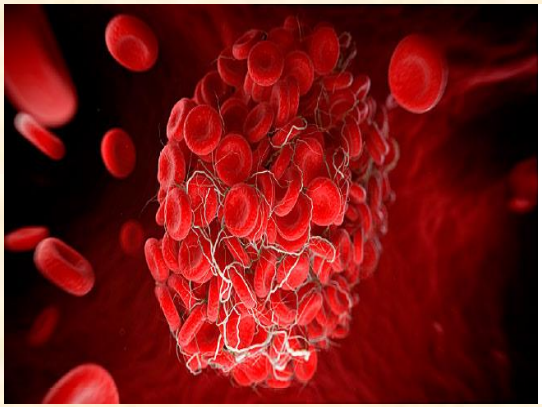
Coagulation disorders in sepsis: Disseminated Intravascular Coagulation



Frantzeska Frantzeskaki
Pulmonologist-Intensivist
2nd Department of Critical Care
Attikon University Hospital

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

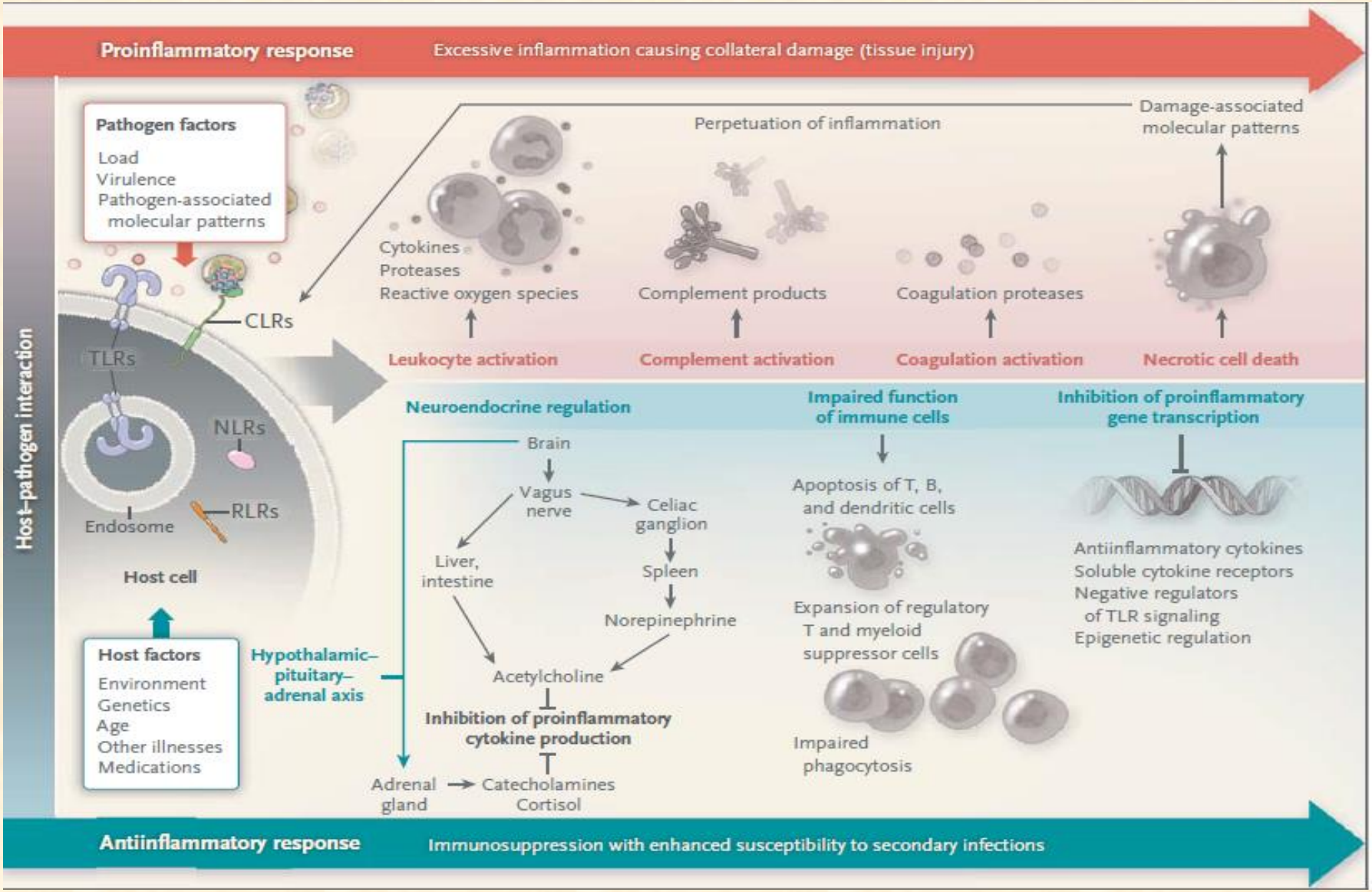
Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

Singer et al. JAMA 2016, 315 (8), 801-810

Sepsis: A life threatening organ dysfunction caused by a dysregulated host response to infection

The body's response injures its own tissues and organs

Immune response in sepsis



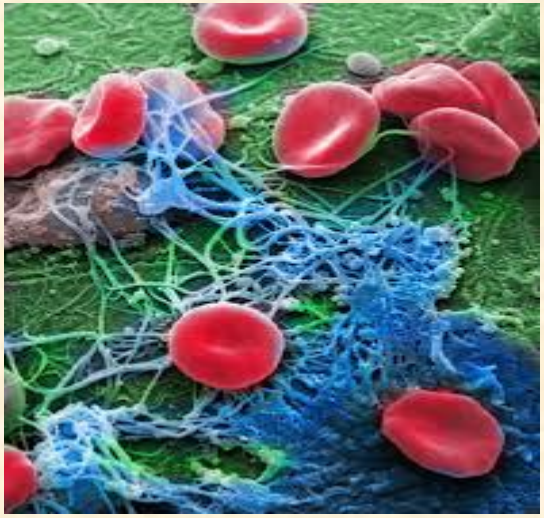
Angus et al. N Engl J Med 2013;369:840-51

TABLE 1. Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/FIO_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

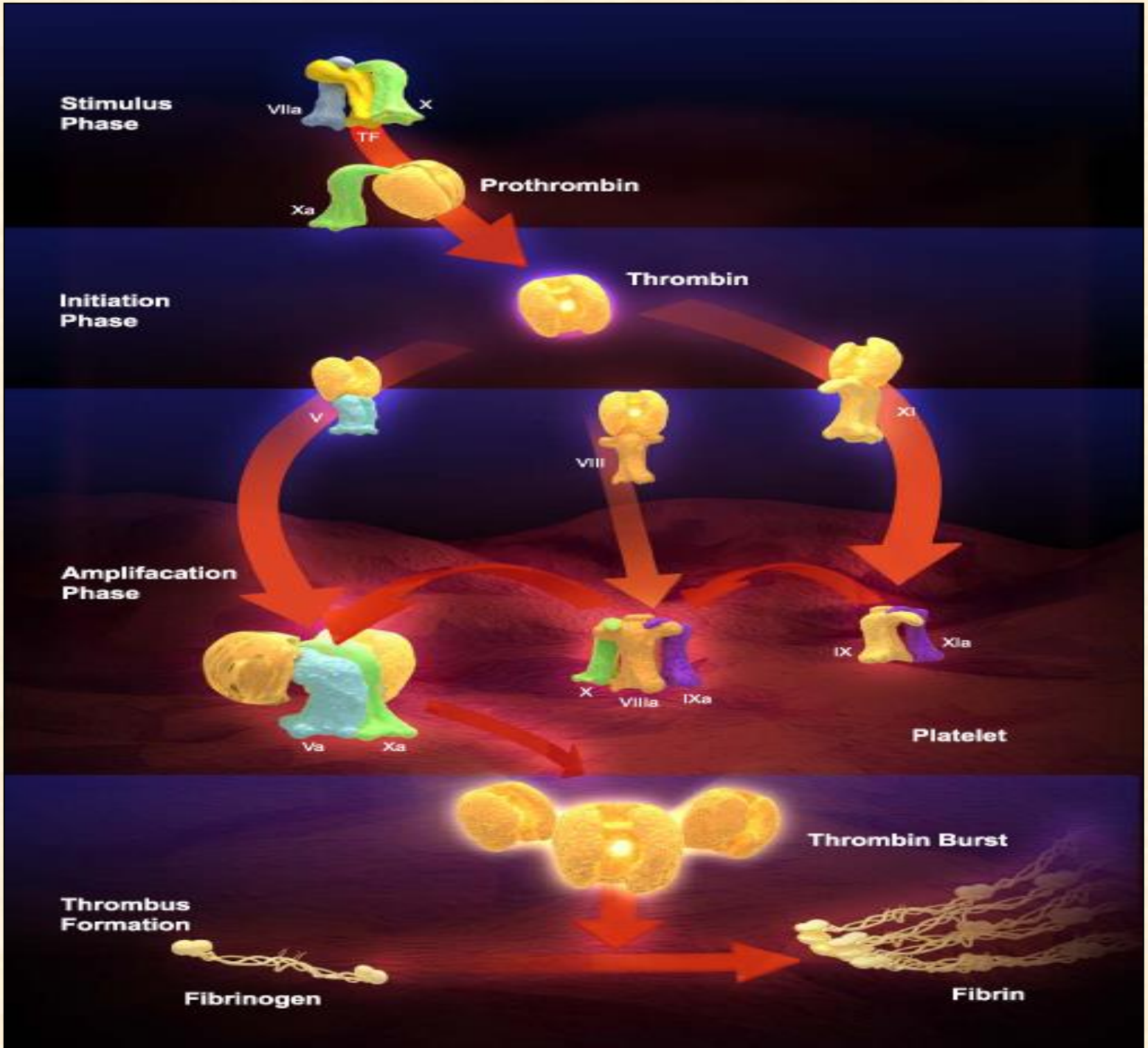
Crit Care Med 2013;41:580-637

Burden of clinically relevant coagulopathy in sepsis

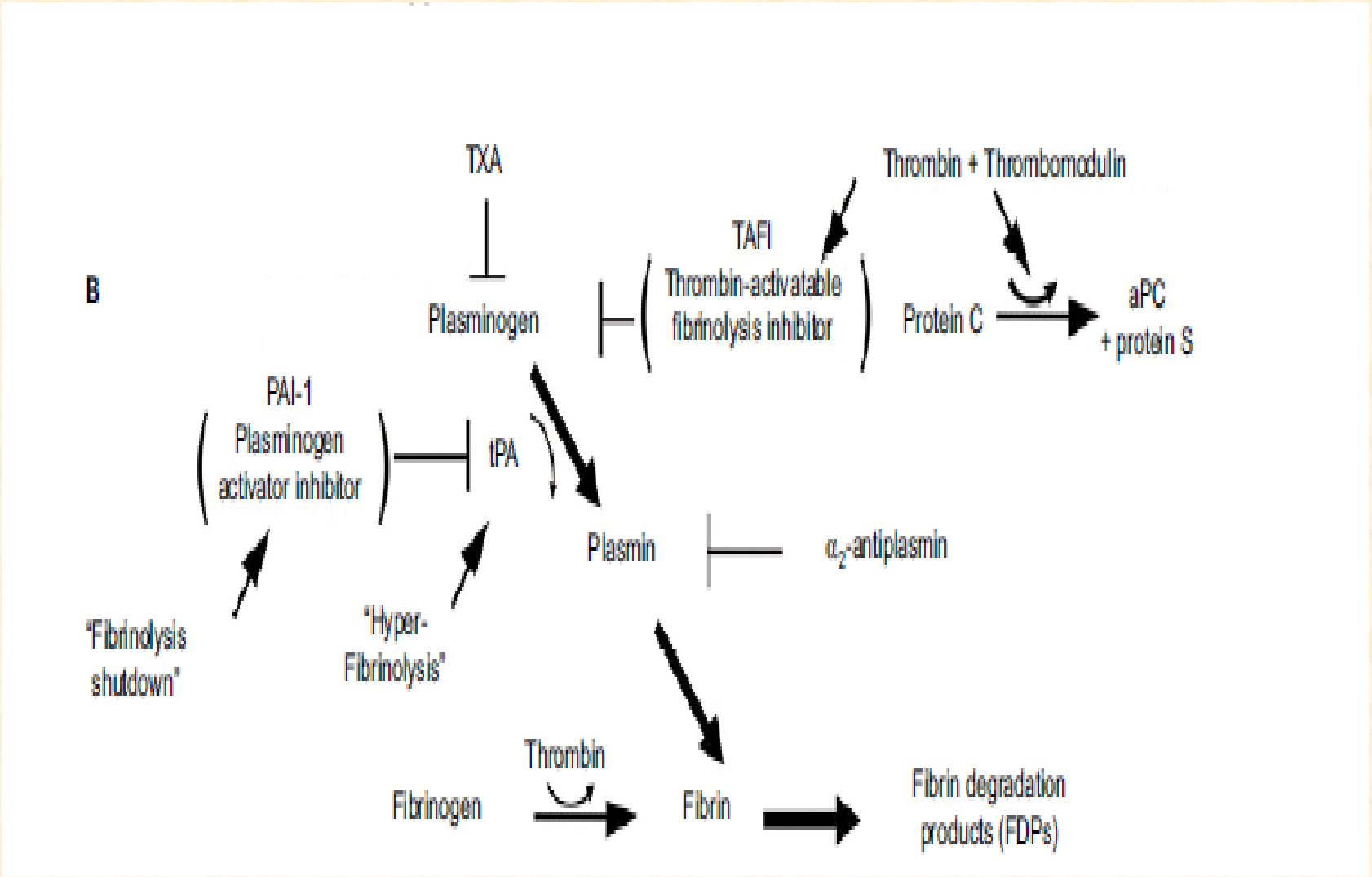


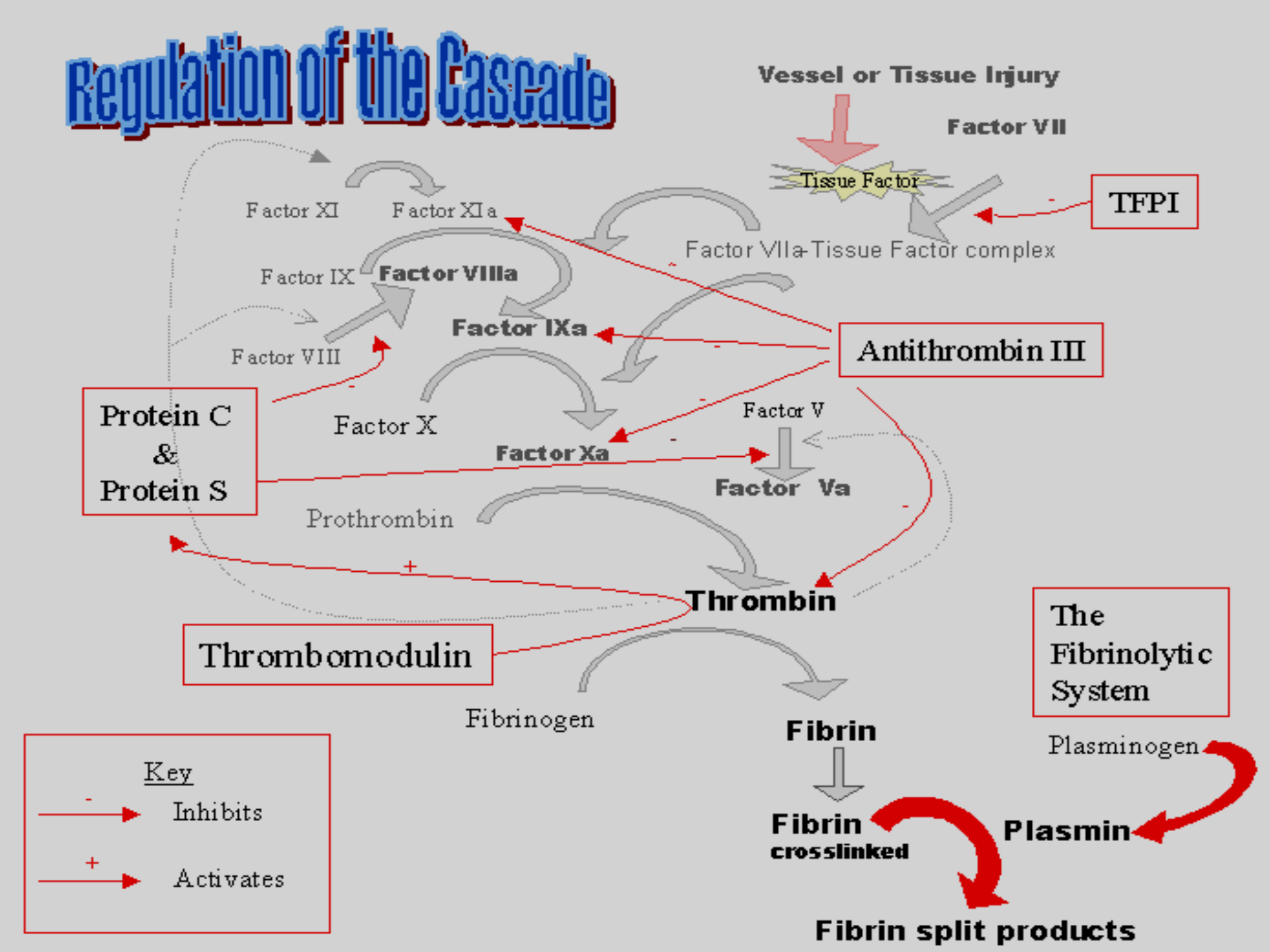
- 50-70% of septic patients
- Wide range
- Delicate activation to DIC
- Thrombocytopenia: <150 x 10^9/l
- Prolonged global assays: 15-30%
- Low physiological anticoagulants: 90%
- 35% DIC

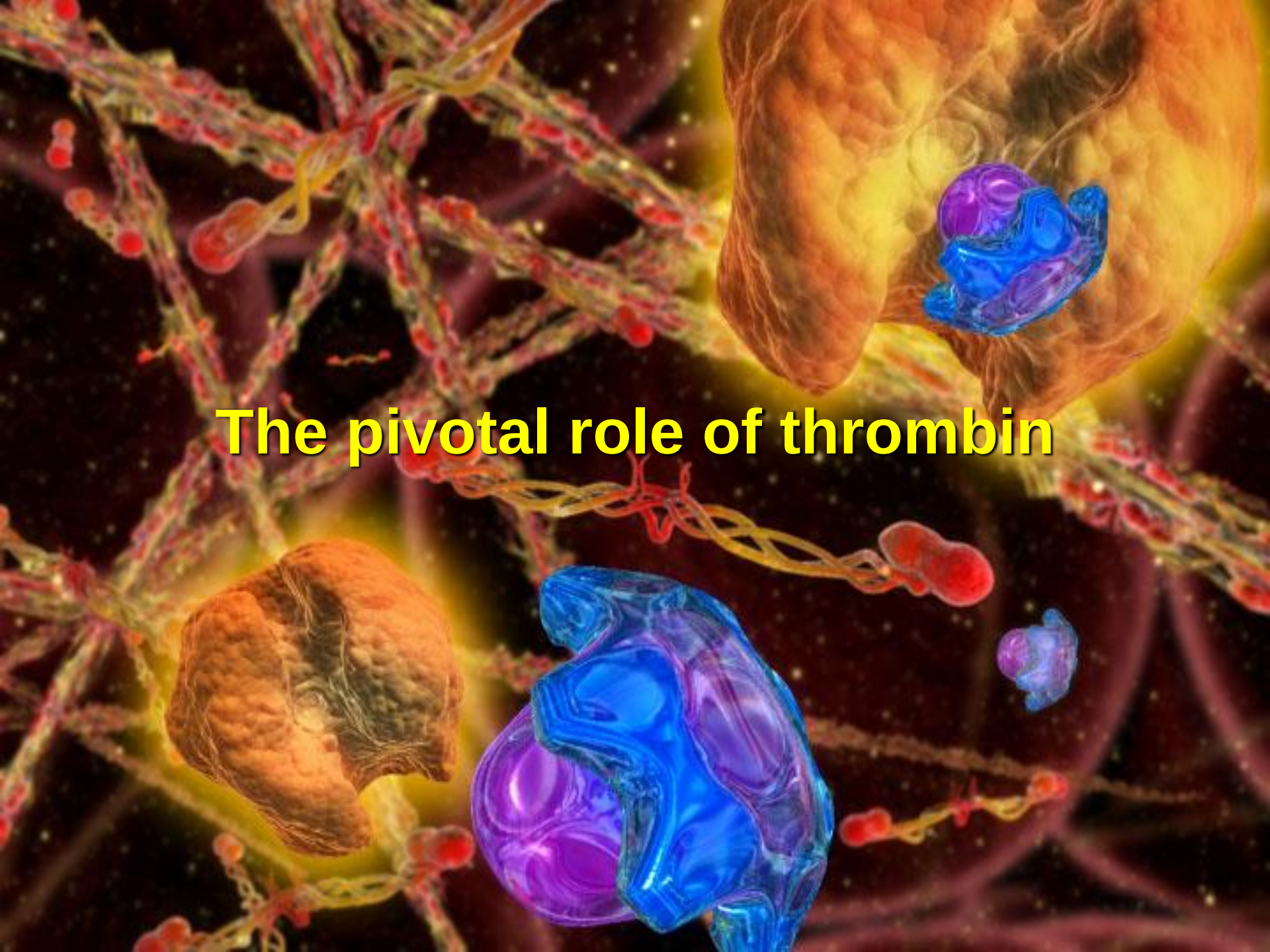
Levi M et al. *Thromb Res* 149 (2017) 38-44


Stimulus Phase
VIIa
X
TF
Xa
Prothrombin
Initiation Phase
Thrombin
V
VIII
XI
Amplifacation Phase
IX
XIa
X
VIIIa
IXa
Va
Xa
Platelet
Thrombin Burst
Thrombus Formation
Fibrinogen
Fibrin

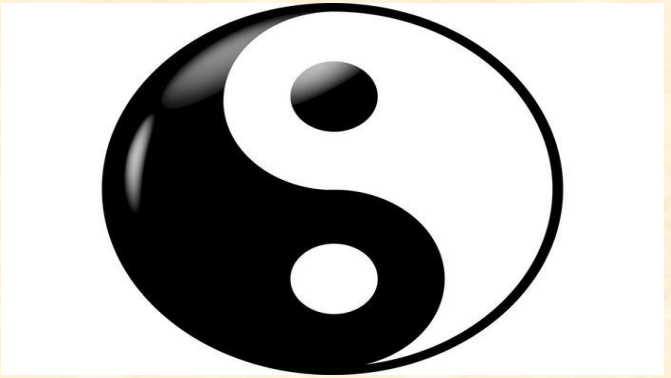
Fibrinolytic pathway and endogenous mediators




Regulation of the Cascade
Vessel or Tissue Injury
Factor VII
Tissue Factor
TFPI
Factor XI
Factor XIa
Factor VIIa-Tissue Factor complex
Factor IX
Factor VIIIa
Factor IXa
Antithrombin III
Factor VIII
Protein C
&
Protein S
Factor X
Factor V
Factor Xa
Factor Va
Prothrombin
Thrombin
Thrombomodulin
Fibrinogen
Fibrin
The
Fibrinolytic
System
Plasminogen
Fibrin
crosslinked
Plasmin
Fibrin split products
Key
Inhibits
Activates

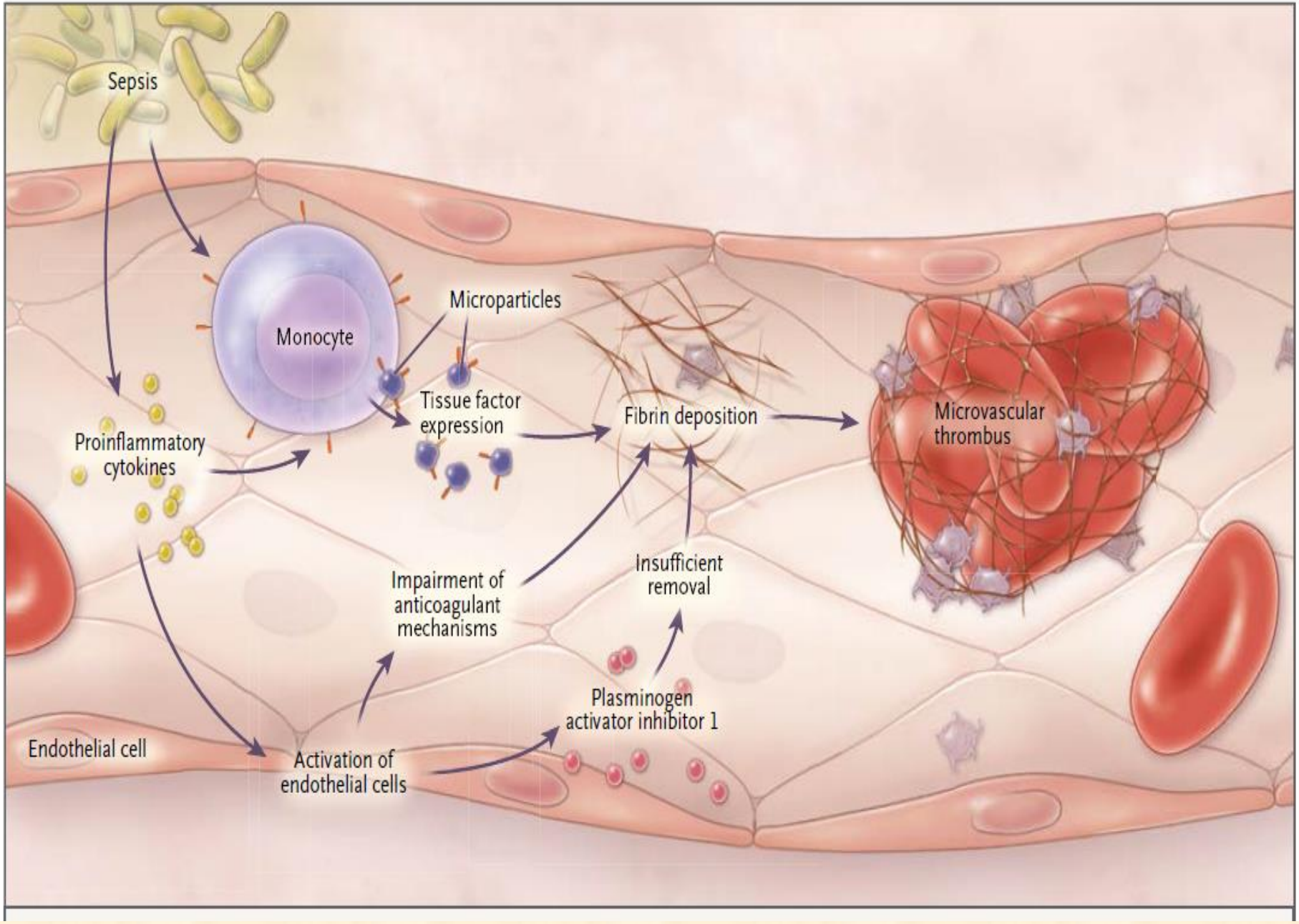

The pivotal role of thrombin

The role of thrombin



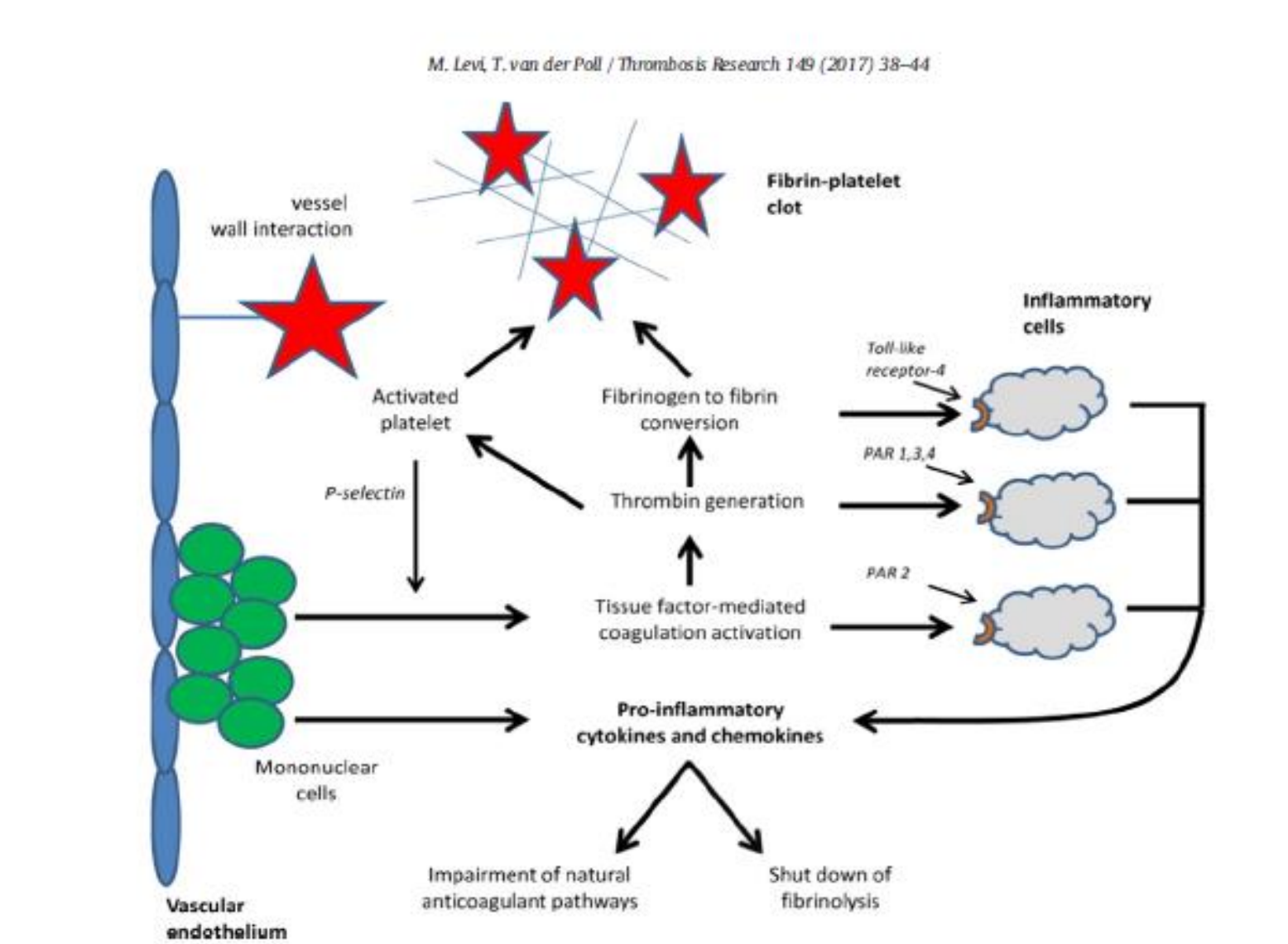
- Thrombus formation (via fibrin network)
- Platelets' activation
- Anticoagulation (via protein C)
- Inhibition of fibrinolysis (TAFI)
- Cytokines production
- Vascular permeability and tone (via endothelial cells receptors)
- Precursor of peptides with antimicrobial properties

Delabranche X et al. *Ann Intensive Care* (2017) 7;117



Hunt B. *N Engl J Med* 2014

Crosstalks between inflammation and coagulation



Immunothrombosis

- The pathophysiological role of coagulation in the innate host response to endothelial damage
- Organized recruitement of innate cells and platelets at the site of endothelial damage, regulated by coagulation proteases and inflammatory mediators
- Microthrombi: Complex with antimicrobiotic properties-inflammatory response, TF expression

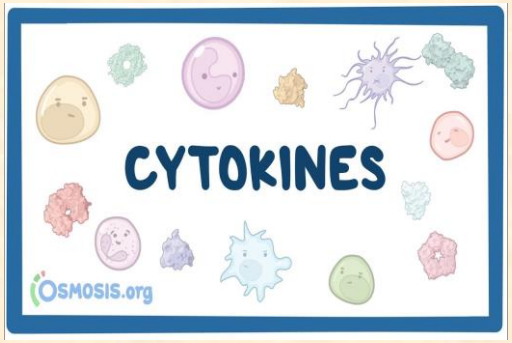
Engelmann B et al. *Nat Rev Immunol* 2013;13(1):34-45

Cells, pathways and cell mediators contributing to immunothrombosis

- Cytokines/chemokines
- Platelets/ Activated endothelial cells
- Tissue factor/ Coagulation proteases
- Neutrophil extracellular traps (NETs)
- Microparticles

Frantzeskaki F et al. *Respiration 2017*;93(3):212-225

Cytokines induced activation of coagulation

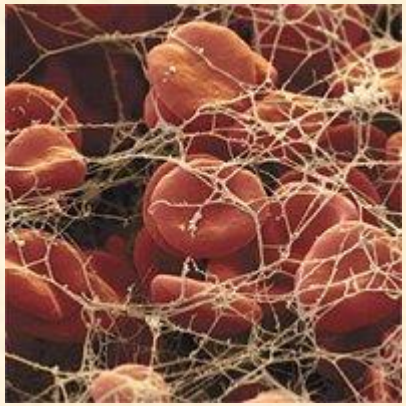


- TNF: The first detectable mediator-procoagulant effects
- IL-6, IL-1
- Antiinflammatory cytokines: IL-10/ inhibition of hemostasis
- Impairment of natural anticoagulant pathways
- Shut down of fibrinolysis

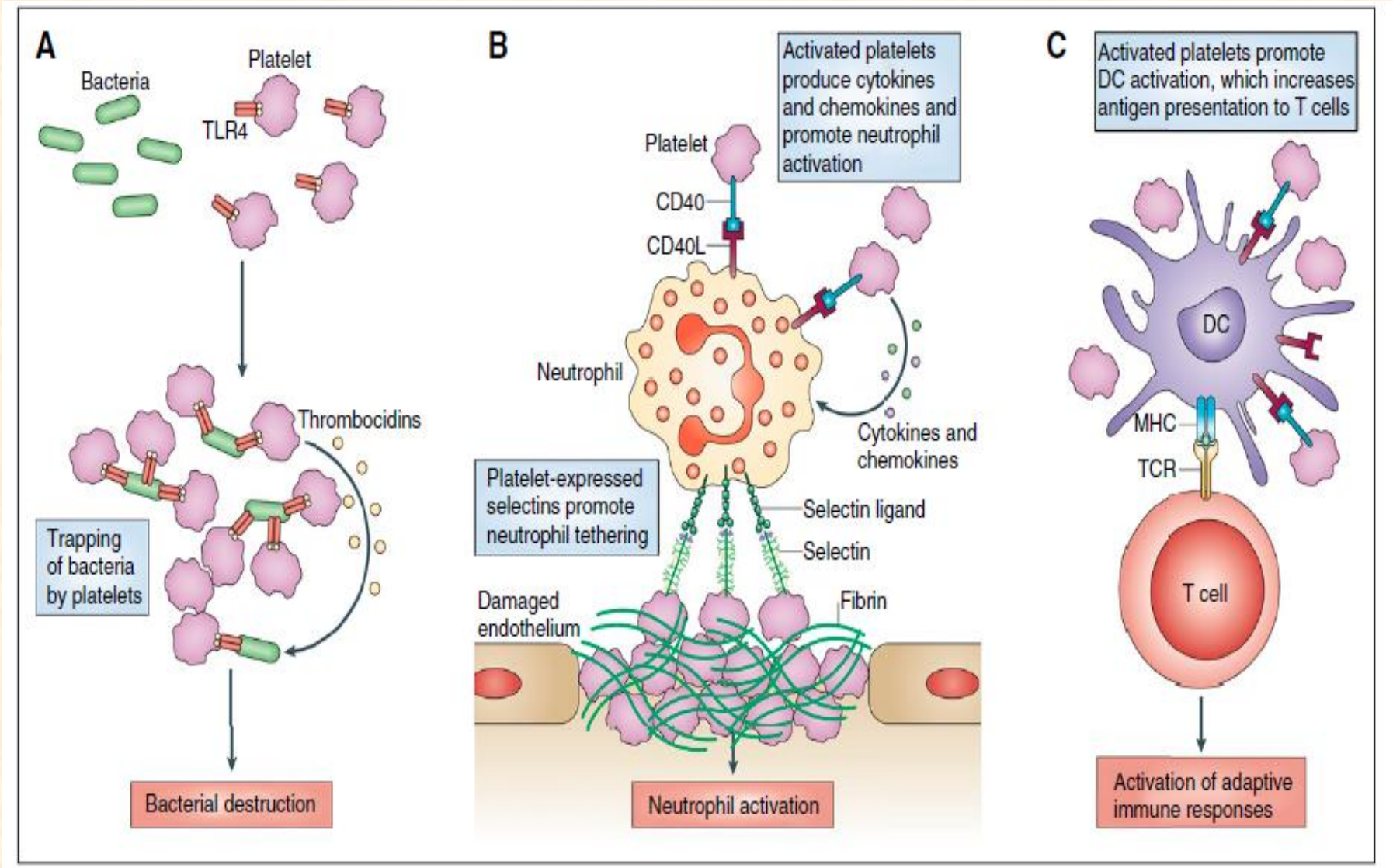
Levi M et al. *Thromb Res;* 149 (2017) 38-44

Platelets: The first defense!

- Aggregation, adhesion, activation
- Triggered by PAF/generated thrombin
- Release of granular contents
- Neutrophils/EC recruitment (p-selectin)
- Expression of TF on monocytes
- Recognition of Pathogen Molecular patterns (PAMPs)
- Antimicrobial peptides (thrombocidins)
- Vascular integrity (Ang-1)



Graham S et al. Blood 2016;127(24)



Graham S et al. Blood 2016;127(24)

Θρομβοπενία στη σήψη

Μειωμένη παραγωγή

TNF-α, IL-6, θρομβοποιητίνη (διεγείρουν την παραγωγή)

M-CSF (αιμοφαγοκυττάρωση)

- Αυξημένη κατανάλωση ή καταστροφή

Παραγωγή θρομβίνης, ανοσολογικοί μηχανισμοί

- Συσσώρευση στο σπλήνα ή στο ενδοθήλιο

Αλληλεπίδραση ενδοθηλιακών κυττάρων-αιμοπεταλίων στην αγγειακή επιφάνεια

Levi M, van der Poll T. *Int Care Med* 2013

Cells, pathways and cell mediators contributing to immunothrombosis

- Cytokines/chemokines
- Platelets/ Activated endothelial cells
- Tissue factor/ Coagulation proteases
- Neutrophil extracellular traps (NETs)
- Microparticles

Frantzeskaki F et al. *Respiration 2017*;93(3):212-225

Tissue factor (TF)

- The most important initiator of thrombin formation
- Membrane protein: fibroblasts of adventitia (brain, lung, kidney)
- Normally encrypted /Released on endothelial damage
- Epithelial, endothelial cells, monocytes, platelets, MP under inflammation- induced by PAMS, IL-6
- Endotoxemia: 125-fold increase in TF in monocytes
- NE degrades TFPI

Levi et al. *Crit Care Med* (2010) S24-34
Franco RF et al. *Blood* 96 (2)(2000)554-559

Normal anticoagulants

- Antithrombin system
- Activated protein C
- Tissue factor pathway inhibitor
- Impaired synthesis, ongoing cosumption, proteolytic degradation (NE)
- Downregulation of thrombomodulin and EPRC

Levi M et al. *Thromb Res* 149 (2017) 38-44

Inflammation and normal anticoagulants

- **Antithrombin**: reducing cytokines receptor expression
- **APC**
  - Attenuates endotoxin-induced TNF,IL-1, IL-6, IL-8 by monocytes
  - Activates the fibrinolytic process
  - Inhibition of PAI
  - Cytoprotective action

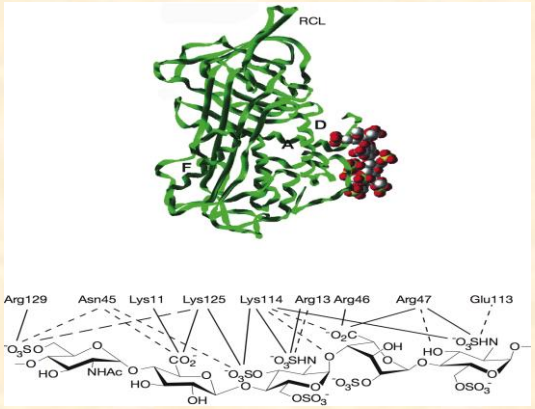
TFPI: antimicrobial activity against *E. coli*

P. aeruginosa

S. aureus

C. albicans,

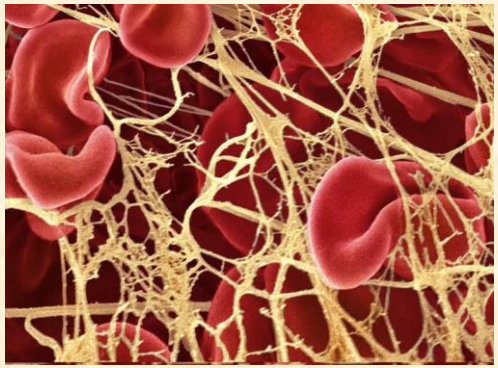
C. parapsilosis



Levi M et al. *Thromb Res* 149 (2017) 38-44

Tang et al. *The american journal of pathology 2007*

Inhibition of fibrinolysis



- Initially: acute release of plasminogen activators
- Increase in PAI-1
- Fibrin(ogen) fundamental to survive infection
- Fibrin formation: pathogen entrapment
- Bacteria: Fibrinolysis activators (omptins)
- Clots: Strong inducer of proinflammatory response
- Dysplasminogenemia: Enhanced survival during infection with *Y.pestis*, *streptococci*, *S.aureus*

Delabranche X et al. *Ann Intensive Care* (2017) 7;117

Protease-activated receptors (PAR)

- The molecular link between inflammation and coagulation
- On immune cells, platelets and endothelial cells
- PAR-1,3, 4: Activated by thrombin
- PAR-1,2: TF, TF/fVIIa, fXa
- Upregulation of inflammatory genes
- Antibacterial and antiviral TLR signaling
- PAR-1: APC, cytoprotective function

Bastarache JA et al, *Thorax 2007;62 (7):608-16*

Cells, pathways and cell mediators contributing to immunothrombosis

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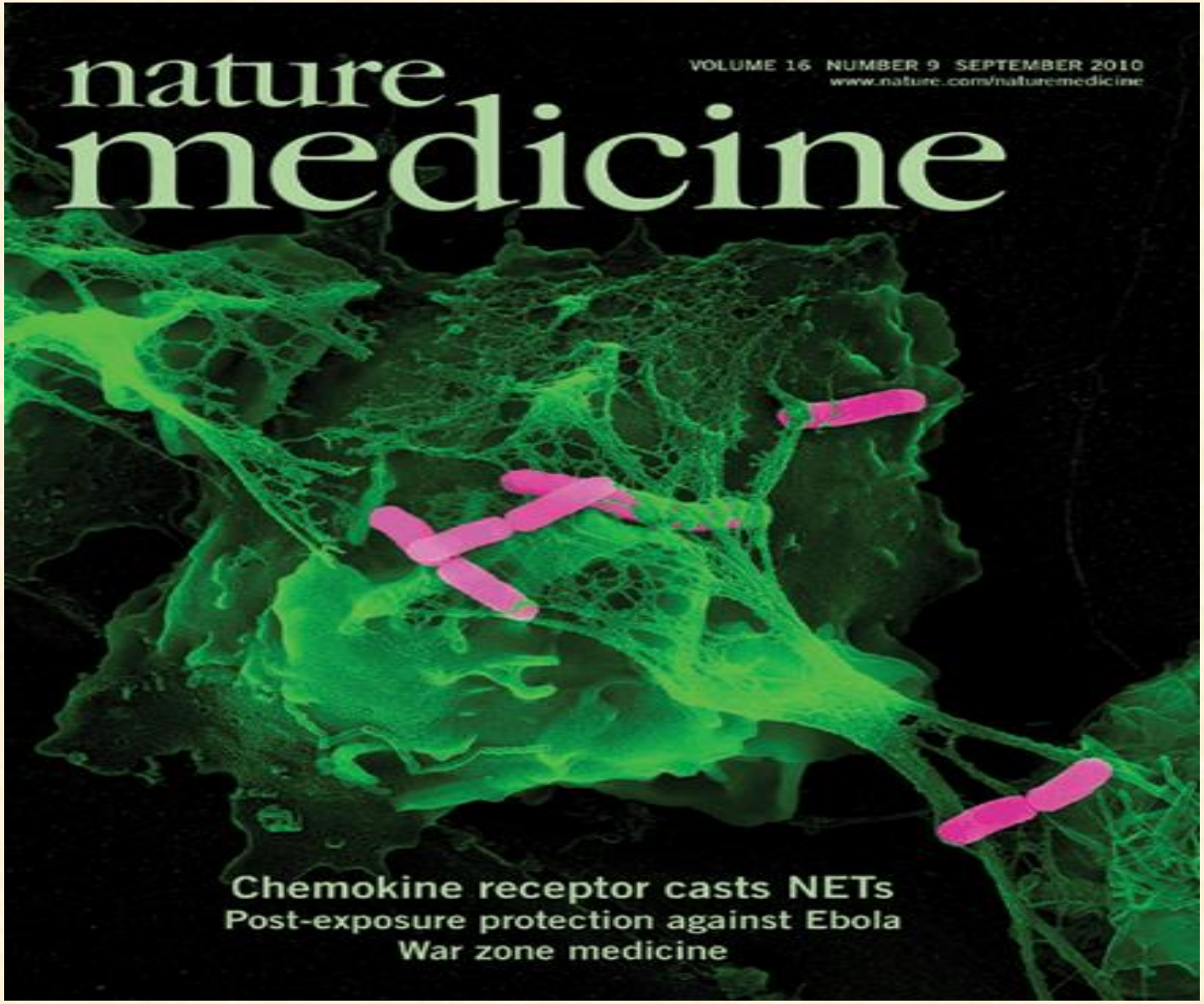
Frantzeskaki F et al. *Respiration 2017*;93(3):212-225

Neutrophil extracellular traps (NETs)

- Released from neutrophils on contact with bacteria
- Chromatine and proteins of activated neutrophils, MPO, NE
- Antimicrobial properties-trapping microorganisms
- Procoagulant activities-delivery of Tissue Factor
- Activation of coagulation factors
- Platelets trapping and activation
- Excessive inflammatory response
- Cytotoxic activity
- TRALI pathophysiology

Kaplan et al. *Journal of immunology* 2012. Sep 15;189 (6) 2689-95


nature
medicine
VOLUME 16 NUMBER 9 SEPTEMBER 2010
www.nature.com/naturemedicine
Chemokine receptor casts NETs
Post-exposure protection against Ebola
War zone medicine

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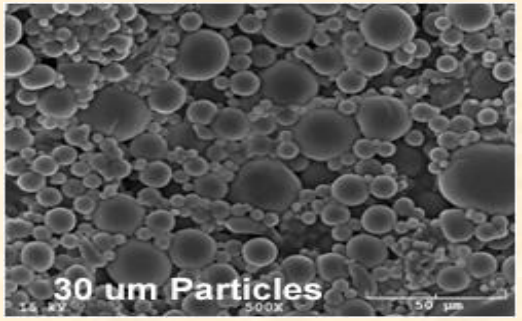
Frantzeskaki F et al. *Respiration 2017*;93(3):212-225

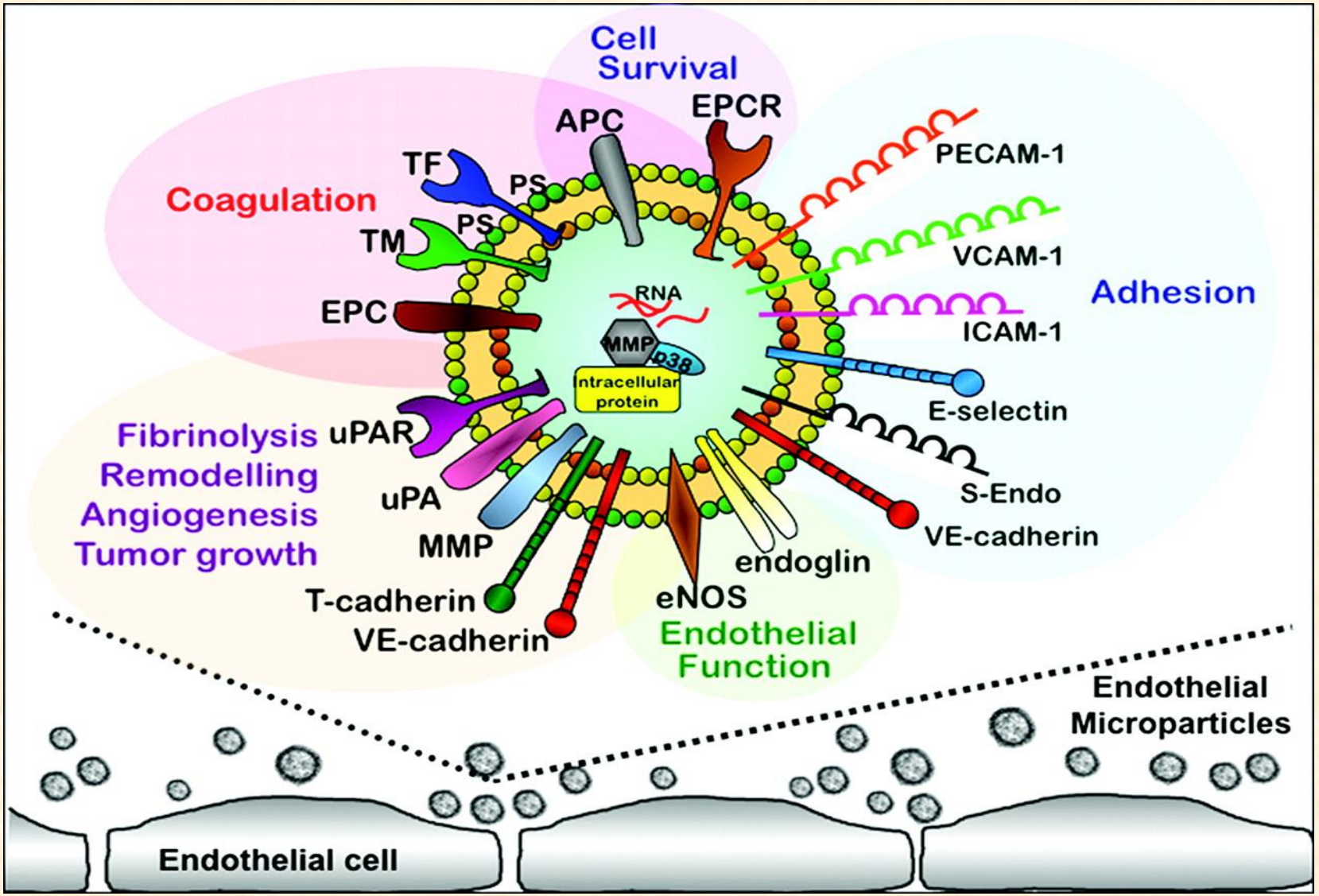
Microparticles

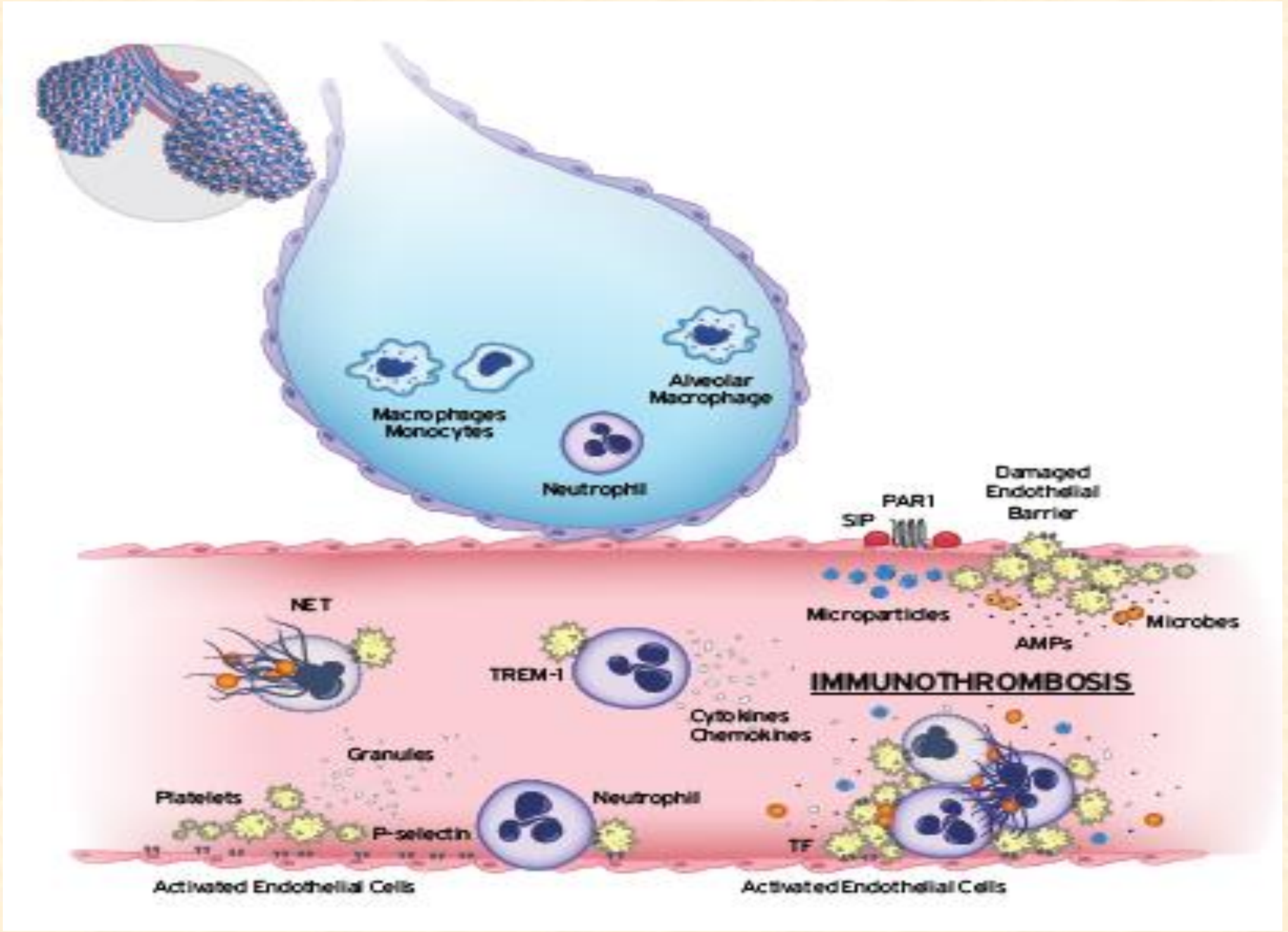


- Small vehicles modulating intracellular communication
- Platelets, EC, neutrophils, leukocytes
- Shed after mechanical injury and inflammation
- Proteins, RNA, phosphatidyloserine membrane
- Increased Tissue factor expression-Decreased TFPI
- 100-fold higher prothrombotic effects than platelets
- Proinflammatory and immunomodulatory effects
- Anticoagulant and anti-inflammatory effects

Bastarache JA et al. *Am J Physiol Lung Cell Mol Physiol 2009*

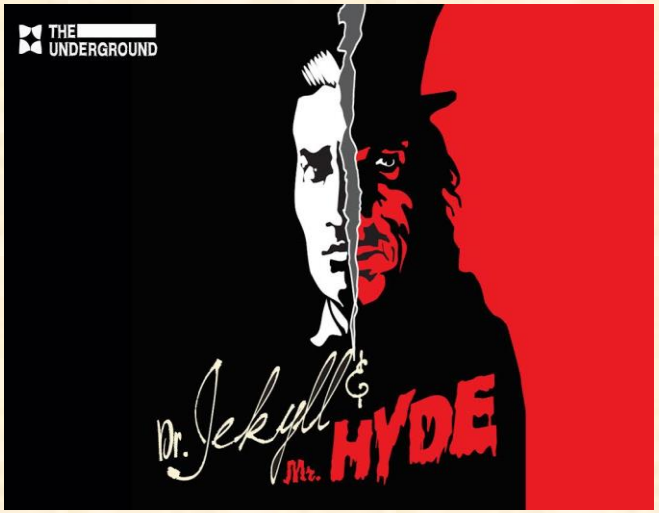
The faces of microparticles





Frantzeskaki F et al. *Respiration 2017*

The two faces of immunothrombosis



- Capturing pathogens
- Preventing tissue invasion
- Concentrating antimicrobial cells
- Thrombin-derived host defense peptides

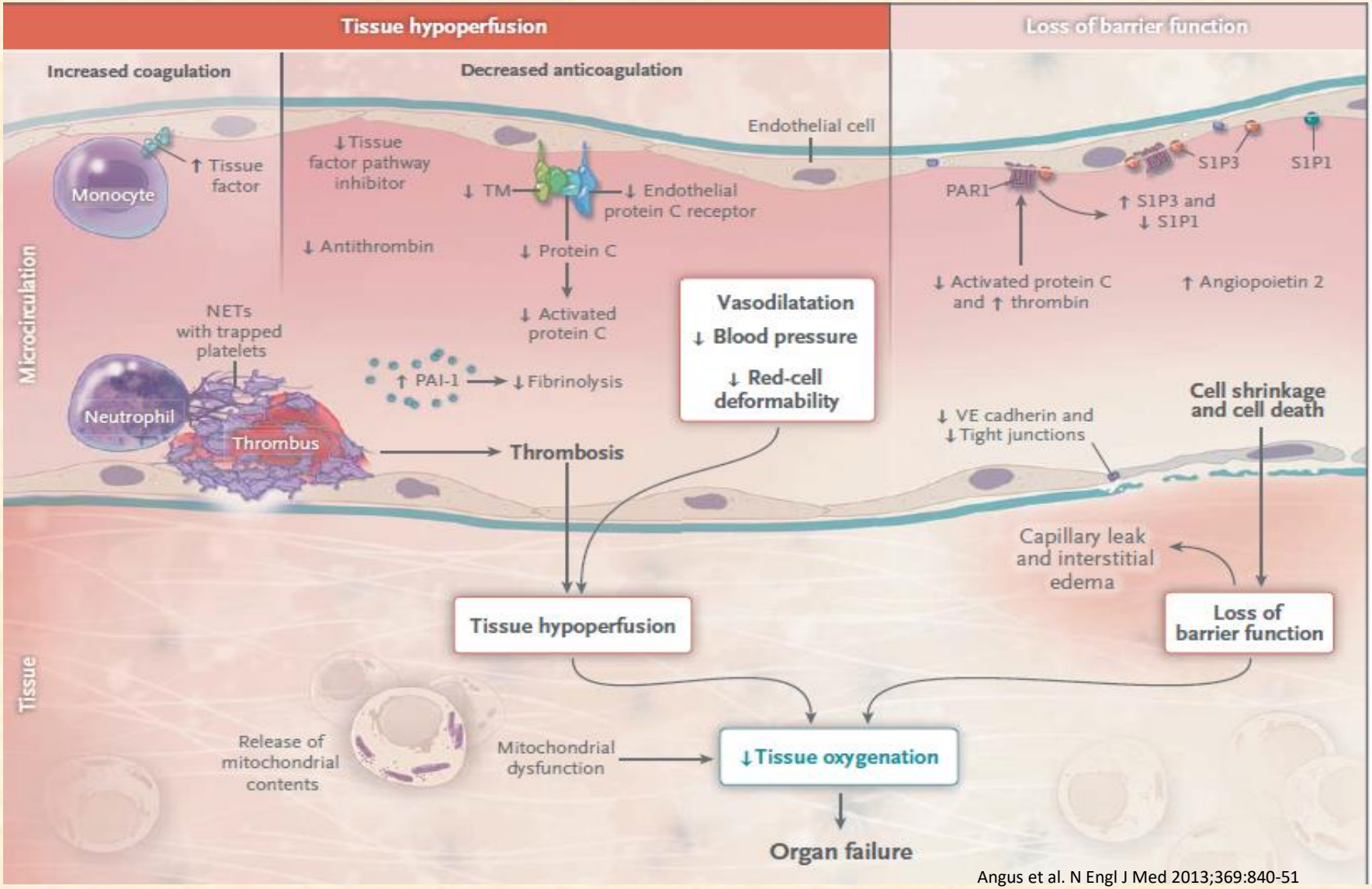
Excessive thrombin formation:
Fibrin deposits in microvessels:
Disseminated intravascular coagulation (DIC)

Delabranche X et al. *Ann Intensive Care* (2017) 7;117

DIC ("Death is coming")-35% of septic pt

"an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" in 2001.[15] The four labora-

International Society of Thrombosis and Hemostasis 2001



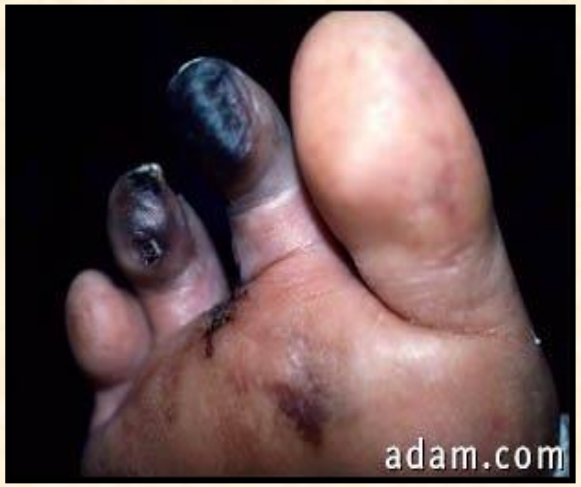
Angus et al. N Engl J Med 2013;369:840-51

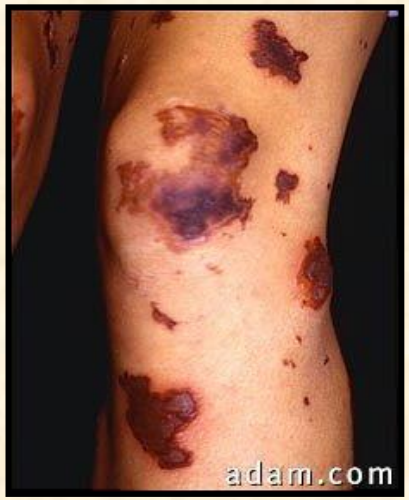
DIC

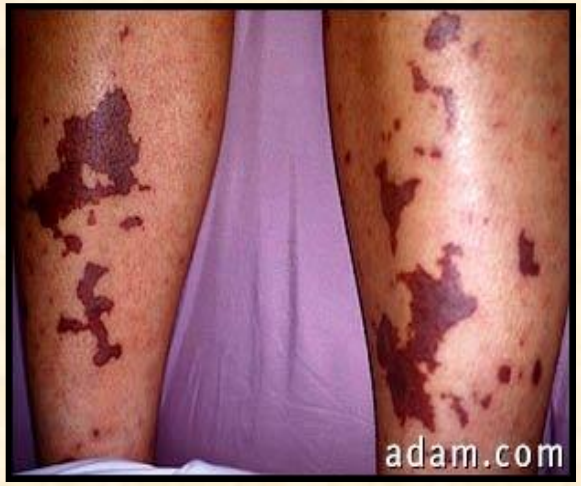
- Asymptomatic
- Haemorrhagic
- Thrombotic (organ failure)
- Massive bleeding (fibrinolytic)

ΚΛΙΝΙΚΗ ΕΙΚΟΝΑ ΔΕΠ

- Προειδοποιητικά στοιχεία είναι η εμφάνιση στο δέρμα πορφύρας, αιμορραγικών πομφολύγων, κυάνωση των άκρων, δερματικές νεκρώσεις και γάγγραινα
- Άλλα συμπτώματα
  - πυρετός, υπόταση,
  - οξέωση, υποξία,
  - αιμορραγία τραυμάτων και σημείων φλεβοκεντήσεων,
  - μεγάλα αιματώματα ή εν τω βάθει αιμορραγία ιστών







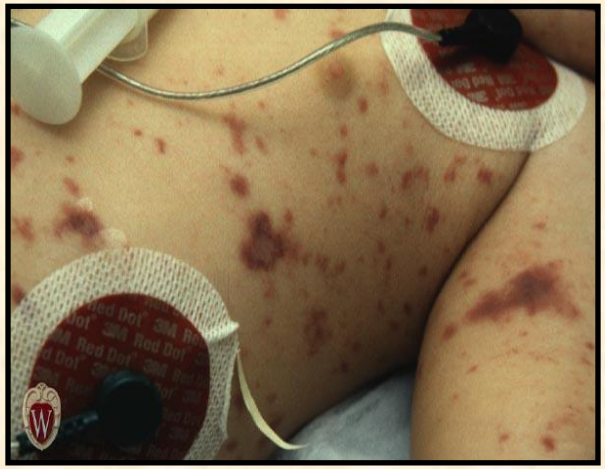


Table 2. Diagnostic Scoring System for Disseminated Intravascular Coagulation (DIC).*

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

- If yes, proceed with this algorithm
- If no, do not use this algorithm

Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)

Score the test results as follows:

- Platelet count: 50,000 to 100,000 per mm^3, 1 point; <50,000 per mm^3, 2 points
- Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points
- Prolonged prothrombin time: <3 sec, 0 points; ≥3 sec but <6 sec, 1 point; ≥6 sec, 2 points
- Fibrinogen level: ≥1 g per liter, 0 points; <1 g per liter, 1 point

Calculate the score as follows:

- ≥5 points: compatible with overt DIC; repeat scoring daily
- <5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

Intensity of coagulopathy:
Strongly associated with
survival rates in critically ill pts

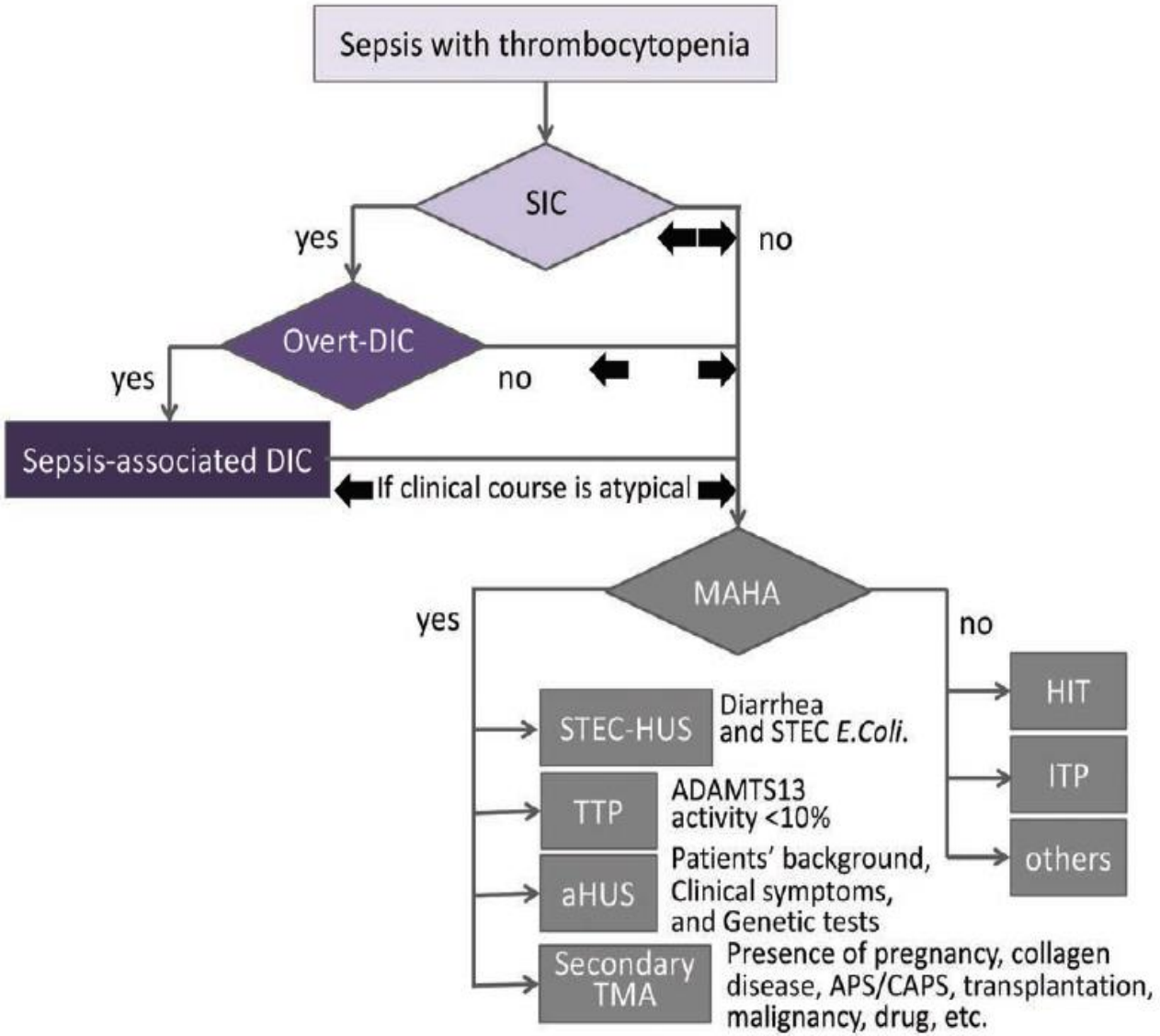
Hunt B. *N Engl J Med* 2014

Table 1. Sepsis-induced Coagulopathy and International Society on Thrombosis and Haemostasis Overt-DIC Scoring Systems

	Points	SIC	Overt DIC
Platelet count ($\times 10^9$ l^{-1})	2	< 100	< 50
	1	≧ 100, < 150	≧ 50, < 100
FDP or D-dimer			Strong increase
			Moderate increase
			–
Prothrombin time–INR			≧ 6 s
			≧ 3, < 6 s
Fibrinogen (g/l)			< 1
Total SOFA score	≧ 2	2	–
	1	1	–

SIC vs DIC
Higher sensitivity
Earlier diagnosis

T.Iba, JH Levy. Anesthesiology 2020; 132, 1238-45



T.Iba, JH Levy. Anesthesiology 2020; 132, 1238-45

Diagnosis of DIC

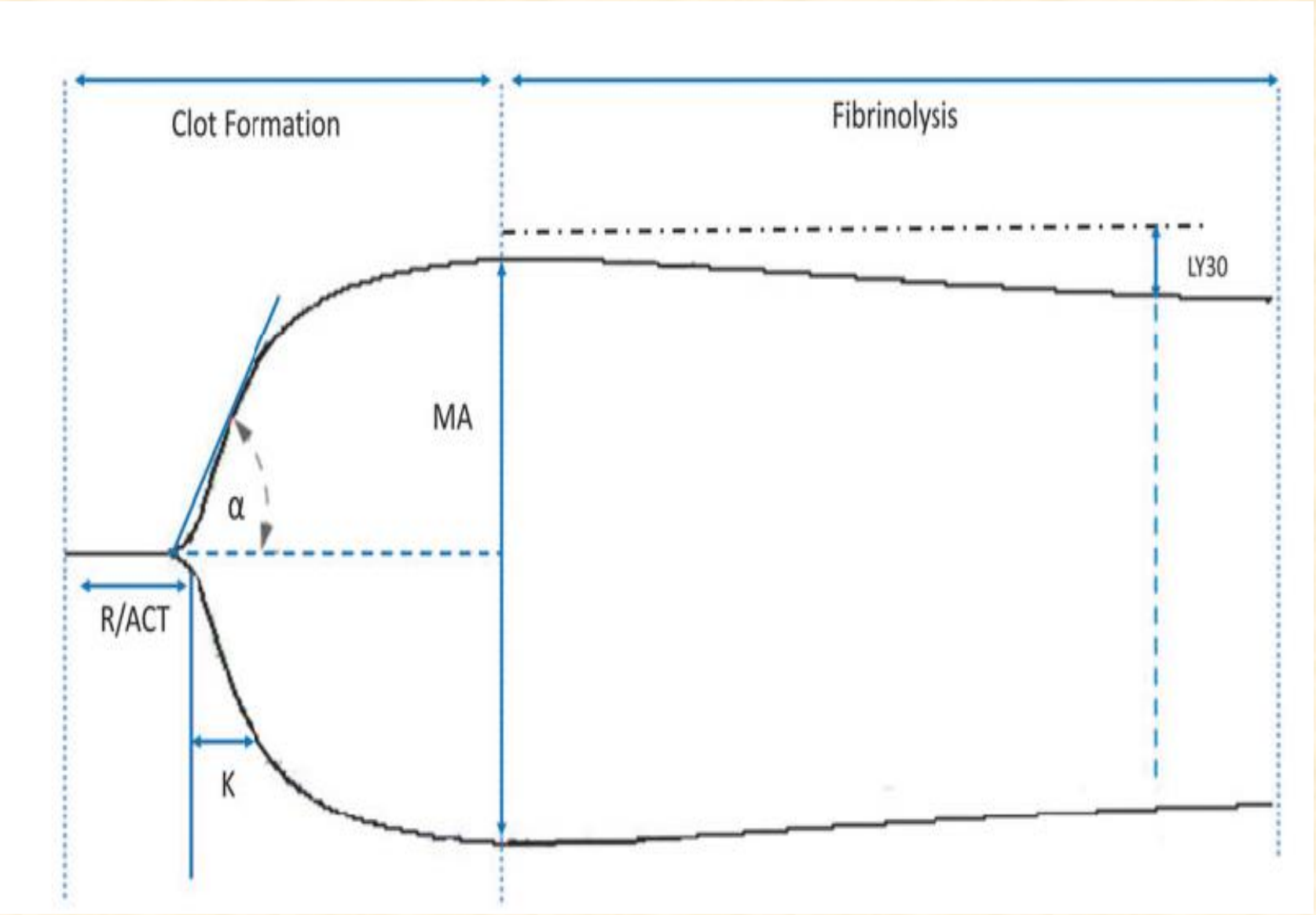
- Presence of underlying disease-MODS
- Elevation PT, aPTT
- Prothrombin fragment 1+2,thrombin-antithrombin complexes
- Fibrinogen degradation products (FDPs), D-dimers
- Fibrinogen: Sensitivity 30%
- Decrease AT, TFPI,PC?
- TEG, ROTEM: To appraise the state of coagulation

Levi M et al. *Thromb Res* 149 (2017) 38-44

POC τεχνικές-Θρομβοελαστογραφία (TEG)

- Σφαιρικές δοκιμασίες: Αρχική παραγωγή θρομβίνης στο πλάσμα
- TEG: Χρόνος έναρξης δημιουργίας θρόμβου, δυναμική και σταθερότητα του θρόμβου, ινωδόλυση, υπερπηκτικές καταστάσεις
- Κατευθυνόμενη αιμοστατική θεραπεία (2C)
- Συσχέτιση αποτελεσμάτων με επιβίωση, οργανική δυσλειτουργία
- Πρώιμοι βιοδείκτες στη σοβαρή σήψη

Meybohm et al.*Critical Care* 2013


Clot Formation
Fibrinolysis
LY30
MA
α
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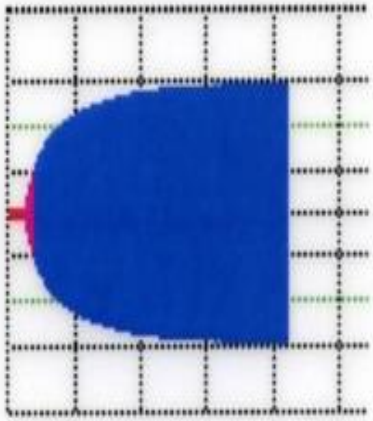

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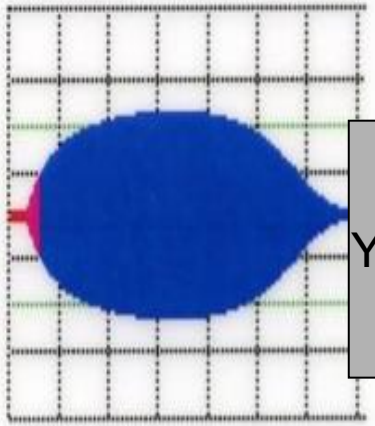
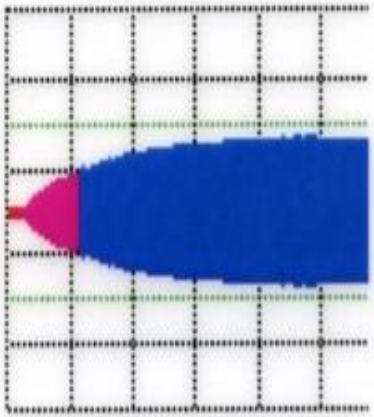


Υπερινωδόλυση



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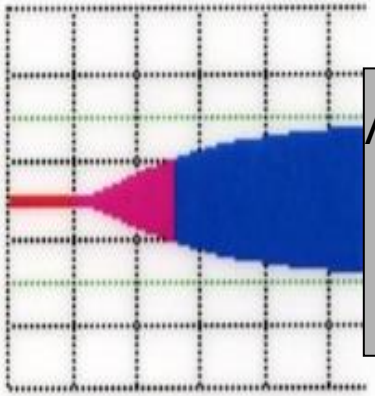


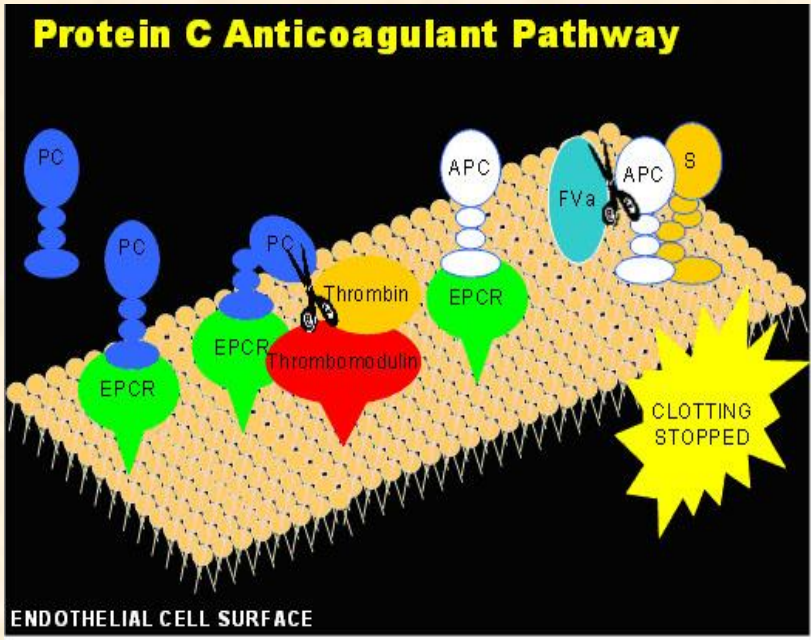
Λήψη ηπαρίνης
ή
έλλειψη
παράγοντα

Supportive treatment in DIC

- Haemostasis is mandatory to survive sepsis
- Rapid and timely treatment of the underlying disease
- Plasma, platelets, fibrinogen: active bleeding or at risk, invasive procedures
- Prothrombin complex concentrate
- Heparin: prophylaxis, thromboembolism, purpura fulminans
- Antithrombin: Shortening of duration of coagulopathy, improvement in organ function

Levy JH et al. *Thromb. Haemost*. 115(4)2016

Recombinant soluble thrombomodulin



A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation.
Vincent JL . *Crit Care Med*. 2013 Sep;41(9):2069-79

750 pts sepsis and DIC
28 d mortality: 17.8% vs 21.6% in placebo group
Lower markers of coagulation
No differences in bleeding

Kato and Matsuura *Thrombosis Journal* (2018) 16:19
https://doi.org/10.1186/s12959-018-0172-6

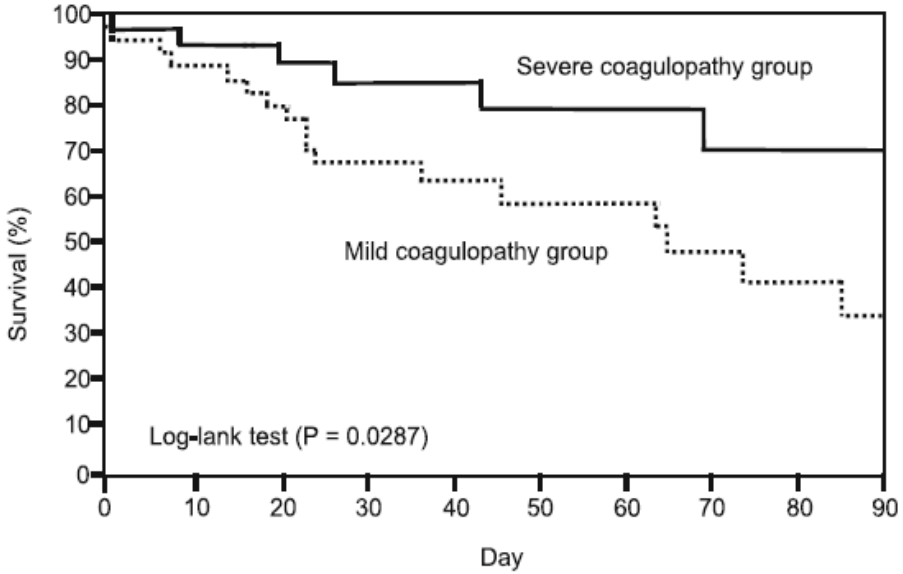
Thrombosis Journal

RESEARCH Open Access

Recombinant human soluble thrombomodulin improves mortality in patients with sepsis especially for severe coagulopathy: a retrospective study

Takahiro Kato[1*] and Katsuhiko Matsuura[2]

69 pts mild or severe coagulopathy (DIC)



New pathways and targets

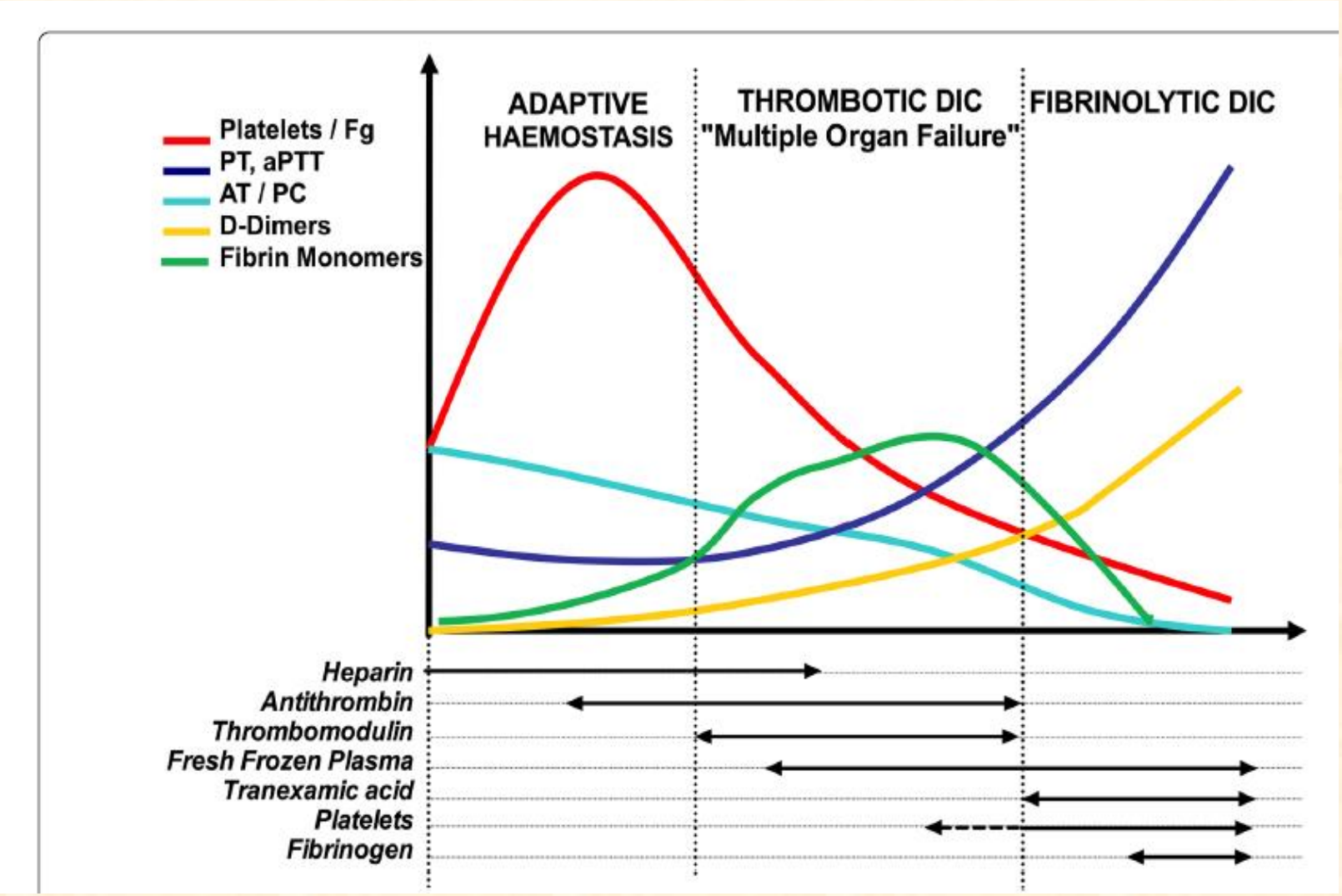
- Past target: restoration of physiological anticoagulation
- Molecules with less anticoagulant properties but with antiinflammatory effects

<u>Non anticoagulant heparin</u>:

- inhibits adhesion molecules
- affects NF-κβ, cytokines
- attenuates endothelial cell dysfunction
- strong affinity with histones-cytotoxic activity

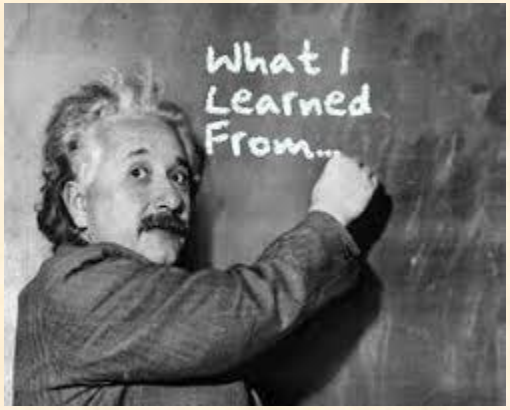
New target: glycocalyx covering the endothelial surface

Natural history of hemostasis during infection and therapeutics

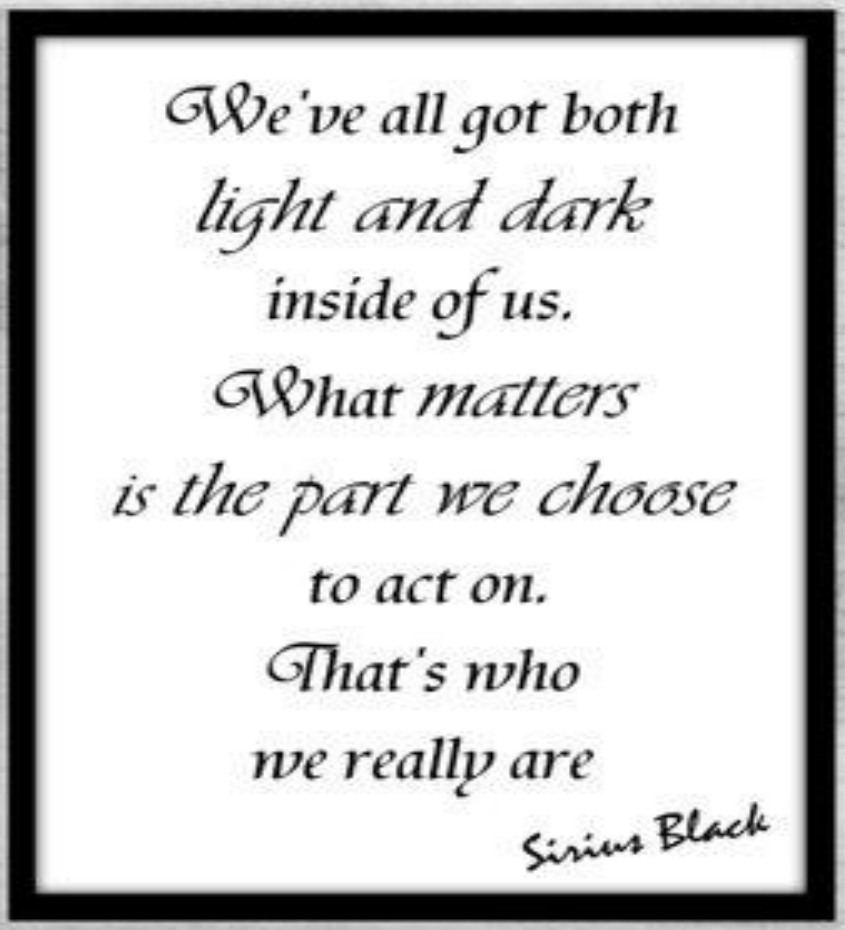


Delabranche X et al. *Ann Intensive Care* (2017) 7;117

Take home messages



- Coagulation disorders in sepsis might be a friend or an enemy
- A continuous crosstalk between immune system and blood coagulation disorders
- Immunothrombosis: the first line of host defense to endothelial injury
- DIC: an overwhelmed haemostasis activation leading to MODS
- Future studies: how to avoid coagulation overactivation without compromising the beneficial contribution on inflammation



Ευχαριστώ πολύ !!!