeostasis is achieved during the resolution phase of sepsis.



Lancet. 2018 Jul 7;392(10141):75-87

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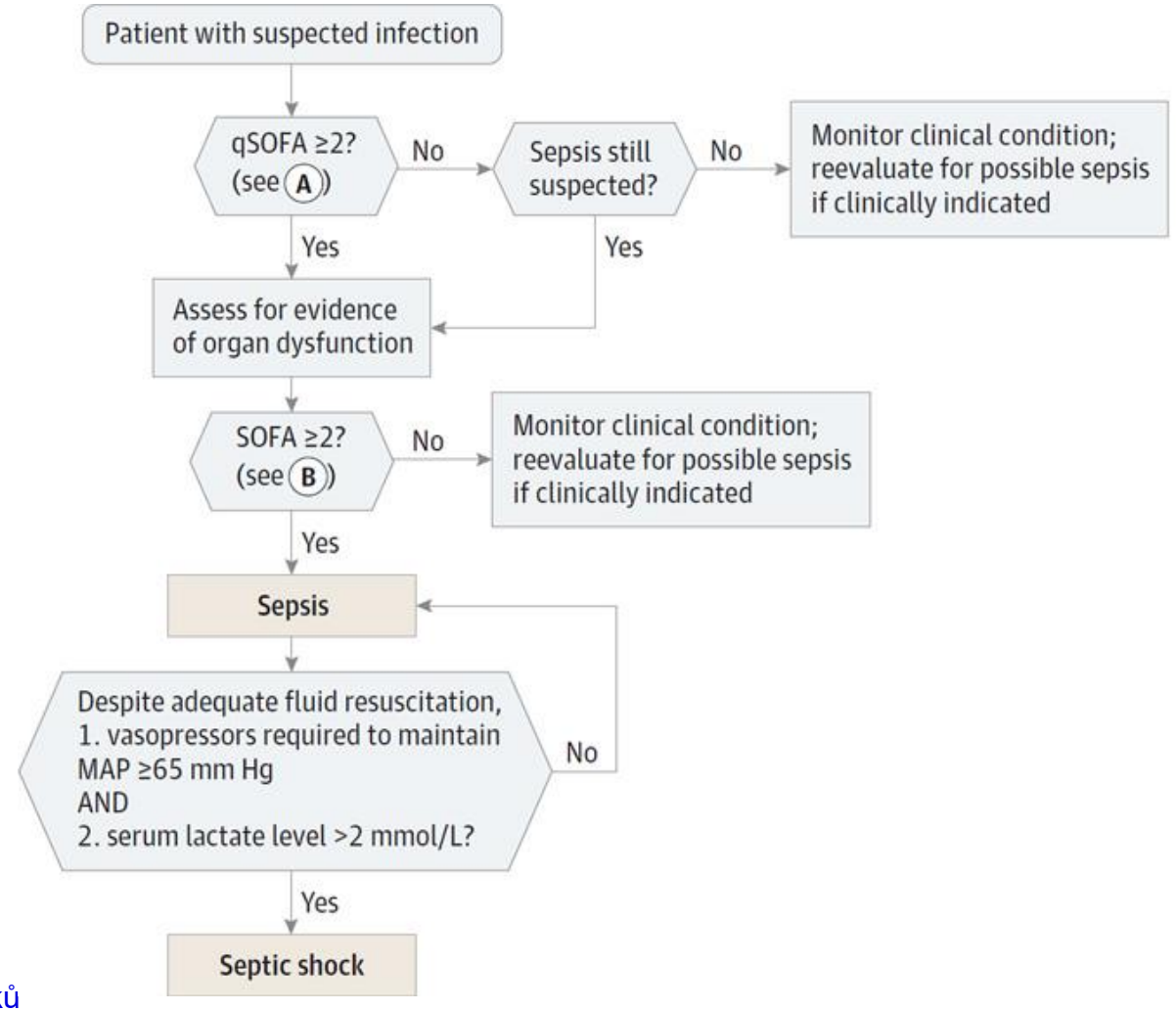
Organ dysfunction during sepsis

- In the intensive care unit (ICU), organ dysfunction is scored according to the sequential organ failure assessment (SOFA) score and Marshall Multiple Organ Dysfunction Score (MMODS), among others.
- They score for dysfunction in respiratory, cardiovascular, hepatic, hematologic, neurologic, and renal systems. As the score increases, so does the mortality. Both the SOFA score and MMODS are very sensitive but not specific for organ failure.

Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.



A qSOFA Variables
- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables
- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

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Septic shock - pathophysiology

- vasodilation
- increased permeability of blood vessels
- hypovolemia
- ventricular dysfunction – decreased cardiac output

Critical Care Clinics ; Volume 34, Issue 1, January 2018, Pages 43-61

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Sepsis and cardiac dysfunction

- Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock occurs when circulatory, metabolic and cellular abnormalities are profound and is defined by a requirement for vasopressor support and persistent hyperlactataemia in the absence of hypovolaemia. Septic shock is classically a form of distributive shock, in which cardiac output is elevated or normal, hypotension results from vasodilatation, and organ dysfunction is attributable, at least in part, to that hypotension, with a contribution from the maldistribution of blood flow with centralization of it.
- Historically, cardiac systolic performance was assumed to be normal in patients with sepsis because cardiac output was high. However, a series of landmark studies in the mid-1980s challenged this view. A radionucleotide angiographic study demonstrated a subgroup of patients with sepsis in whom left ventricular (LV) ejection fraction (EF) was decreased. The absence of myocardial lactate production, noted in blood sampled from the coronary sinus, excluded myocardial ischaemia as a cause of this LV dysfunction. Although LV systolic dysfunction should have resulted in a substantially decreased cardiac output, concurrent LV dilatation resulted in a preserved stroke volume, provided that fluid resuscitation was adequate. Paradoxically, patients with reversible decreases in EF had better outcomes than those without a decreased EF.

Nature Reviews Cardiology **volume 18**, pages424–434 (2021)

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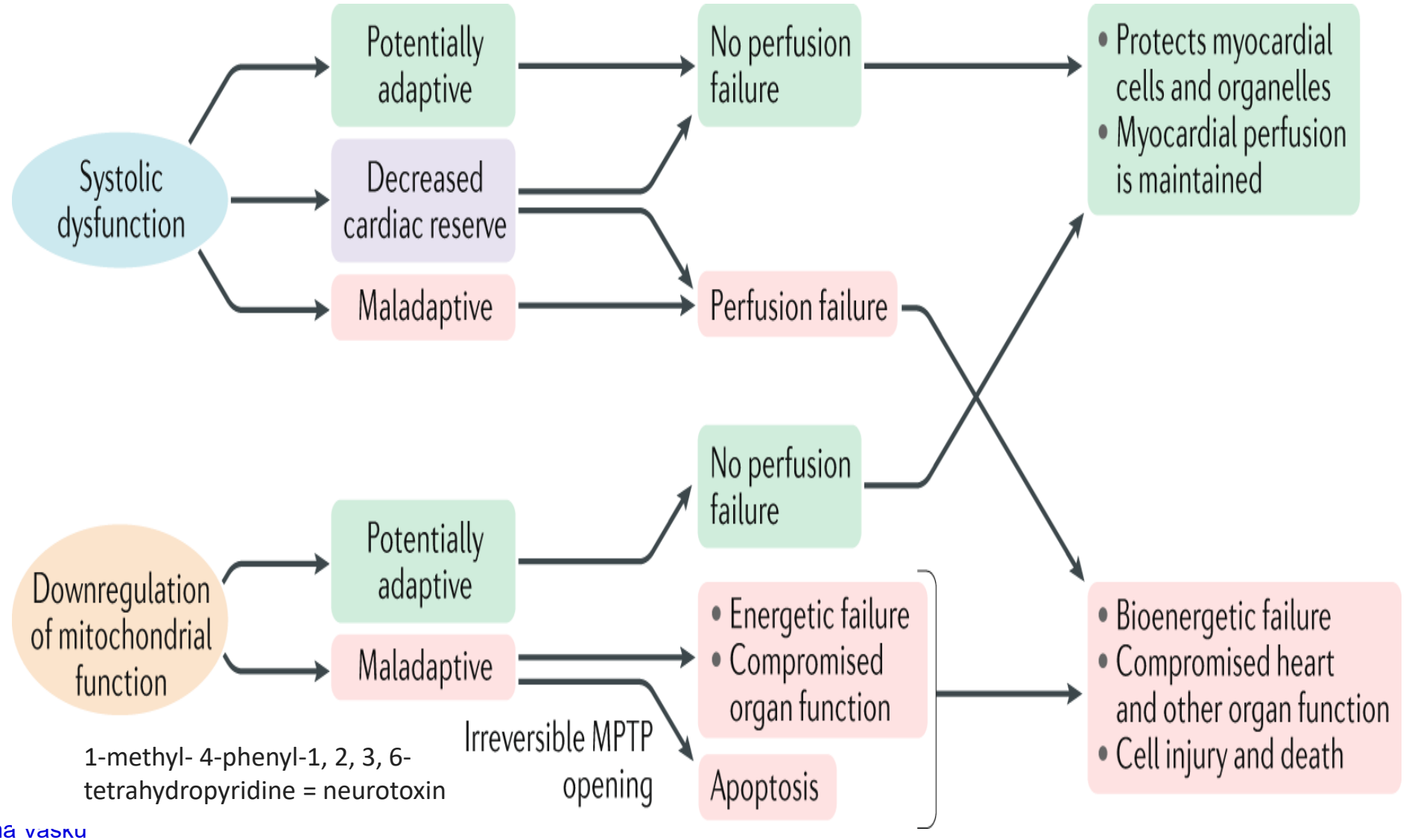
Potential pathophysiological implications of systolic dysfunction and downregulation of mitochondrial function in sepsis-induced cardiomyopathy.



1-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine = neurotoxin

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Pathophysiology of sepsis

- Immune activation in response to the offending organisms is initiated when microbial pathogen-associated molecular patterns are recognized by cellular pattern-recognition receptors
- Neutrophils, macrophages and T cells release pro-inflammatory cytokines and other mediators
- Counter-regulatory responses can lead to a subsequent hypo-inflammatory state
- The precise mechanisms of cell injury and sepsis-induced organ dysfunction are incompletely understood
- Vascular dysfunction is predominantly microvascular

Septic shock - pathophysiology

- Disequilibrium between necessities of tissues and possibilities of cardiovascular system
- Loss of reactivity of smooth muscle cells of vessels (ischemia?) leading to vasodilation
- SNS activation: catocholamines levels in blood are extremely high; they reflect severity of septic state
- RAS system activation
- Deficiency of vasopressin?

- Critical Care Clinics ; Volume 34, Issue 1, January 2018, Pages 43-61

Summary

- Sepsis is associated with alterations in immune effector cells including defects in antigen presentation, quantitative and qualitative alternation in neutrophils, defective NK cell-mediated immunity, defective T and B cell-mediated immunity, relative increases in regulatory T cells (Tregs), an increased expression of PD-1/PD-L1
- Programmed Cell Death Protein 1 (PD-1) plays a vital role in inhibiting immune responses and promoting self-tolerance through modulating the activity of T-cells, activating apoptosis of antigen-specific T cells and inhibiting apoptosis of regulatory T cells.
- Programmed Cell Death Ligand 1 (PD-L1) is a trans-membrane protein that is considered to be a co-inhibitory factor of the immune responses, decreased immunoglobulin levels, hypercytokinemia, and complement consumption.

Front Immunol. 2018; 9: 595.

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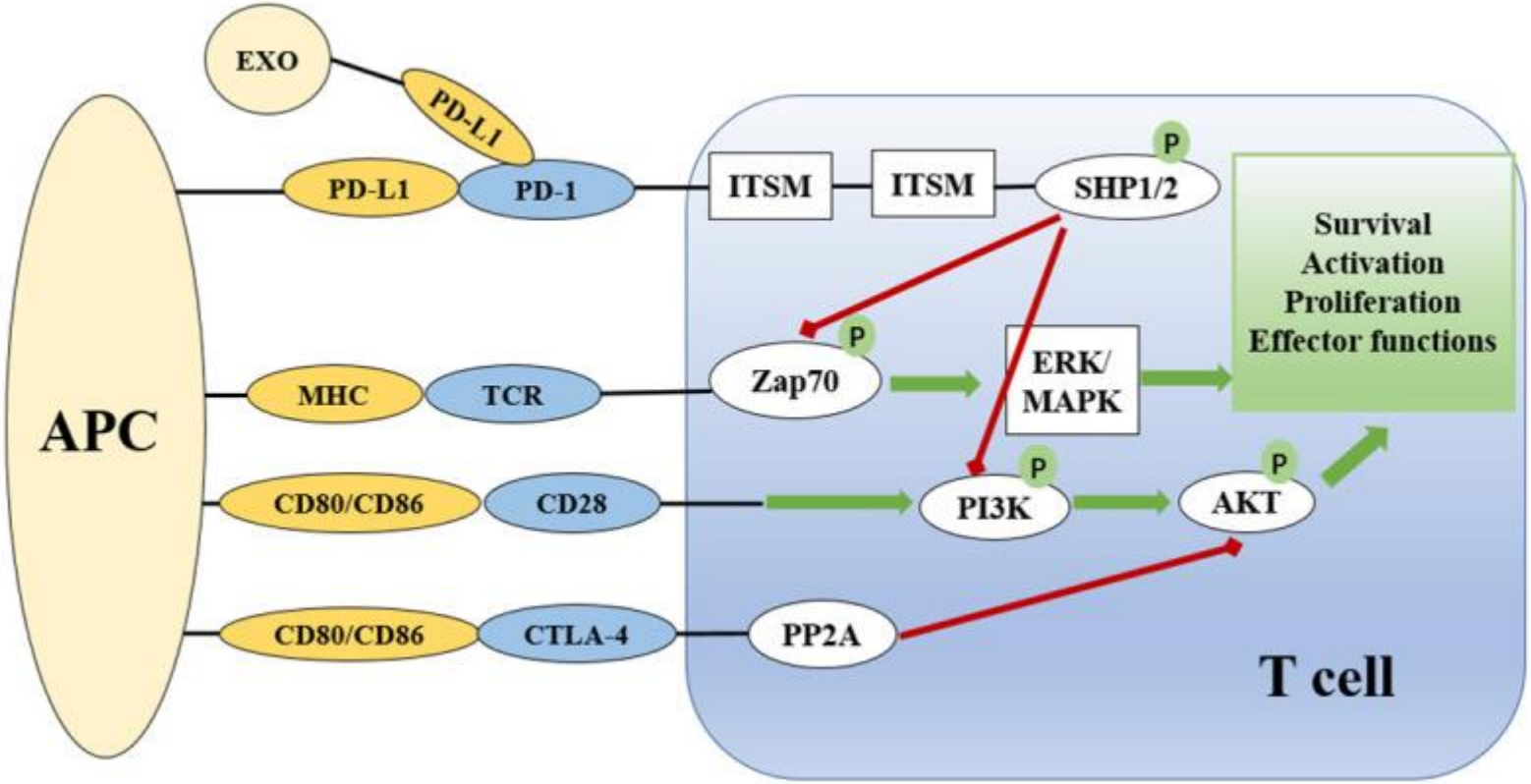

APC, antigen presenting cell; TCR, T cell receptor; MHC, major histocompatibility complex; PD-1, programmed death-1; CTLA4, cytotoxic T lymphocyte antigen-4; ZAP70, zeta chain of T cell receptor associated protein kinase 70; PI3K, phosphoinositide 3 kinase; PP2A, protein phosphatase 2A; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; AKT, protein kinase B; ITIM, immunoreceptor tyrosine-based inhibition motif; ITSM, immunoreceptor tyrosine-based motif; SHP, Src homology region 2 domain-containing phosphatase

Overview of the PD-1 and PD-L1 checkpoints and signaling pathways associated with them.

The presentation of antigen by MHC on APCs to the TCR complex on T cells activates T cells *via* the Zap70 and ERK/MAPK signaling pathways. CD28 on T cells binds to CD80/86 on APCs to provide co-stimulatory signals. PD-1/PD-L and CTLA-4 signaling suppress the AKT signaling pathway to limit T cell activation. CTLA-4 suppresses the AKT pathway directly by recruiting PP2A, while PD-1 signaling includes SHP-mediated regulation of Zap20 and the PI3K/AKT signaling pathway. Green lines indicate stimulatory messages, while red lines represent inhibitory ones. ITSM and ITIM are intracellular domains of immunological checkpoints that are responsible for intracellular signaling..

Zhang T, Yu-Jing L, Ma T. Role of regulation of PD-1 and PD-L1 expression in sepsis. Front Immunol. 2023 Mar 9;14:1029438.

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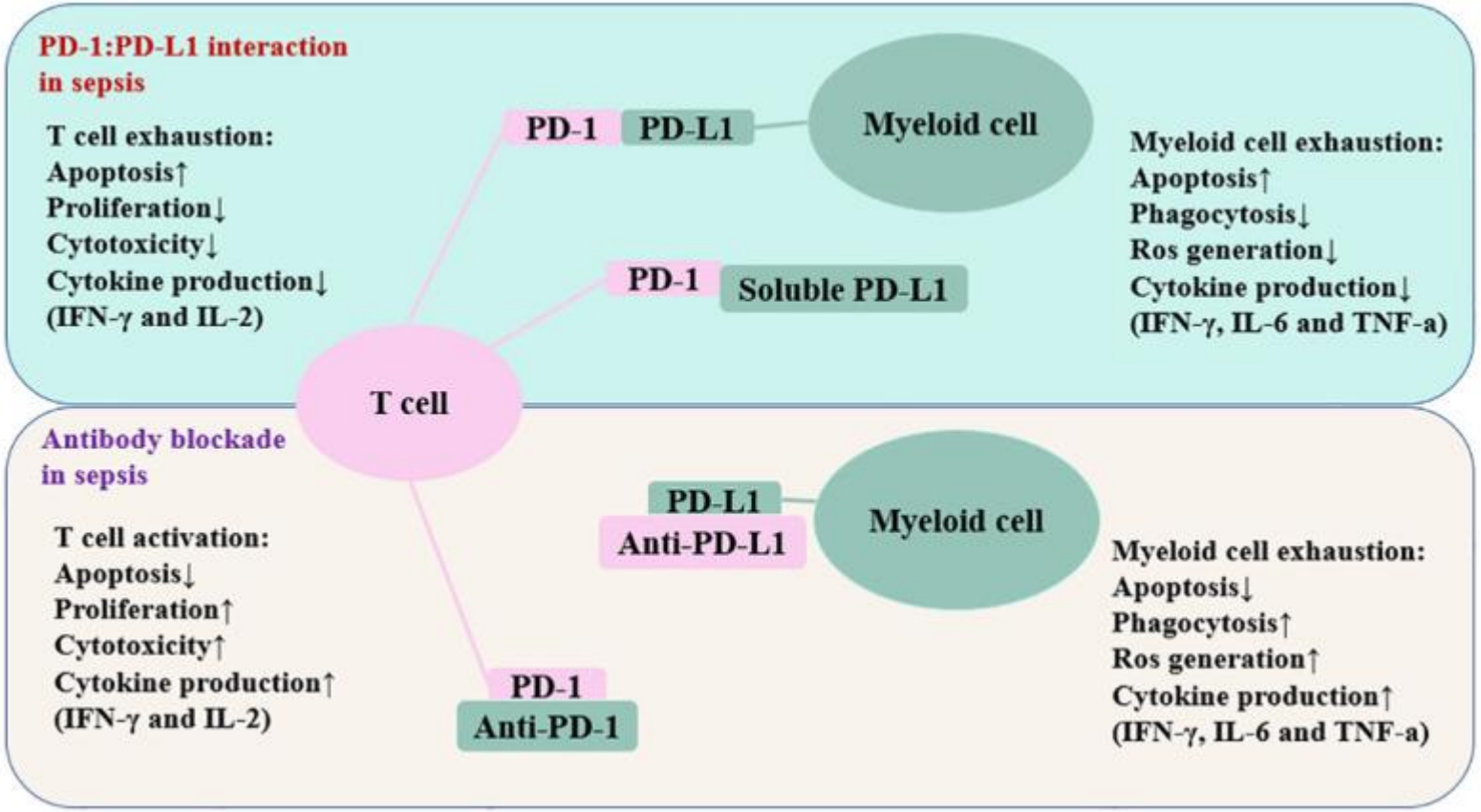
Biomarkers of sepsis

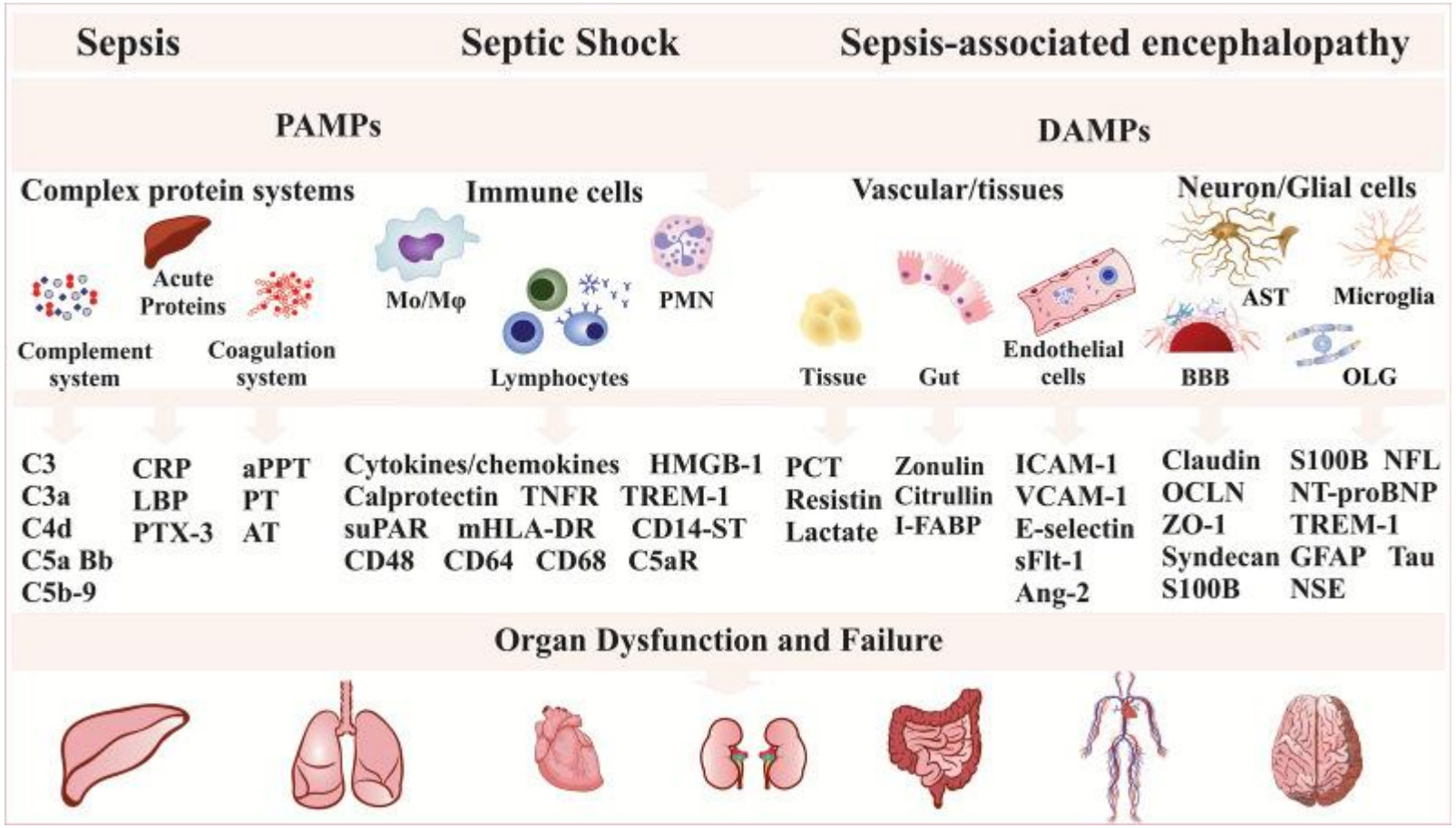
- Procalcitonin (PCT) is a prohormone of calcitonin and in healthy individuals PCT is produced in thyroid C cells, from a calcitonin gene-related peptide I (CALC-1) located on chromosome 11. The mRNA product is known as preprocalcitonin. It is further modified to 116-amino acid procalcitonin, and all the PCT formed in thyroid C cells is converted to calcitonin, so no PCT is released into the circulation and its level in healthy subjects is very low (0.05 ng mL-1). During systemic infection PCT is produced mainly by two alternative mechanisms: the direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolites from microbes and the indirect pathway induced by various inflammatory mediators such as IL-6, tumor necrosis factor-α (TNF-α), etc. The increase of PCT was observed in 3–4 hours after intravenous injection of endotoxin and was maintained for 24 hours in healthy volunteers. The measurement of PCT helps to guide and shorten the antibiotic therapy in septic patients, but recent studies showed that use of PCT did not affect the frequency of diagnostic or therapeutic procedures. Additionally, the cut-off range of PCT concentration for sepsis confirmation depends on clinical settings, source of infection and co-morbidities.
  C-reactive protein level may be increased during both infectious or non-infectious processes and in contrast to PCT, the hepatic synthesis of CRP starts 6 to 8 hours after onset and peak concentrations are reached between 36 to 50 hours after infection has started. The half-life of CRP is 19 hours and it is cleared by the liver.
  Interleukin-6 belongs to the group of pro-inflammatory cytokines. Similarly to TNF-α and IL-1 it is an endogenous pyrogen but in contrast to them it has a longer half-life. The synthesis of IL-6 is regulated by various factors, including endotoxin, which stimulates its formation in monocytes and fibroblasts as well as glucocorticoids which inhibit its formation. The highest level is achieved most often in 2-3 hours after stimulation with endotoxin. IL-6 is considered as useful in septic patients but increase of its level is not specifically linked to infectious conditions.



Schematic depiction of the PD-1/PD-L1 related immune cell dysfunction.
The interaction between PD-1 and PD-L1 impairs T cell function and myeloid cell function.
Antibodies against these inhibitory molecules restore the immune system's function and boost resistance to infection in patients suffering from sepsis. The up arrow represents an increase, whereas the down arrow denotes a decrease.
PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; IFN-γ, interferon-gamma; IL-2, interleukin-2; IL-6, inerleukin-6.

Also non-immune cells, such as the lung, liver, kidney, colon, small intestine, and tissue endothelial cells express PD-L1. Therefore, PD-1/PD-L1 signaling has been associated with organ damage induced by sepsis.

Zhang T, Yu-Jing L, Ma T. Role of regulation of PD-1 and PD-L1 expression in sepsis. Front Immunol. 2023 Mar 9;14:1029438.



Sepsis, septic shock, and sepsis-associated encephalopathy biomarkers.
The infection triggers a cascade of signaling pathways that activate several transcription factors and promote proinflammatory mediators such as acute-phase proteins, cytokines, chemokines, and antimicrobial peptides necessary to eliminate the invading pathogens. The unbalanced host immune response triggers vascular endothelial damage, increasing gut and BBB permeability, culminating in organ dysfunction.

Zhang T, Yu-Jing L, Ma T. Role of regulation of PD-1 and PD-L1 expression in sepsis. Front Immunol. 2023 Mar 9;14:1029438

Ang-2 (angiopoietin-2), APP (acute phase proteins), aPPT (activated partial thromboplastin), AST (astrocytes), AT (antithrombin), BBB (blood–brain barrier), C5aR (complement component 5a receptor), CD (cluster of differentiation), CD14-ST (soluble subtype of CD14), CRP (C reactive protein), DAMPs (damage-associated molecular patterns), GFAP (glial fibrillary acidic protein), HMGB-1 (high mobility group box 1), ICAM-1 (intercellular adhesion molecule 1), I-FABP (intestinal fatty acid binding protein), LBP (lipopolysaccharide binding protein), mHLA-DR (monocytic human leukocyte antigen DR), Mo (macrophage), NFL (neurofilament light), NSE (neuron specific enolase), NT-proBNP (N-terminal pro-brain natriuretic peptide), OCLN (occludin), OLG (oligodendrocyte), PAMPs (pathogen-associated molecular patterns), PCT (procalcitonin), PMNL (polymorphonuclear leukocytes), PT (prothrombin), PTX-3 (pentraxin-3), S100B (calcium-binding protein B), sFlt-1 (soluble fms-like tyrosine kinase 1), suPAR (soluble form of the urokinase plasminogen activator receptor), TNFR (tumor necrosis factor receptor type), TREM-1 (triggering receptor expressed on myeloid cells 1), VCAM-1 (vascular cell adhesion molecule 1), ZO-1 (zonula-occluden 1)

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Key points

- Procalcitonin is a biomarker generally elevated in bacterial infections but not viral.
- Procalcitonin guidance may aid physicians in modestly reducing antibiotic use in critically ill patients.
- However, impact in settings with low baseline antibiotic use may be muted, and effect on antibiotic resistance is unclear.
- As with all tests, procalcitonin will require extensive observational and interventional studies to best determine its role.

Thank you for your attention

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