2017

Progetto Ematologia Romagna

La Coagulazione Intravascolare Disseminata

Inquadramento del problema

Marco Marietta - Modena

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

Partecipazione ad Advisory Board per l' Azienda Novo-Nordisk

Relazioni a congressi per la ditta Kedrion, Orphan, Novo-Nordisk, Werfen

2017

PROGETTO EMATOLOGIA – ROMAGNA Rimini, 8 aprile 2017

«Se vi è l'impronta dev'esserci stato qualcosa di cui è l'impronta».

«Ma diverso dall'impronta, mi dite».

«Certo. Non sempre un'impronta ha la forma del corpo che l'ha impressa e non sempre nasce dalla pressione di un corpo.

Talora […] è l'impronta di un'idea.

L'idea è segno delle cose, e l'immagine è segno dell'idea, segno di un segno.

Ma dall'immagine ricostruisco, se non il corpo, l'idea che altri ne aveva».

Umberto Eco. Il nome della rosa

L'immagine è segno dell'idea, segno di un segno...

- ✓ Plt 98.000/mmc
- ✓ PT INR 1.4
- ✓ Fibrinogeno 182 mg/dl
- ✓ D-dimero 11280 ng/ml

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C. H. TOH
COAGULA

Table 1 Scoring system for overt Disseminated Intravascular Coagulation (DIC)

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

   If yes: Proceed.

   If no: Do not use this algorithm.

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

3. Score global coagulation test results.

- Platelet count
  (>100 = 0; <100 = 1; < 50 = 2) — 1
- Elevated fibrin related marker (e.g. D-dimers; fibrin degradation products)
  (no increase = 0; moderate increase = 2; strong increase = 3) — 3
- Prolonged prothrombin time
  (< 3 s = 0; > 3 but < 6 s = 1; > 6 s = 2) — 1
- Fibrinogen level
  (>1.0g L^{-1} = 0; < 1.0g L^{-1} = 1) — 0

5. Calculate score

If ≥ 5: compatible with overt DIC: repeat score daily

If < 5: suggestive (not affirmative) for non-overt DIC: repeat next 1–2 days.

PROGET

L'immagine è segno dell'idea, segno di un segno...

LA PROMIELOCITICA

TRAUMA

- ✓ Plt 98.000/mmc
- ✓ PT INR 1.4
- ✓ Fibrinogeno 182 mg/dl
- ✓ D-dimero 11280 ng/ml

SEPSI

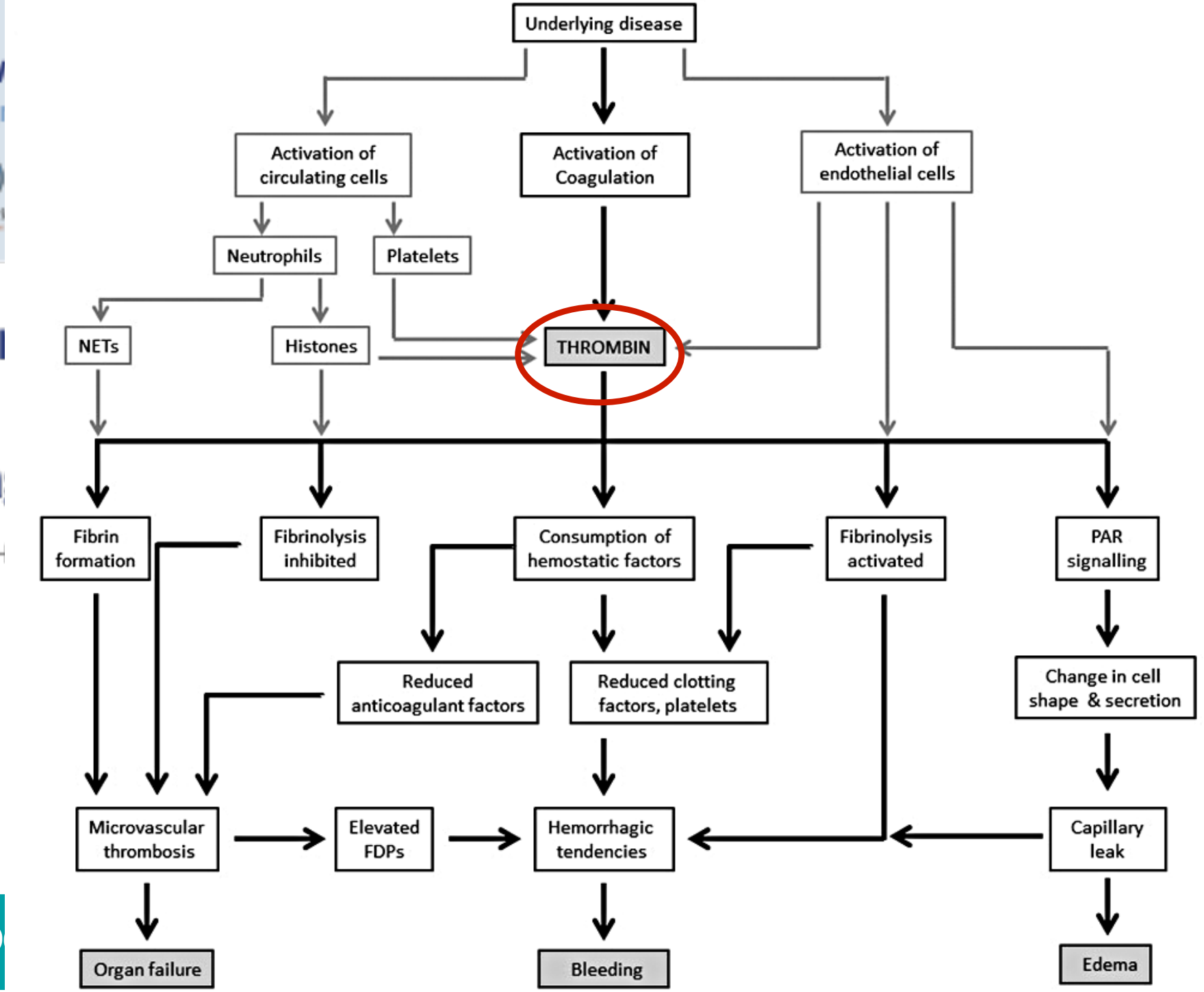
OFFICIAL COMMUNICATION OF THE SSC

J Thromb Haemost 2013; **11**: 761–7.

Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines

H. WADA,* J. THACHIL,† M. DI NISIO,‡§ P. MATHEW,¶ S. KUROSAWA,** S. GANDO,†† H.K. KIM,‡‡ J.D. NIELSEN,§§ C-E. DEMPFLE,¶¶ M. LEVI,§ C-H. TOH***††† and THE SCIENTIFIC AND STANDARDIZATION COMMITTEE ON DIC OF THE ISTH

- ✓ Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood coagulation, which generates intravascular fibrin, leading to thrombosis of small and medium-sized vessels, and eventually organ dysfunction.
- ✓ DIC may occur as a complication of infections, solid cancers, hematologic malignancies, obstetric diseases, trauma, aneurysm, and liver diseases
- ✓ ***Each type of DIC presents characteristic features related to the underlying disorder.***


Underlying disease
Activation of circulating cells
Activation of Coagulation
Activation of endothelial cells
Neutrophils
Platelets
NETs
Histones
THROMBIN
Fibrin formation
Fibrinolysis inhibited
Consumption of hemostatic factors
Fibrinolysis activated
PAR signalling
Reduced anticoagulant factors
Reduced clotting factors, platelets
Change in cell shape & secretion
Microvascular thrombosis
Elevated FDPs
Hemorrhagic tendencies
Capillary leak
Organ failure
Bleeding
Edema

Thromb Haemost 2011; 106: 1020–1033

Thr

Focu

Jolanta

	Thrombin functions in coagulation
Procoagulant properties	• cleavage of fibrinogen and liberation of fibrinopeptide A and B (10) • activation of factors: V (128), VIII (129), XI (130) and XIII (131) • induction of platelet aggregation, platelet secretion and platelet procoagulant activity (132) • release of adenosine diphosphate from platelets (132) • expression of P-selectin on endothelial cells (133, 134) • stimulation of expression of the platelet activating factor (PAF)
Antifibrinolytic properties	• activation of thrombin-activable fibrinolysis inhibitor (TAFI) (136) • release of the plasminogen activator inhibitor-1 (137)

Thromb Haemost 2011; 106: 1020–1033

Thrombin as a multi-functional enzyme

Focus on *in vitro* and *in vivo* effects

Jolanta M. Siller-Matula[1]; Michael Schwameis[2]; Andrew Blann[3]; Christine Mannhalter[4]; Bernd Jilma[2]

Anticoagulant properties	• binding to thrombomodulin (TM) and activation of protein C • decrease in the binding of von Willebrand factor (vWF) to glycoprotein (GP) Ib (135) • decrease in ristocetin-induced agglutination (135)
Fibrinolytic properties	• release of the tissue plasminogen activator (138)

REVIEW ARTICLE

J Thromb Haemost 2016; **14**: 1908–16.

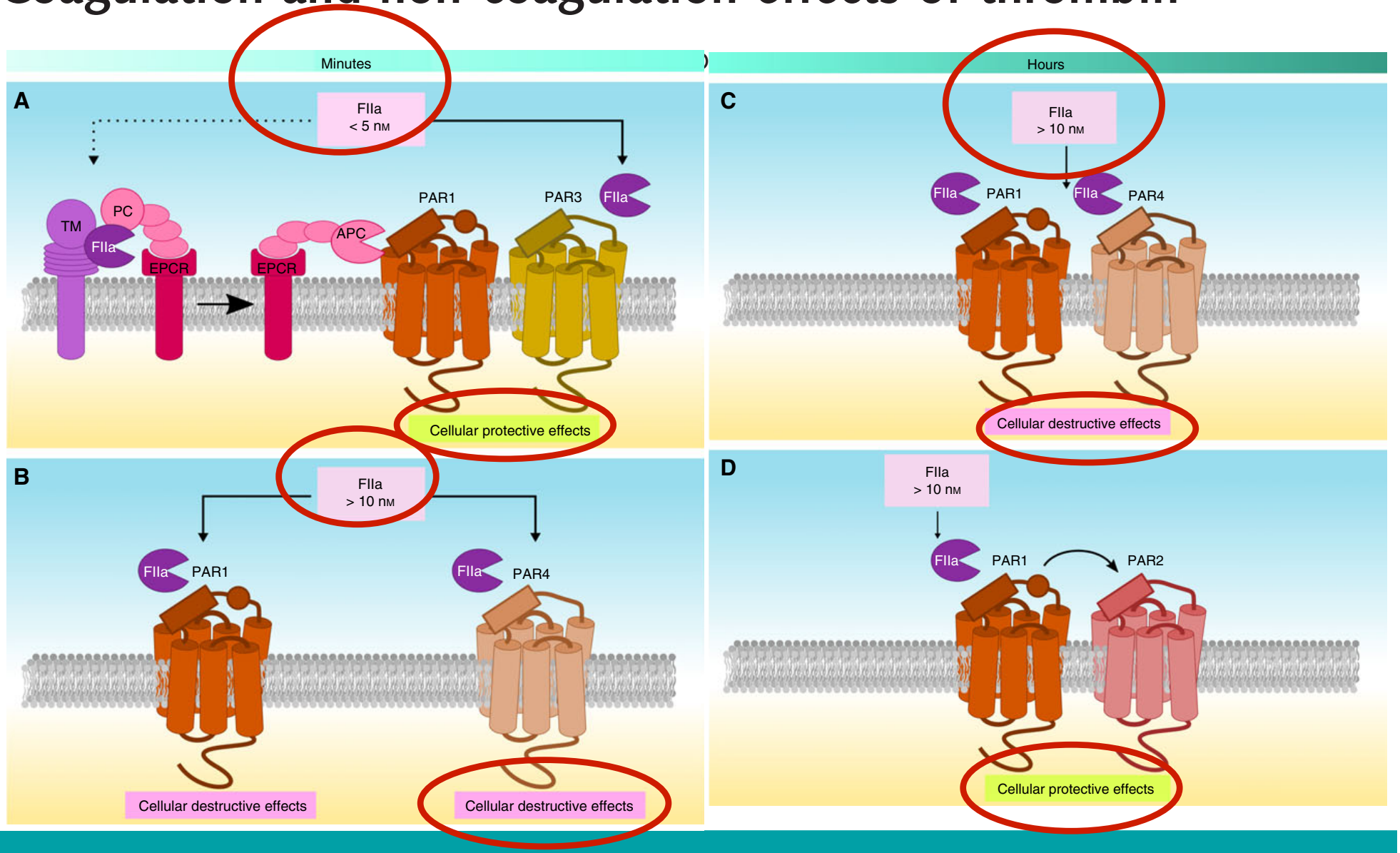
Coagulation and non-coagulation effects of thrombin

J. J. N. POSMA, J. J. POSTHUMA and H. M. H. SPRONK

- ✓ Thrombin mainly regulates cellular responses through activation of **PARs**, but can have opposite effects on the same cell, depending on vari- ous conditions, such as the concentration, the location, the exposure time, and the presence of cofactors .
- ✓ Through activation of PARs, thrombin can regulate physiologic processes such as embryonic development and wound healing, but also pathophysiologic processes such as sepsis, cancer, fibrosis, and inflammation.
- ✓ Activation of PARs by thrombin can lead to ***2224 different intracellular phosphorylations in the cell***, making investigation of the various effects of thrombin on cellular pathways challenging

J Thromb Haemost 2016; **14**: 1908–16.

Coagulation and non-coagulation effects of thrombin



bjh review

Bleeding related to disturbed fibrinolysis

Krasimir Kolev[1] and Colin Longstaff[2]

- ✓ DIC is a common severe complication of systemic infection (sepsis) and extensive tissue destruction (major trauma).
- ✓ DIC is defined as *'an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction' (ISTH, 2001).*
- ✓ *Depending on the nature of the provoking factor and the stage of the disease, the phenotype of DIC can be either thrombotic or haemorrhagic.*

REVIEW Journal of Intensive Care (2017) 5:14

Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype

Mineji Hayakawa

Table 1 Characteristics of DIC phenotypes

	Fibrinolytic phenotype	Thrombotic phenotype

REVIEW Journal of Intensive Care (2017) 5:14

Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype

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Table 1 Characteristics of DIC phenotypes

	Fibrinolytic phenotype	Thrombotic phenotype
Representative cause	Acute promyelocitic leukemia	Sepsis
Coagulation	Activated	Activated
Fibrinolysis	Activated	Suppressed
PAI-1	Low	High
Clinical symptom	Bleeding	Organ dysfunction

DIC disseminated intravascular coagulation, *PAI* plasminogen activator inhibitor

The Coagulopathy of Acute promyelocytic leukaemia

- ✓ Acute promyelocytic leukaemia(APL) is characterized by a high rate of life-threatening haemorrhagic events related to hyperfibrinolysis.
- ✓ **Low TAFI activity** has been reported in APL patients probably due to excessive inactivation of TAFI by plasmin
- ✓ PML-RAR-a enhances the expression of S100A10 (p11), a member of the S100 family of calcium-binding proteins which forms a eterotetrameric (S100A10)2-(annexin A2)2 complex on the surface of various cells
- ✓ **The (S100A10)2-(annexin A2)2 complex provides a template for plasminogen activation on the cell surface** and protects plasmin against plasma inhibitors in a similar way to fibrin.
- ✓ These S100A10-related pro-fibrinolytic effects are consistent with the bleeding profile in APL

Kolev K, BJH 2016

The Coagulopathy of Acute promyelocytic leukaemia

- ✓ ATRA treatment reverses the S100A10 and annexin A2 induction in PML-RAR-a positive cells and suppresses plasmin generation on their surface
- ✓ An additional factor for the profibrinolytic state in APL could be the release of neutrophil elastase from the leukaemic promyelocytes
- ✓ The evidence justifies the classification of the haemostatic imbalance in APL as **primary hyperfibrinolysis**, and this conclusion is supported by the typical laboratory findings in the blood of APL patients

Kolev K, BJH 2016

REVIEW Journal of Intensive Care (2017) 5:14

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DIC disseminated intravascular coagulation, *PAI* plasminogen activator inhibitor

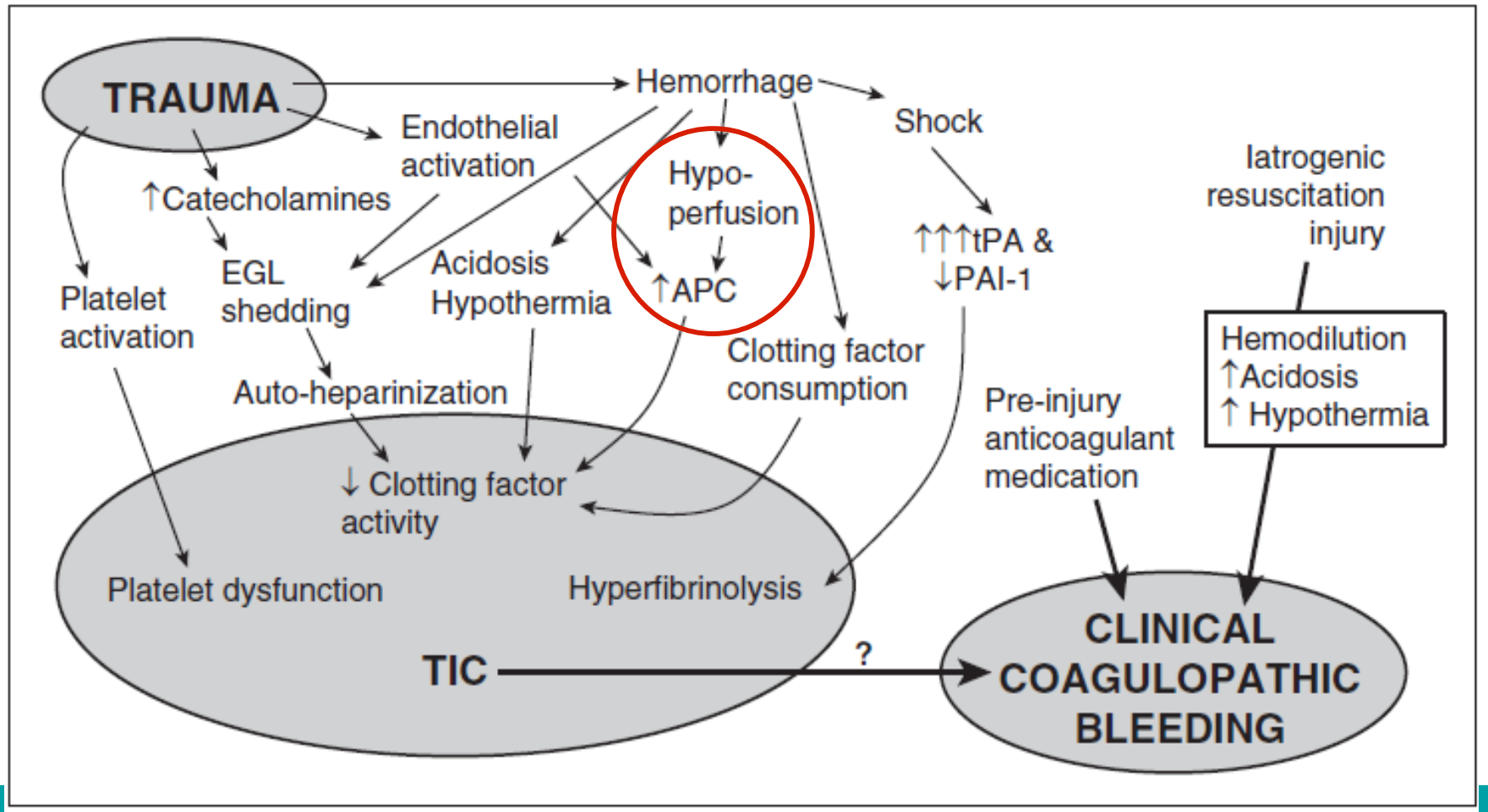
Review Article

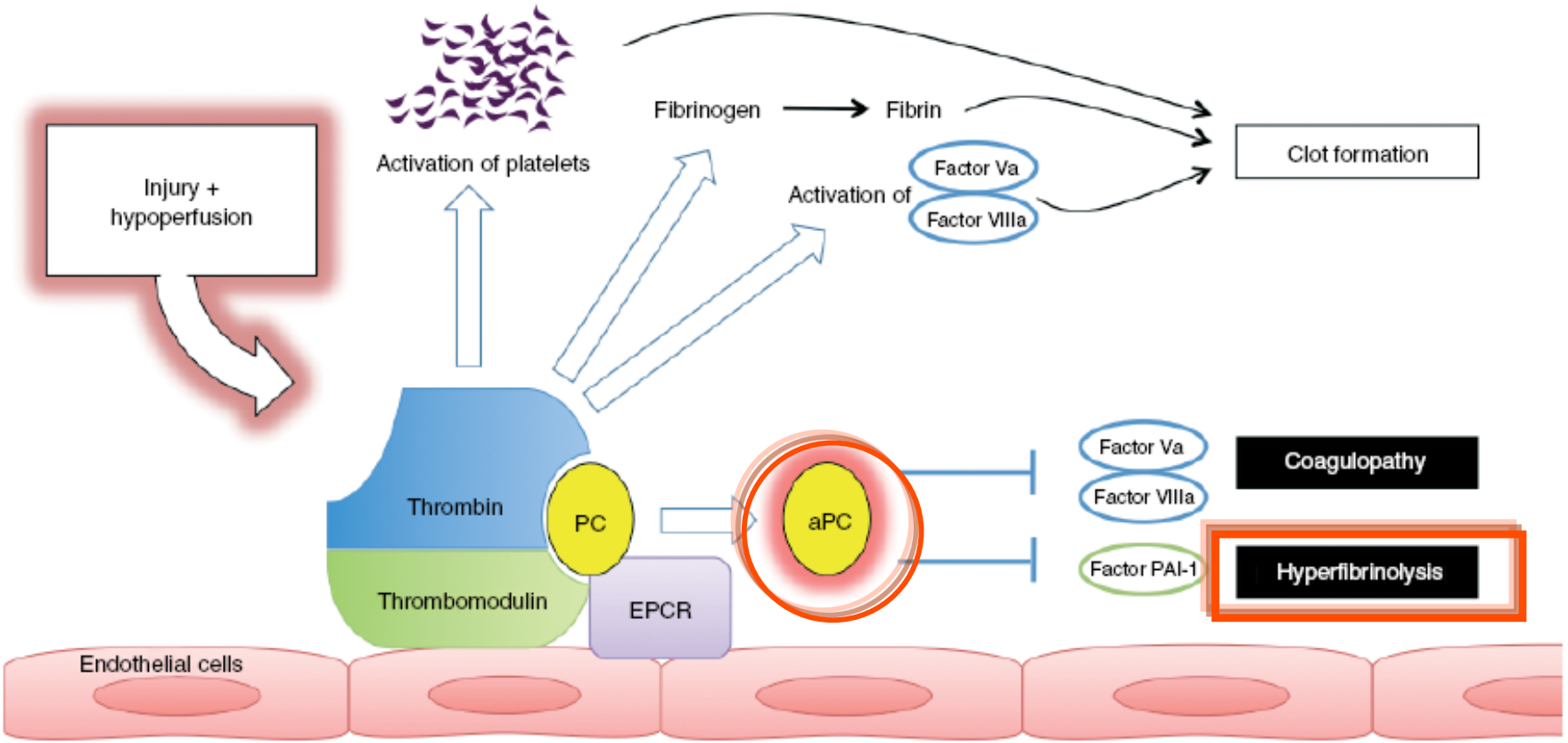
Blood 2016;128(8):1043-1049

blood

Advances in the understanding of trauma-induced coagulopathy

Ronald Chang,[1,2] Jessica C. Cardenas,[1,2] Charles E. Wade,[1,2] and John B. Holcomb[1,2]





Thorsen K et al. Br J Surg 2011;98:894-907

Pathoph coagulo coagulat pe

Mineji Hayakawa

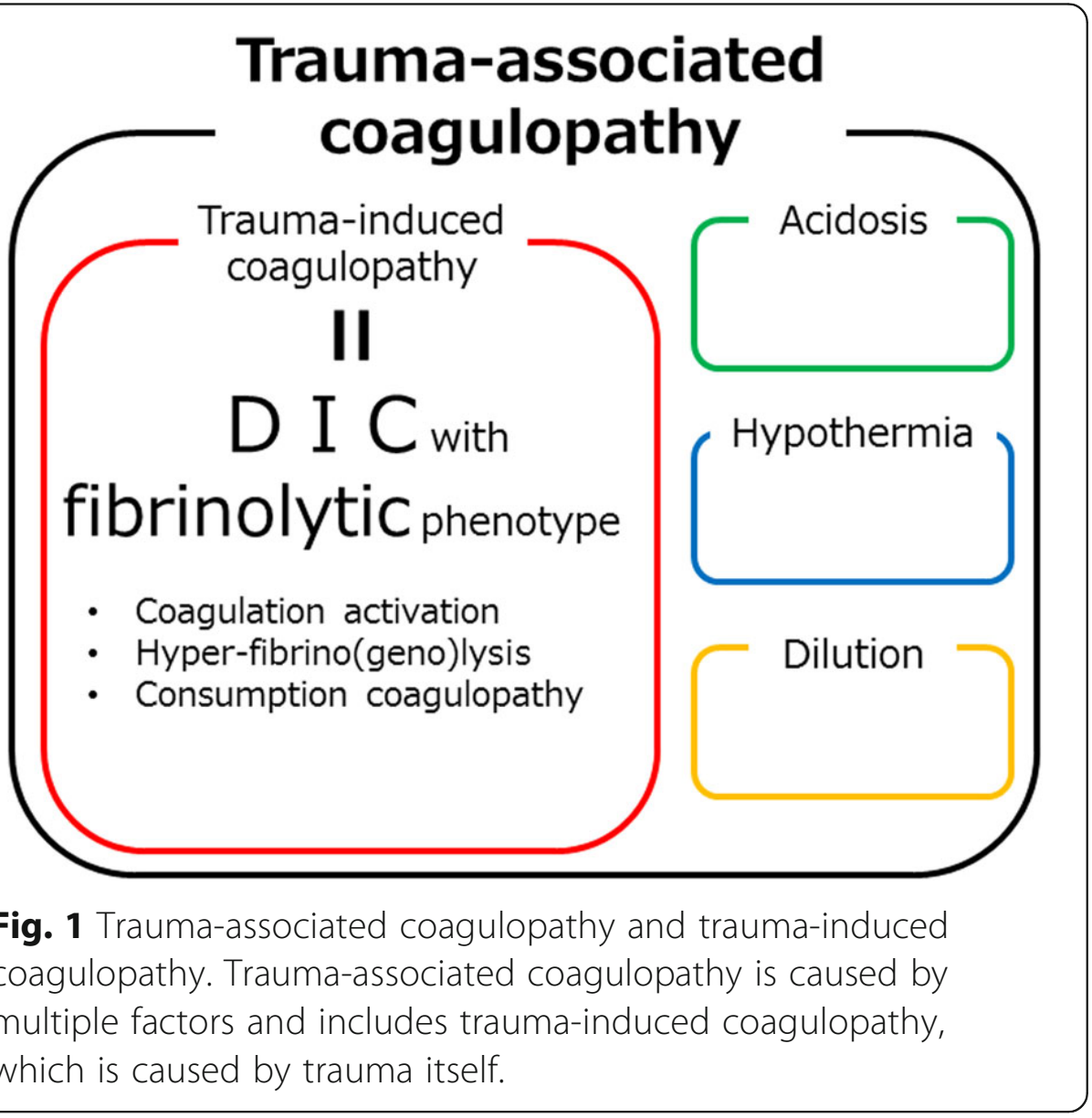
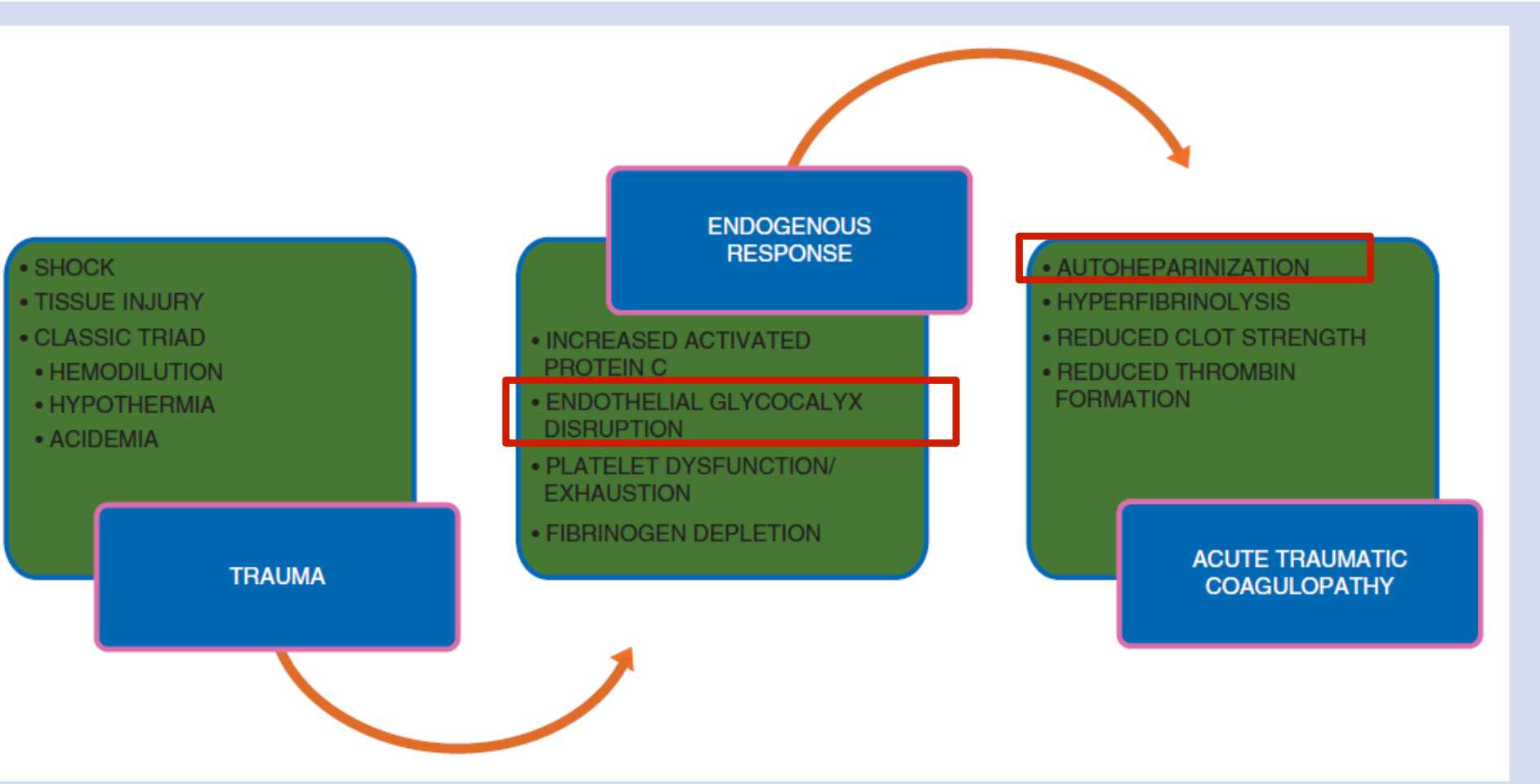


Fig. 1 Trauma-associated coagulopathy and trauma-induced coagulopathy. Trauma-associated coagulopathy is caused by multiple factors and includes trauma-induced coagulopathy, which is caused by trauma itself.

Acute traumatic coagulopathy: pathophysiology and resuscitation

British Journal of Anaesthesia, 117 (S3): iii31–iii43 (2016)

J. W. Simmons* and M. F. Powell



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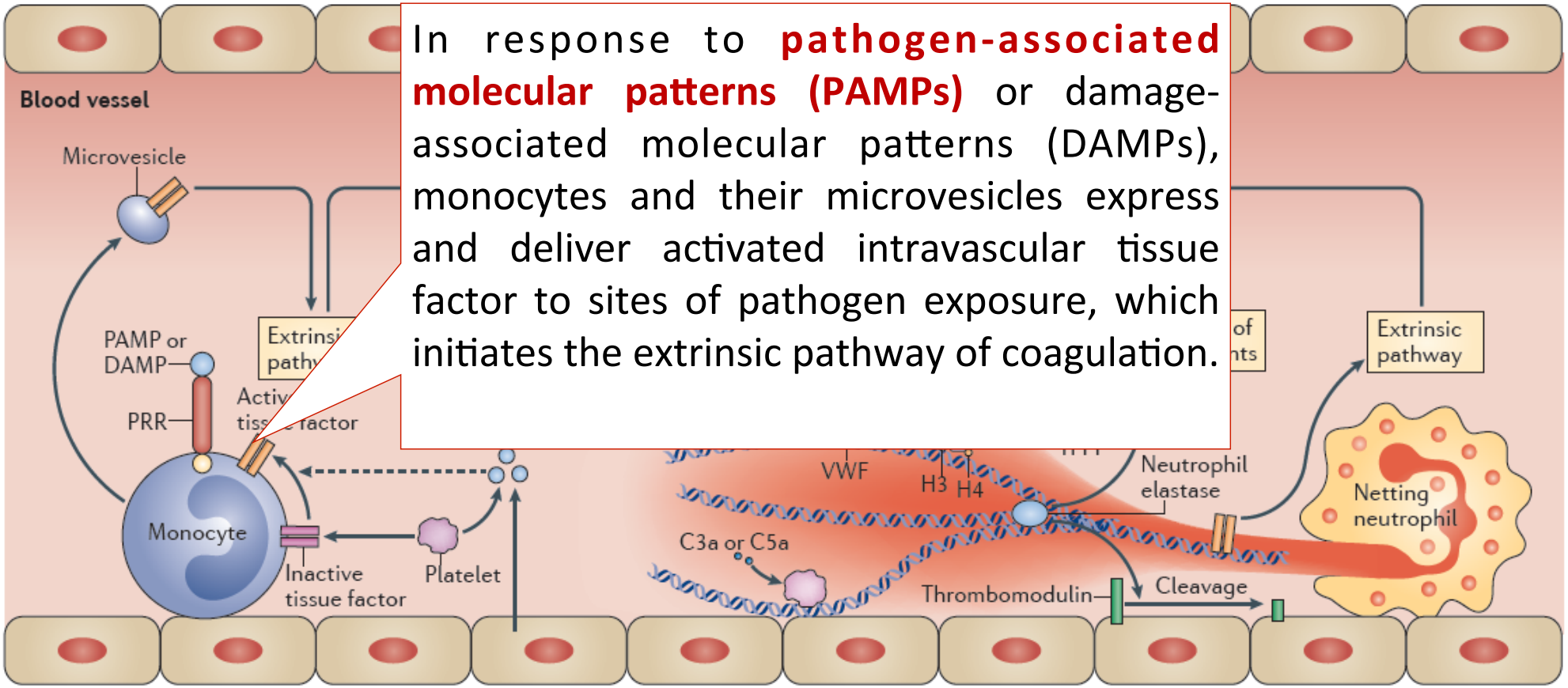
DIC disseminated intravascular coagulation, *PAI* plasminogen activator inhibitor

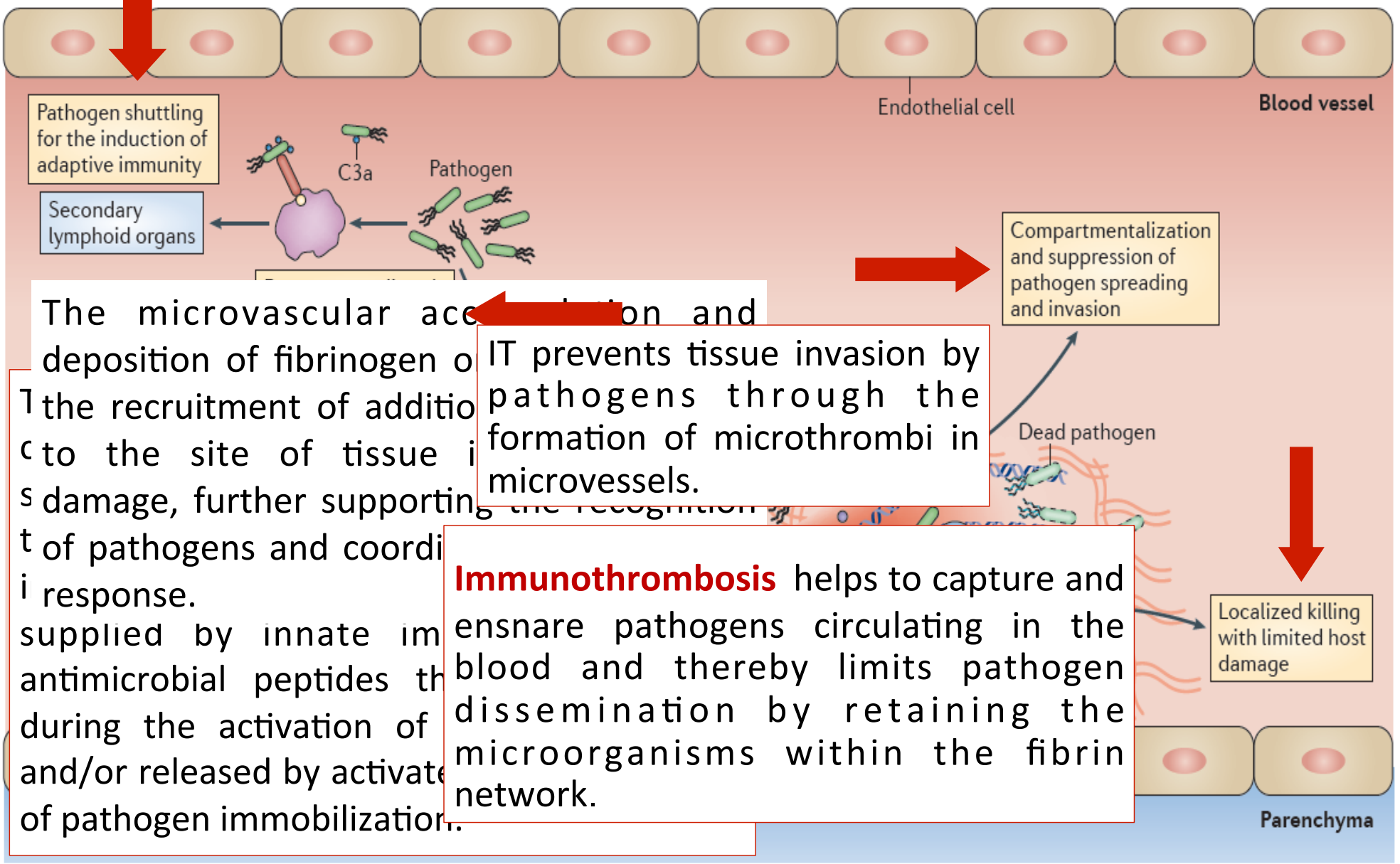
Innate immune cells have evolved cell-specific prothrombotic pathways that operate in intact blood vessels to protect hosts from non-self and altered-self.



In response to **pathogen-associated molecular patterns (PAMPs)** or damage-associated molecular patterns (DAMPs), monocytes and their microvesicles express and deliver activated intravascular tissue factor to sites of pathogen exposure, which initiates the extrinsic pathway of coagulation.

Nat Rev Immunol 2013;13:34

2017

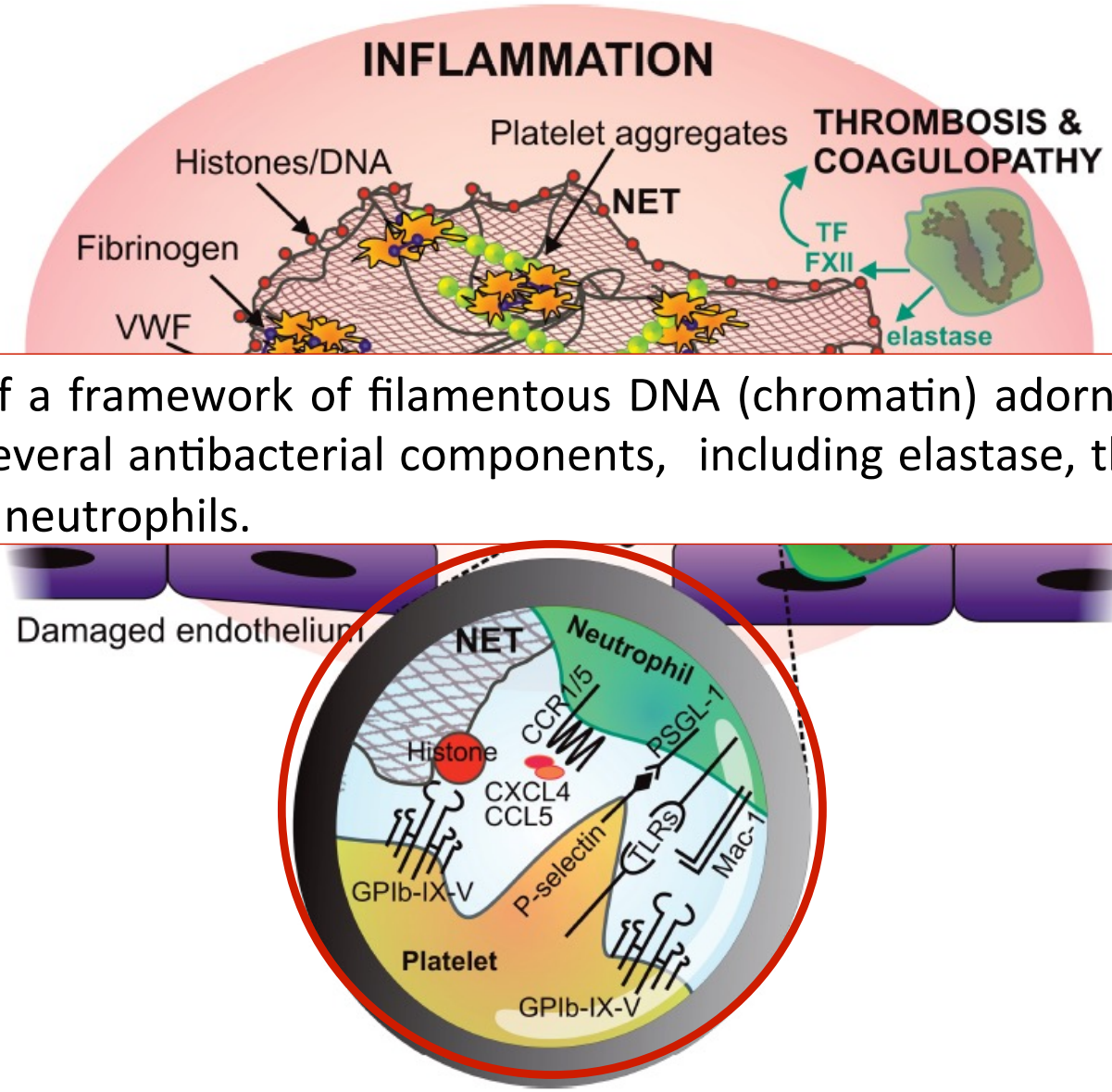


The microvascular acc on and deposition of fibrinogen o
the recruitment of additio to the site of tissue i damage, further supporting the recognition of pathogens and coordi response.
supplied by innate im
antimicrobial peptides th
during the activation of
and/or released by activate
of pathogen immobilization.

IT prevents tissue invasion by pathogens through the formation of microthrombi in microvessels.

Immunothrombosis helps to capture and ensnare pathogens circulating in the blood and thereby limits pathogen dissemination by retaining the microorganisms within the fibrin network.

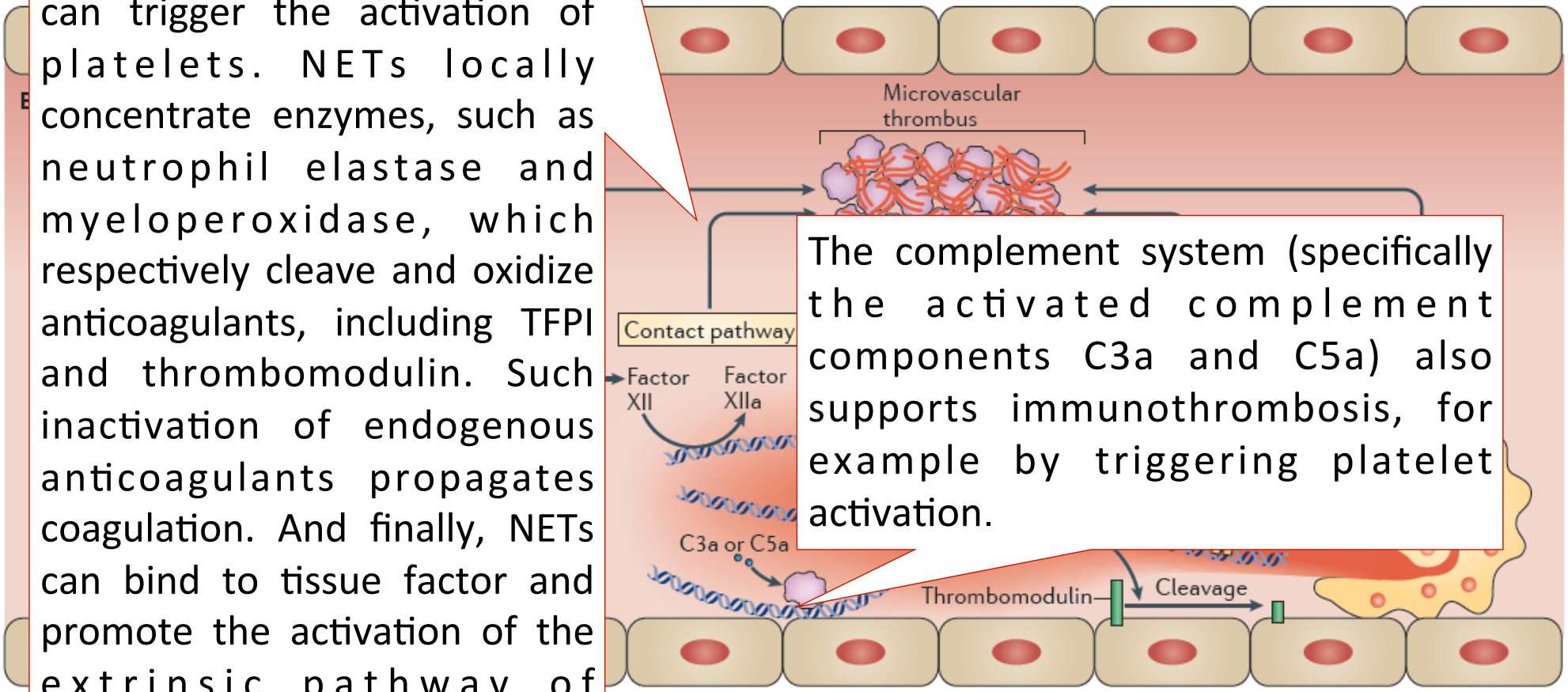
Nat Rev Immunol 2013;13:34



NETs consist of a framework of filamentous DNA (chromatin) adorned with histone proteins and several antibacterial components, including elastase, that are expelled from activated neutrophils.

NETs can directly activate factor XII (the contact pathway of coagulation). They bind to von Willebrand factor (VWF) and support the recruitment of platelets. Histones H3 and H4 can trigger the activation of platelets. NETs locally concentrate enzymes, such as neutrophil elastase and myeloperoxidase, which respectively cleave and oxidize anticoagulants, including TFPI and thrombomodulin. Such inactivation of endogenous anticoagulants propagates coagulation. And finally, NETs can bind to tissue factor and promote the activation of the extrinsic pathway of coagulation.

…olved cell-specific prothrombotic pathways that …to protect hosts from non-self and altered-self.



The complement system (specifically the activated complement components C3a and C5a) also supports immunothrombosis, for example by triggering platelet activation.

Nat Rev Immunol 2013;13:34

Thrombosis Research 151, Suppl. 1 (2017) S56–S60

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

The clinical presentation of DIC may be the results of the following mechanisms.

✓***Endothelial dysfunction and platelet activation*** In HELLP syndrome, a systemic inflammatory response is associated with markedly increased circulating pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 which can lead to expression of TF by leukocyte and endothelial cells

✓***Trophoblast properties and activation of the coagulation system***

The trophoblast is both

- **anticoagulant**: in the intervillous space by expression of anticoagulation proteins;
- **procoagulant:** at the maternal fetal interface by expression of placental TF

In any condition that disrupts the integrity of the trophoblast such as placental abruption and amniotic fluid embolism large amount of TF are released.

Thrombosis Research 151, Suppl. 1 (2017) S56–S60

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

✓ ***Impaired liver function***

In HELLP syndrome or in acute fatty liver of pregnancy the injury to the liver leads to a reduction in the production of anticoagulation proteins and coagulation factors leading to increase susceptibility of the mother to both hemorrhage and thrombosis.

✓ **Post-partum hemorrhage**.

Obstetrical complications causing PPH are: uterine atony, retained placenta or membranes, uterine rupture, placenta accreta, or severe cervical or vaginal lacerations. The loss os large amount of coagulation factors and natural inhibitors of coagulation can worse bleeding leading to a consumption coagulopathy and to an overt DIC, which in turn worses the bleeding

Thrombosis Research 151, Suppl. 1 (2017) S56–S60

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Table 1
Comparison among the pregnancy modified DIC score by Erez et al. and the other DIC scores in current clinical use.

Parameters	ISTH score	Pregnancy Modified ISTH score	
		Erez et al. [2]	Clark et al. [51]
Platelet count (10^9/L)	>100 = 0 <100 = 1 <50 = 2	>185 = 0 100–185 = 1 50–100 = 2 <50 = 1	>100 = 0 50–100 = 1 <50 = 2
Fibrin-related markers (e.g. soluble fibrin monomers/ fibrin degradation products)	no increase: 0 moderate increase: 2 strong increase: 3		
Prothrombin time (value of patient/normal value)	<3 s = 0 ≥3 s but <6 s = 1 ≥6 s = 2	<0.5 = 0 0.5–1 = 5 1.0–1.5 = 12 >1.5 = 25	<25% increase = 0 25–50% increase = 1 >50% increase = 2
Fibrinogen level (g/L)	<1.0 = 1 >1.0 = 0	3.0 = 25 3.0–4.0 = 6 4.0–4.5 = 1 >4.5 = 0	<2.0 = 1 >2.0 = 0
Calculated score	>5: compatible with overt DIC; repeat scoring daily <5: suggestive (not affirmative) for non-overt DIC; repeat next 1–2 days	>26 high probability for DIC	>3 compatible with overt DIC in pregnancy

ISTH, International Society for Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; SIRS, systemic inflammatory response syndrome.

2017

« Dubium sapientiae initium »

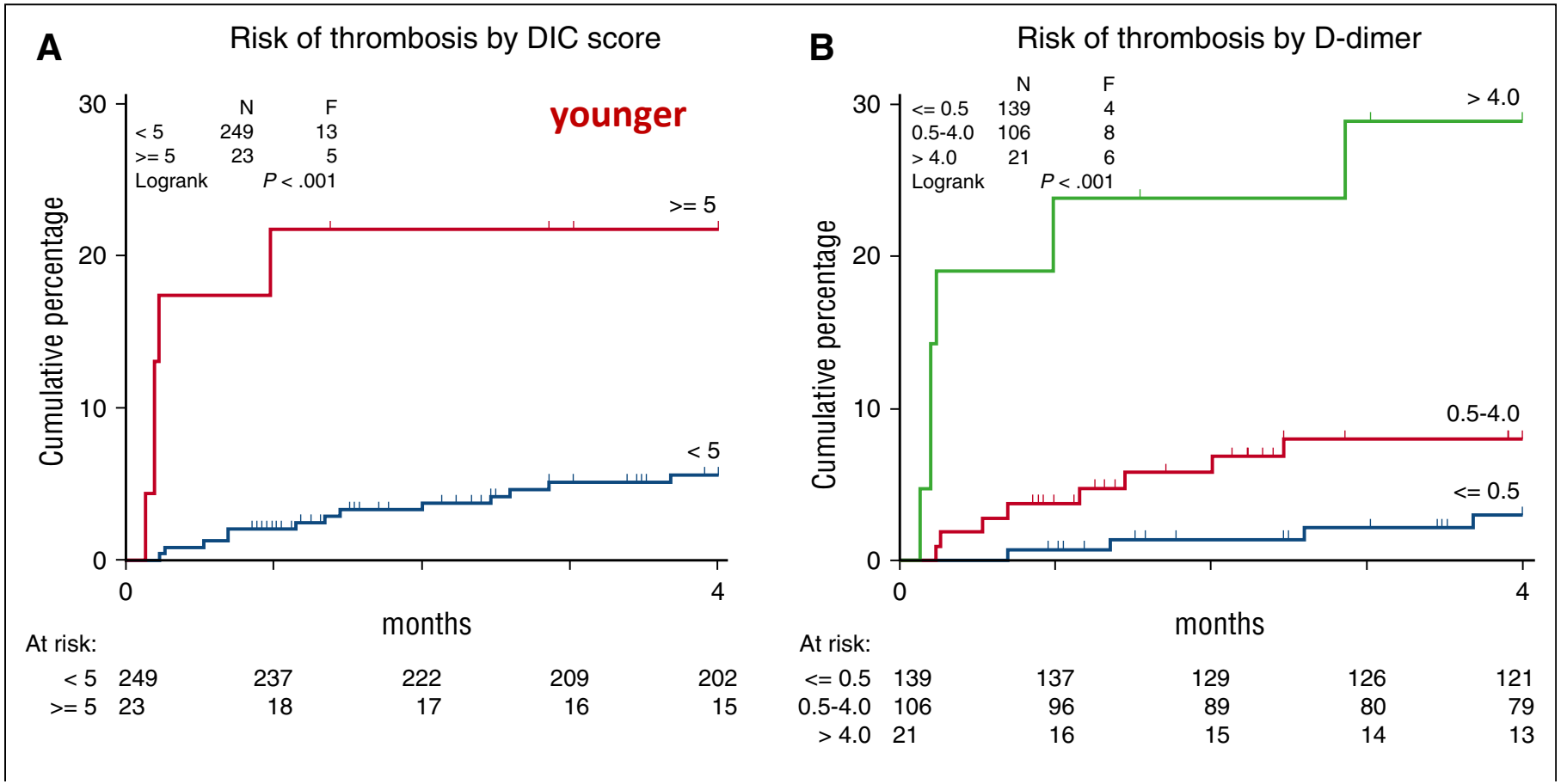
René Descartes, *Meditationes de prima philosophia*

PROGETTO EMATOLOGIA – ROMAGNA Rimini, 8 aprile 2017

(*Blood*. 2016;128(14):1854-1861)

Disseminated intravascular coagulation at diagnosis is a strong predictor for thrombosis in acute myeloid leukemia

Eduard J. Libourel,[1,2] Clara P. W. Klerk,[3] Yvette van Norden,[4] Moniek P. M. de Maat,[2] Marieke J. Kruip,[2] Pieter Sonneveld,[2] Bob Löwenberg,[2] and Frank W. G. Leebeek[2]



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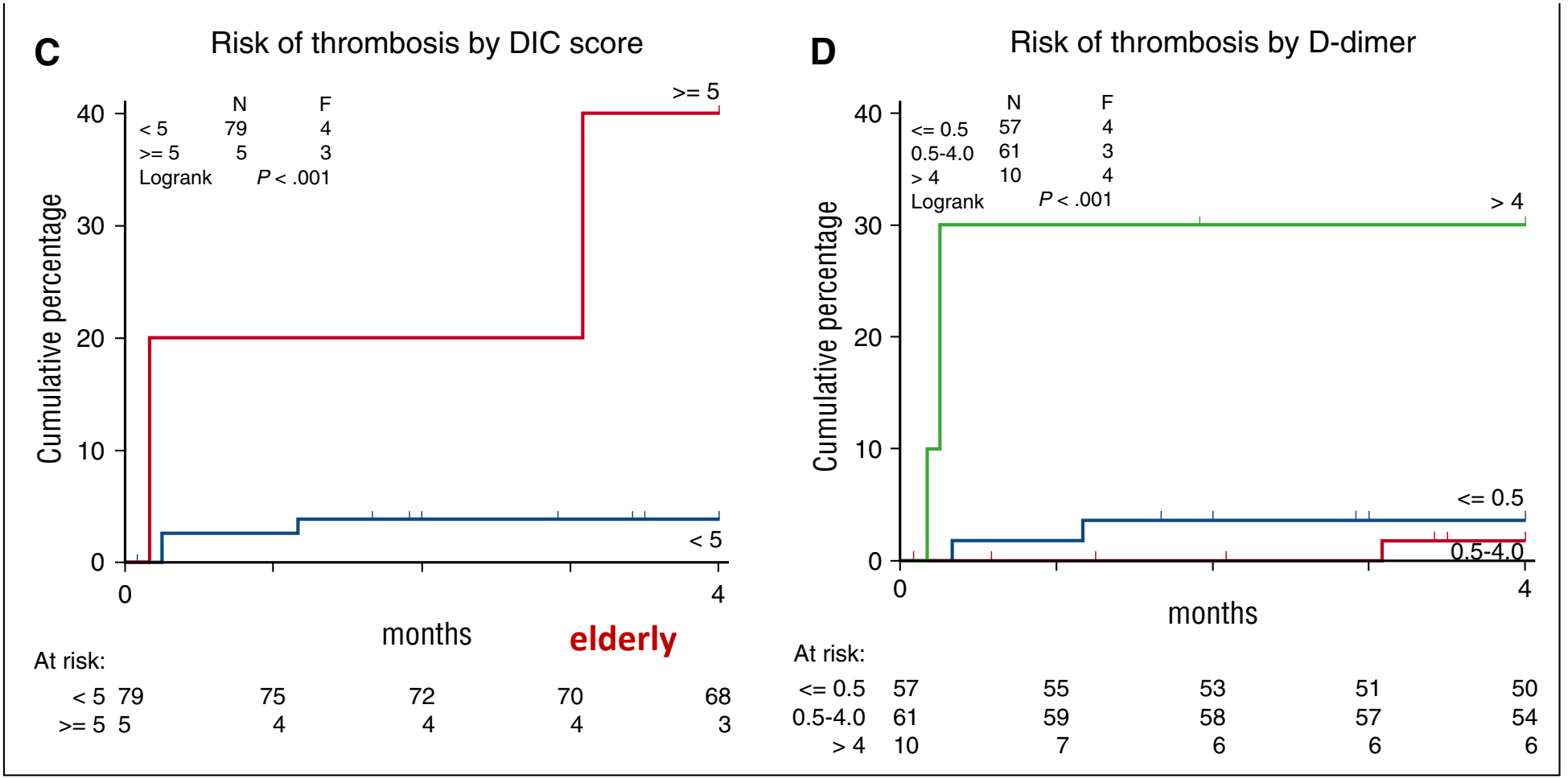

Dalla fisiopatologia alla clinica…

- ✓ DIC con fenotipo iperfibrinolitico → antifibrinolitici?
- ✓ DIC con fenotipo protrombotico → anticoagulanti naturali?

2017

Dalla fisiopatologia alla clinica…

PROGETTO EMATOLOGIA – ROMAGNA Rimini, 8 aprile 2017

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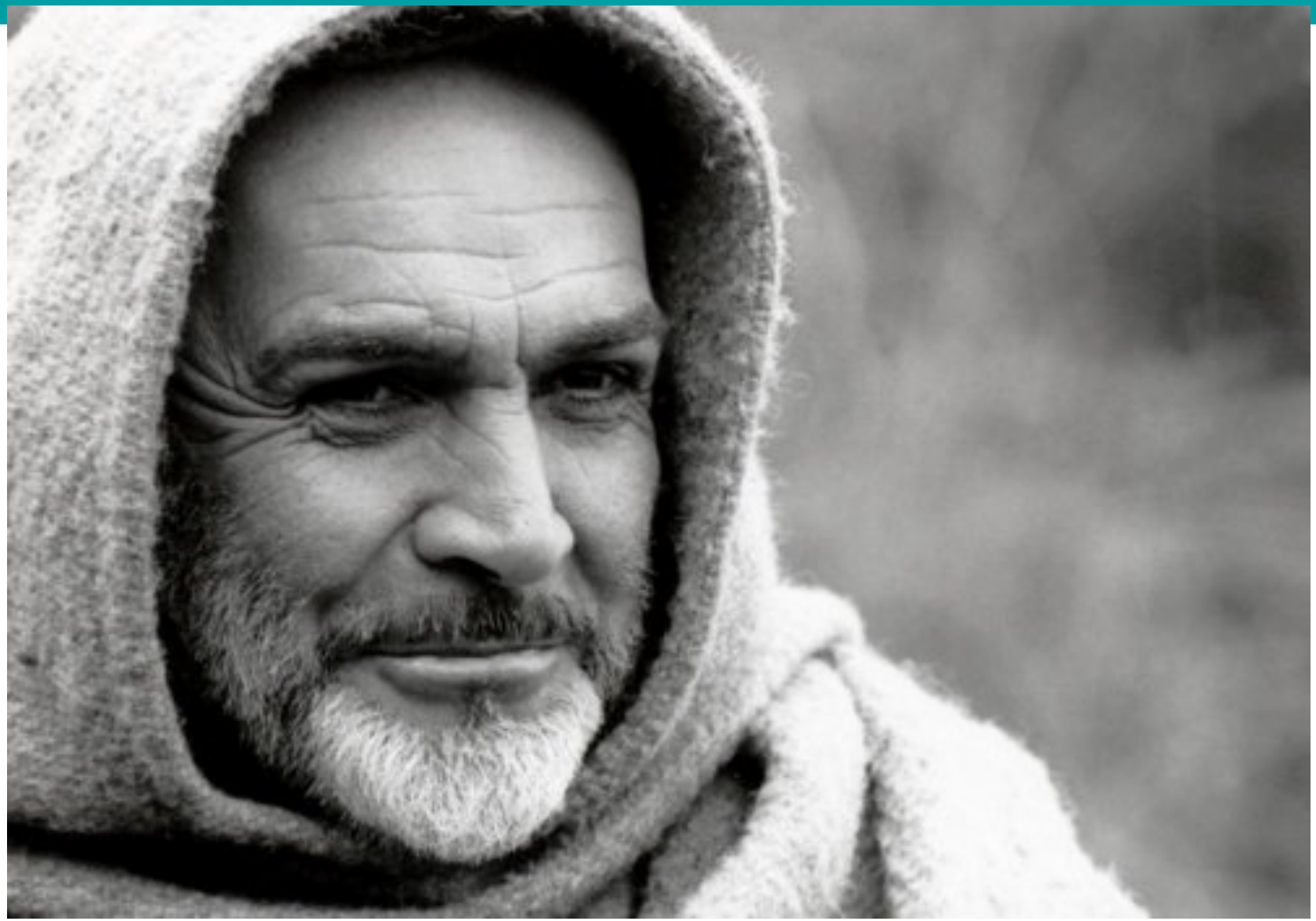

PROGETTO EMATOLOGIA – ROMAGNA Rimini, 8 aprile 2017

«Voglio dirti solo una parola, ragazzo. Solo una parola»
«Sì, signore». «Mi ascolti?». «Sì, signore».

«Trombina». Pausa. «Credo di non avere capito, signore».
«Trombina, Ben. Il futuro è nella trombina»

Il Laureato – 1967

Schöchl *et al. Critical Care* (2017) 21:51
DOI 10.1186/s13054-017-1636-y

- Bacterial invasion prompts a compelling upregulation of the coagulation system and inhibits anticoagulant and fibrinolytic pathways, which results in widespread microvascular fibrin deposition
- Dual inhibition of activated FII and activated FX (SATI) diminishes thrombin formation and preserves anticoagulant and fibrinolytic pathways
- SATI administration strongly ameliorates IL-6 release in severe sepsis
- SATI robustly attenuates sepsis-induced organ damage and protects organ function