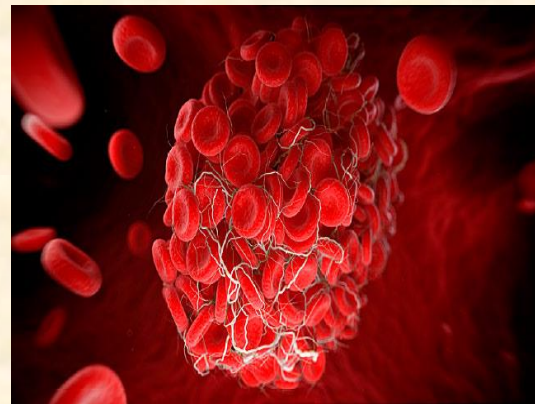


# Coagulation disorders in sepsis: Disseminated Intravascular Coagulation

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Pulmonologist-Intensivist  
2<sup>nd</sup> 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)

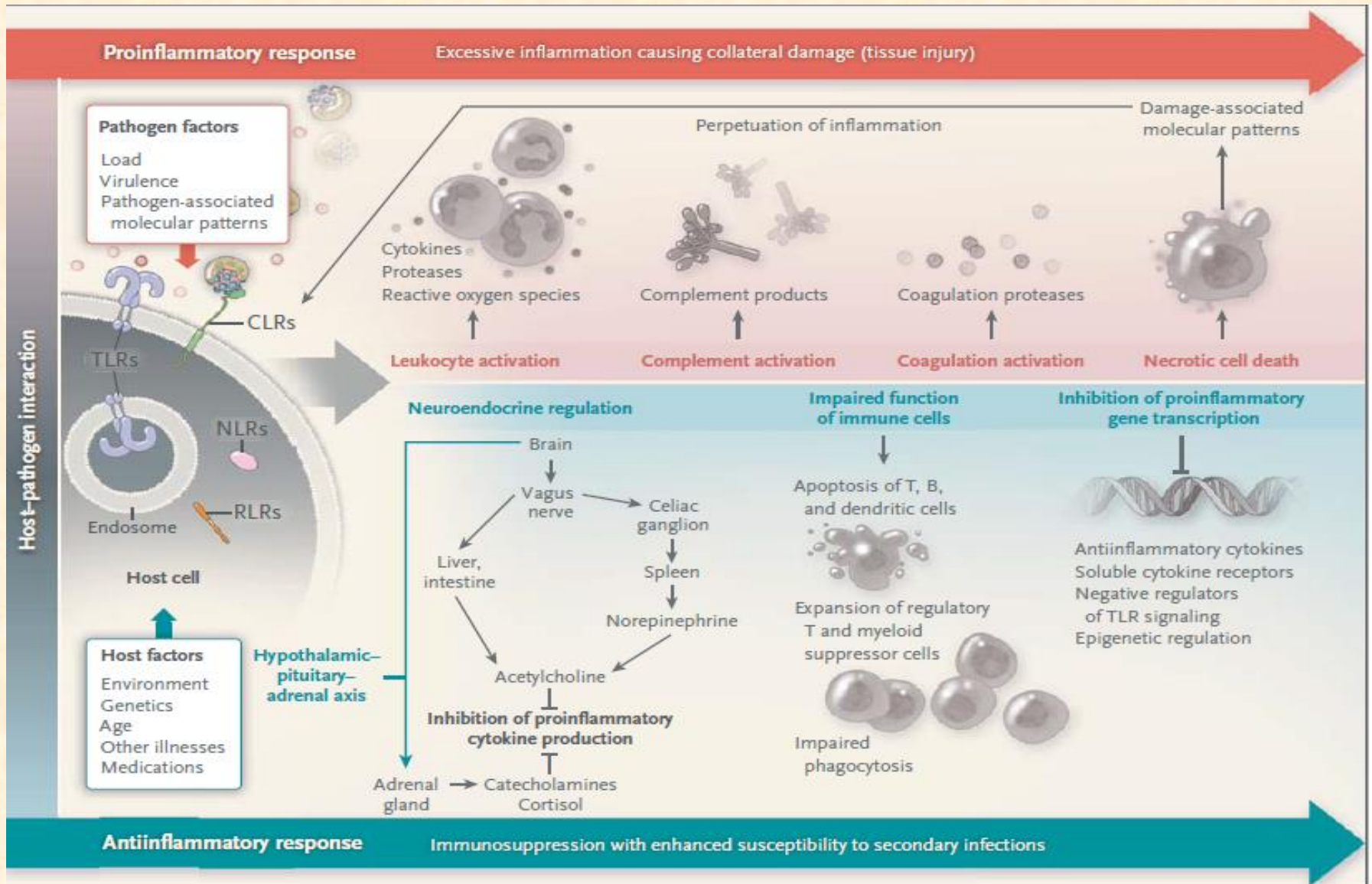
Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell 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



**TABLE 1. Diagnostic Criteria for Sepsis**

**Infection, documented or suspected, and some of the following:**

General variables

- Fever ( $> 38.3^{\circ}\text{C}$ )
- Hypothermia (core temperature  $< 36^{\circ}\text{C}$ )
- Heart rate  $> 90/\text{min}^{-1}$  or more than two SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance ( $> 20\text{ mL/kg}$  over 24 hr)
- Hyperglycemia (plasma glucose  $> 140\text{ mg/dL}$  or  $7.7\text{ mmol/L}$ ) in the absence of diabetes

Inflammatory variables

- Leukocytosis (WBC count  $> 12,000\ \mu\text{L}^{-1}$ )
- Leukopenia (WBC count  $< 4000\ \mu\text{L}^{-1}$ )
- 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  $< 90\text{ mm Hg}$ , MAP  $< 70\text{ mm Hg}$ , or an SBP decrease  $> 40\text{ mm Hg}$  in adults or less than two SD below normal for age)

Organ dysfunction variables

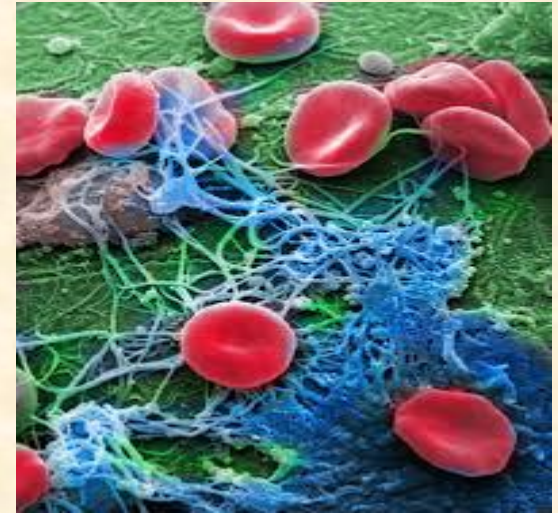
- Arterial hypoxemia ( $\text{Pao}_2/\text{Fio}_2 < 300$ )
- Acute oliguria (urine output  $< 0.5\text{ mL/kg/hr}$  for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase  $> 0.5\text{ mg/dL}$  or  $44.2\ \mu\text{mol/L}$
- Coagulation abnormalities (INR  $> 1.5$  or aPTT  $> 60\text{ s}$ )
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count  $< 100,000\ \mu\text{L}^{-1}$ )
- Hyperbilirubinemia (plasma total bilirubin  $> 4\text{ mg/dL}$  or  $70\ \mu\text{mol/L}$ )

Tissue perfusion variables

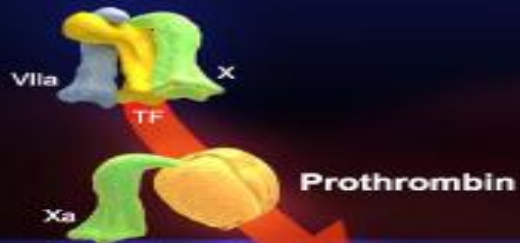
- Hyperlactatemia ( $> 1\text{ mmol/L}$ )
- Decreased capillary refill or mottling

# Burden of clinically relevant coagulopathy in sepsis

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



**Stimulus Phase**



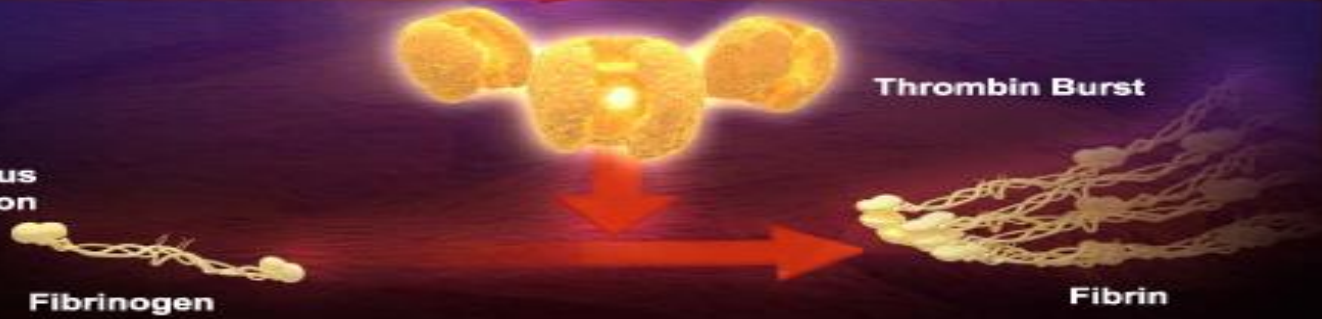
**Initiation Phase**



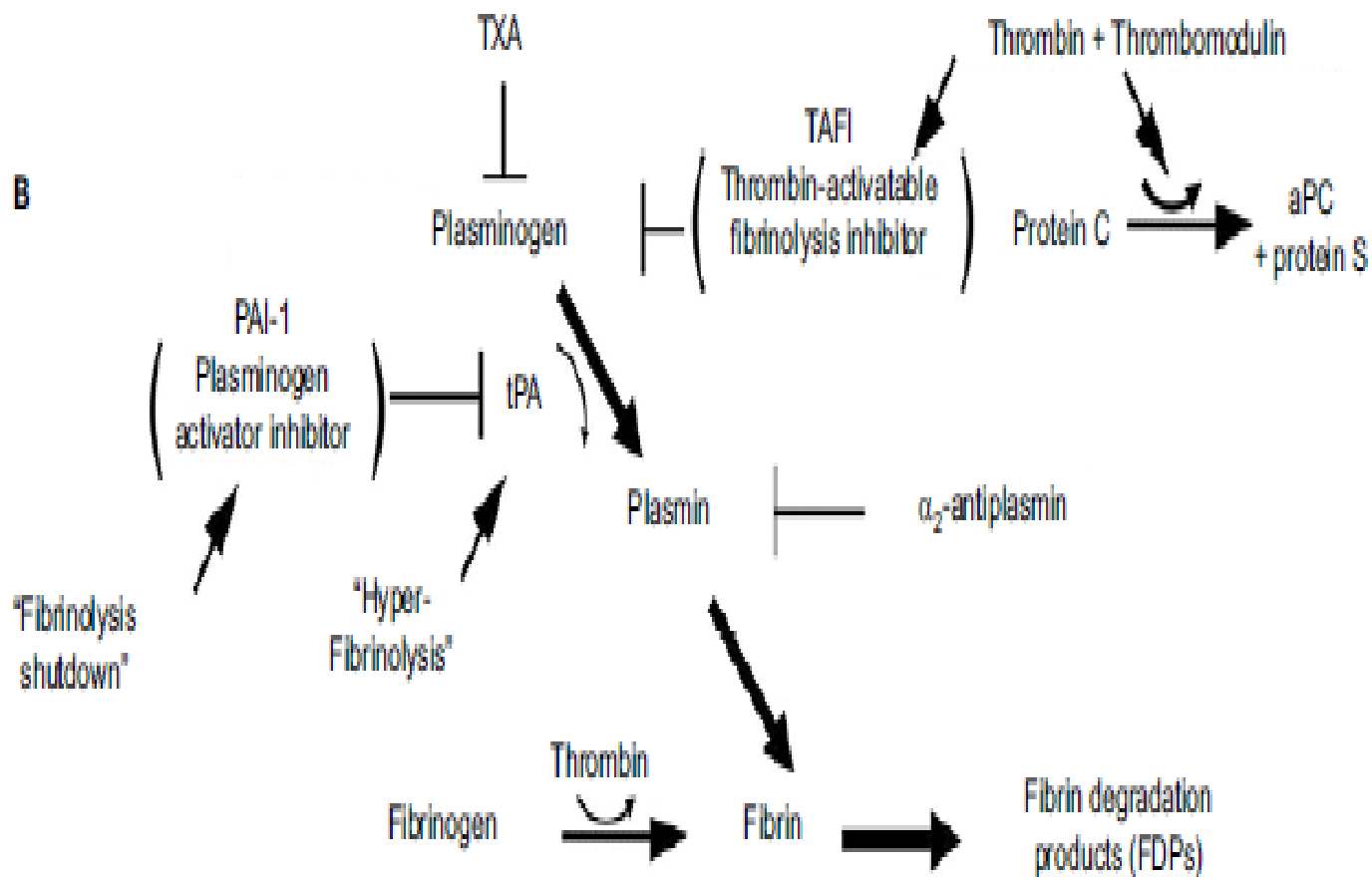
**Amplification Phase**



**Thrombus Formation**



# Fibrinolytic pathway and endogenous mediators



# Regulation of the Cascade

Vessel or Tissue Injury

Factor VII

Tissue Factor

TFPI

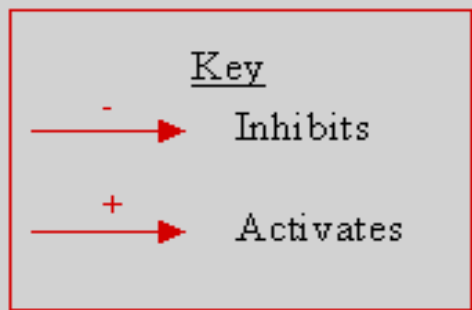
Factor VIIa-Tissue Factor complex

Antithrombin III

Protein C & Protein S

Thrombomodulin

The Fibrinolytic System



Factor XI

Factor XIa

Factor IX

**Factor VIIIa**

**Factor IXa**

Factor VIII

Factor X

**Factor Xa**

Factor V

**Factor Va**

Prothrombin

**Thrombin**

Fibrinogen

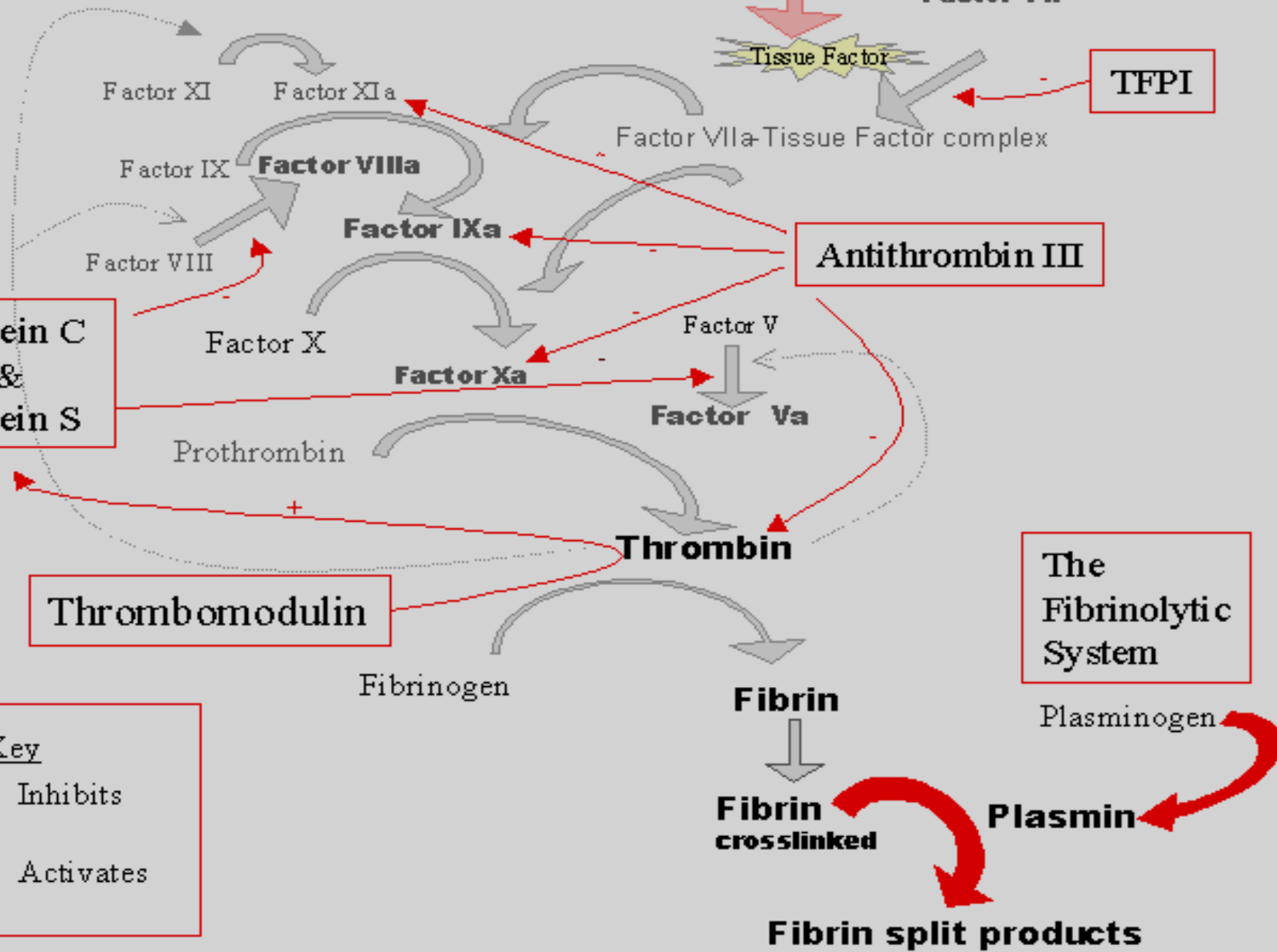
**Fibrin**

**Fibrin crosslinked**

**Plasmin**

**Fibrin split products**

Plasminogen

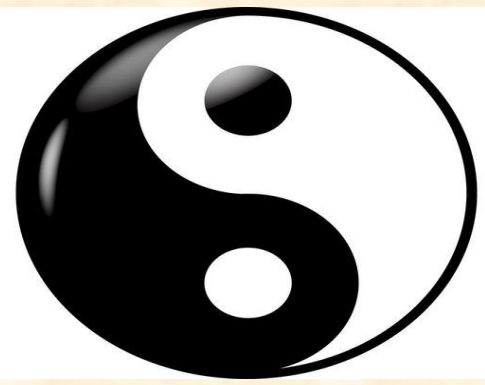




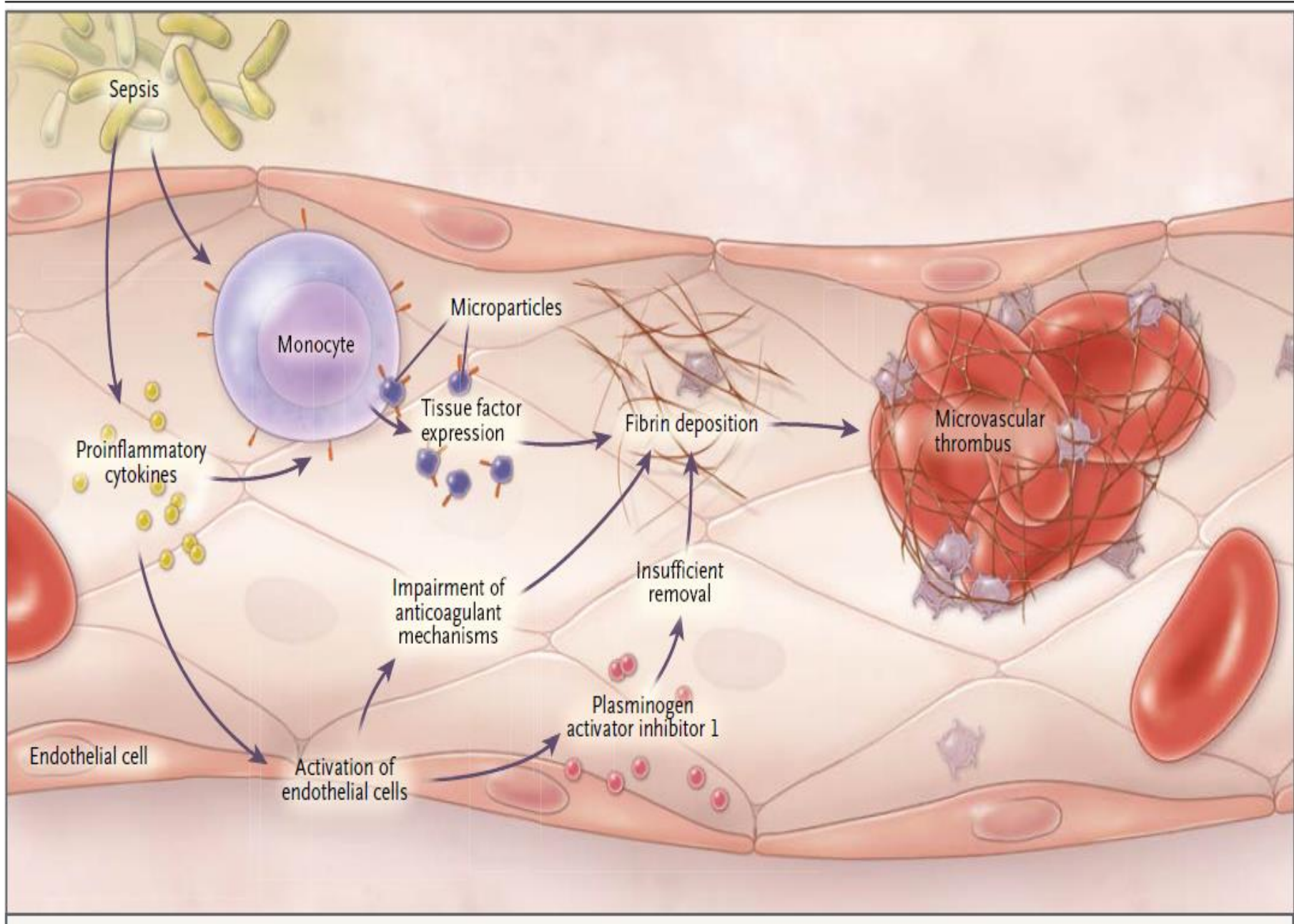
A 3D scientific illustration showing a large, textured brown blood clot at the top right. Below it, several blue and purple translucent structures represent thrombin molecules. The background features a network of yellow and red vessels, with small red and blue particles scattered throughout. The text "The pivotal role of thrombin" is centered in yellow.

# The pivotal role of thrombin

# The role of thrombin

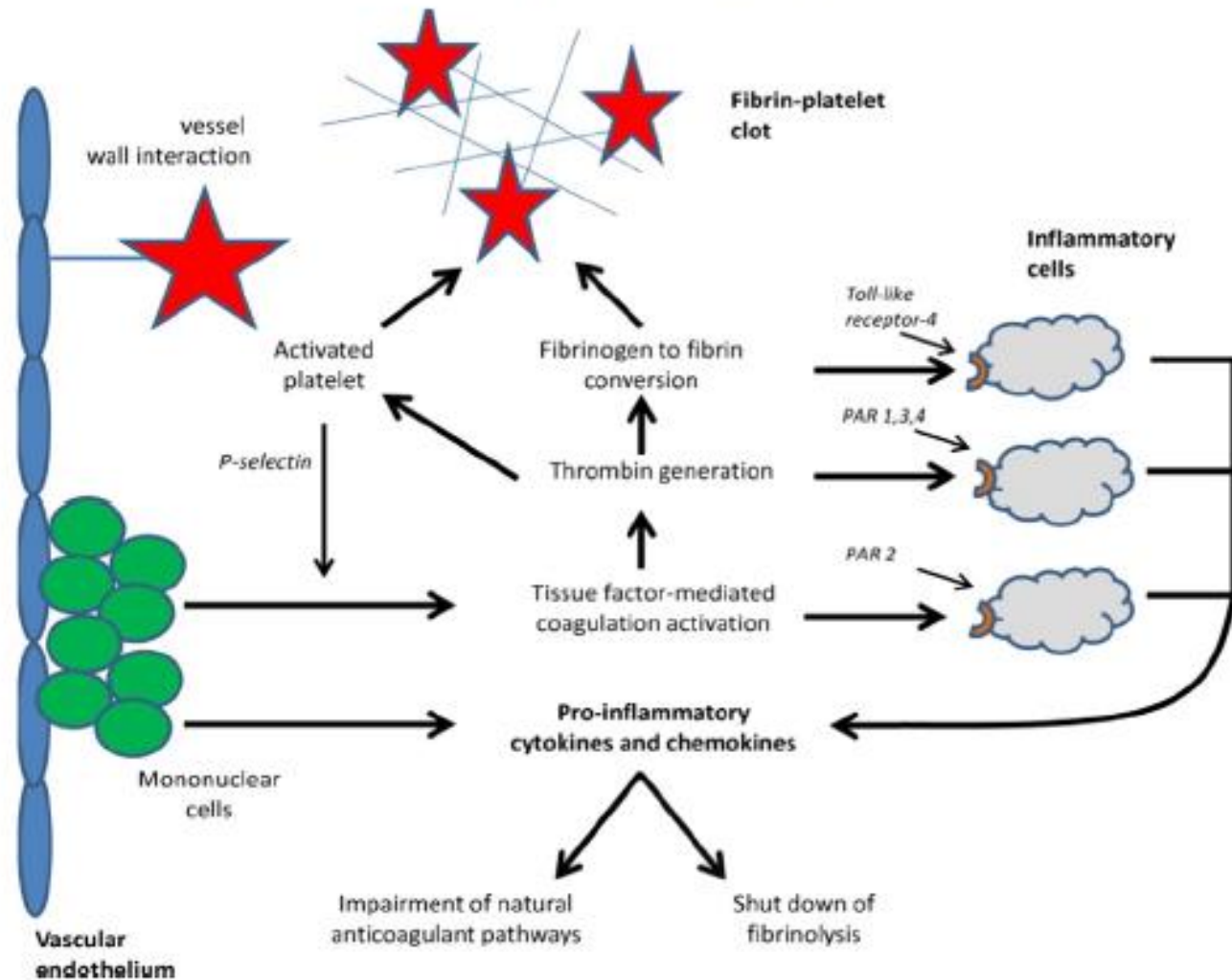


- Thrombus formation (via fibrin network)
- Platelets' activation
- Anticoagulation (via protein C)
- Inhibition of fibrinolysis (TAFI)
- Cytokines production
- Vascular permeability and tone (via endothelial cells receptors)
- Precursor of peptides with antimicrobial properties



# Crosstalks between inflammation and coagulation

M. Levi, T. van der Poll / *Thrombosis Research* 149 (2017) 38–44



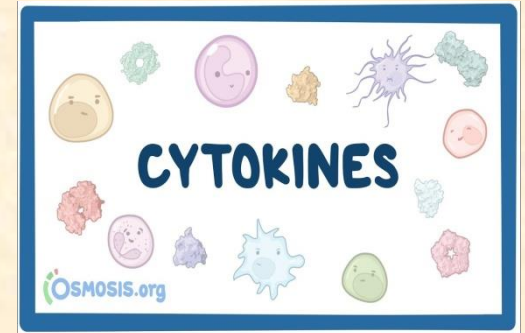
# Immunothrombosis

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

# Cells, pathways and cell mediators contributing to immunothrombosis

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

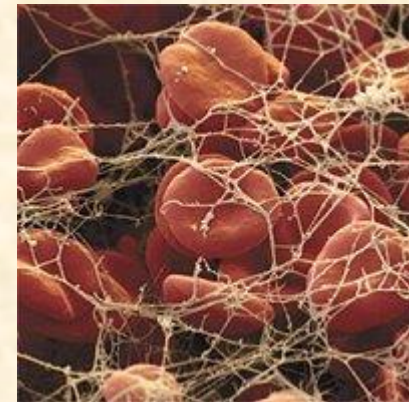
# Cytokines induced activation of coagulation



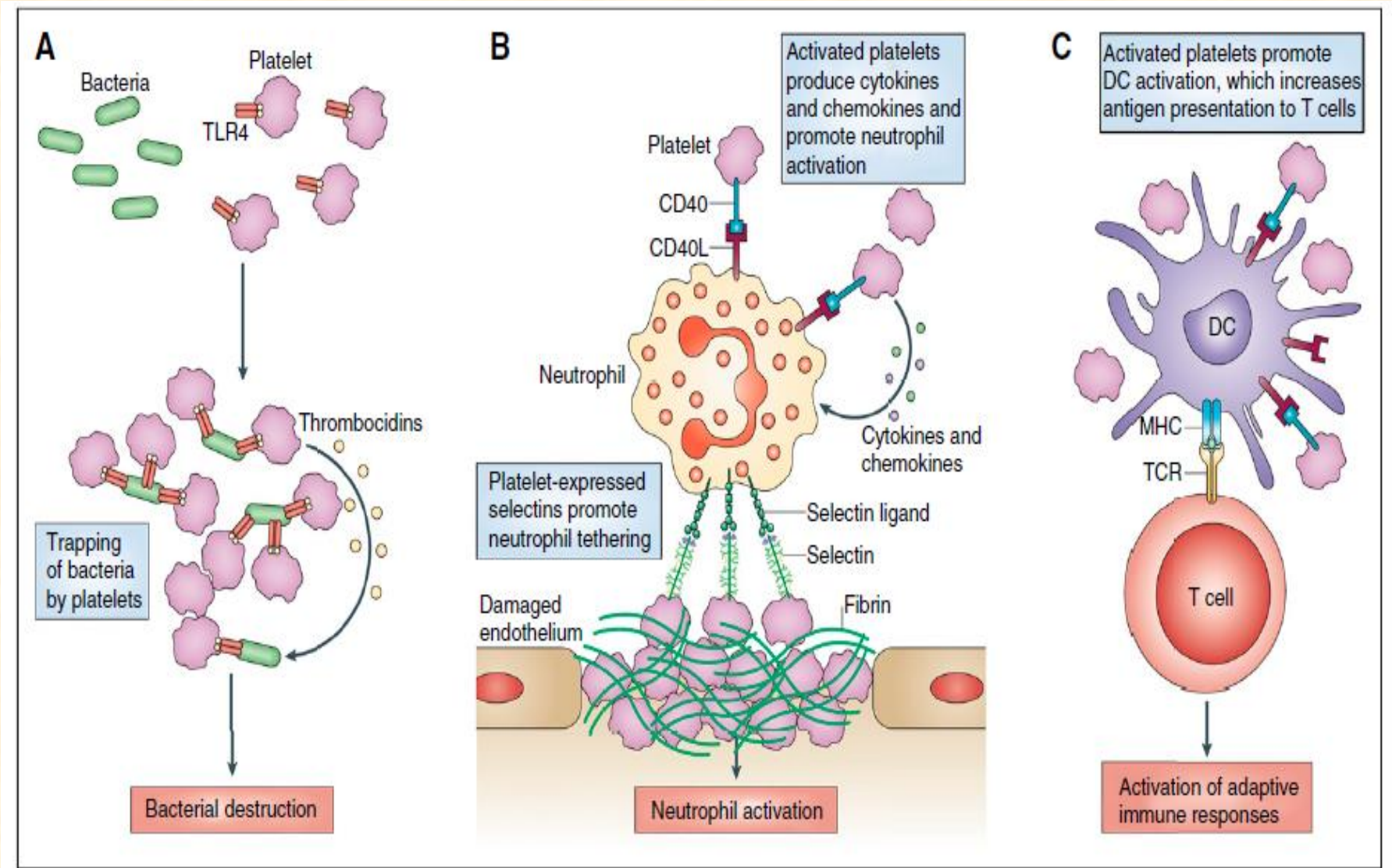
- TNF: The first detectable mediator-procoagulant effects
- IL-6, IL-1
- Antiinflammatory cytokines: IL-10/ inhibition of hemostasis
- Impairment of natural anticoagulant pathways
- Shut down of fibrinolysis

# 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)







# Θρομβοπενία στη σήψη

## Μειωμένη παραγωγή

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

M-CSF (αιμοφαγοκυττάρωση)

- Αυξημένη κατανάλωση ή καταστροφή

Παραγωγή θρομβίνης, ανοσολογικοί μηχανισμοί

- Συσώρευση στο σπλήνα ή στο ενδοθήλιο

Αλληλεπίδραση ενδοθηλιακών κυττάρων-αιμοπεταλίων στην αγγειακή επιφάνεια

# Cells, pathways and cell mediators contributing to immunothrombosis

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

# 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 consumption, proteolytic degradation (NE)
- Downregulation of thrombomodulin and EPCR

# 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

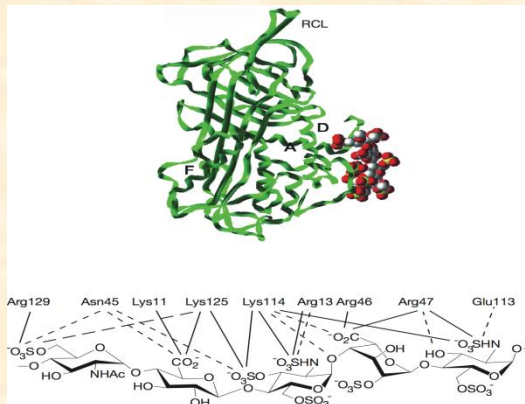
**TFPI:** antimicrobial activity against *E. coli*

*P. aeruginosa*

*S. aureus*

*C. albicans,*

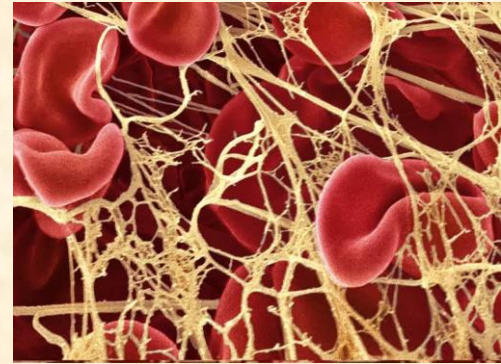
*C. parapsilosis*



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*

# 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



# Cells, pathways and cell mediators contributing to immunothrombosis

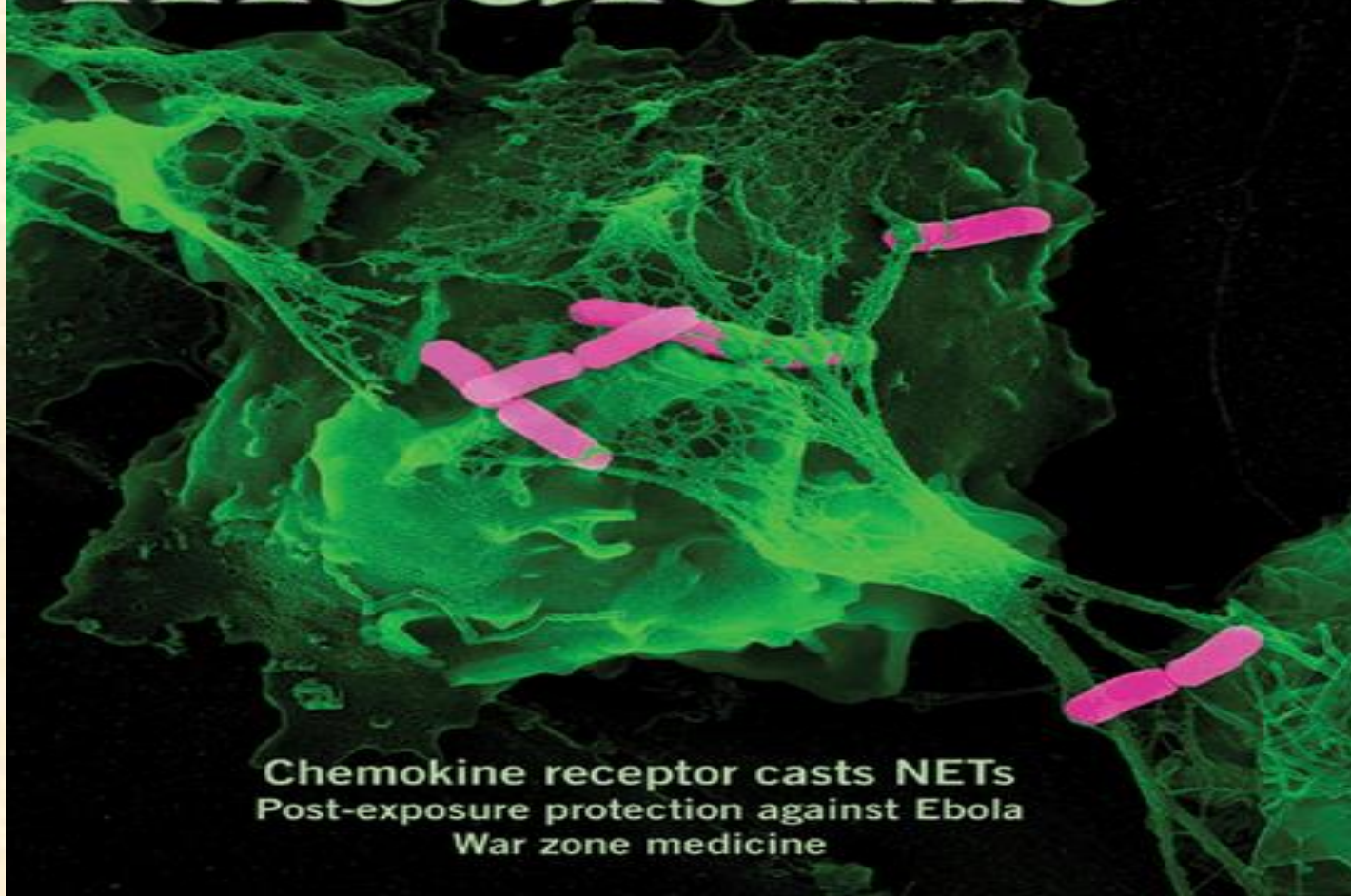
- Cytokines/chemokines
- Platelets/ Activated endothelial cells
- Tissue factor/ Coagulation proteases
- Neutrophil extracellular traps (NETs)
- Microparticles

# 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

# nature medicine

VOLUME 16 NUMBER 9 SEPTEMBER 2010  
[www.nature.com/naturemedicine](http://www.nature.com/naturemedicine)

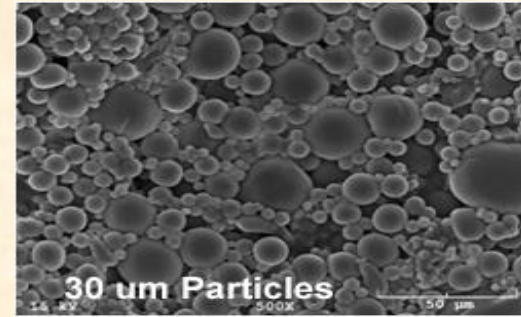


**Chemokine receptor casts NETs**  
Post-exposure protection against Ebola  
War zone medicine

# Cells, pathways and cell mediators contributing to immunothrombosis

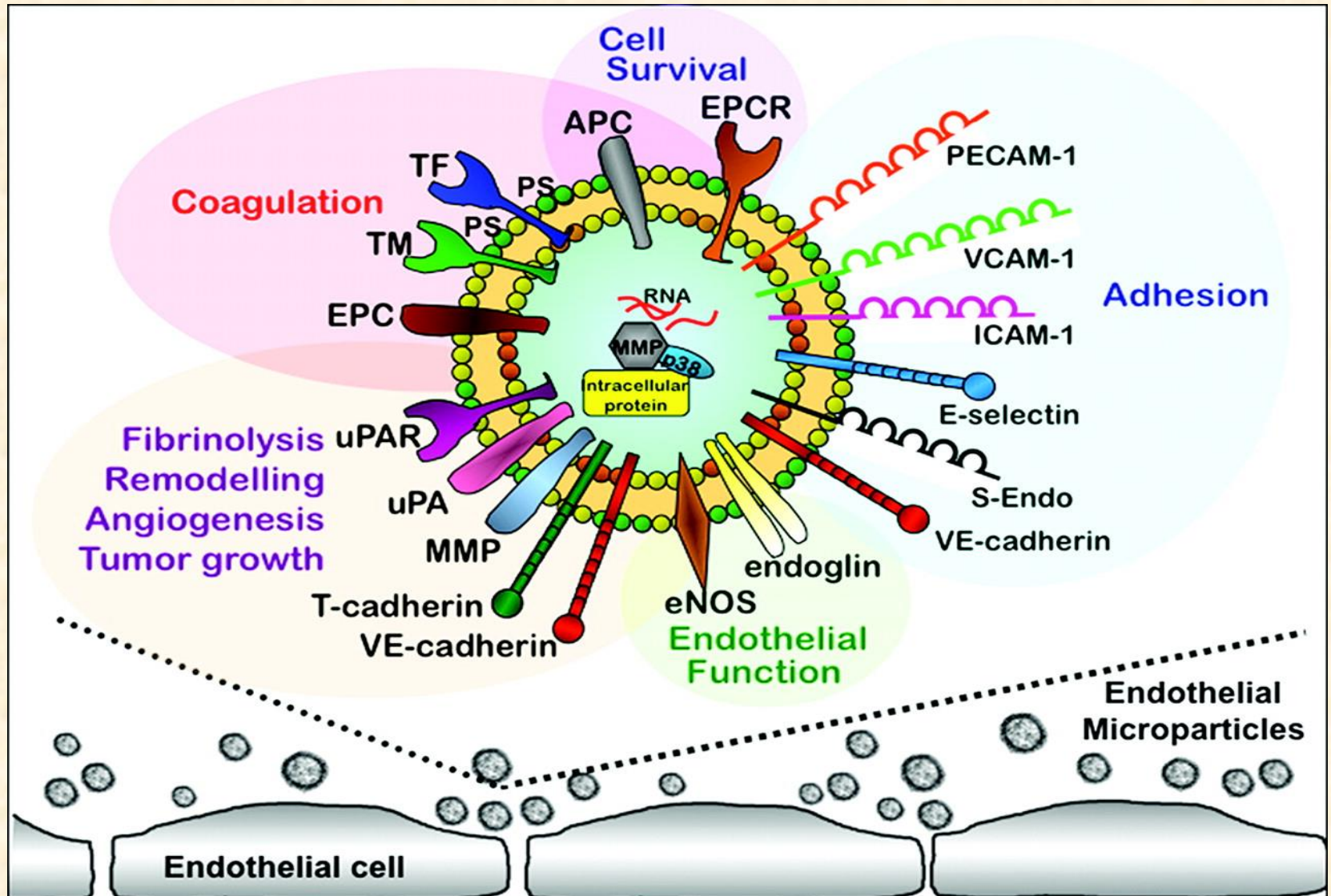
- Cytokines/chemokines
- Platelets/ Activated endothelial cells
- Tissue factor/ Coagulation proteases
- Neutrophil extracellular traps (NETs)
- **Microparticles**

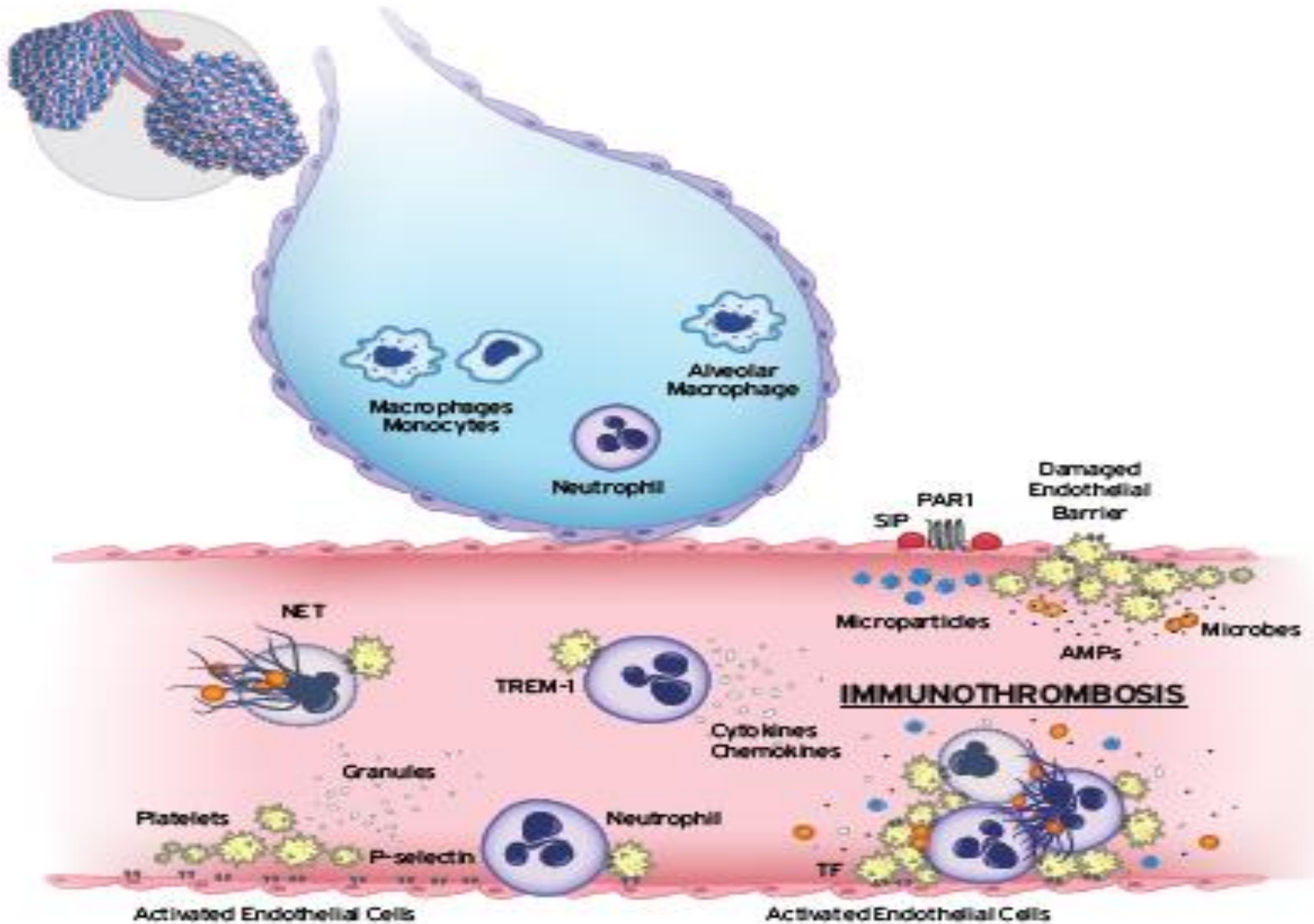
# Microparticles



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

# The faces of microparticles

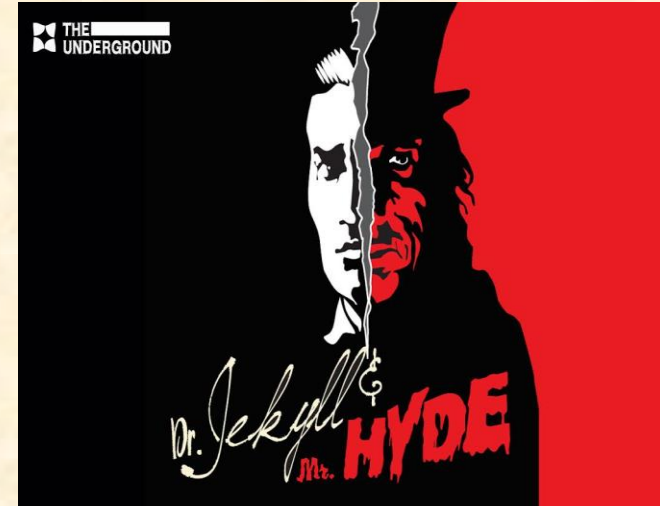




# The two faces of immunothrombosis

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

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

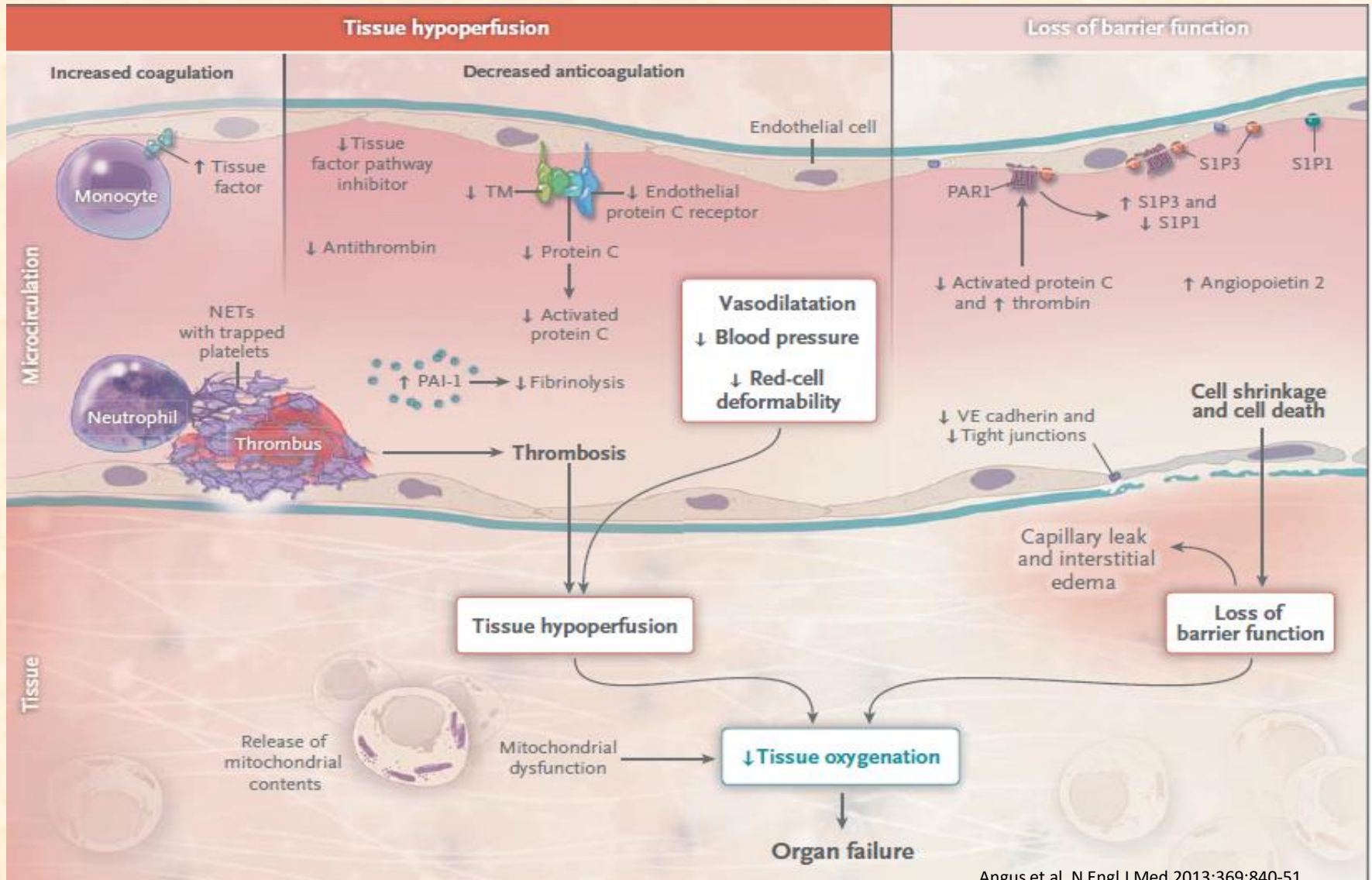




# DIC (“Death is coming”)-35% of septic pt

“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.<sup>15</sup> The four labora-

International Society of Thrombosis and Hemostasis 2001



# DIC

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

# ΚΛΙΝΙΚΗ ΕΙΚΟΝΑ ΔΕΤ

- 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  $\text{mm}^3$ , 1 point;  $<50,000$  per  $\text{mm}^3$ , 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;  $\geq 3$  sec but  $<6$  sec, 1 point;  $\geq 6$  sec, 2 points

Fibrinogen level:  $\geq 1$  g per liter, 0 points;  $<1$  g per liter, 1 point

Calculate the score as follows:

$\geq 5$  points: compatible with overt DIC; repeat scoring daily

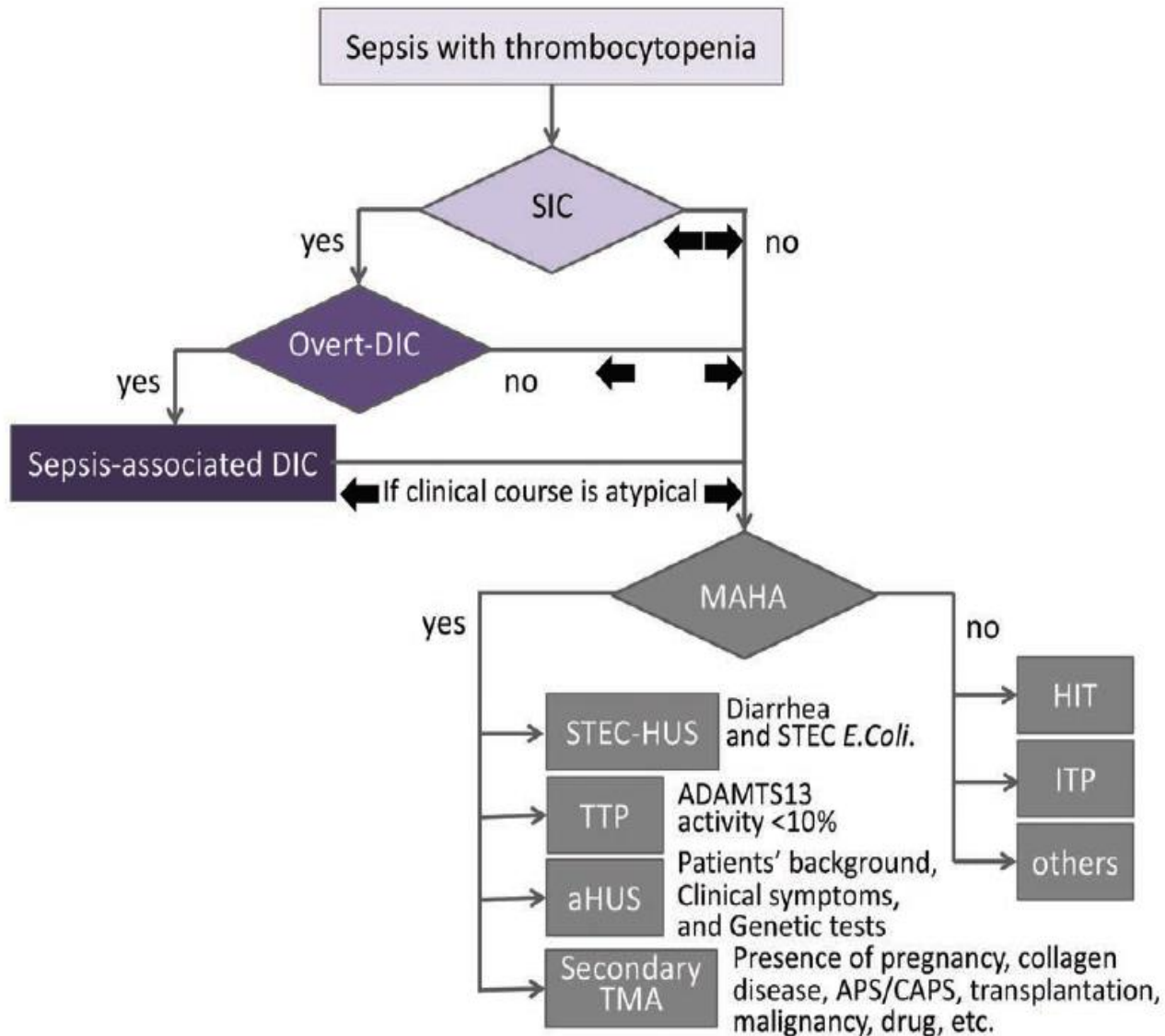
$<5$  points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

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

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

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

SIC vs DIC  
Higher sensitivity  
Earlier diagnosis



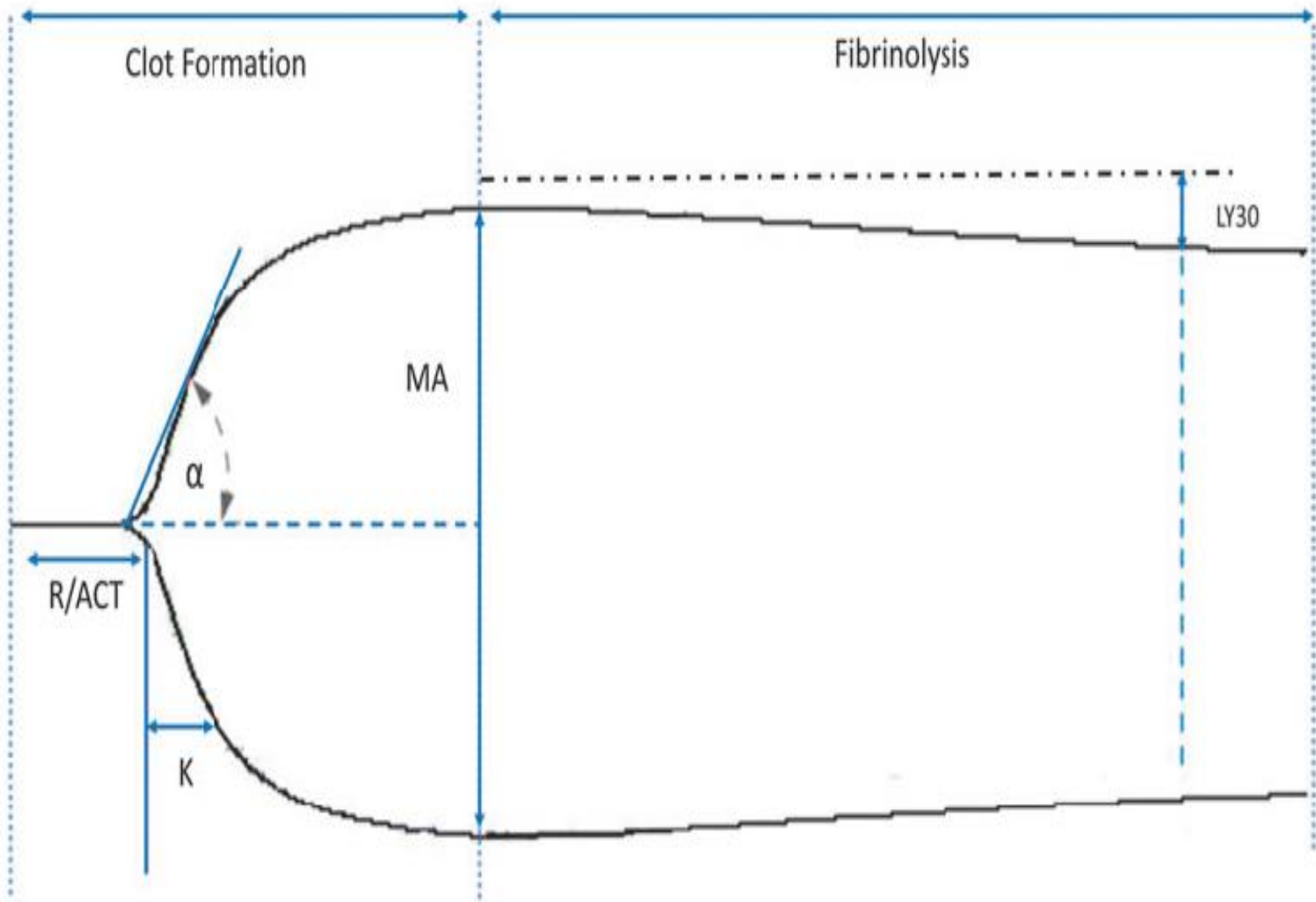
# Diagnosis of DIC

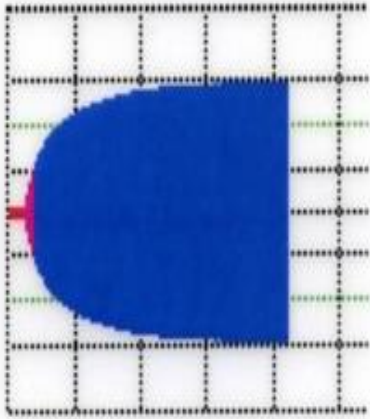
- Presence of underlying disease-MODS
- Elevation PT, aPTT
- Prothrombin fragment 1+2,thrombin-antithrombin complexes
- Fibrinogen degradation products (FDPs), D-dimers
- Fibrinogen: Sensitivity 30%
- Decrease AT, TFPI,PC?
- TEG, ROTEM: To appraise the state of coagulation



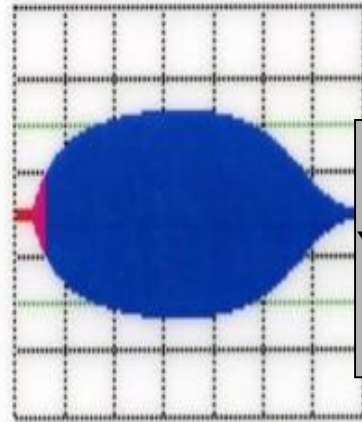
# ΡΟC τεχνικές-Θρομβοελαστογραφία (TEG)

- 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

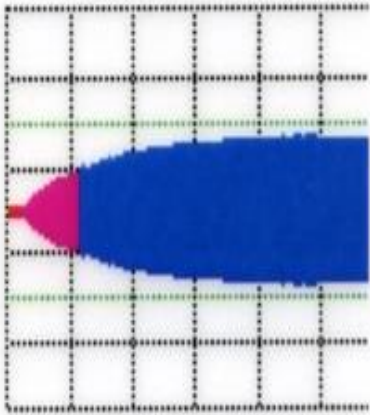




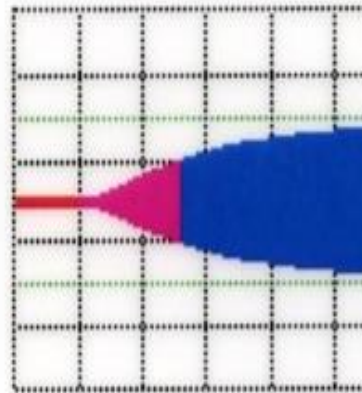
φυσιολογικό



Υπερνωδόλυση



Θρομβοπενία  
ή  
χαμηλό ινωδογόνο

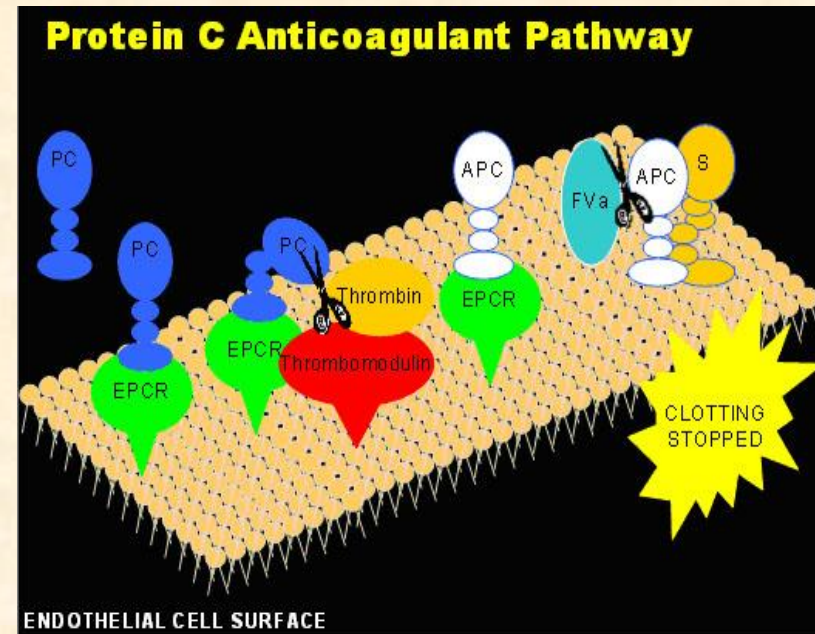


Λήψη ηπαρίνης  
ή  
έλλειψη  
παράγοντα

# 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

# 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

RESEARCH

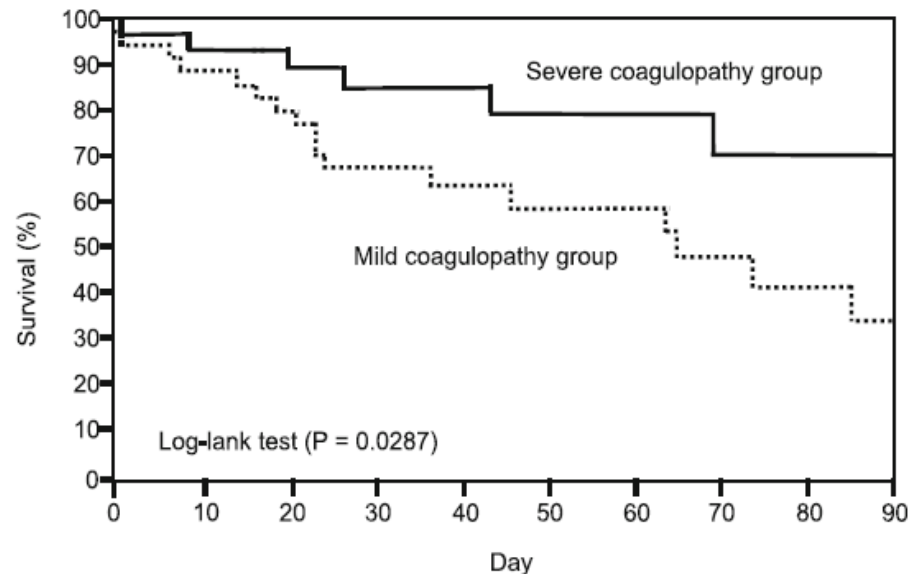
Open Access



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

Takahiro Kato<sup>1\*</sup> and Katsuhiko Matsuura<sup>2</sup>

69 pts mild or severe coagulopathy (DIC)



# New pathways and targets



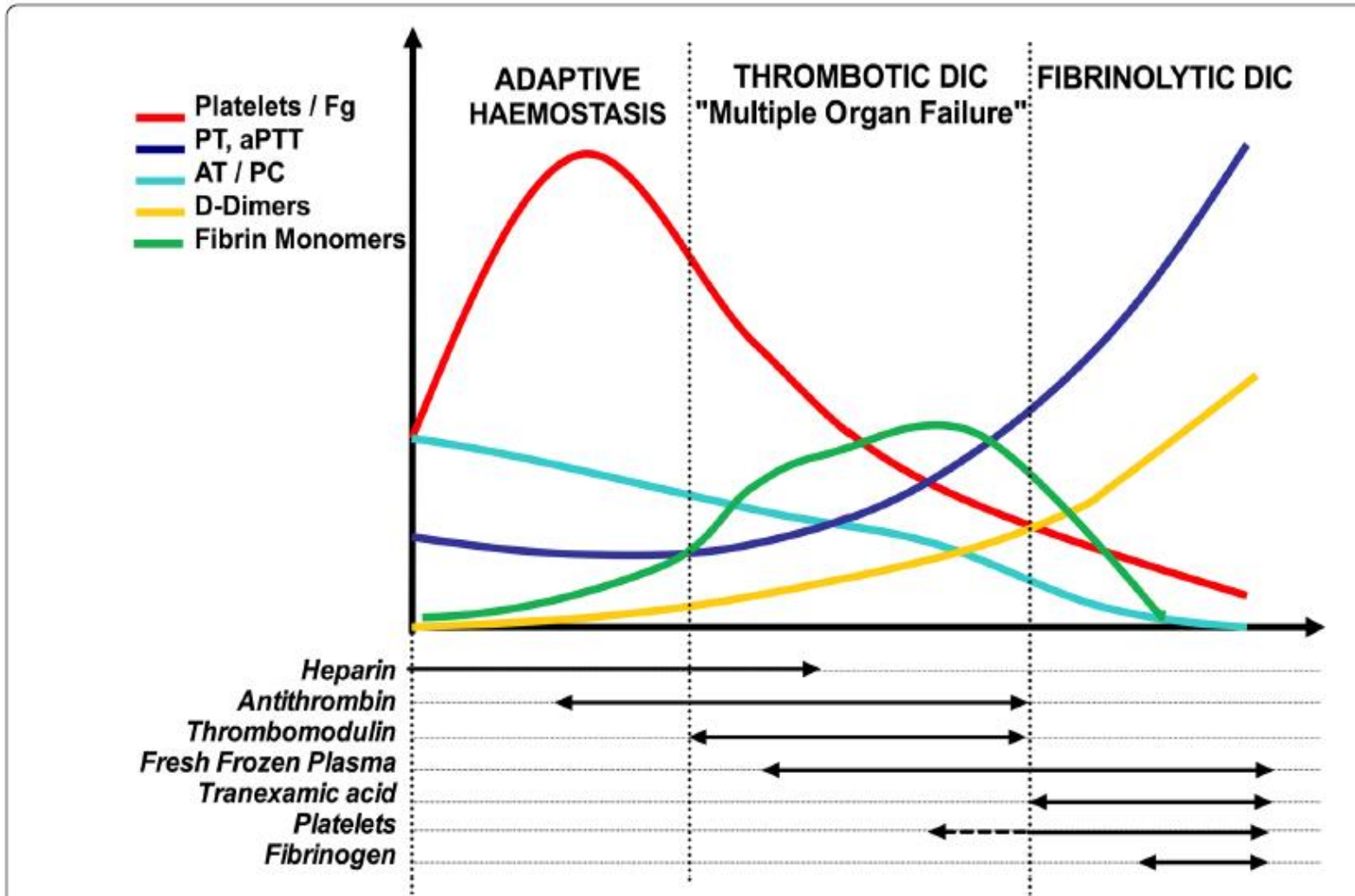
- Past target: restoration of physiological anticoagulation
- Molecules with less anticoagulant properties but with antiinflammatory effects

## **Non anticoagulant heparin:**

- inhibits adhesion molecules
- affects NF- $\kappa$  $\beta$ , cytokines
- attenuates endothelial cell dysfunction
- strong affinity with histones-cytotoxic activity

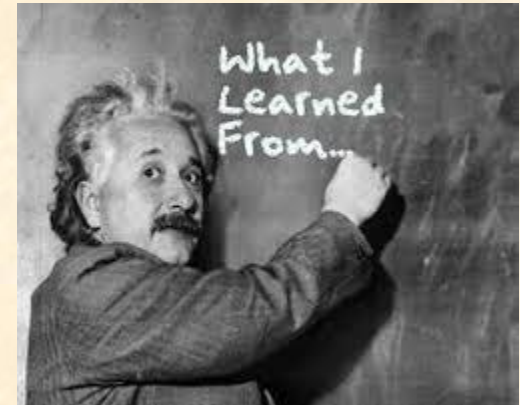
**New target: glycocalyx covering the endothelial surface**

# Natural history of hemostasis during infection and therapeutics





# 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

*We've all got both  
light and dark  
inside of us.  
What matters  
is the part we choose  
to act on.  
That's who  
we really are*

*Sirius Black*

Ευχαριστώ πολύ !!!