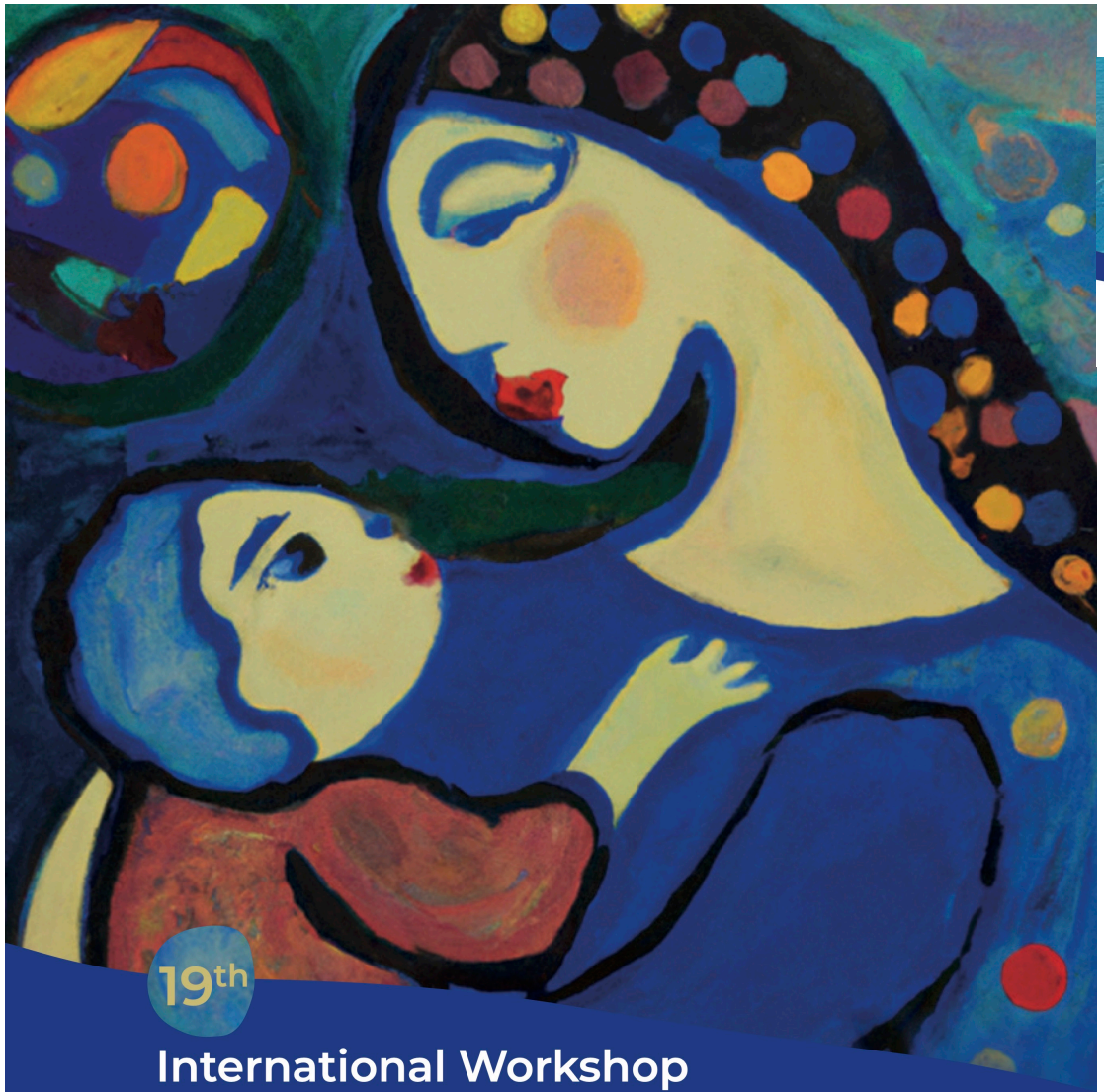


19th

International Workshop on Neonatology and Pediatrics

President: Vassilios Fanos

FROM WOMB TO AGING, FROM MEDICAL HISTORY TO ARTIFICIAL INTELLIGENCE

18th-21th October 2023 | T Hotel, Cagliari

GIOVEDÌ 19 OTTOBRE

CONGRESSO
SESSIONI IN ITALIANO
Sala principale

IV SESSIONE: IMMUNITÀ, INFEZIONI, MICROBIOTA, PROBIOTICI

Presidente: Giovanni Corsello (Palermo)
Moderatori: Francesca Birocchi (Cagliari), Danila Manus (Cagliari)
Discussant: Valentina Masile (Cagliari)

17.10	**Key Note Lettura** Nutrizione e immunità nel neonato *Fabio Mosca (Milano)*
17.30	Biomarkers delle infezioni neonatali *Michele Mussap (Bologna e Cagliari)*
17.50	Infiammazione in epoca perinatale *Cristina Loddo (Cagliari)*
18.10	Antibiotici e danno al microbiota *Nicola La Forgia (Bari)*
18.30	Probiotici in Terapia Intensiva Neonatale: sogno o realtà? *Andrea Dotta (Roma)*
18.40	Compilazione test ECM
	Discussione
19.00	Chiusura del Congresso

Michele Mussap, MD
Laboratory Medicine, Dpt. Surgical Science, School of Medicine
University of Cagliari
Laboratorio Metabolomica e Microbiomica Valsambro, Bologna

VALSAMBRO LABORATORIO ANALISI
INNOVATION RESEARCH

NEONATAL SEPSIS

Neonatal sepsis is a devastating, and expensive disease with life-long impact plagued by a lack of accurate diagnostic and prognostic testing

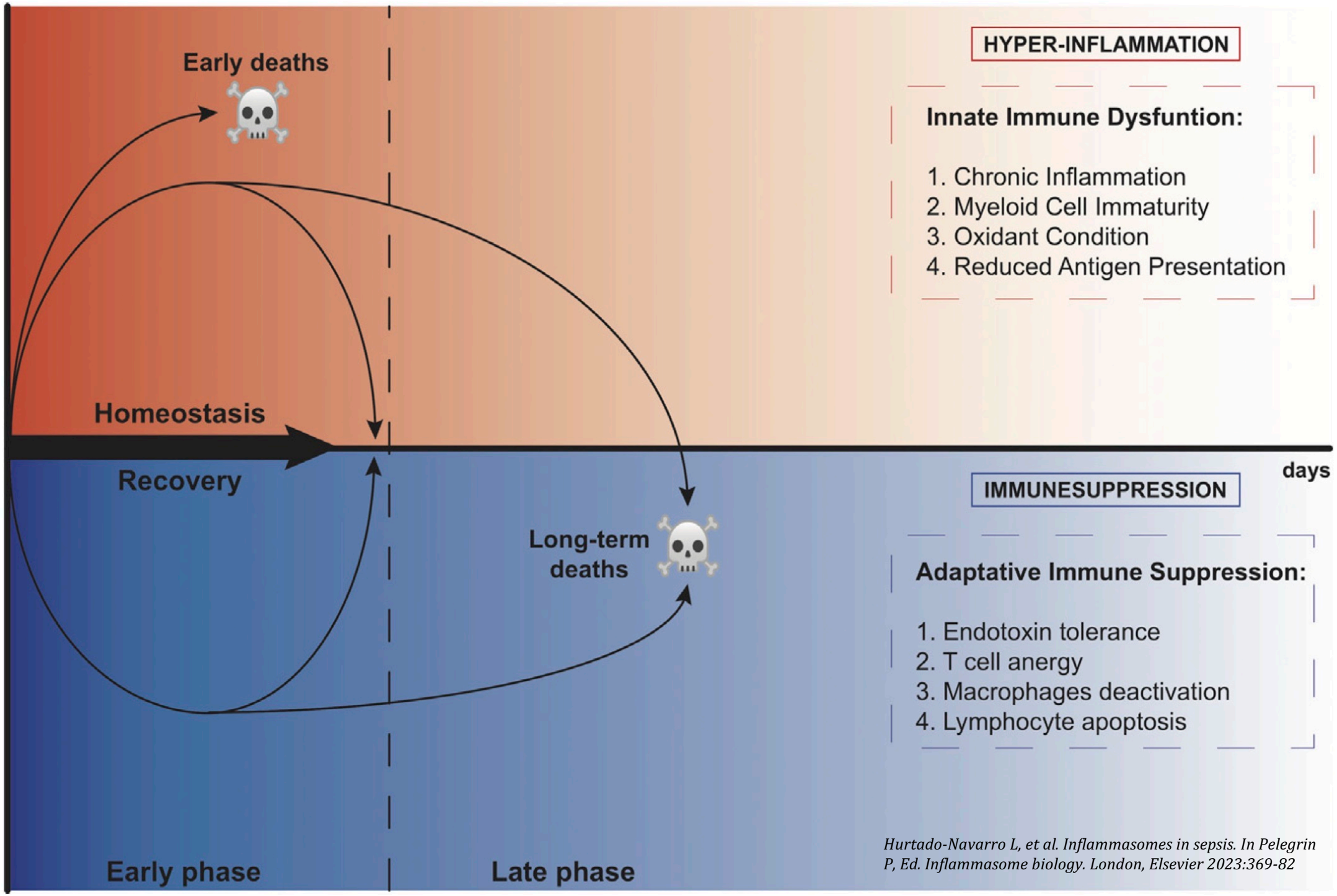
Management options and outcomes have not changed for the last 30 years

- The pathogenesis of the sepsis syndrome is critically dependent on activation of the **innate immune response**
- Innate immunity plays a direct role in the development of sepsis and is also crucial for the activation and modulation of later antigen-specific adaptive immune responses
- Nearly all of the clinical manifestations of sepsis can be attributed to components of the innate immune response

HOST IMMUNE RESPONSE IN SEPSIS

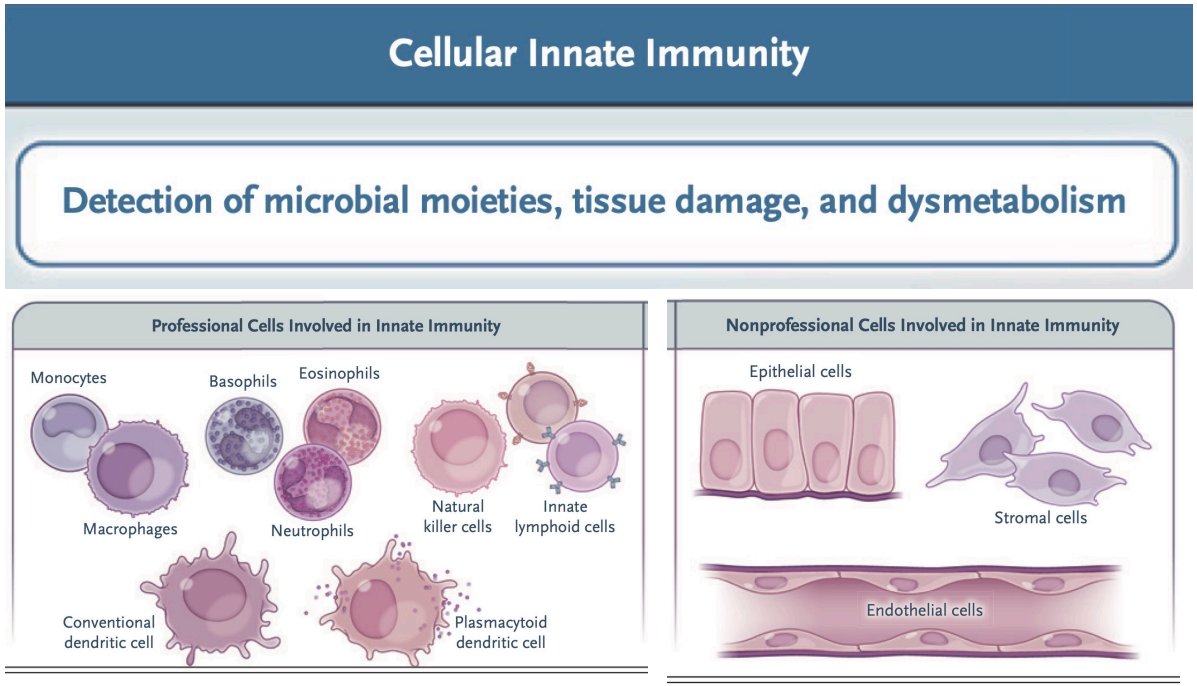
- Hyperinflammatory and immunosuppressive responses can occur concurrently at early times of sepsis
- The **early inflammatory response** and cytokine storm has been associated with the development of multiple-organ dysfunction and early death
- The **antiinflammatory response** is associated with nosocomial and/or reactivation of latent viral infections and delayed mortality
- Persistent dysfunctional innate immune response and suppressed adaptative immunity:
  - derives from long hospital stays or readmission that in turn lead to further health deterioration and deaths in the long term
  - could contribute to sepsis-associated immunopathology (organ injury, infectious complications, cardiovascular events) which varies among septic patients

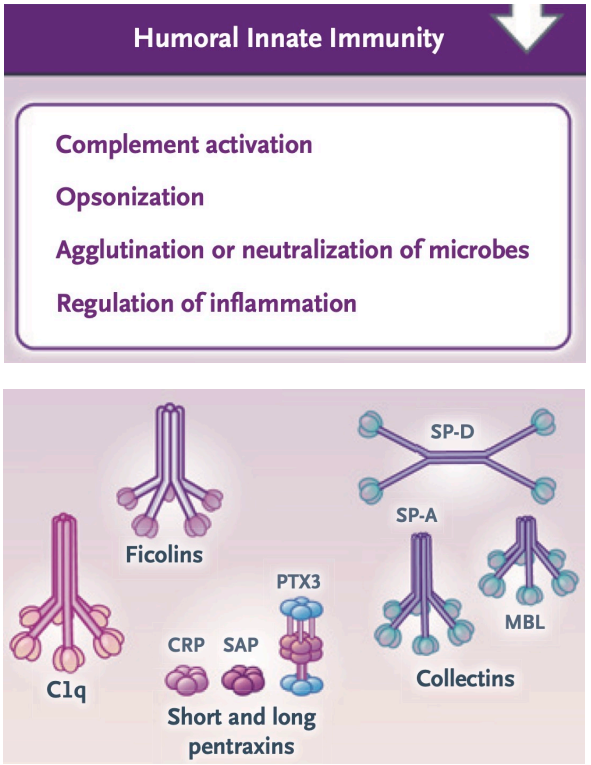
Hurtado-Navarro L, et al. Inflammasomes in sepsis. In Pelegrin P, Ed. Inflammasome biology. London, Elsevier 2023:369-82



Hurtado-Navarro L, et al. Inflammasomes in sepsis. In Pelegrin P, Ed. Inflammasome biology. London, Elsevier 2023:369-82

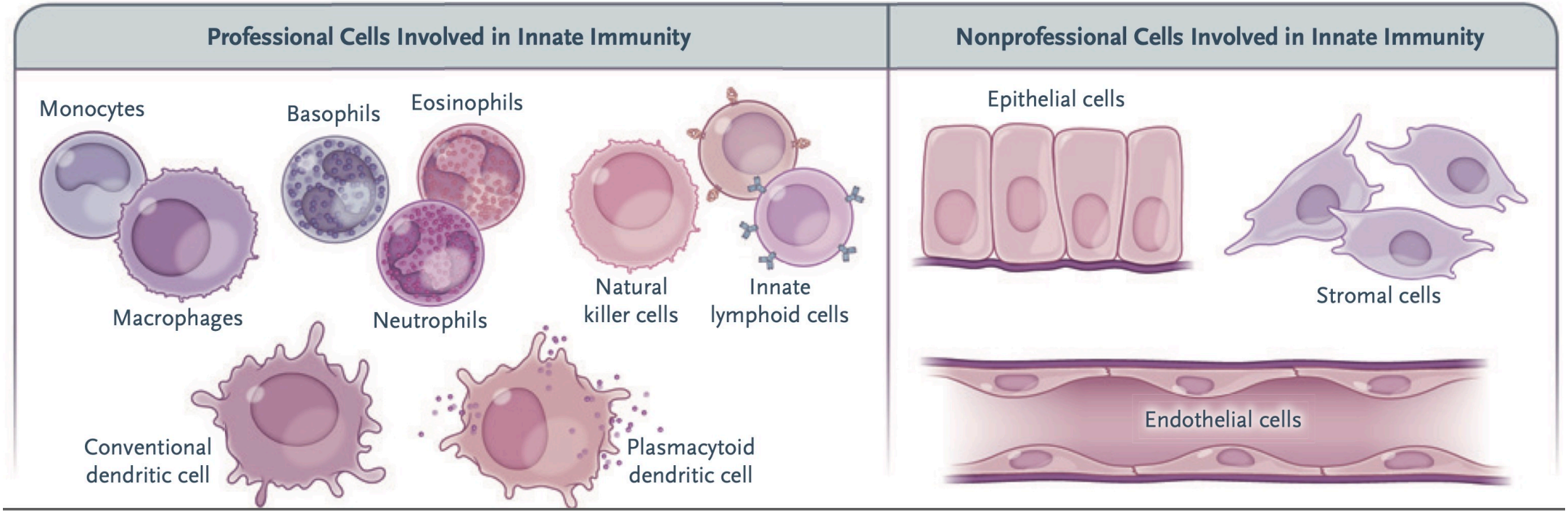
THE CONTEXT: CELLULAR AND HUMORAL INNATE IMMUNITY





Innate immunity is a first line of resistance against microbial pathogens and is involved in the activation of adaptive immune responses, as well as in tissue repair. Innate immunity is made up of a cellular arm and a humoral arm. The molecular strategies used by the cellular arm to sense microbial moieties and tissue damage

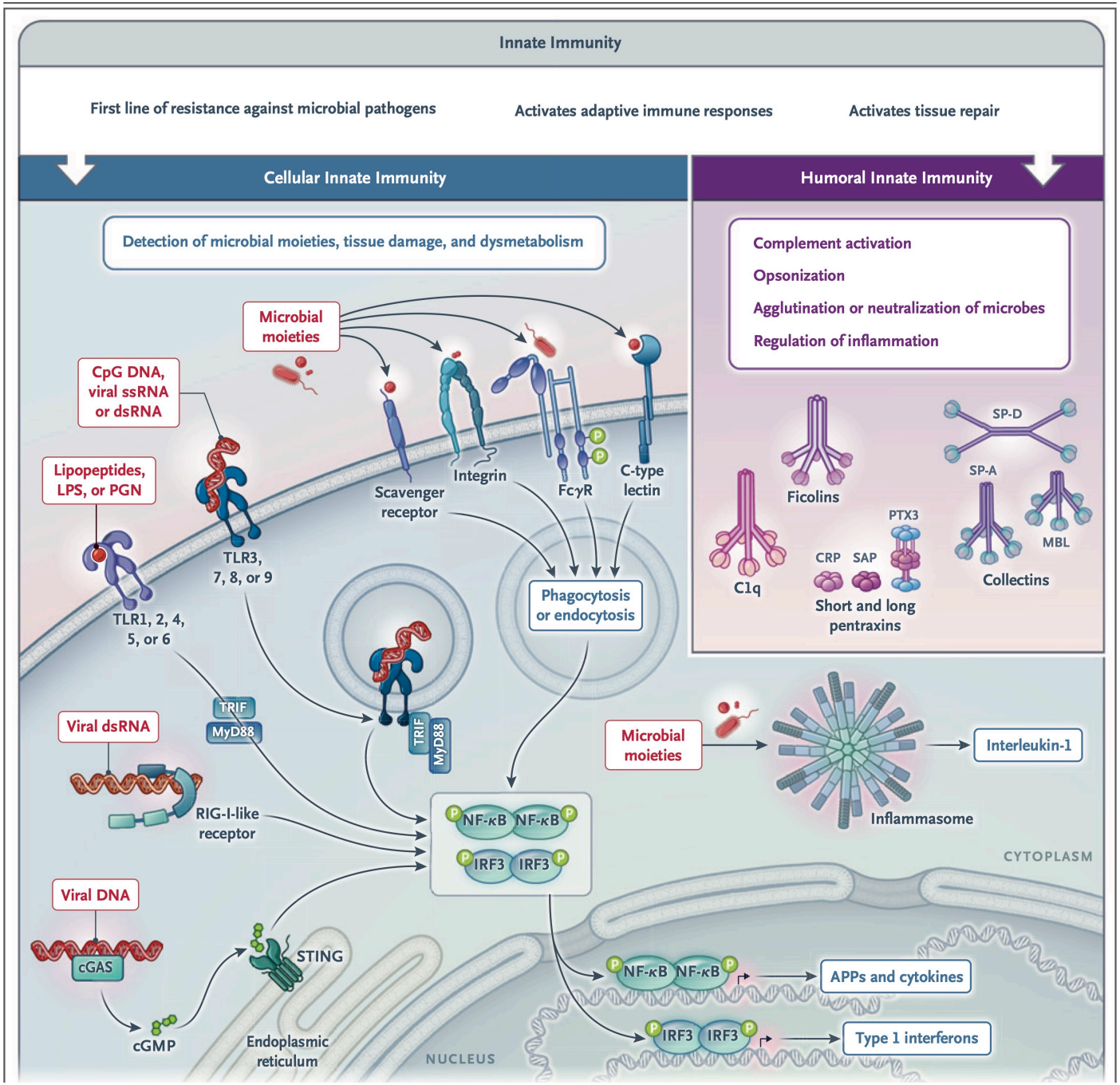
N Engl J Med 2023;388:439-52.



Cellular sensors of tissue damage, infection, and dysmetabolism are strategically localized on the cell surface, in the endosomal compartment, and in the cytoplasm, in both

- ***professional innate immune cells*** (i.e., those with innate immunity as their principal function)
- ***nonprofessional innate immune cells*** (i.e., those with other principal functions), such as hepatocytes, a major source of acute-phase proteins.

N Engl J Med 2023;388:439-52.



NOD: nucleotide-binding oligomerization domain; RIG-I: retinoid acid-inducible gene I; STING: stimulator of interferon genes

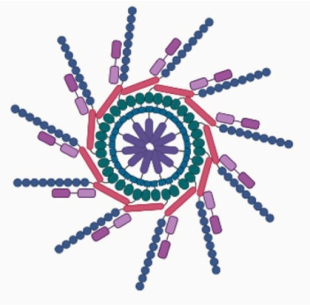
Innate immunity involves cell-associated pattern-recognition molecules located in plasma membrane, endosomes, and cytoplasm, belonging to different molecular families:

- TLRs
- NOD–like receptors
- RIG-I–like receptors
- Inflammasomes
- STING
- C-type lectins
- Scavenger receptors

Their activation leads to the expression of:

- ➢ cytokines (including interferons and chemokines)
- ➢ adhesion molecules
- ➢ antimicrobial effectors
- ➢ phagocytosis

N Engl J Med 2023;388:439-52.



INFLAMMASOMES

- Inflammasomes are a group of protein complexes (supramolecular structures) in the cytoplasm of activated immune cells, built around several proteins, including NLRP3, NLRC4, AIM2 and NLRP6
- Inflammasomes recognize a diverse set of inflammation-inducing stimuli that include PAMPs and DAMPs and that control the production of important pro-inflammatory cytokines (IL-1β, IL-18)
- Inflammasomes regulate other important aspects of inflammation and tissue repair such as pyroptosis, a form of cell death that combines characteristics of apoptosis (DNA fragmentation) and necrosis (inflammation and cytokine release)
- The most widely studied inflammasome is the NLRP3 inflammasome, shown to be involved in antibacterial, viral, fungal and parasitic immune responses

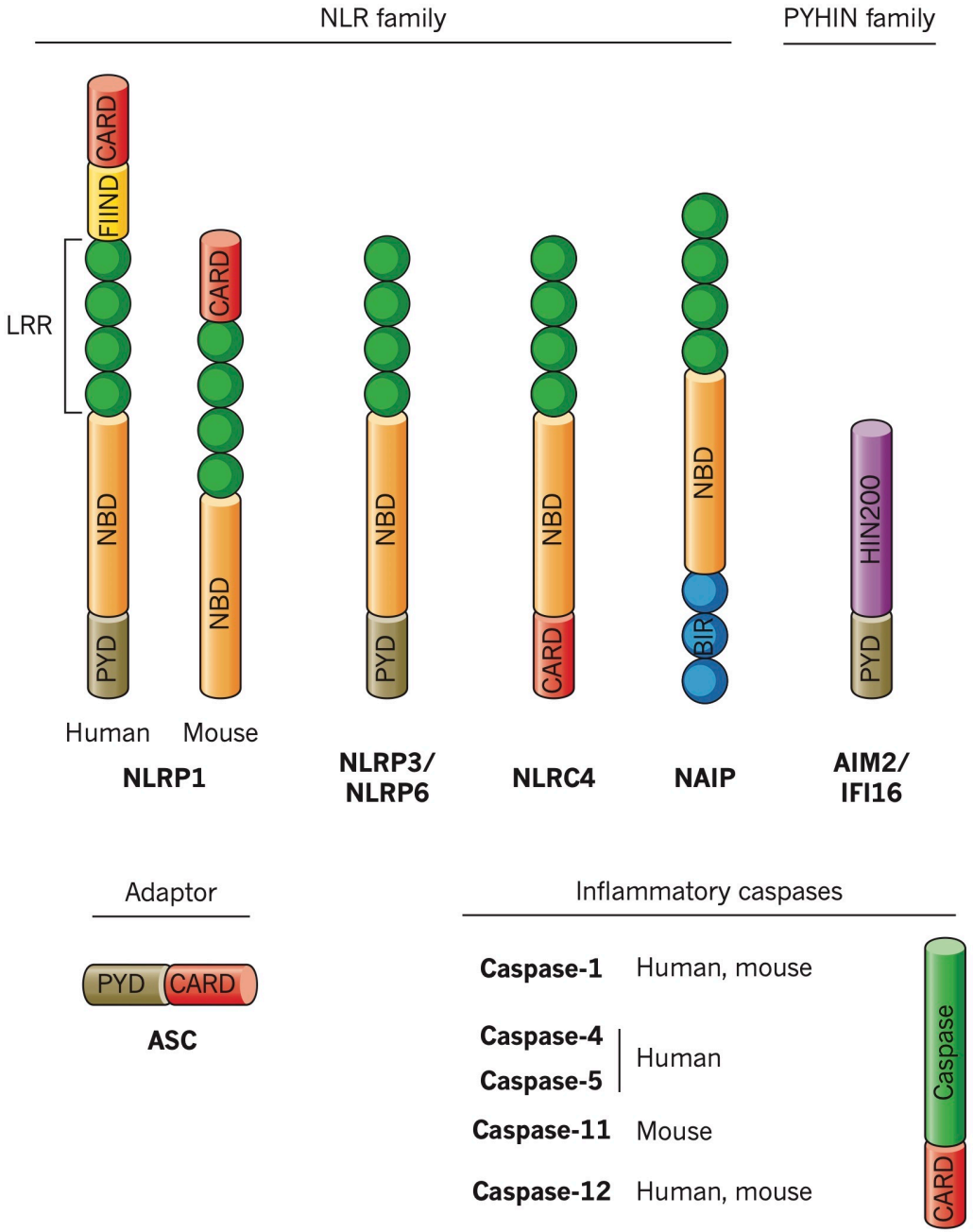
NOD LIKE RECEPTOR PROTEIN 3 INFLAMMASOME

The Nod Like Receptor Protein 3 (NLRP3) inflammasome consists of:

- a sensor (NLRP3)
- an adaptor (ASC - apoptosis-associated speck-like protein containing a CARD - Caspase Activation and Recruitment Domain; also known as PYCARD)
- an effector (caspase 1)

The sensor NLRP3 is a tripartite protein that contains an amino-terminal pyrin domain (PYD), a central nucleotide binding domain domain (NBD) and a carboxy-terminal leucine-rich repeat domain (LRR)

DOMAIN ORGANIZATION OF INFLAMMASOME PROTEINS



The identified **core components** belong to 2 families, the NOD-like receptor **(NLR)** family, and **PYHIN** family [pyrin and HIN200 domain-containing protein (HIN200 = hemato-poietic interferon-inducible nuclear antigens with 200 amino acid repeats)

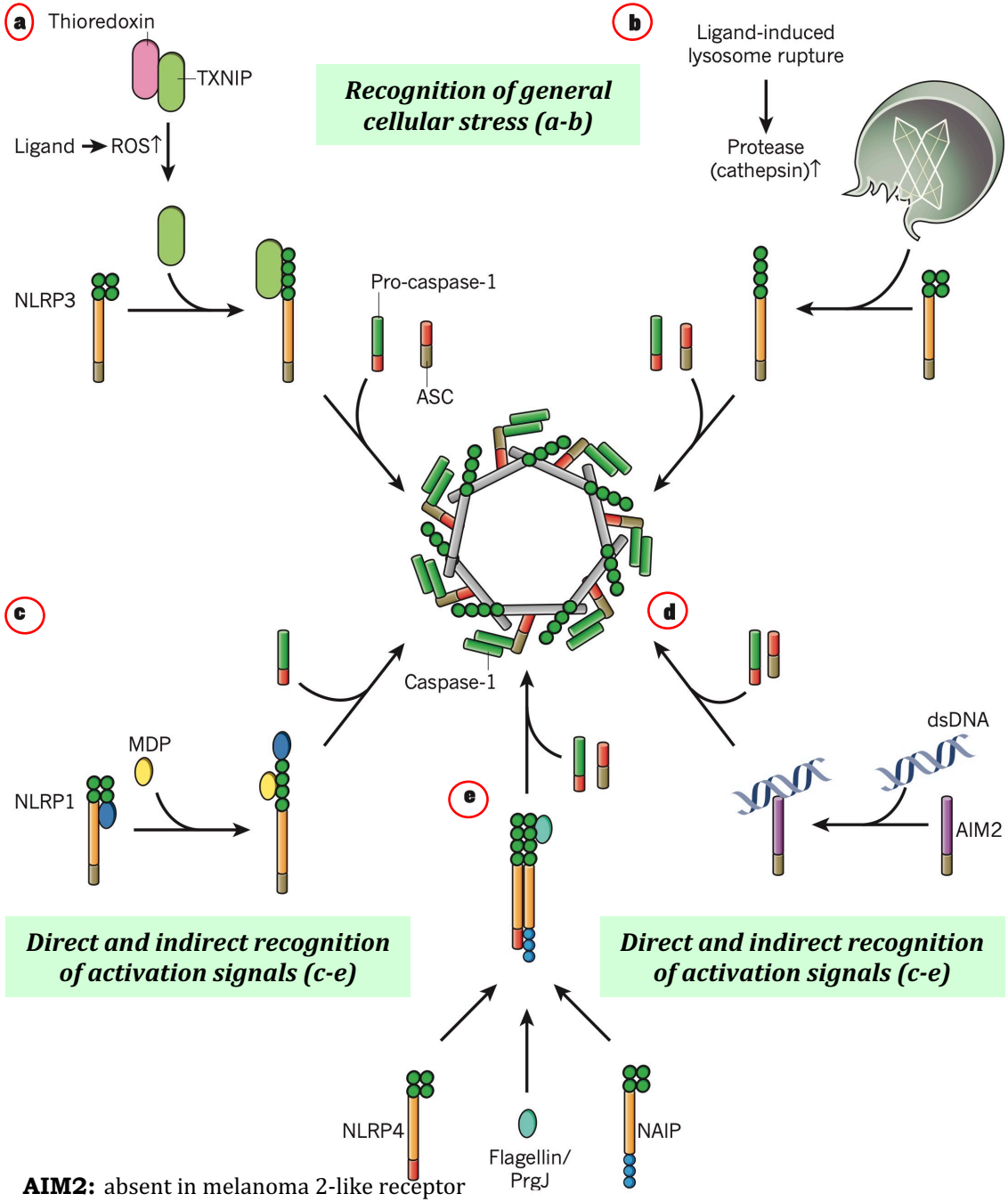
The NLR family members include:

- NLRP1
- NLRP2
- NLRP3
- NLRP6
- NLRC4
- NLRP12

They all contain a nucleotide-binding domain (NBD), carboxy-terminal leucine-rich repeat (LRR), and can contain either a PYD or a caspase activation and recruitment domain (CARD) or both

Strowig T, et al. Nature 2012;481:278-86

MODELS FOR INFLAMMASOME ACTIVATION



AIM2: absent in melanoma 2-like receptor

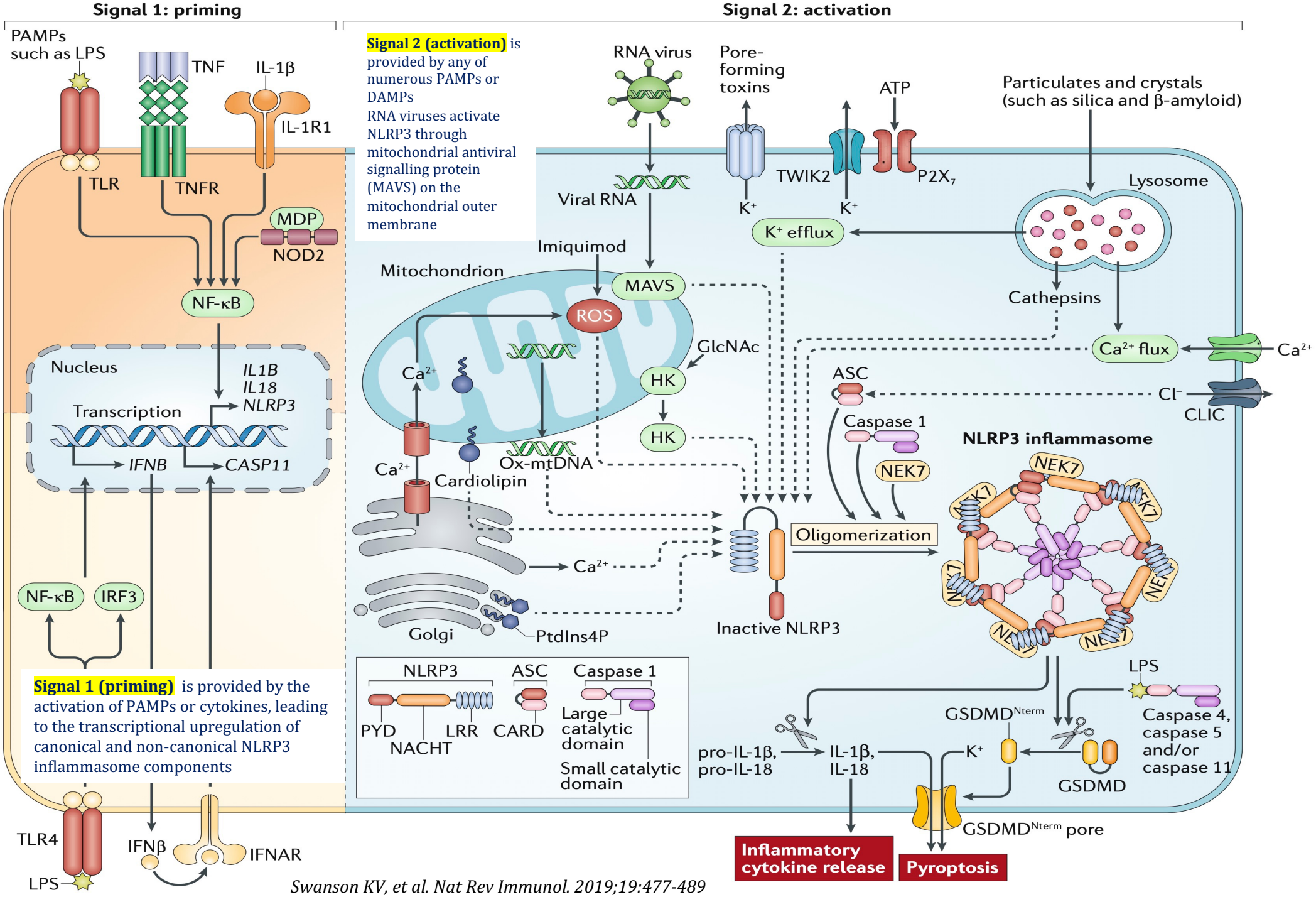
(a) NLRP3 senses the ROS, which is produced in mitochondria directly or indirectly by activators of the NLRP3 inflammasome

(b) NLPR3 is activated after lysosome destabilization, due to the phagocytosis of specific crystalline and particulate structures → release of proteases → proteolytic inactivation of a negative regulator or proteolytic activation of a positive regulator of NLRP3 → **inflammasome assembly**

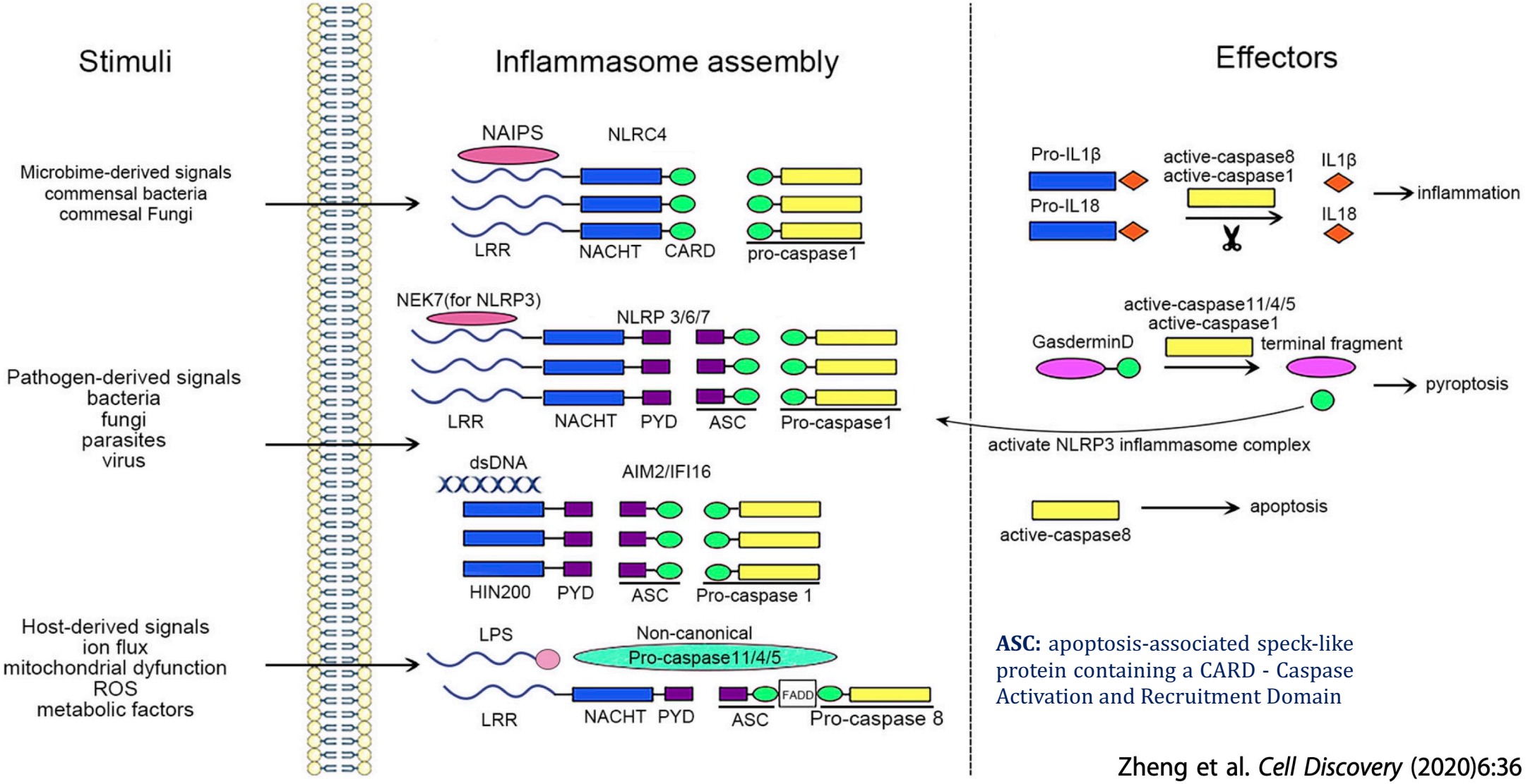
(c,d) NLRP1 and AIM2 sense the ligand directly. The direct binding of specific ligands (muramyl dipeptide (MDP) and double-stranded DNA) can lead to conformational changes in NLRP1 and AIM2, resulting in **inflammasome activation.**

(e) NAIP proteins sense bacterial proteins resulting in the recruitment of NLRC4 and assembly of the NLRC4 inflammasome

Strowig T, et al. Nature 2012;481:278-86



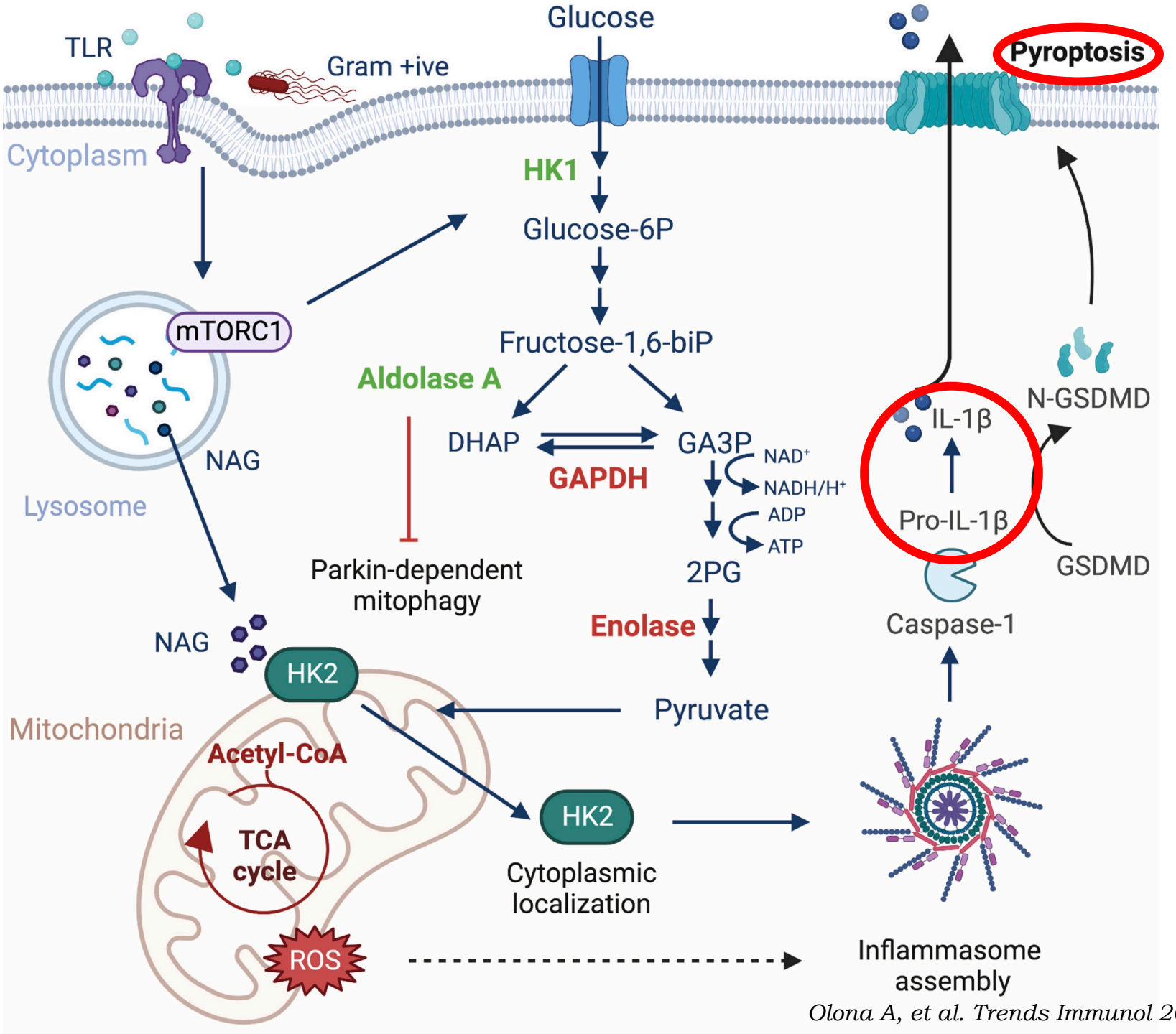
Swanson KV, et al. Nat Rev Immunol. 2019;19:477-489



ASC: apoptosis-associated speck-like protein containing a CARD - Caspase Activation and Recruitment Domain

Zheng et al. *Cell Discovery* (2020)6:36

Upon activation, the inflammasome sensors initiate the canonical inflammasome assembly by recruiting and forming pro-caspase-1 filaments, with or without the ASC adapter. The active caspase-1 or caspase-8 leads to the maturation and secretion of inflammatory IL-1β and IL-18, and triggers the cleavage of **Gasdemin D (GSDMD)**, which can either cause pyroptosis or activate the NLRP3 inflammasome complex. The active caspase-8 mediates apoptosis.



Olona A, et al. Trends Immunol 2022;43:978-89

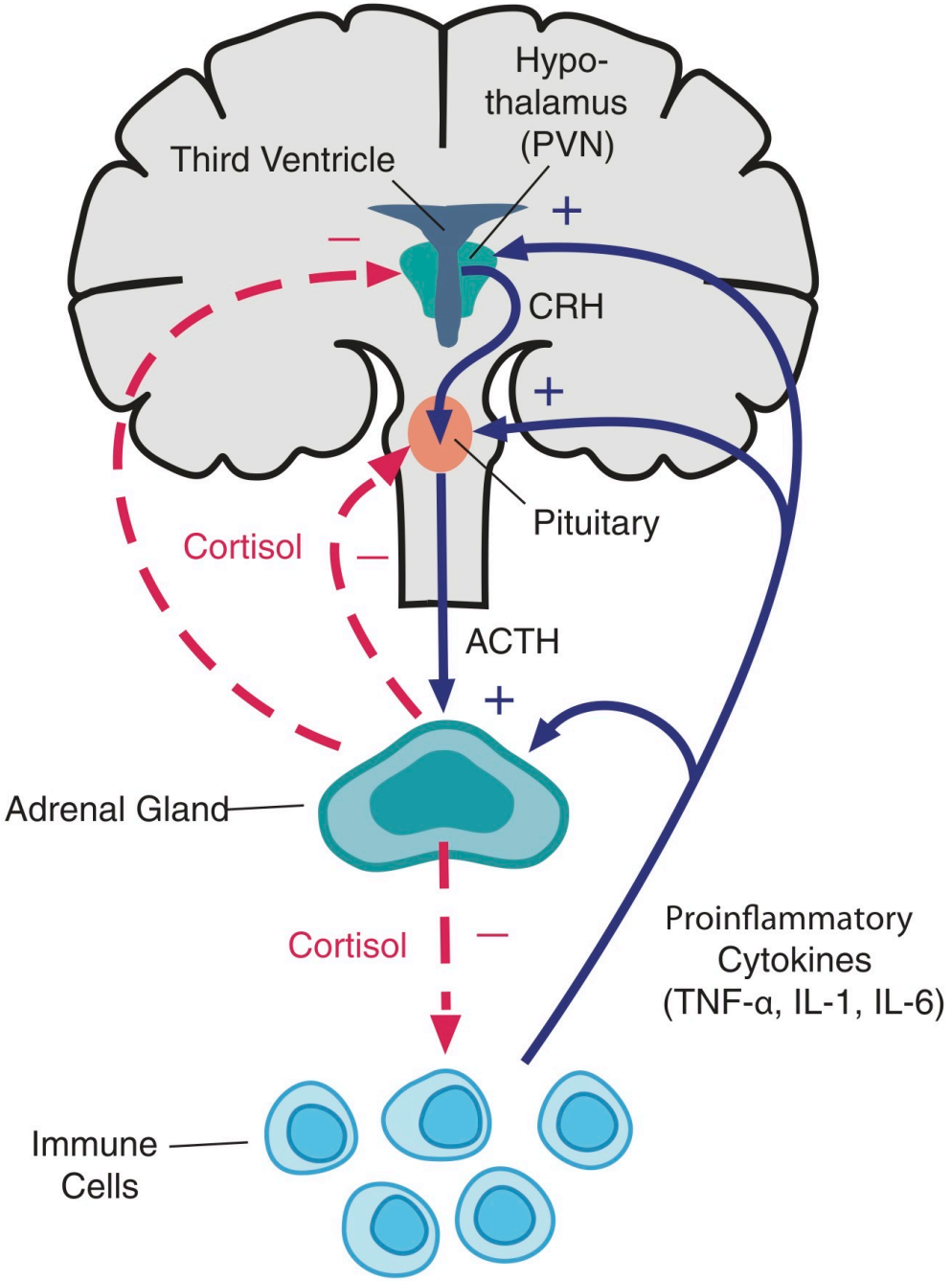
UPSTREAM OF THE ACUTE-PHASE RESPONSE: THE CYTOKINE CASCADE

Primary inflammatory cytokines, typically IL-1, IL-6, and TNFα, induce production of secondary mediators in tissues:

- IL-6 itself
- Chemokines
- Colony-stimulating factors
- Endothelial adhesion molecules
- Prostaglandins
- NO (nitric oxide)

These mediators amplify leukocyte recruitment, effector functions, and local innate immunity

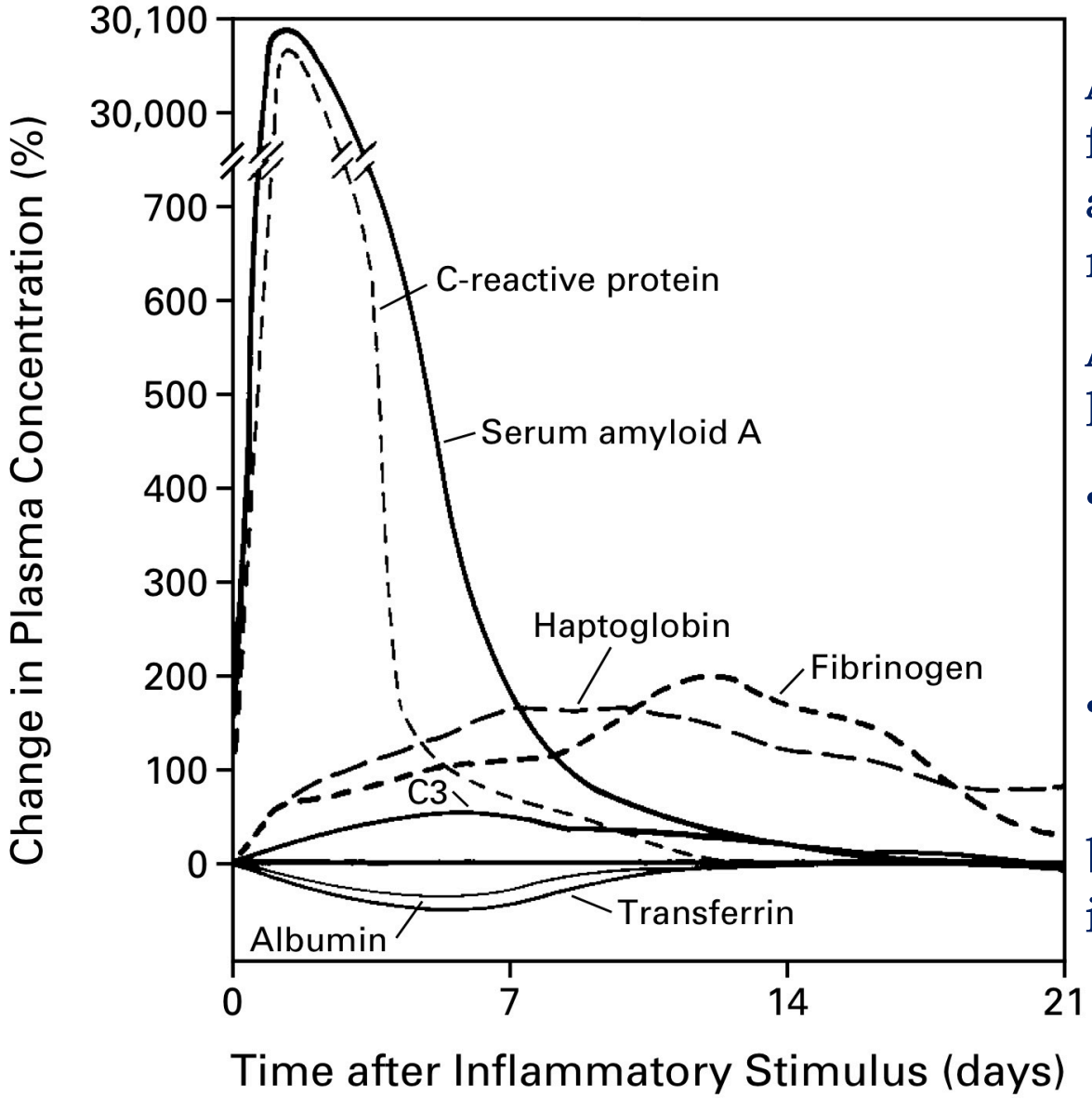
IL-6 is a potent inducer of the production of acute-phase proteins in the liver through reprogramming and reorientation of metabolic functions (e.g., decrease in albumin and increased acute-phase proteins)



- Inflammatory cytokines act on the CNS through their activation of the **hypothalamus–pituitary–adrenal axis**, resulting in production of ACTH and glucocorticoid hormones
- Glucocorticoid hormones act as negative regulators of inflammation by suppressing IL-1 and inducing the IL-1 decoy receptor IL-1R2
- Antiinflammatory cytokines (IL-10, TGF-β, and IL-1Ra) are also part of pathways of negative regulation
- IL-1Ra (the IL-1R antagonist) is a liver-derived acute-phase protein also produced by macrophages and other cell types in tissues

Silverman MN, et al. Ann N Y Acad Sci 2012;1261:55-63

ACUTE-PHASE PROTEINS AND OTHER SYSTEMIC RESPONSES TO INFLAMMATION



A large number of changes, distant from the site(s) of inflammation and involving many organ systems, may accompany inflammation

An acute-phase protein (reactant) has been defined as:

- one whose plasma concentration increases (positive acute-phase proteins)
- or decreases (negative acute-phase proteins)

by at least **25 percent** (1/4) during inflammatory disorders

Gabay C & Kushner I. N Engl J Med. 1999;340:448-54

Table 1. Main Acute-Phase Proteins and Their Role in Covid-19.*

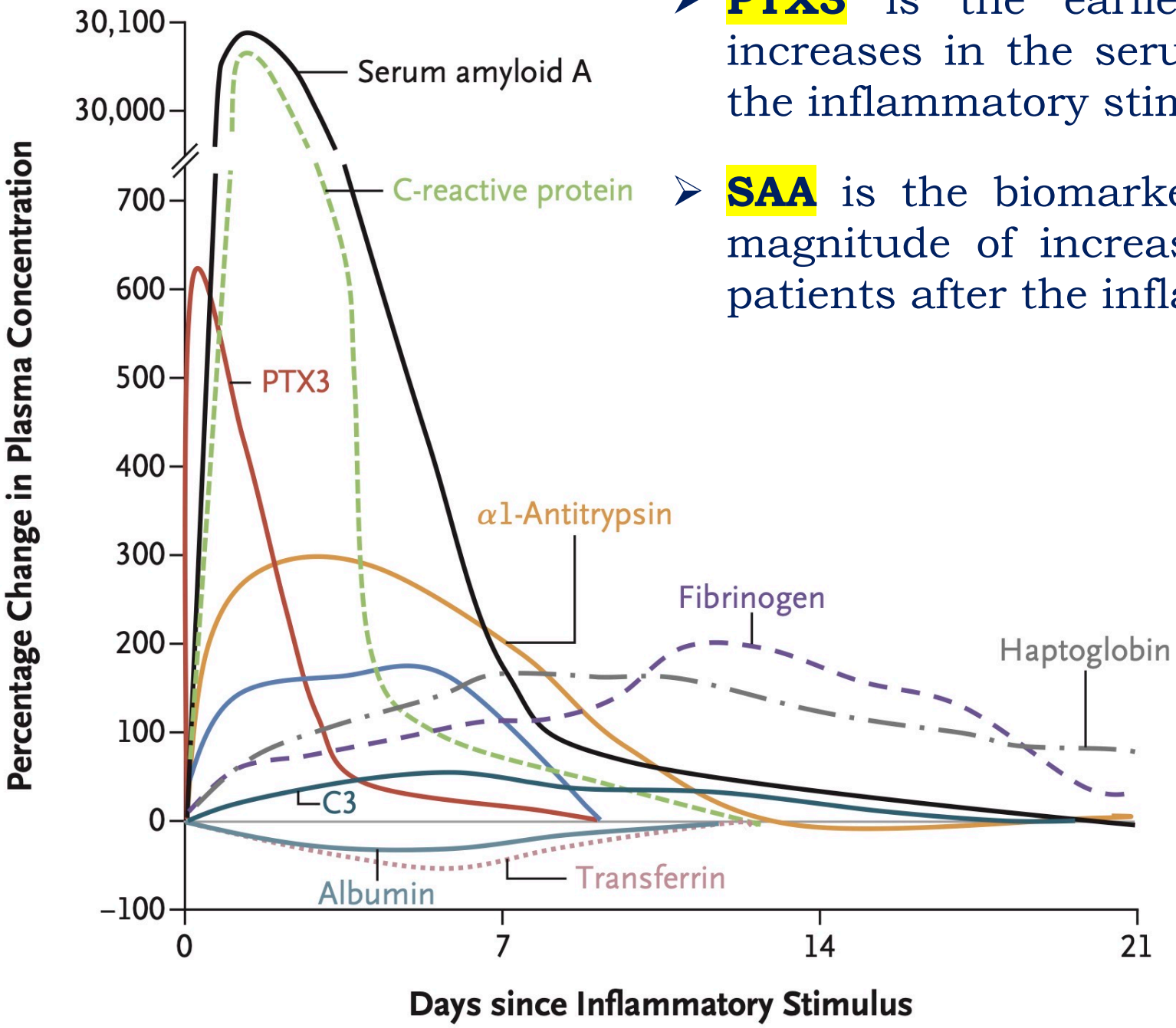
Function and Protein or Proteins	Degree and Type of Change in Inflammatory Conditions†	Role or Roles in Covid-19 and Associated Conditions‡
Humoral innate immunity		
C-reactive protein	↑↑↑↑	Association with death, ICU admission, need for interleukin-6 inhibition, and PASC[11-14]
Serum amyloid P	↑ or →	ND
Serum amyloid A	↑↑↑↑	Association with severity[15]
PTX3	↑↑↑	Association with death, lung lesions on CT, response to interleukin-6 inhibition, intubation, thrombotic events, and PASC[16-19]
C1q, C3, and C4	↑	Association with pathogenesis[20,21]
C4-binding protein	↑	ND
Mannose-binding lectin	↑↑ or →	Viral inhibition, association with thromboembolism[22]
Interleukin-1Ra	↑↑	Association between anti–interleukin-1Ra autoantibodies and severity, MIS-C, or myocarditis after SARS-CoV-2 vaccination[23]

HEPATIC AND NONHEPATIC SOURCES OF ACUTE-PHASE PROTEINS

- Approximately 200 acute-phase proteins are produced mainly by hepatocytes, but other cell types also contribute to the acute-phase reaction
- These cell types include organ-infiltrating monocytes and tissue-resident macrophages such as Kupffer cells, hepatic stellate cells, and endothelial cells macrophages
- Endothelial cells can produce complement components, serum amyloid A (SAA), iron transporters, α_1-antitrypsin, Pentraxin 3 (PTX3), and IL-1Ra
- Adipose tissue is an important source of the overall systemic concentration of acute-phase proteins in response to proinflammatory stimuli
- Adipocytes express large amounts of complement factors (C3, D, and B), α_1-acid glycoprotein, lipocalin-2, plasminogen activator inhibitor 1 (PAI-1), and serum amyloid A3

N Engl J Med 2023;388:439-52.

- **PTX3** is the earliest biomarker that increases in the serum of patients after the inflammatory stimulus
- **SAA** is the biomarker with the highest magnitude of increase in the serum of patients after the inflammatory stimulus



N Engl J Med 2023;388:439-52.

MOLECULES AND FUNCTIONS

1. Pentraxins (PTX)

Pentraxins are a family of evolutionarily conserved proteins characterized by a cyclic multimeric structure and by the presence of a conserved 200-amino acid pentraxin domain

- **PTX1: C-reactive protein (CRP)**
- **PTX2: serum amyloid P component (SAP)**
- **PTX3: Pentraxin 3**

CRP and SAP are pentameric short pentraxins; PTX3 is an octameric molecule

CRP, SAP, and PTX3 bind bacteria, fungi, and viruses, promoting innate immune responses to these pathogens

PTX also bind to phospholipids and small nuclear ribonucleoproteins in apoptotic cells, promoting the disposal of these cells in a non-inflammatory mode

N Engl J Med 2023;388:439-52.

1. Pentraxins (PTX)

The pentraxin trio of CRP–SAP–PTX3 plays a role in the amplification of innate resistance to selected pathogens and in the regulation of tissue remodeling

In humans, CRP plasma levels increase by as much as 1000 times in response to an acute-phase stimulus, in particular to IL-6, whereas SAP is constitutively present in plasma

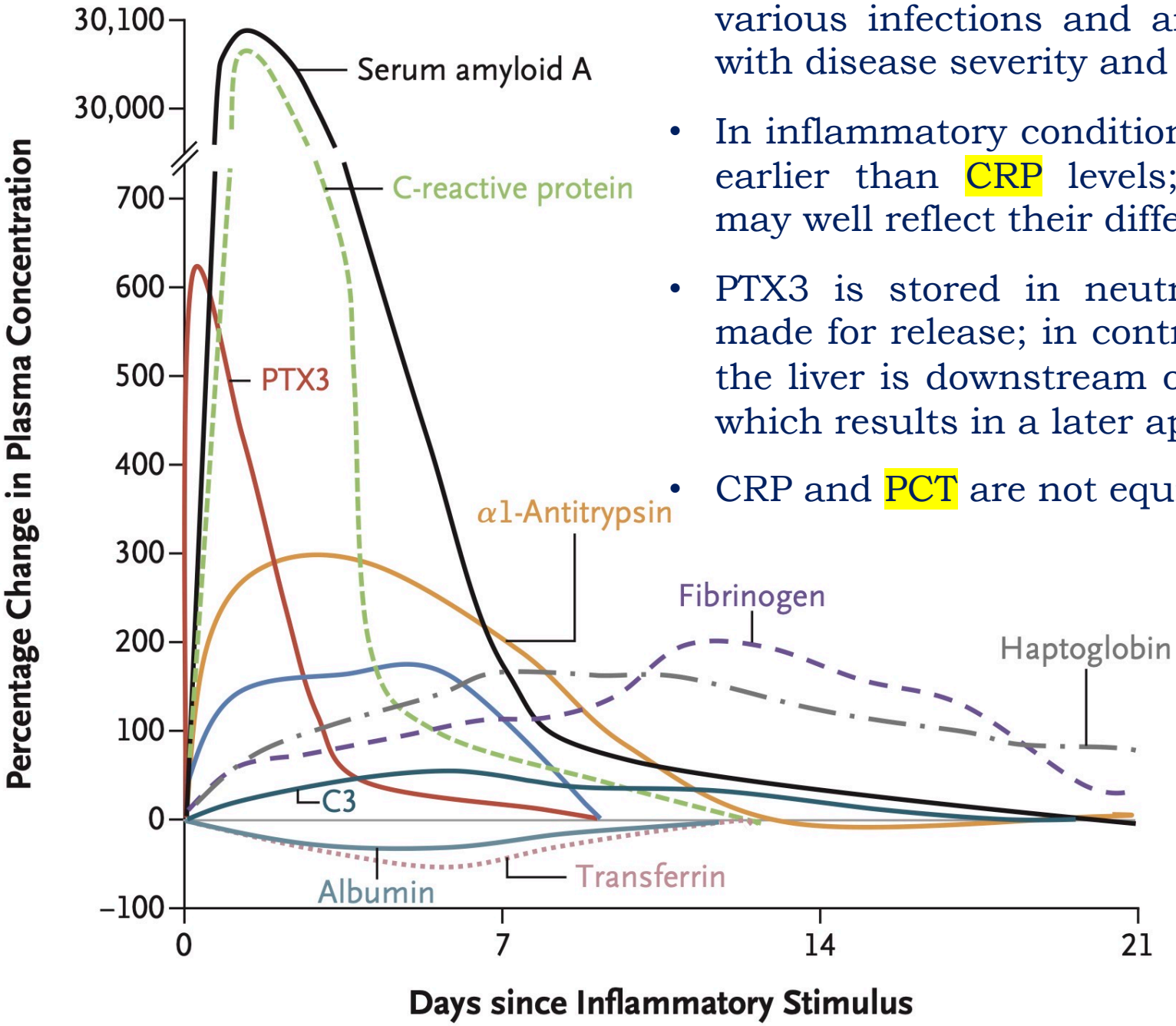
In contrast, PTX3 is rapidly induced in response to IL-1 and TNF or microbial components in various cell types, in particular, myelo-monocytic cells (monocytes, macrophages, dendritic cells), vascular and lymphatic endothelial cells, and stromal cells

Neutrophils synthesize PTX3 during myelopoiesis, store it in lactoferrin-positive granules, and rapidly release it after microbial recognition

Thus, PTX3 differs from short pentraxins in terms of structure, cell source, and regulation

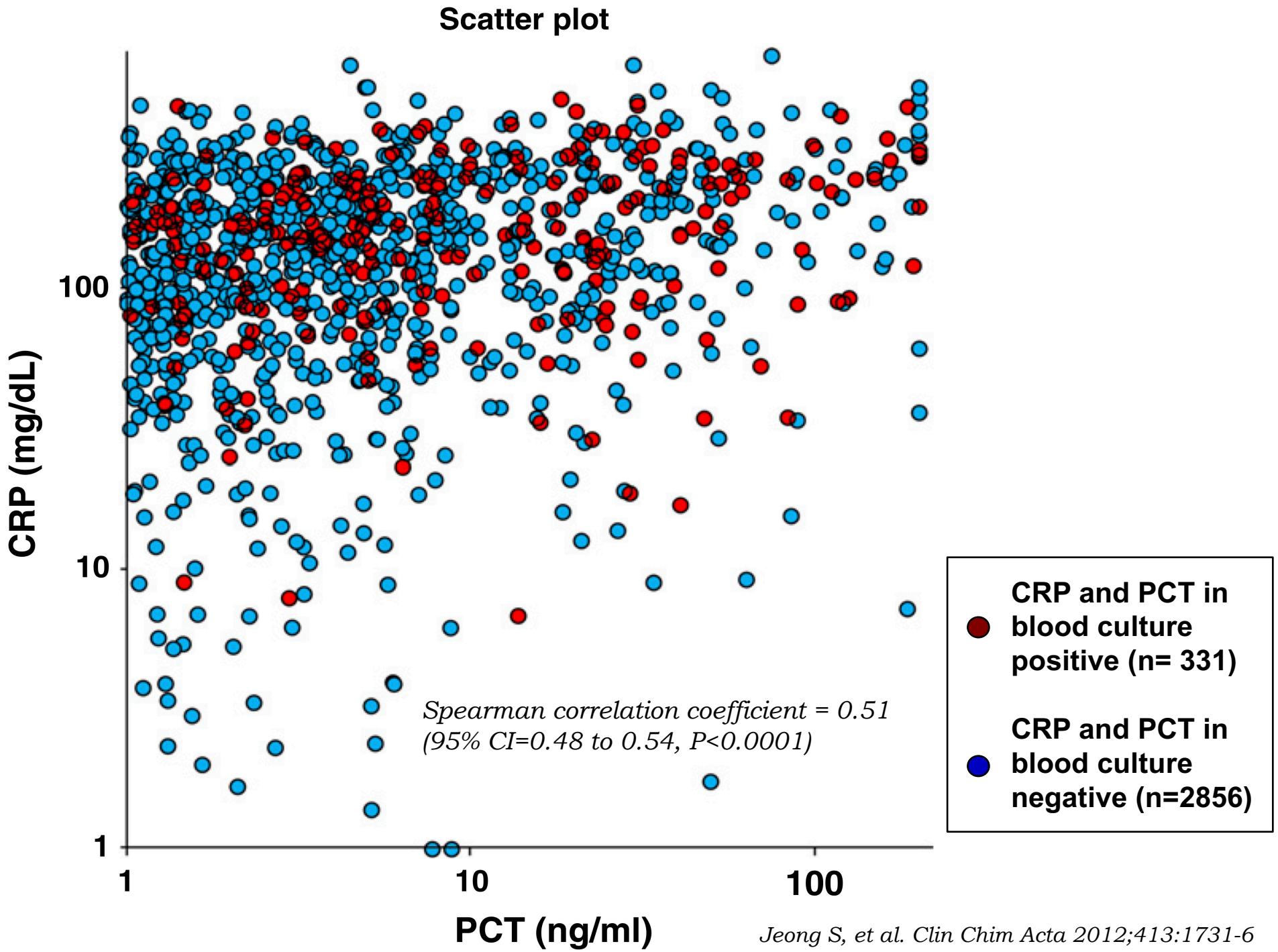
PTX3 and SAP genetic polymorphisms have been associated with susceptibility to fungal and bacterial infections

N Engl J Med 2023;388:439-52.



- PTX3 plasma levels increase rapidly during various infections and are positively associated with disease severity and the risk of death
- In inflammatory conditions, PTX3 levels increase earlier than CRP levels; the different kinetics may well reflect their different cellular sources
- PTX3 is stored in neutrophil granules, ready-made for release; in contrast, CRP production in the liver is downstream of the cytokine cascade, which results in a later appearance
- CRP and PCT are not equivalent to each other

N Engl J Med 2023;388:439-52.



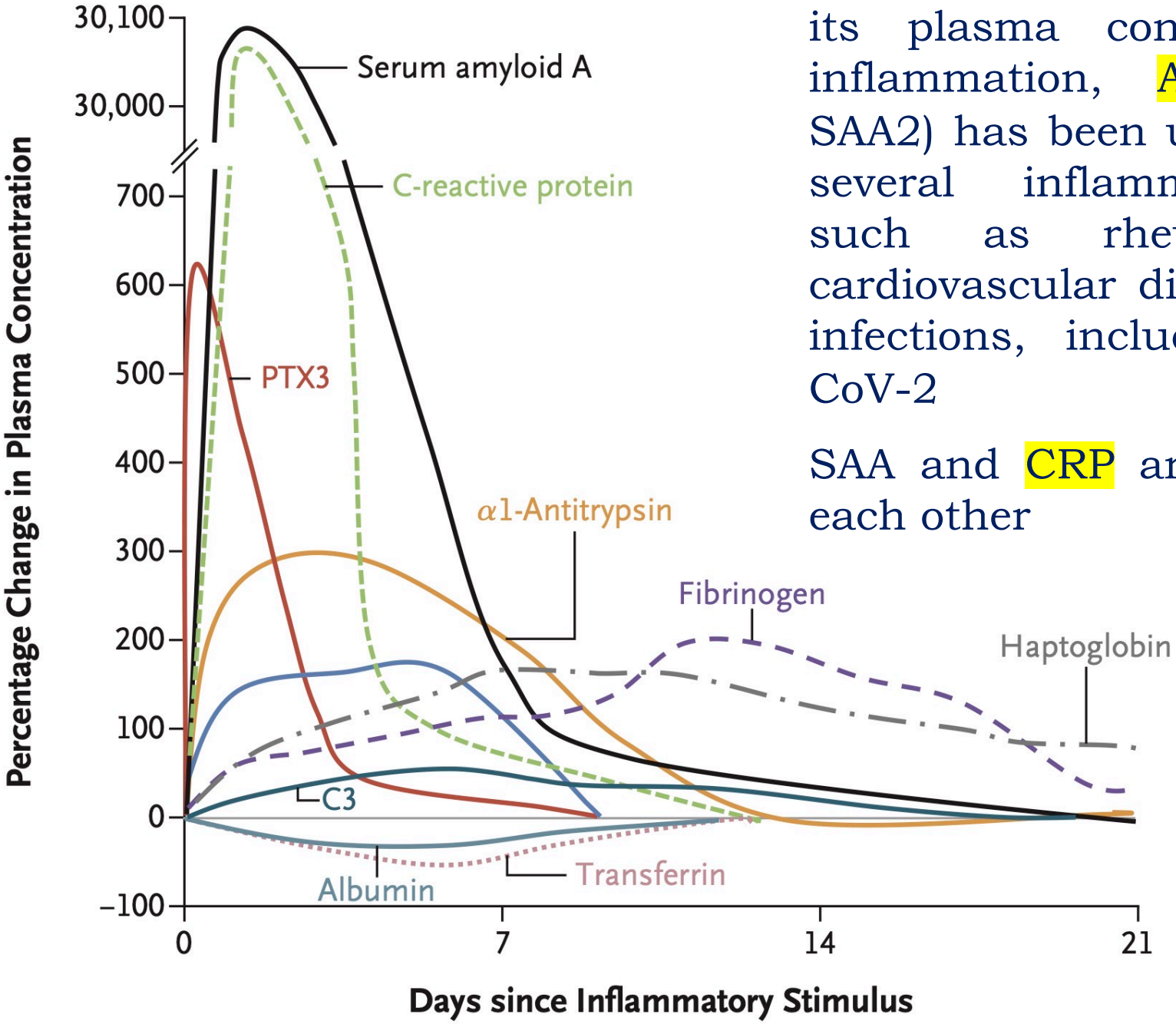
Jeong S, et al. Clin Chim Acta 2012;413:1731-6

2. Serum Amyloid A (SAA)

- Members of the SAA family are major acute-phase proteins in humans
- In humans, 4 genes encode different members of the family; SAA1 and SAA2 are typical liver-derived acute-phase proteins and are collectively termed A-SAA.
- In the small intestine, SAA is induced in epithelial cells by IL-22 and promotes local T helper 17 cell differentiation and effector function, favoring barrier integrity
- Long-term or recurrent high plasma SAA concentrations (e.g., due to tuberculosis or rheumatoid arthritis) in association with SAA1 allelic variants or other, unknown factors can lead to amyloid A amyloidosis

N Engl J Med 2023;388:439-52.

B

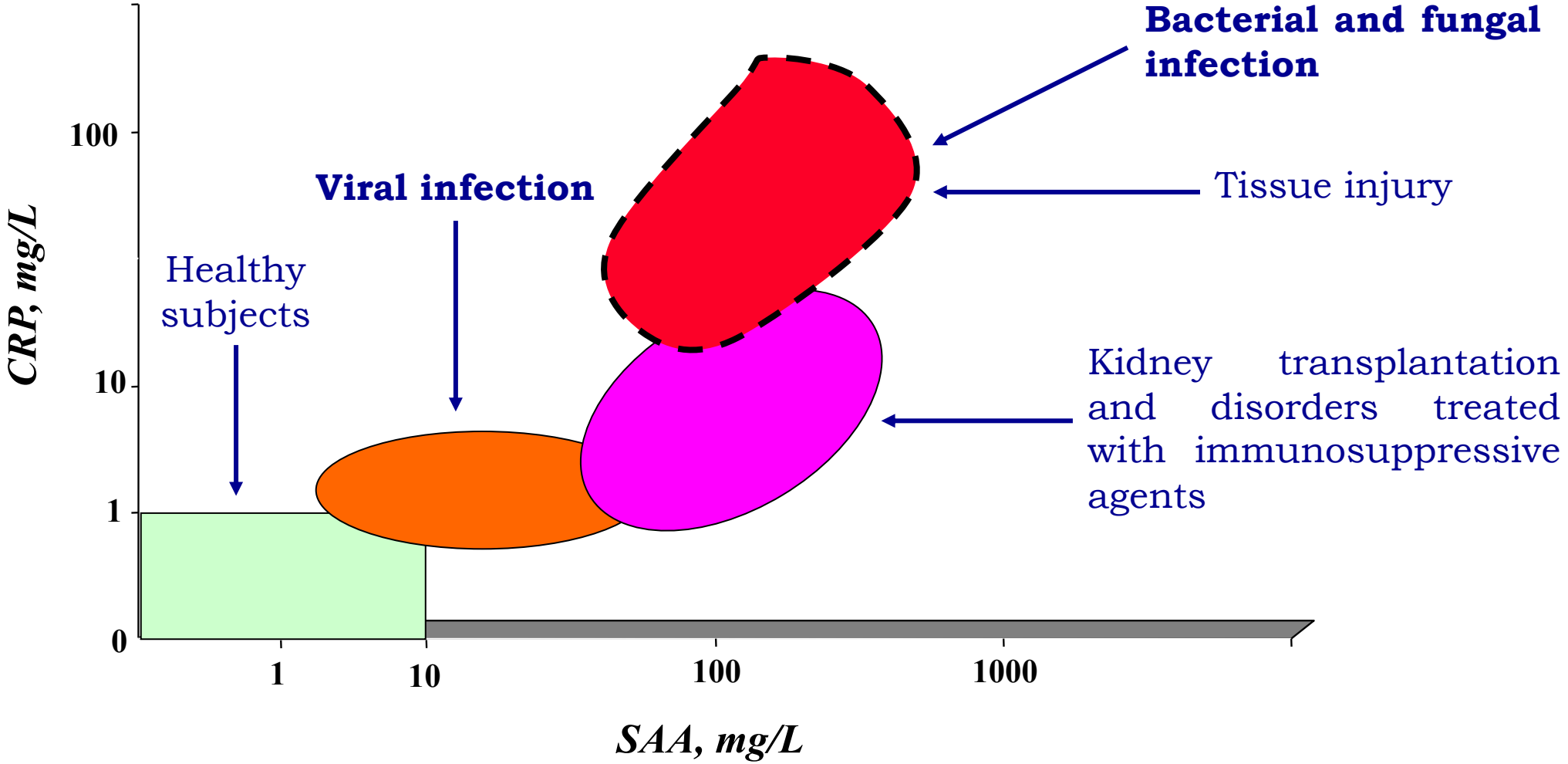


Because of the massive increase in its plasma concentrations during inflammation, A-SAA (SAA1 and SAA2) has been used as a marker in several inflammatory conditions, such as rheumatoid arthritis, cardiovascular diseases, cancer, and infections, including severe SARS-CoV-2

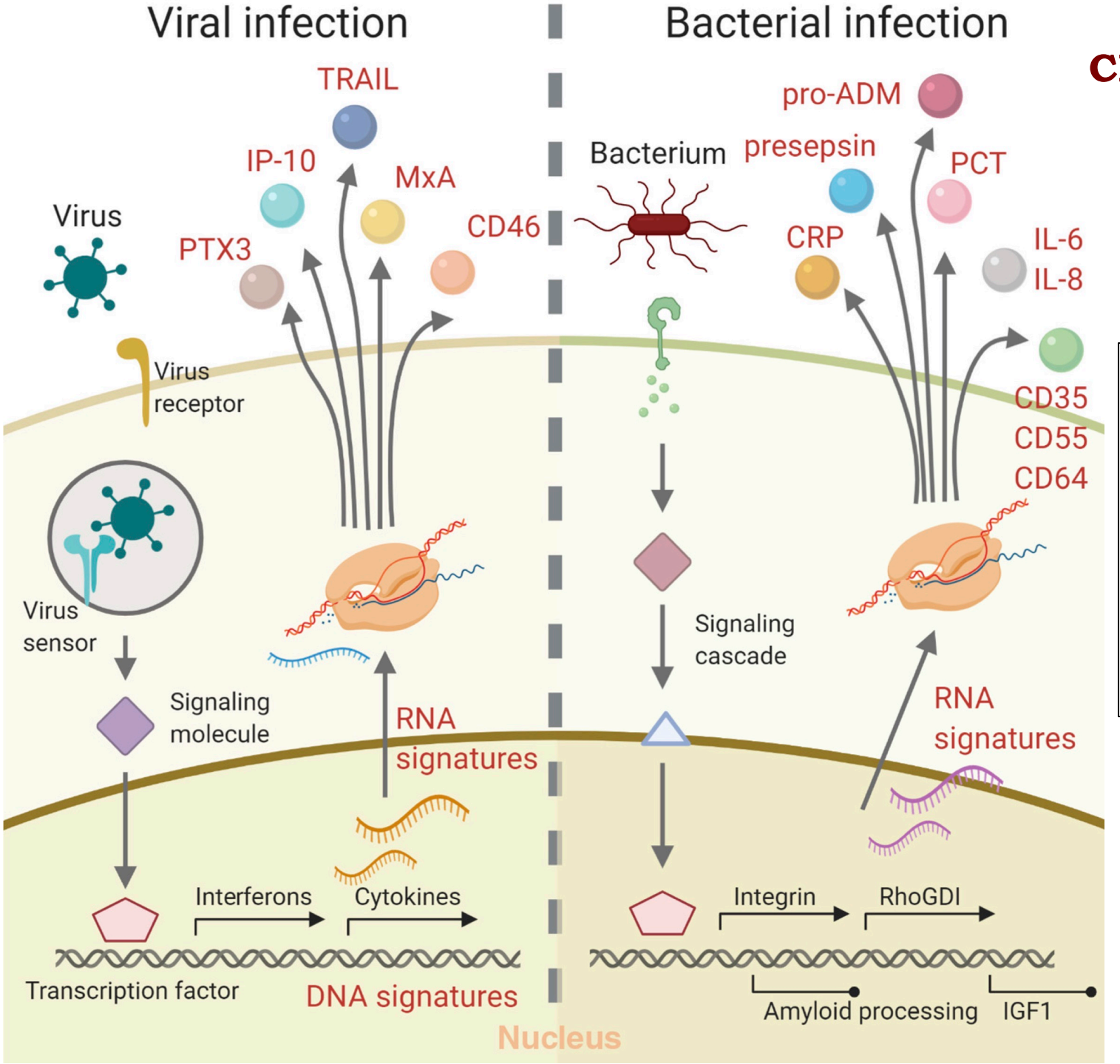
SAA and CRP are not equivalent to each other

N Engl J Med 2023;388:439-52.

SERUM AMYLOID A AND C-REACTIVE PROTEIN



CELLULAR RESPONSES TO BACTERIAL AND VIRAL INFECTIONS



- **Viruses** are more likely to trigger IFN-related signatures
- **Bacteria** are more likely to induce integrin-related signatures

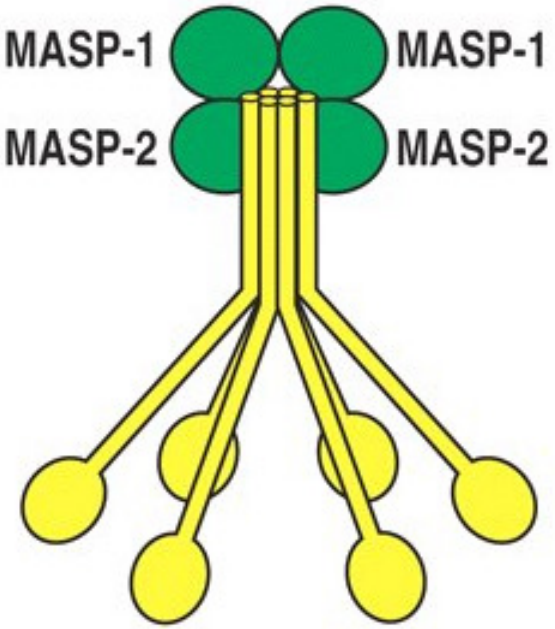
Tsao YT, et al. Trends Mol Med 2020;26:1118-32

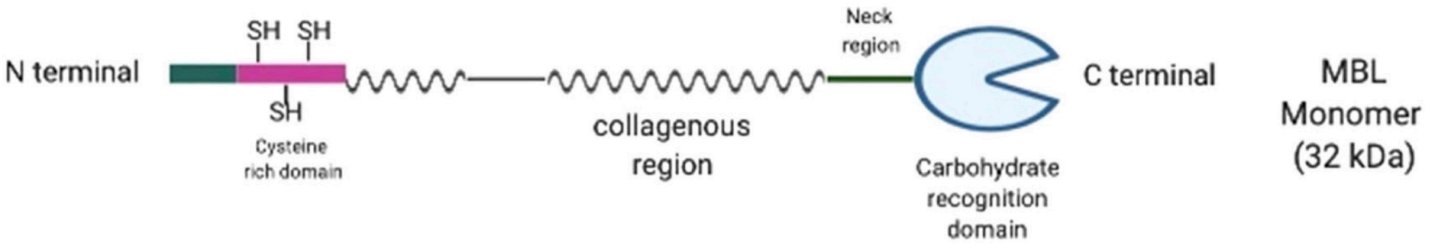
3. Mannose-Binding Lectin (MBL)

- MBL, also called Mannan-Binding Protein (MBP), is a liver-derived C-type plasma lectin, a class of pattern-recognition molecules (PRM) composed of a Ca^{2+}-type lectin domain (also called the carbohydrate-recognition domain) and a collagen-like domain
- MBL acts as a humoral PRM with high affinity for mannose and *N*-acetyl glucosamine (GlcNAc) exposed on microbes
- MBL opsonizes pathogens for phagocytosis and leads to the activation of MBL-associated serine proteases, initiating the complement cascade through the lectin pathway, in an antibody-independent manner
- MBL binds yeasts, viruses, and Gram- bacteria and also Gram+ bacteria with low affinity

N Engl J Med 2023;388:439-52.

Mannose-Binding Lectin (MBL)



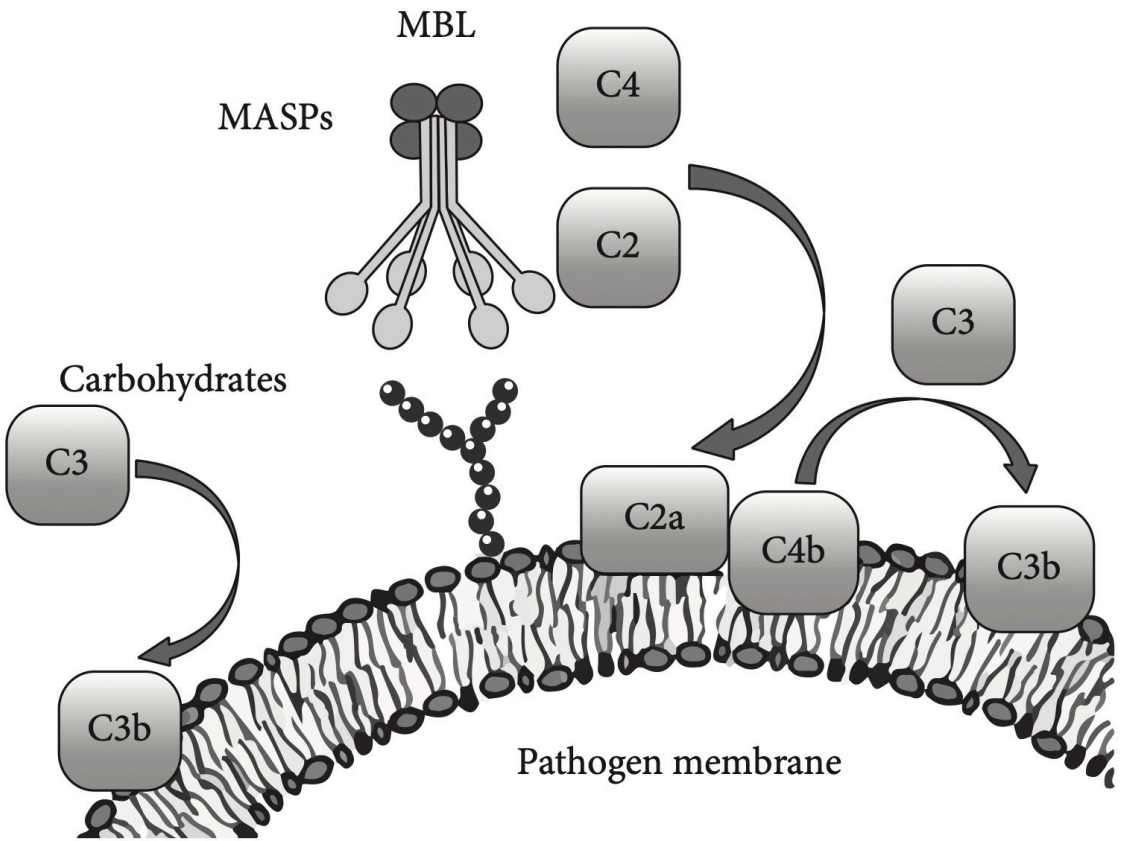


MBL forms clusters of 2 to 6 carbohydrate-binding heads around a central collagen-like stalk, and complexes with MBL-associated serine proteases 1 (MASP-1) and 2 (MAPS-2)

On binding of MBL to bacterial surfaces, these serine proteases become activated and can then activate the complement system by cleaving and activating C4 and C2

MBL, acting as a preformed, pluripotent, pathogen-pattern recognition molecule, plays a significant role in the early response to infections by:

- opsonizing invading organisms
- promoting the complement-mediated pathogen lysis
- modulating an appropriate pro-inflammatory cytokine response



Auriti C, et al. J Immunol Res 2017;2017:7045630

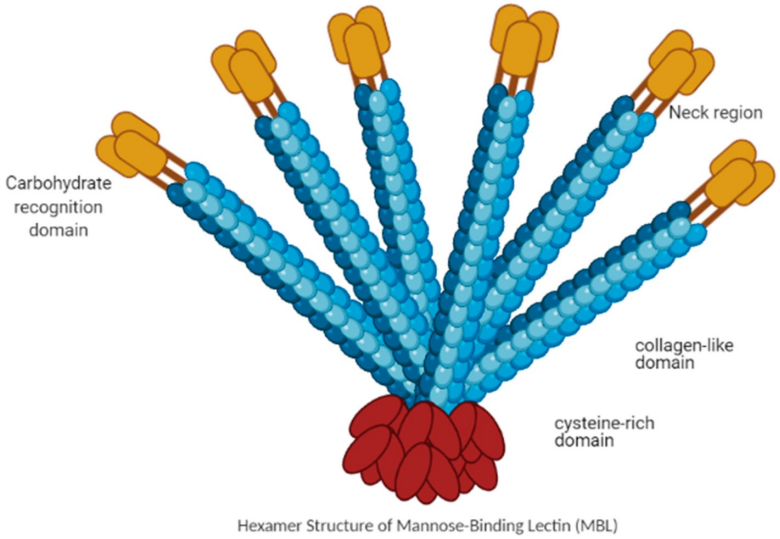
Lower circulating MBL levels are associated with a poor outcome

MBL: CLINICAL SIGNIFICANCE

- Likewise to proteins of the acute phase of inflammation, MBL blood levels increase in response to infections (3-4-fold compared to the baseline level)
- MBL **deficiency** in adults has been defined as plasma levels <0.5 mg/L
- Adults with a MBL serum level below 0.5 mg/L are characterized by a higher risk, severity, and frequency of infections in a number of clinical settings
- However, **high MBL activity** in adults has been associated with inflammatory autoimmune diseases such as the Systemic Lupus Erythematosus; even other pathological conditions are associated, such as transplant rejection, diabetic nephropathy, enhanced uptake of mycobacteria and *Leishmania*, and primary biliary cirrhosis

Auriti C, et al. J Immunol Res 2017;2017:7045630

Mannose-Binding Lectin (MBL)



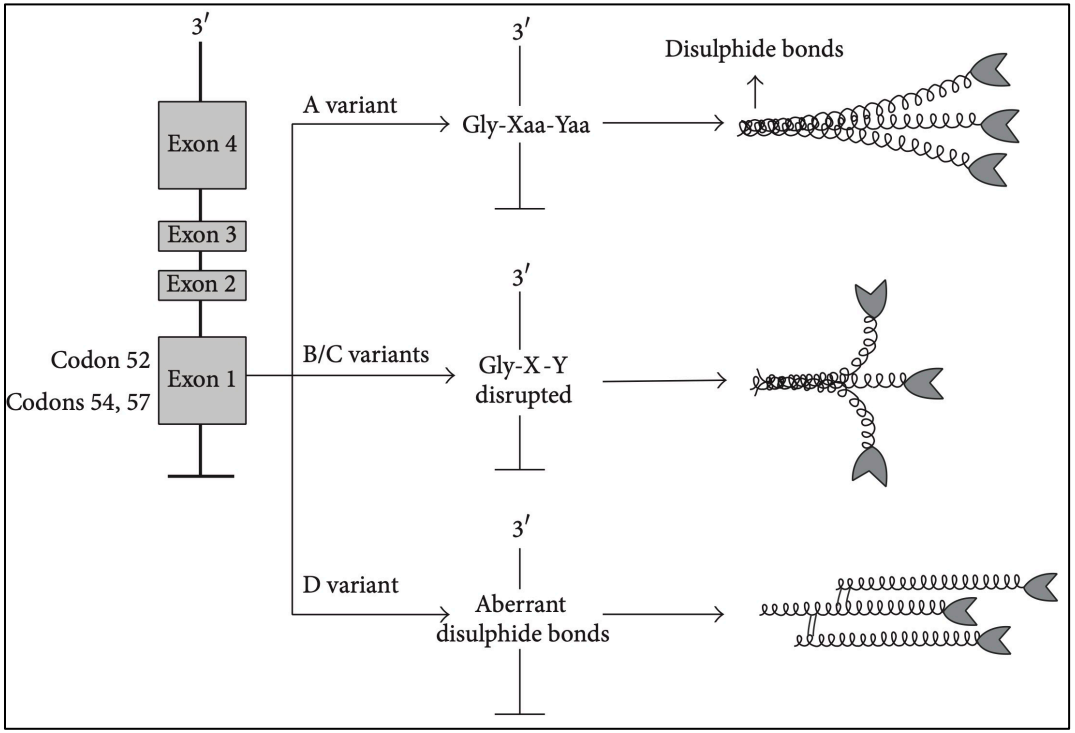
Hexamer Structure of Mannose-Binding Lectin (MBL)

- Low MBL levels **(<1.0 mg/L**) seem to represent a **risk factor** for the development of neonatal infections (often observed in **prematures**)
- Low MBL serum levels on **admission to the NICU** are associated with an increased risk of nosocomial sepsis, independently on GA
- Low MBL concentrations already in the **cord blood** were found to correlate with a higher incidence of Gram-negative sepsis
- A possible role of MBL as biomarker for the early identification of neonates at risk for infection has been suggested

Auriti C, et al. J Immunol Res 2017;2017:7045630

- The human MBL gene (*MBL2)* is located in the chromosome 10q11.1-q21

- Variant alleles of the *MBL2* gene encoding 3 different structural variants of the MBL polypeptide is strongly associated with MBL deficiency



- 5 single nucleotide polymorphisms (SNPs) in the *MBL2* gene lead to variations in quantity or function of MBL in serum

- However, Auriti et al observed that only 13.8% of **preterm babies** carried a genetically deficient *MBL2* haplotype, while 43.1% of babies had deficient MBL levels (<0.7 mg/L) on admission to the unit

- The finding of a discrepancy between MBL genotypes and serum MBL levels in preterm newborns supports the role of immaturity in causing low MBL levels in neonates

Auriti C, et al. J Immunol Res 2017;2017:7045630

MBL: CLINICAL SIGNIFICANCE

- Not only MBL **deficiency** but also MBL **hyperproduction** seems to have potentially harmful effects
- The onset of an excessive and uncontrolled inflammatory response by the neonatal intestine after the exposure to luminal bacteria may trigger the onset of necrotizing enterocolitis (NEC)
- Polymorphisms of the *MBL2* gene associated with high expression of active serum and tissue proteins may predispose **preterm neonates** to develop NEC and generate the pathophysiology of NEC, which contributes to the disease progression
- MBL has been found strongly expressed in enterocytes, in endothelial cells, and in histiocytes of the small intestine and colon of **preterm infants with NEC**
- MBL levels may affect the outcome of NEC, supporting the hypothesis of a role of high MBL levels in contributing to intestinal damage

Auriti C, et al. J Immunol Res 2017;2017:7045630

6. MBL: Future Perspectives

The observation that low MBL levels represent a risk factor for infection development and severity suggested that the external administration of MBL may be beneficial. Therefore, MBL replacement treatments in critically ill neonates with severe infections are currently discussed, although still far to be applied in clinical practice. However, considering the increased risk of some disorders which have been associated with an uncontrolled production of the MBL (as described above in the text), the potential prophylactic/therapeutic MBL administration should be carefully investigated prior to embarking upon potentially dangerous strategies [12, 118].

NEONATAL SEPSIS

- Our understanding of neonatal sepsis is hampered by a static definition associated with continued limitations in diagnostic accuracy because sepsis is a dynamic, complex, and heterogeneous condition

- Neonates are developmentally immature and may be encountering infection for the first time

- ***The core of treatment relies on accurate laboratory diagnosis for commencement of antibiotics therapy***

RESEARCH LETTER

Antibiotic Use Among Infants Admitted to Neonatal Intensive Care Units

JAMA Network™

- This repeated cross-sectional cohort study used the Premier Healthcare Database
- The analysis included 1,395,791 infants birth from January 1, 2009, to December 31, 2021:
- 763 498 males (54.7%)
- 632 293 females (45.3%)
- from 735 NICUs
- Most NICUs were urban (77.7%) and nonteaching (65.6%)
- The median (IQR) length of stay was 5 (3-13) days.

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Table. Antibiotic Use Trends Among 1 395 791 Infants Admitted to Neonatal Intensive Care Units From 2009 to 2021

	Antibiotic use, No. (%)[a]			Absolute difference, %[b,a]	Relative difference, %[c,a]	Annual absolute or relative difference (95% CI), %[d,a]	*P* value
	Overall	2009	2021				
DOT[e,a]	273.7	373.6	191.6	−181.9	−48.7	−6.9 (−8.1 to −5.7)	<.001
Any antibiotic	625 208 (44.8)	36 021 (54.8)	32 931 (35.9)	−18.9	−34.4	−1.9 (−2.6 to −1.3)	<.001
Ampicillin	591 421 (42.4)	33 858 (51.5)	30 674 (33.4)	−18.0	−35.0	−1.9 (−2.5 to −1.3)	<.001
Gentamicin	572 145 (41.0)	31 564 (48.0)	29 840 (32.5)	−15.5	−32.3	−1.8 (−2.3 to −1.2)	<.001
Vancomycin	49 905 (3.6)	3233 (4.9)	2429 (2.6)	−2.3	−46.8	−0.2 (−0.3 to −0.1)	<.001
Cefotaxime	31 368 (2.2)	3444 (5.2)	261 (0.3)	−5.0	−95.5	−0.4 (−0.5 to −0.3)	<.001
Cefazolin	15 379 (1.1)	632 (1.0)	1172 (1.3)	0.3	31.2	0.03 (−0.004 to 0.06)	.09
Cefepime	12 421 (0.9)	508 (0.8)	1325 (1.4)	0.7	90.6	0.04 (−0.05 to (0.1)	.39
Ceftazidime	8414 (0.6)	217 (0.3)	1092 (1.2)	0.9	272.7	0.06 (0.02 to 0.1)	.001
Piperacillin-tazobactam	10 463 (0.7)	377 (0.6)	677 (0.7)	0.2	34.9	0.02 (−0.02 to 0.05)	.34
Antistaphylococcal[f]	11 670 (0.8)	550 (0.8)	1027 (1.1)	0.3	35.9	0.02 (−0.01 to 0.06)	.22
Carbapenem[g]	5687 (0.4)	274 (0.4)	422 (0.5)	0.04	9.6	−0.01 (−0.03 to 0.01)	.44

Abbreviation: DOT, days of therapy.

[a] All proportions and DOT values were rounded to 1 significant decimal place. The absolute and relative differences were calculated using the respective values before rounding and were then rounded to 1 significant decimal place.

[b] Absolute difference calculated as 2009 value subtracted from 2021 value.

[c] Relative difference calculated as absolute difference divided by 2009 value.

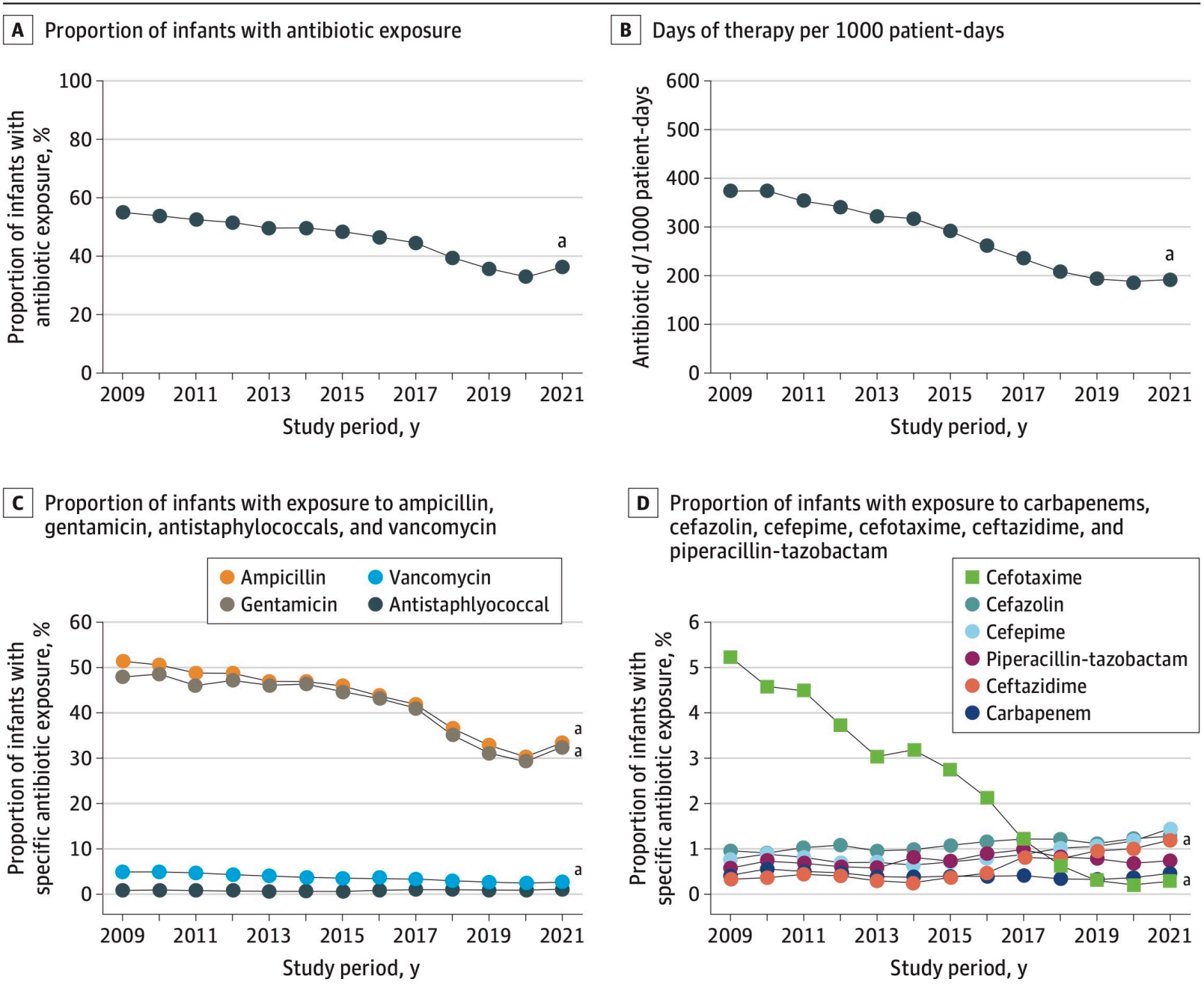
[d] Generalized linear regression was used to estimate annual absolute or relative difference with 95% CI and *P* value, accounting for clustering by neonatal intensive care unit. Annual relative difference of antibiotic days per patient-days was reported for DOT, whereas annual absolute difference of proportion of infants with antibiotic exposure during admission was reported for antibiotic exposure.

[e] DOT were defined as antibiotic days/1000 patient-days.

[f] Antistaphylococcal includes nafcillin and/or oxacillin.

[g] Carbapenem includes meropenem, ertapenem, imipenem, and/or doripenem.

Figure. Trends of Antibiotic Use Among Infants Admitted to Neonatal Intensive Care Units From 2009 to 2021



[a] Statistically significant absolute or relative annual change.

What Is the Role of a Clinical Laboratorian in Care of a Septic Patient?

Alison Woodworth[1*]

grazie!

- The key to reducing sepsis-related mortality is ***early diagnosis*** and initiation of targeted therapy
- 13 years ago, it was demonstrated that a 1-h delay in appropriate antimicrobial therapy translated to increases in mortality of 7-10%
- The speed of the ***etiological*** diagnosis has been considerably improved by automation coupled with the mass spectrometry