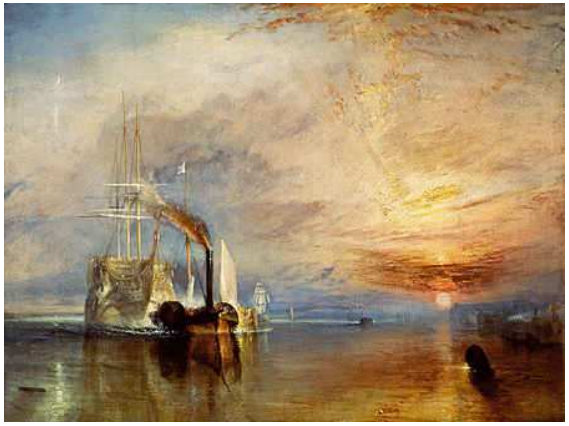
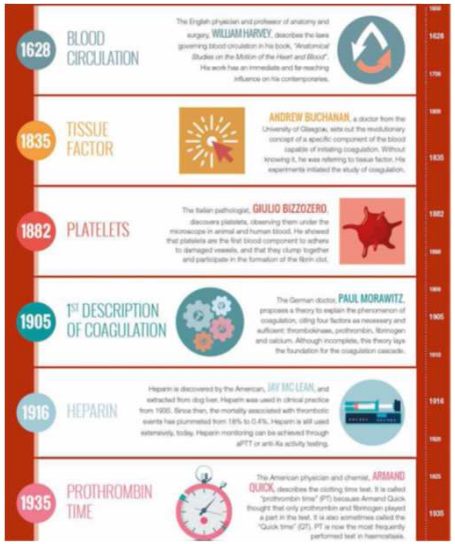


William Turner, 1839, The Fighting Temeraire

La fisiopatologia dell'emostasi

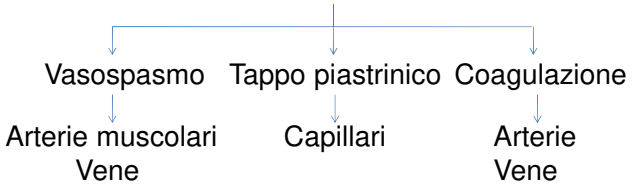


https://www.stago.com/haemostasis/history-of-coagulation/

Emostasi

L'insieme delle reazioni cellulari e biochimiche finalizzate ad arrestare l'emorragia

Meccanismi emostatici



Le fasi dell'emostasi

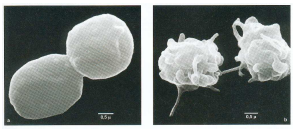
1. Fase vascolare: intensa vasocostrizione (riduzione del flusso di sangue nell'area interessata; espressione di molecole pro-aggreganti)
2. Fase piastrinica (primaria): attivazione, adesione, aggregazione (tappo bianco), liberazione di fattori atti ad amplificare il processo ed attivare alcuni fattori della coagulazione.
3. Fase plasmatica o emocoagulativa (secondaria): attivazione dei fattori della coagulazione per la formazione del coagulo stabile (trombo rosso)
4. Fase risolutiva: dissoluzione del coagulo ad opera della plasmina

1. Fase vascolare (vasocostrizione)

- Risposta diretta delle cellule muscolari in risposta al trauma
- Riflesso neurovegetativo
- Liberazione locale di sostanze vasocostrittrici (endotelina)

2. Fase piastrinica

Le piastrine



- Cellule discoidi anucleate
  - Diametro 2-3 µm
  - Vita media 9-12 gg
- Livello normale: 150 000 – 400 000/µl
- Piastrinopoiesi stimolata da trombopoietina, interleuchina 1

Il fattore di von Willebrand

- Presente nel sangue come multimero (n. variabile di omodimeri di ca. 500 kDa). Rilasciato da **megacariociti e cellule endoteliali** (da corpi Weibel-Palade in risposta a stimolazione).
- **Media l'adesione al collagene sottovasale**. La proteina ad alto PM è 100 volte più attiva nel legare il collagene (es VHMW vW presente nei corpi di WP)
- **Media l'associazione fra le piastrine**
- **Protegge il fattore VIII dall'inattivazione Proteina C-dipendente**

Acta Haematologica
Acta Haematol 2012;128:158–169
DOI: 10.1159/000339426

von Willebrand Factor: More Than a Regulator of Hemostasis and Thrombosis

Gui-Ping Luo Bing Ni Xia Yang Yu-Zhang Wu

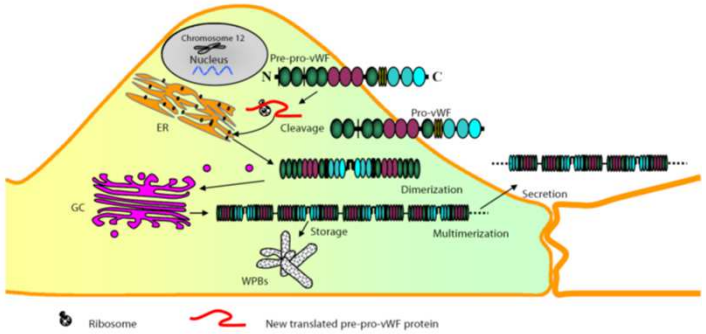


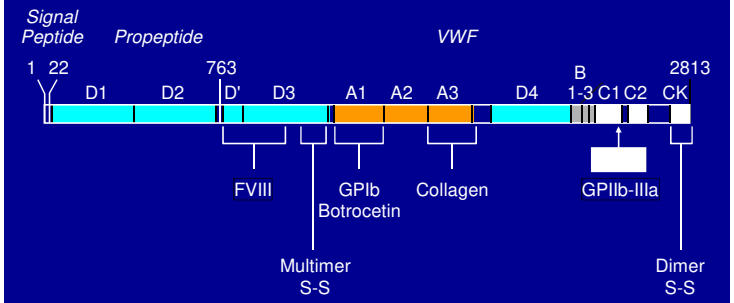
Table 1. vWF secretion pathways induced by agonists or inhibitors

Secretagogue	Mediator	Receptor
VEGF	Ca^{2+}	VEGFR2
NAADP	Ca^{2+}	H1R
Histamine	Ca^{2+}	H1R
Thrombin	Ca^{2+}	Thrombin receptor
Estrogen	Ca^{2+}	Estrogen receptor
LTs, ROIs, calcium ionophore A23187/ionomycin, PMA, C5a and C5b-9, superoxide anions	Ca^{2+}	UNK
Purine nucleotides	Ca^{2+}/camp	P2yR/A2R
Vasopressin (DDAVP)	cAMP	V2R
Epinephrine	cAMP	β2-AR
5-HT, adenosine, prostacyclin	cAMP	UNK
Dopamine	Not Ca^{2+} or cAMP	D2, D3, D4
NO	GCy, cGMP, NSF, Ca^{2+}	UNK
H_2O_2	Ca^{2+}	UNK

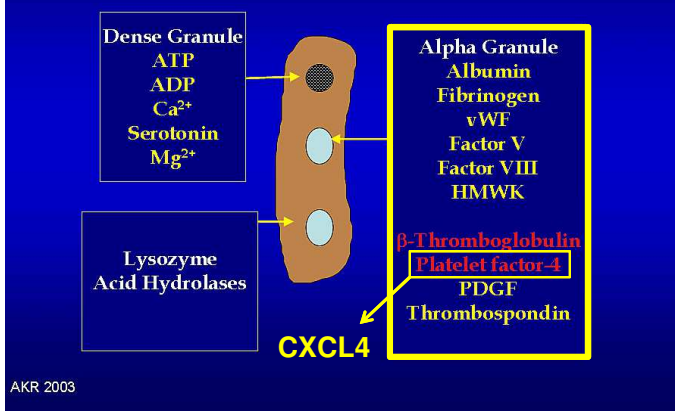
cAMP = Cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GCy = guanylate cyclase; UNK = unknown; A2R = adenosine A2 receptor; β2-AR = β2-adrenergic receptor; H1R = histamine H1 receptor; P2yR = P2y purinergic receptor; V2R = vasopressin 2 receptor.

In response to pathological stimuli, such as inflammation, the circulatory concentration of vWF increases rapidly. Secretion of stored vWF from endothelial cells occurs through both a constitutive and a regulated pathway [8]. Megakaryocytes, however, lack the regulatory pathway, and once they are stimulated, vWF is constitutively secreted

The Von Willebrand Factor Precursor



Platelet Granule Constituents



Blood Reviews 23 (2009) 177–189

Contents lists available at ScienceDirect

Blood Reviews

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

REVIEW

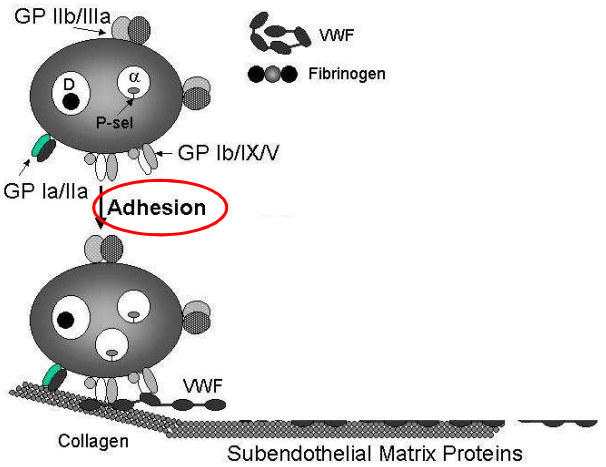
Platelet α-granules: Basic biology and clinical correlates

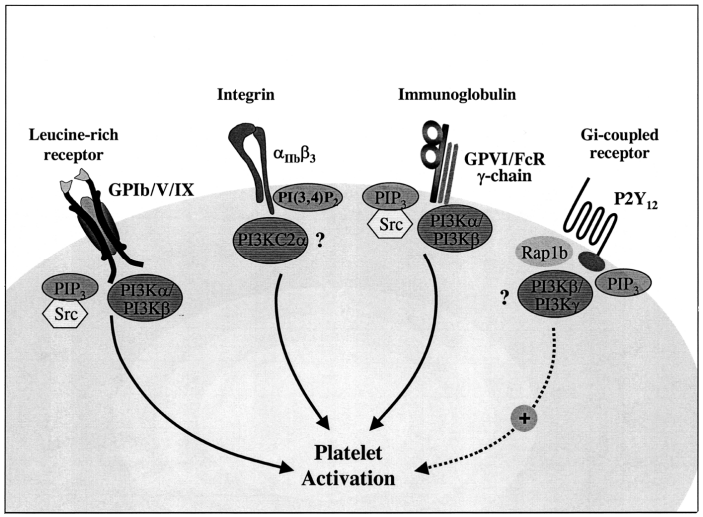
Price Blair, Robert Flaumenhaft *

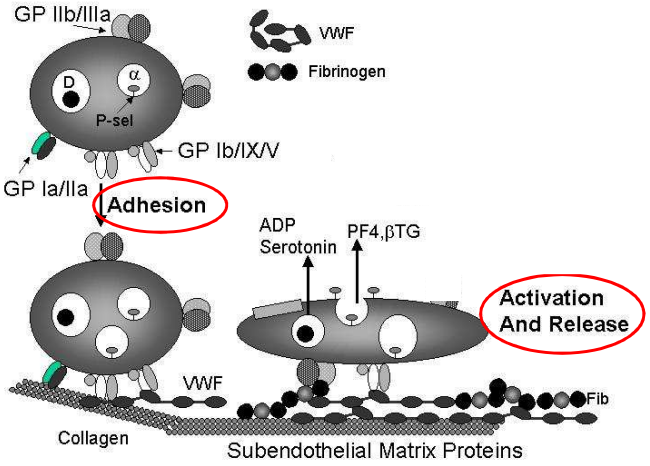
Department of Medicine, Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

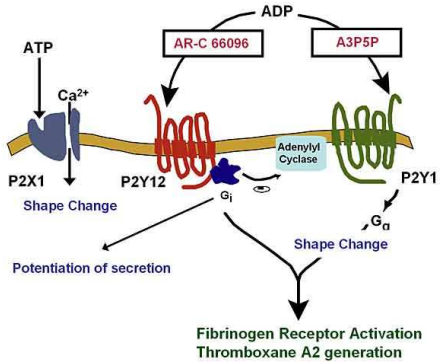
Proteomic studies suggest that hundreds of soluble proteins are released by α-granules.

α-Granules contain a wide range of chemokines including CXCL1 (GRO-α), CXCL4, CXCL5 (ENA-78), CXCL7 (PBP, β-TG, CTAP-III, NAP-2), CXCL8 (IL-8), CXCL12 (SDF-1α), CCL2 (MCP-1), CCL3 (MIP-1α), and CCL5 (RANTES).[133] Among these, CXCL4 and CXCL7 are the most abundant.[134] For example, platelets contain 20 μg of CXCL4/10^9 cells, and following thrombin stimulation the serum concentration of CXCL4 rises to 5–10 μg/ml, approximately 1000-fold greater than normal plasma.[135,136] Platelets are considered the major cellular source of CXCL4 and CXCL7, whereas platelet secretion of other chemokines is thought to merely augment their secretion by other cells.[121] CXCL4 has been shown to induce neutrophil adhesion and degranulation, monocyte activation, and monocyte differentiation to macrophages and foam cells.[137–139] In coordination with CCL5, CXCL4 is also able to induce adhesion of monocytes to endothelial cells.

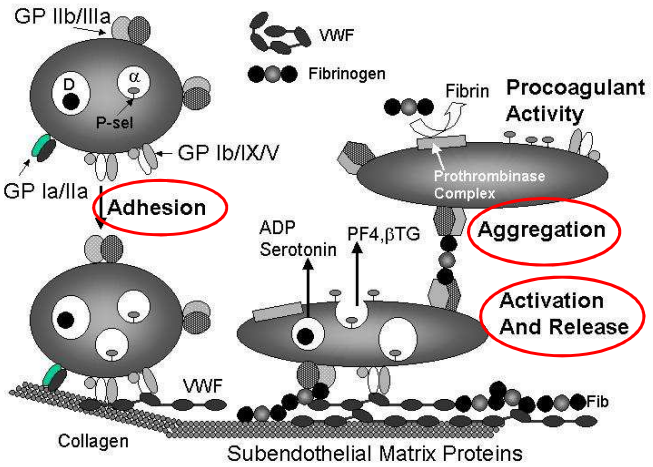


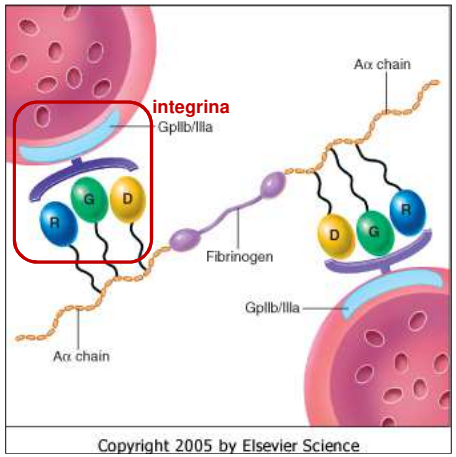


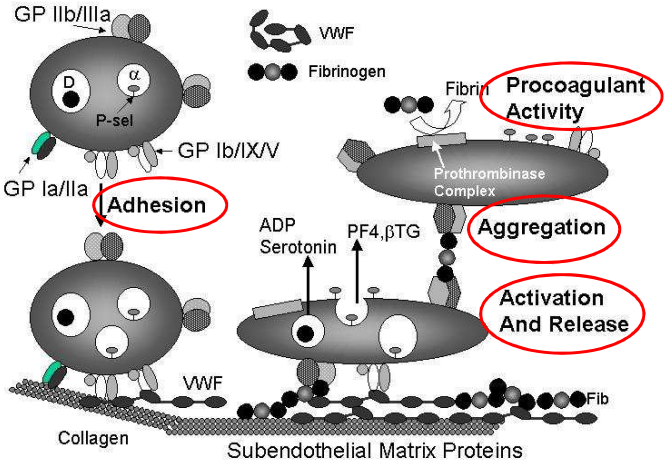




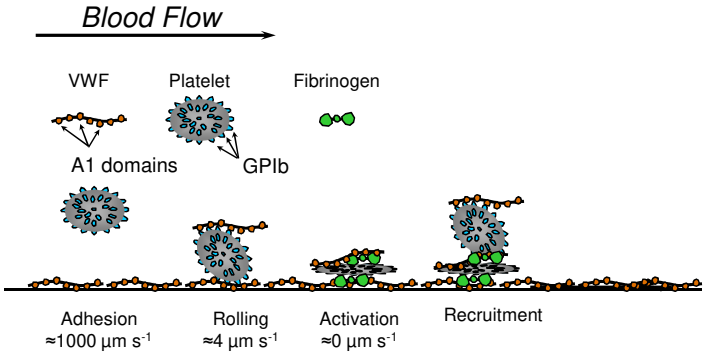
Trombina
TxA_2
PAF
→ Gq GPCR →
Produzione TxA_2
Secrezione
Cambio di forma
Modifica affinità integrine







VWF and Platelet Adhesion



VWF Cleaving Protease (ADAMTS13)

A Disintegrin-like And Metalloprotease with a ThromboSpondin type 1 motif, member 13

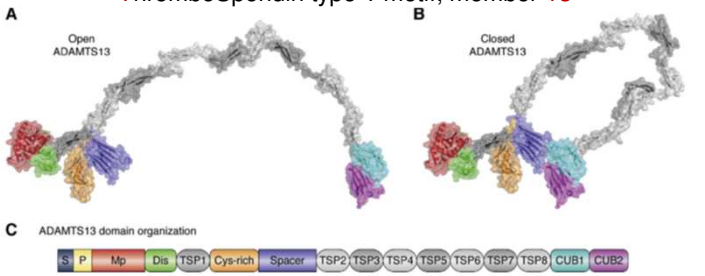
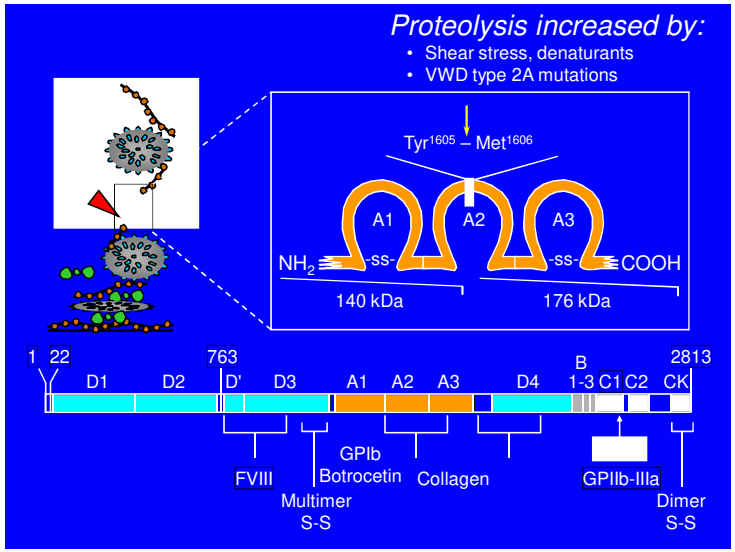
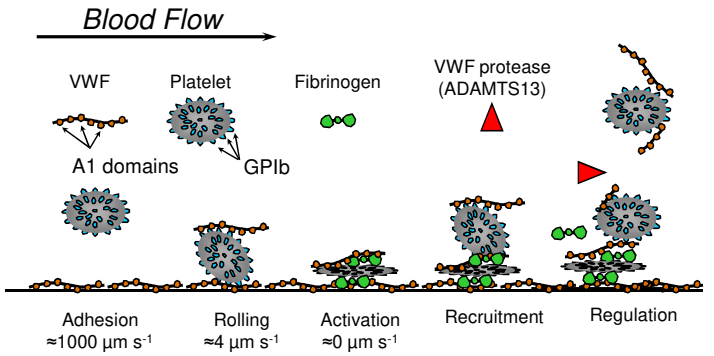


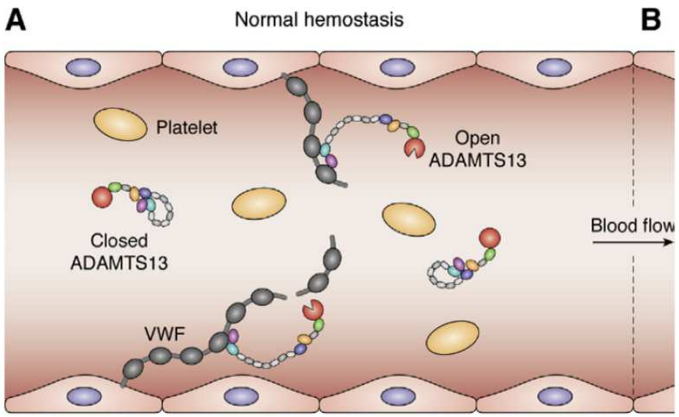
Figure 2. ADAMTS13 structure. *A*, three-dimensional model of ADAMTS13 in the "open conformation". In this conformation, the spacer domain (*blue*) releases its interactions with the CUB domains (*cyan* and *magenta*). This image was created based on the full-length ADAMTS13 3D model in panel *B*. *B*, three-dimensional model of ADAMTS13 in the "closed conformation". The MDTCS structure is determined by X-ray crystallography (18); three-dimensional structure of the CUB domains was taken from the study by Kim *et al.* (32); the structure of TSP2-8 was determined by homology modeling as described (49). *C*, the ADAMTS13 domains are depicted schematically as a signal peptide (S; *black*), propeptide (P; *yellow*), metalloprotease (MP; *red*) domain with active site followed by disintegrin-like (Dis; *green*), central thrombospondin type 1-like (TSP; *gray*) repeat, cysteine-rich (Cys-rich; *orange*), spacer (*purple*) domains, TSP2-8 (*gray*), CUB1 (*cyan*), and CUB2 (*magenta*). ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CUB, complement C1r/C1s, Uegf, Bmp1; MDTCS, metalloprotease, disintegrin-like domain, thrombospondin type 1 repeat.

J. Biol. Chem. (2021) 297(4) 101132

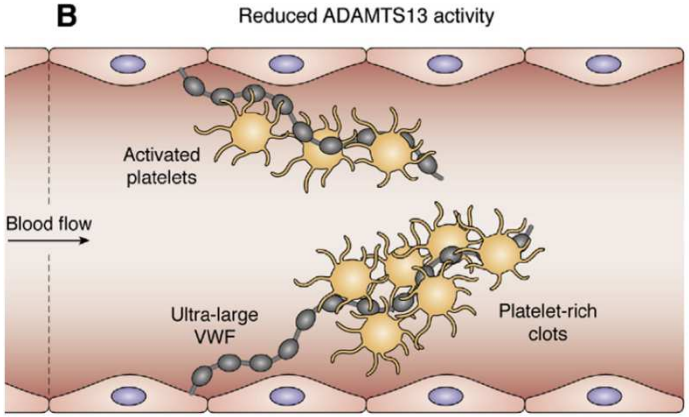


VWF and Platelet Adhesion





J. Biol. Chem. (2021) 297(4) 101132

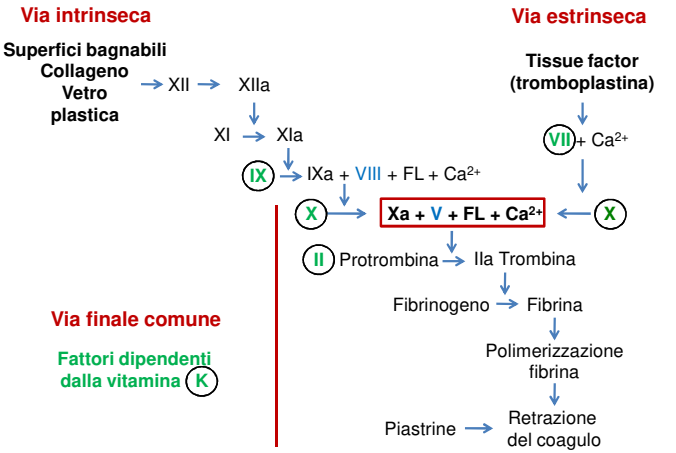


J. Biol. Chem. (2021) 297(4) 101132

Coagulo

Sangue solidificato per attivazione dei meccanismi coagulativi *in vivo* o *in vitro*

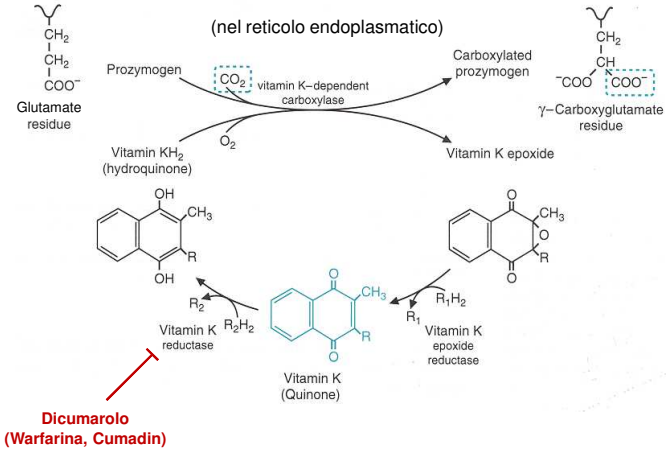
3. Fase emocoagulativa



Vitamina K

- **K**oagulation
- Liposolubile
- Presente nella dieta e prodotta dalla flora batterica intestinale
- Interviene nella sintesi epatica dei fattori II, VII, IX, X

La γ-carbossilazione



Dicumarolo

- Anticoagulante
- Antagonista della vit. K
- Presente nel trifoglio dolce
- Causa emorragie mortali nei bovini

Warfarina

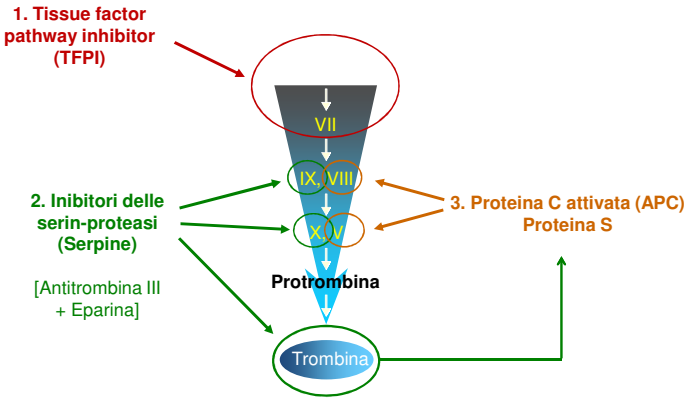
(Wisconsin Alumni Research Foundation + cumarin)

- Anticoagulante derivato dal dicumarolo
- Principio attivo del Cumadin

Cumadin

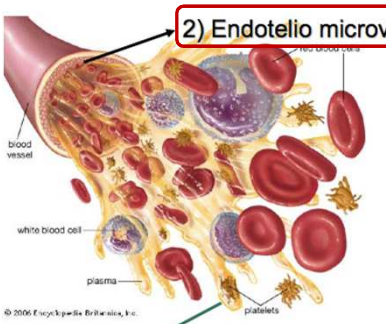
- Usato nella terapia della fibrillazione atriale
- Usato nelle esche topicida (attenti ai cani!)
- Farmaco di difficile gestione, perché condizionato dall'apporto dietetico di vit. K
- Sostituibile con Eliquis, inibitore diretto del fattore X

Regolazione negativa della coagulazione



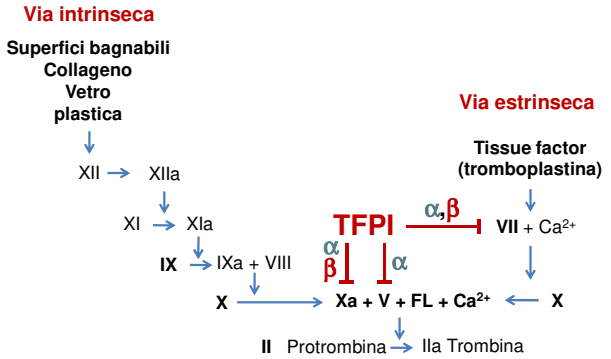
1. Tissue factor pathway inhibitor (TFPI)

Distribuzione:
1) Nel plasma (2-2.5 nM, poco) libero o associato a lipoproteine.



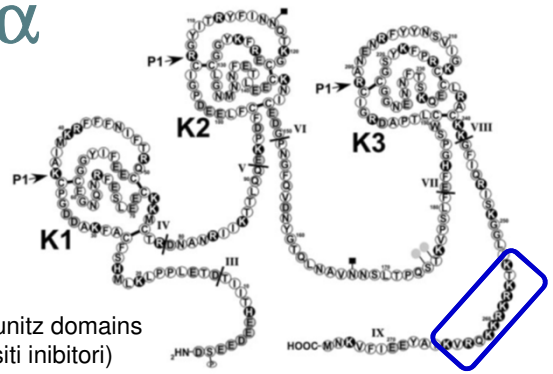
Sintesi:
- Cellule endoteliali
- Megacariociti

Forme di TFPI:
- Full length (43 kDa)
- Varie forme (34-40 kDa)



1. Tissue factor pathway inhibitor (TFPI)

α



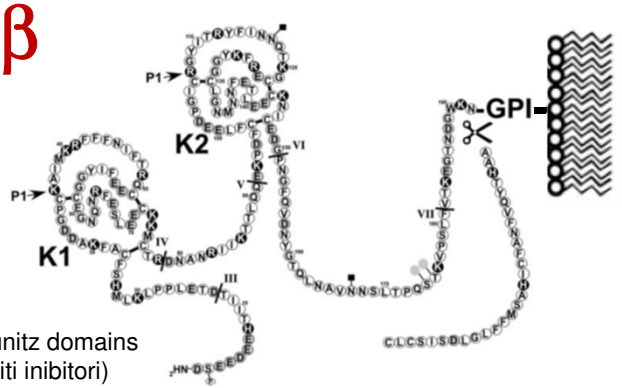
K, Kunitz domains
(siti inibitori)

Residui basici

Crawley and Lane (2008)
Arterioscler Thromb Vasc Biol 2008;28:233-242

1. Tissue factor pathway inhibitor (TFPI)

β



K, Kunitz domains
(siti inibitori)

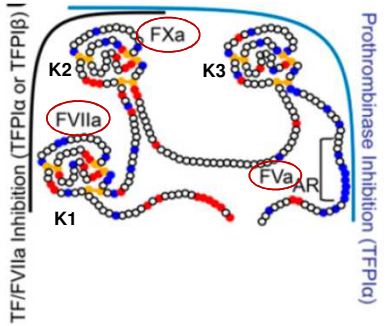
Crawley and Lane (2008)
Arterioscler Thromb Vasc Biol 2008;28:233-242

Tissue factor pathway inhibitor-alpha inhibits prothrombinase during the initiation of blood coagulation

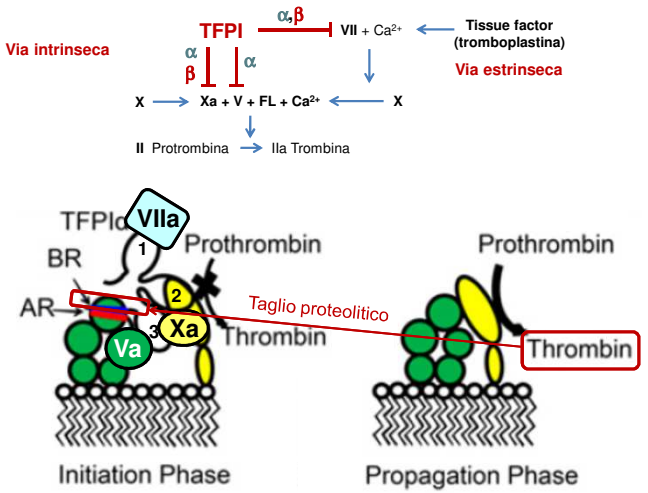
17838–17843 | PNAS | October 29, 2013 | vol. 110 | no. 44

Jeremy P. Wood[a], Matthew W. Bunce[b], Susan A. Maroney[a], Paula B. Tracy[c], Rodney M. Camire[b,d], and Alan E. Mast[a,e,1]

[a]Blood Research Institute, Blood Center of Wisconsin, Milwaukee, WI 53226; [b]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA 19104; [c]Department of Biochemistry, University of Vermont College of Medicine, Burlington, VT 05405; [d]Department of Pediatrics, University of Pennsylvania, Philadelphia, PA 19104; and [e]Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI 53226



Based on the studies reported here, it is proposed that TFPIα inhibits early events in blood coagulation through two separate mechanisms, thereby preventing small procoagulant or inflammatory stimuli from inducing intravascular thrombosis (Fig. 7*B*). First, TFPIα and TFPIβ rapidly inhibit small amounts of intravascular tissue factor on activated endothelial cells or monocytes, thereby preventing "subthreshold" intravascular inflammatory stimuli from developing into occlusive thrombi, a function mediated by K1 and K2 (7, 16). Second, platelet and plasma TFPIα rapidly inhibit early forms of prothrombinase that assemble on the surface of platelets activated by subthreshold stimuli within the vasculature, a function mediated by K2 and the basic C terminus. In both cases, the inhibitory capacity of TFPI is overcome by strong prothrombotic stimuli, producing feedback activation



of factors VIIIa and Va, removal of the entire B domain from FVa, and a resultant thrombin burst.

These findings lend unique insight into therapeutic agents to treat hemophilia that are directed against different structural regions of TFPI, some of which are currently in phase 1 clinical trials (26, 45, 46). As hemostasis in hemophilia is modulated by the TFPIα present in plasma (47) or in platelets (26), agents designed to specifically block TFPIα-mediated inhibition of prothrombinase may be therapeutically effective as they would promote clot formation at the site of the platelet plug, while leaving functional TFPIβ-mediated anticoagulant activity throughout the vasculature.

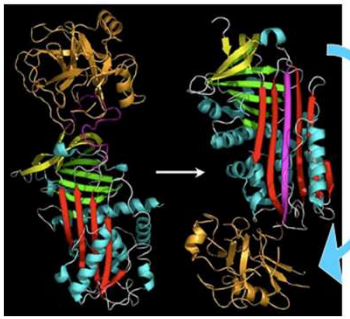
Tissue factor (TF) pathway inhibitor (TFPI) is a well-characterized activated factor X (FXa)-dependent inhibitor of TF-initiated coagulation produced in two alternatively spliced isoforms, TFPIα and TFPIβ. The TFPIα C terminus has a basic sequence nearly identical to a portion of the factor V (FV) B domain necessary for maintaining FV in an inactive conformation via interaction with an acidic region of the B domain. We demonstrate rapid inhibition of prothrombinase by TFPIα mediated through a high-affinity exosite interaction between the basic region of TFPIα and the FV acidic region, which is retained in FXa-activated FVa and platelet FVa. This inhibitory activity is not mediated by TFPIβ and is lost upon removal of the acidic region of FVa by thrombin. The data identify a previously undescribed, isoform-specific anticoagulant function for TFPIα and are a unique description of physiologically relevant inhibition of prothrombinase. These findings, combined with previous descriptions of differential expression patterns of TFPIα and TFPIβ in platelets and endothelial cells, suggest that the TFPI isoforms may act through distinct mechanisms to inhibit the initial stages of intravascular coagulation, with TFPIβ acting to dampen TF expressed on the surface of vascular cells, whereas TFPIα dampens the initial prothrombinase formed on the activated platelet surface.

2. Inibitori delle serin-proteasi (Serpine)

[Antitrombina III + Eparina]

Famiglia antichissima di proteine monomeriche, frequentemente extracellulari, ma anche intracellulari.

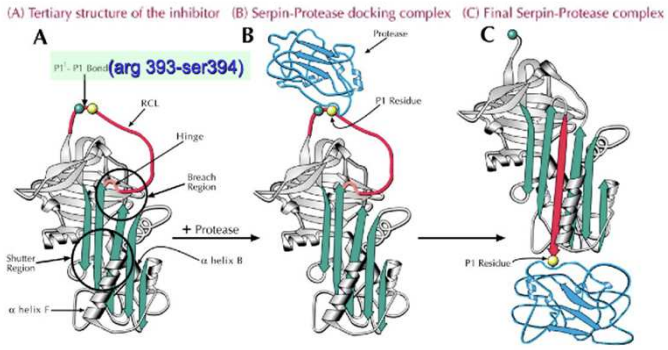
L'ATIII appartiene a questa famiglia.



Proteine parzialmente stabili nella loro forma attiva.

In seguito all'azione di una serin proteasi posson divenir molto più stabili.

Meccanismo di inibizione da parte delle serpine: trappola o suicidio molecolare



Si complessano irreversibilmente alle proteasi mediante legame estere fra il gruppo carbonilico in P1 dell'inibitore e l'ossidrile serinico della proteasi → complesso stabile a pH neutro

Sistema antitrombina-eparina

Antitrombina (ATIII)

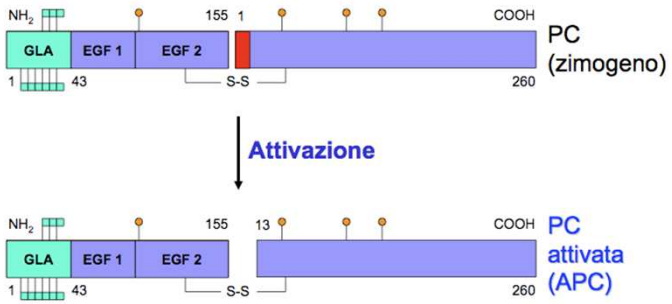
- Anticoagulante plasmatico
- Appartiene alla famiglia delle SERPINE (inibitori delle serin proteasi)
- Inibisce **trombina**, FXa e altre serin proteasi della coagulazione (FIXa, FXIa, FXIIa)
- L'attività inibitoria viene potenziata dall'interazione con il proprio cofattore (eparina)

Eparina

- Glicosaminoglicano (GAG) altamente solforato.
- Prodotta e rilasciata dai mastociti associati all'endotelio.
- Azione anticoagulante indiretta: cofattore dell'ATIII.

3. Proteina C attivata (APC)

Glicoproteina vit K-dipendente, con sito catalitico serin proteasico



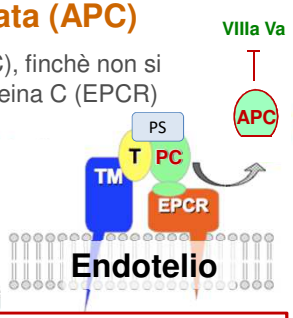
Questo enzima, attivato per taglio proteolitico, ne inattiverà altri sempre mediante tagli proteolitici!

3. Proteina C attivata (APC)

Circola nel plasma come zimogeno (PC), finchè non si lega al Recettore Endoteliale della Proteina C (EPCR)

Per essere attivata necessita della trombina e della trombomodulina

TM = Trombomodulina, anch'essa proteina trasmembrana, espressa costitutivamente dalle cellule endoteliali



La trombina complessata alla trombomodulina attiva la proteina C

La reazione è stimolata dalla proteina S, fattore vitamina K-dipendente che ha anche un ruolo nella regolazione del complemento

La PC attivata (APC) si stacca da EPCR e inattiva i fattori

- VIIIa e Va

Regulated endothelial protein C receptor shedding is mediated by tumor necrosis factor-α converting enzyme/ADAM17

D. QU,* Y. WANG,* N. L. ESMON*† and C. T. ESMON*‡†§

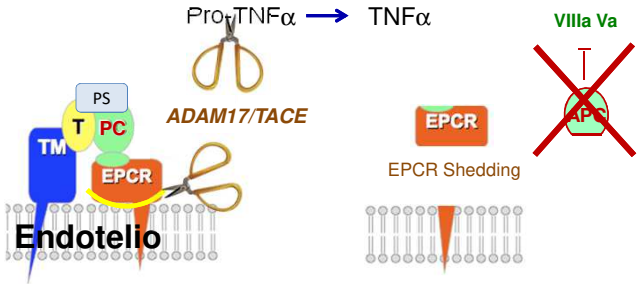
*Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK; †Departments of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; and ‡Howard Hughes Medical Institute, Oklahoma City, OK; §Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

To cite this article: Qu D, Wang Y, Esmon NL, Esmon CT. Regulated endothelial protein C receptor shedding is mediated by tumor necrosis factor-α converting enzyme/ADAM17. *J Thromb Haemost* 2007; **5**: 395–402.

Summary. Endothelial protein C receptor (EPCR) plays an important role in the protein C anticoagulation pathway. Previously, we have reported that EPCR can be shed from the cell surface, and that this is mediated by an unidentified metalloproteinase. In this study, we demonstrate that tumor necrosis factor-α converting enzyme/ADAM17 (TACE) is responsible for EPCR shedding. Phorbol-12-myristate 13-acetate (PMA)-stimulated EPCR shedding is reduced by approximately 50% in HEK293 cells transfected with human EPCR cDNA and by 60% in human umbilical vein endothelial cells after transfection of TACE small interfering RNA (siRNA) into these cells. PMA-stimulated EPCR shedding is completely blocked in fibroblasts from TACE-deficient mice transfected with human EPCR cDNA, and restored by transfection of TACE cDNA into this cell line. To characterize the EPCR sequence requirement for shedding, we generated several mutants of EPCR. Replacing amino acids from residue 193 to residue 200 with the FLAG™ sequence (DYKDDDDK) completely blocks EPCR shedding, whereas a single amino acid substitution in this region has less effect on EPCR shedding.

3. Proteina C attivata (APC)

Circola nel plasma come zimogeno (PC), finchè non si lega al Recettore Endoteliale della Proteina C (EPCR)



La PC attivata (APC) si stacca da EPCR e inattiva i fattori

- VIIIa e Va

Molecular Aspects of Medicine 29 (2008) 258–289

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Review

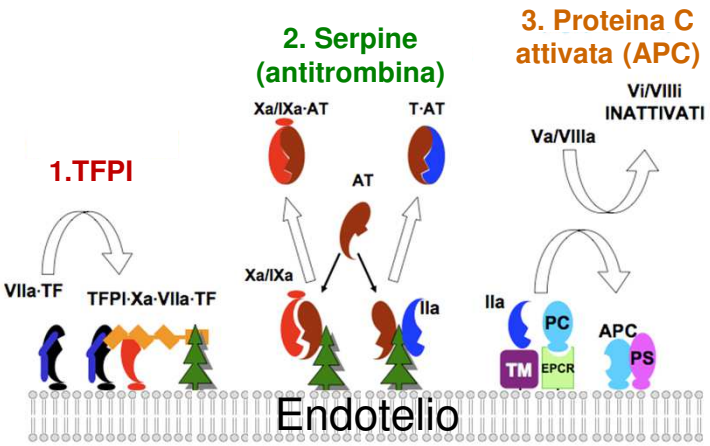
The ADAM metalloproteinases

Dylan R. Edwards *, Madeleine M. Handsley, Caroline J. Pennington

Biomedical Research Centre, School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ, UK

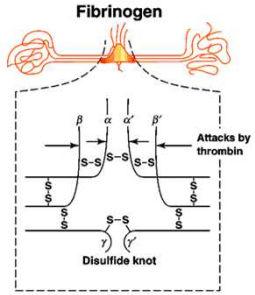
The ADAMs (a disintegrin and metalloproteinase) are a fascinating family of transmembrane and secreted proteins with important roles in regulating cell phenotype via their effects on cell adhesion, migration, proteolysis and signalling. Though all ADAMs contain metalloproteinase domains, in humans only 13 of the 21 genes in the family encode functional proteases, indicating that at least for the other eight members, protein–protein interactions are critical aspects of their biological functions. The functional ADAM metalloproteinases are involved in "ectodomain shedding" of diverse growth factors, cytokines, receptors and adhesion molecules. The archetypal activity is shown by ADAM-17 (tumour necrosis factor-α convertase, TACE), which is the principal protease involved in the activation of pro-TNF-α, but whose sheddase functions cover a broad range of cell surface molecules. In particular, ADAM-17 is required for generation of the active forms of Epidermal Growth Factor Receptor (EGFR) ligands, and its function is essential for the development of epithelial tissues. Several other ADAMs have important sheddase functions in particular tissue contexts. Another major family member, ADAM-10, is a principal player in signalling via the Notch and Eph/ephrin pathways. For a growing number of substrates, foremost among them being Notch, cleavage by ADAM sheddases is essential for their subsequent "regulated intramembrane proteolysis" (RIP), which generates cleaved intracellular domains that translocate to the nucleus and regulate gene transcription. Several ADAMs play roles in spermatogenesis and sperm function, potentially by effecting maturation of sperm and their adhesion and migration in the uterus. Other non-catalytic ADAMs function in the CNS via effects on guidance mechanisms. The ADAM family are thus fundamental to many control processes in development and homeostasis, and unsurprisingly they are also linked to pathological states when their functions are dysregulated, including cancer, cardiovascular disease, asthma, Alzheimer's disease. This review will provide an overview of current knowledge of the human ADAMs, discussing their structure, function, regulation and disease involvement.

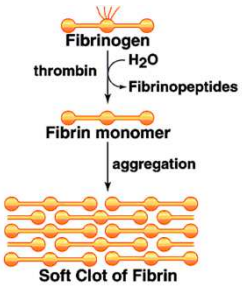
Sistemi anticoagulanti endogeni



Fibrinogeno → fibrina

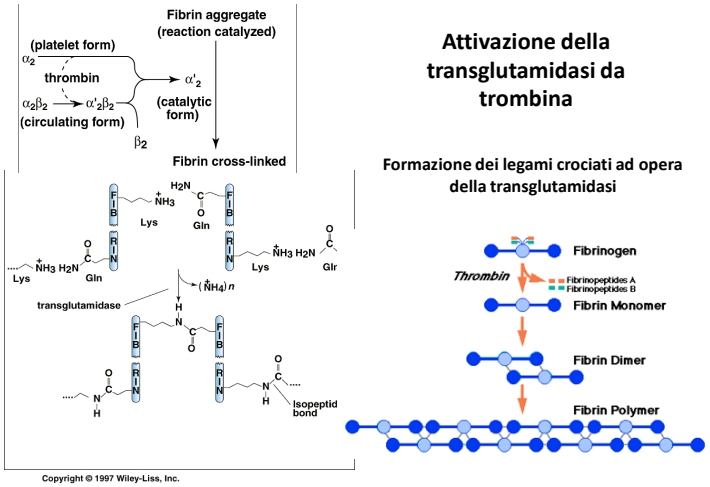
- 3 g/l in plasma, sintetizzato nel fegato $(\alpha\beta\gamma)_2$
- $T_{1/2}$= 4 g
- Trombina converte fibrinogeno solubile in fibrina insolubile
- Stabilizzazione con XIII





La regione N terminale delle subunità αα' e ββ' per repulsione di carica previene aggregazione dei monomeri di fibrina.
Contiene molecole di plasminogeno

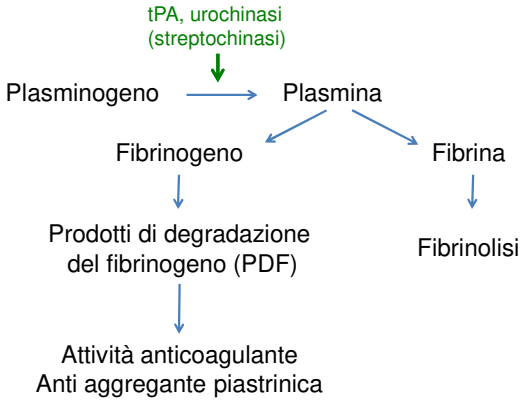
La transglutamidasi (FXIII)

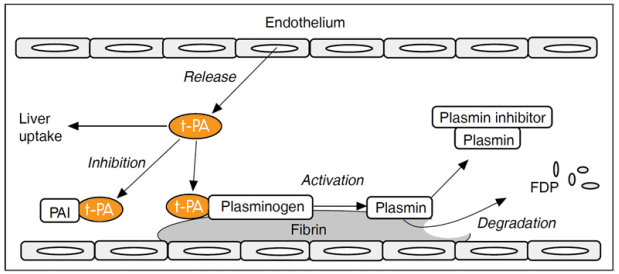


Attivazione della transglutamidasi da trombina

Formazione dei legami crociati ad opera della transglutamidasi

4. Fase risolutiva (fibrinolisi)

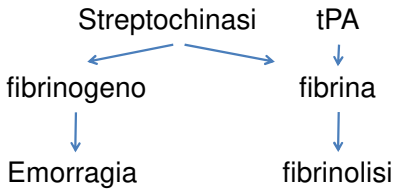




The fibrinolytic system in vivo. Plasminogen is the proenzyme of plasmin, whose primary target is the degradation of fibrin in the vasculature. The activation of plasminogen to plasmin in blood is catalyzed by t-PA secreted from endothelial cells. Fibrin provides binding sites for both plasminogen and t-PA, thereby optimizing contact between them. ***This mechanism ensures a high concentration of plasminogen and t-PA at the site of fibrin formation and localizes the action of plasmin****. Further regulation of the system is provided by PAI-1 and plasmin inhibitor. Free t-PA, as well as complexed t-PA/PAI-1, is cleared from the circulation by receptors in the liver. Abbreviations: t-PA; tissue-type plasminogen activator, PAI-1; plasminogen activator inhibitor 1, FDP; fibrin degradation products.*

https://diapharma.com/tissue-plasminogen-activator-tpa/

Gli attivatori del plasminogeno differiscono per la specificità nei confronti del substrato



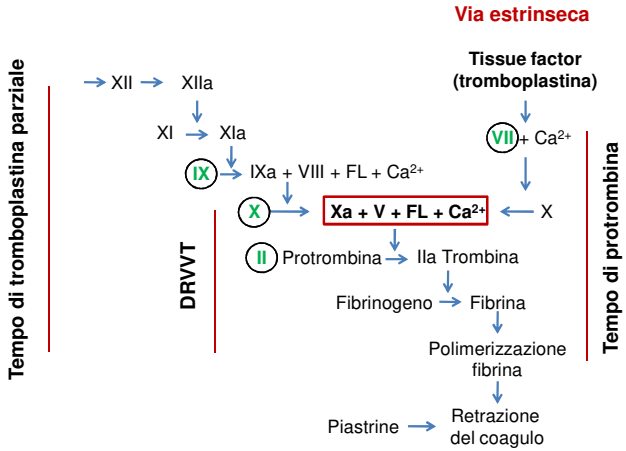
La streptochinasi è il farmaco fibrinolitico più usato

Farmaco	Streptochinasi	Urochinasi umana ricombinante	tPA umano ricombinante	tPA umano ricombinante tripla sostituzione	Stafilochinasi batterica ricombinante
Specificità per la fibrina	No	+	++	+++	++++
Costo (USD)	280	Non noto	2.200	Non noto	Non noto

Esami per lo studio della patologia dell'emostasi

- Conta piastrinica
- Tempo di sanguinamento: 1-9 min
- Tempo di coagulazione: 5-15 min a 37° C
- Tempo di tromboplastina parziale: 10-15 secondi
- Tempo di protrombina: 10-15 secondi
- Dilute Russell Venom Viper Test (DRVVT)

Coagulazione



Patologia dell'emostasi: porpore

Classificazione delle emorragie in base alle dimensioni e morfologia

- Emorragie capillari cutanee
- Forma e numero variabile
- Dimensione: dalla petecchia a emorragie confluenti

Petecchie – emorragie puntiformi, < 2 mm diametro, cute, mucose e visceri
Ecchimosi – emorragie piatte, > 2 mm diamentro, sottocutaneo e sottomucosa. Lividi
Ematomi – raccolte di sangue, volume variabile, in cute tumefazione visibile

William Turner, The Battle of Trafalgar (1806-1808)

Porpore generalizzate

1. Da difetto vascolare

- Scòrbuto
- Tifo petecchiale
- Porpora anafilattoide

James Lind (1716-1794)

Lind thought that scurvy was due to putrefaction of the body which could be helped by acids, and thus included a dietary supplement of an acidic quality in the experiment. This began after two months at sea when the ship was afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition,

group one was given a **quart of cider** daily
group two twenty-five drops of **elixir of vitriol** (sulfuric acid)
group three six spoonfuls of **vinegar**
group four half a pint of **seawater**
group five received **two oranges and one lemon**, and the
last group a **spicy paste plus a drink of barley water**

The treatment of group five stopped after six days when they ran out of fruit, but by that time one sailor was fit for duty while the other had almost recovered. Apart from that, **only group one also showed some effect of its treatment**.
In 1753 Lind published A treatise of the scurvy, which was virtually ignored. On the insistence of senior officers, led by Rear Admiral Alan Gardner, **in 1794 lemon juice was issued on board the Suffolk on a twenty-three-week, non-stop voyage to India.** The daily ration of two-thirds of an ounce mixed in grog contained just about the minimum daily intake of **10 mg vitamin C**. **There was no serious outbreak of scurvy.**

SCURVY

STEPHEN R. BOWN

HOW A SURGEON, A MARINER,
AND A GENTLEMAN SOLVED THE
GREATEST MEDICAL MYSTERY
OF THE AGE OF SAIL

THOMAS DUNNE BOOKS
ST. MARTIN'S GRIFFIN ■ NEW YORK

The Battle of Trafalgar on October 21, 1805. The British tore the heart out of Napoleon's navy and thwarted the invasion of England. The defeat of scurvy played a significant role in their supreme victory.

When Nelson died at Trafalgar, he was at the pinnacle of a brilliant naval career. He was Britain's greatest commander, a national hero associated more closely than any other with naval supremacy during the Age of Sail. During the era of his stunning victories, in the late 1790s and early 1800s, scurvy was no longer a threat to the Royal Navy. It had been reduced to a menacing phantom, rarely occurring since Blane had persuaded the Admiralty to issue a daily dose of lemon juice as a preventative in 1795. Yet Nelson might easily have perished, like many others, before ever realizing his potential. Perhaps remembering his own encounter with scurvy as a young captain, he was devoted to the health of his men, which he knew contributed to the strength of his fighting force. He purchased additional supplies of lemon juice, above the Admiralty's regular issue. In February 1805, just a month before he set off on the pursuit of Villeneuve that culminated in the Battle of Trafalgar, he ordered for the Mediterranean fleet an astonishing twenty thousand gallons of lemon juice to supplement the regular issue of thirty thousand gallons. Despite having been months at sea without any significant time in port, the British sailors at Trafalgar were free from scurvy.

Scòrbuto

- Carenza dietetica di vit. C, essenziale per la idrossilazione di lisina e prolina nel protocollageno
- Il collageno della membrana basale è difettoso e causa mancato ancoraggio ai capillari con porpore da microtraumi

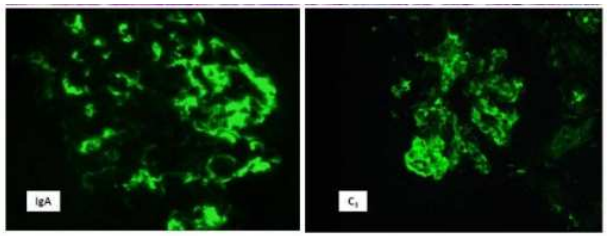
Tifo petecchiale

- *Rickettsia prowazecki,* Batterio gram-negativo (Coccobacillo)
- Intracellulare obbligato (non sintetizza ATP)
- Viene trasmessa dal pidocchio infettatosi succhiando il sangue di individui affetti
- Depositato con le feci sulla cute, entra in circolo e infetta le cellule endoteliali in cui si replica
- La morte delle cellule endoteliali causa porpore (cutanee, cerebrali, cardiache)

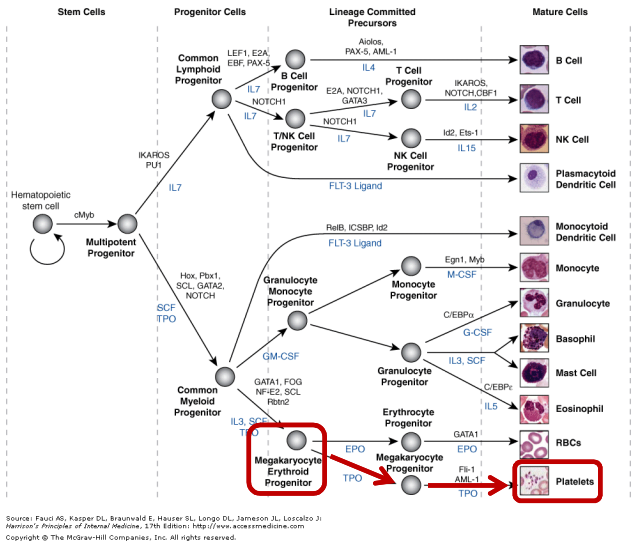
Porpora anafilattoide o di Schonlein-Henoch

- Vasculite da deposizione di immunocomplessi di IgA
- Attivazione del complemento e danno endoteliale cutaneo e sistemico
- Frequente in età pediatrica

Immunofluorescenza



Anti-IgA **Anti-C3**



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Porpore generalizzate

2. Da difetto piastrinico

- Trombocitopeniche
  - Insufficiente produzione
    - Aplasia midollare
    - Sostituzione midollo rosso
  - ↑ distruzione
    Ipersplenismo
    Anticorpi:
    - Morbo di Werlhof
    - Porpora da Sedormid
    - Porpore nella malattie diffuse del connettivo
    - Trombocitopenia trombotica indotta da eparina (HIT)
    - Trombocitopenia trombotica immune da vaccino (VITT)
  - ↑ consumo
    Malattia di Moschowitz
    Componente della sindrome uremico-emolitica di Gasser
- Trombocitopatiche
  - Sindrome di Bernard-Soullier
  - Iatrogene
  - Tromboastenia di Glanzmann

Sintomi

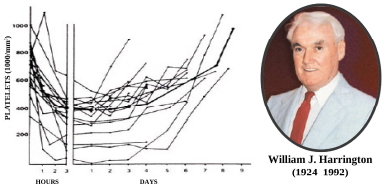
- Cutanei
- Glomerulonefrite focale
- Gastrointestinali
- SNC
- Cardiaci

○ ↑ distruzione

Morbo di Werlhof
(porpora trombocitopenica primaria idiopatica)

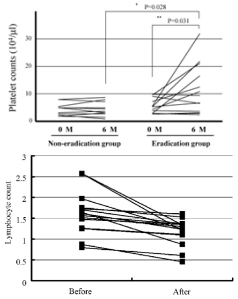
- Malattia immunopatologica
- Autoanticorpi contro le piastrine
- Aumentata emocateresi splenica
- Possibile reazione crociata con anticorpi prodotti contro *H. pilori*
- Terapia antibiotica per eradicare *H. pilori* sulla trombocitopenia
- Efficacia alta in Giappone ed Italia, bassa nel resto d'Europa e Stati Uniti
- Altre terapie: Splenectomia, cortisone

The Harrington–Hollingsworth Experiment



William J. Harrington
(1924 1992)

Graph shows rapid development of thrombocytopenia, followed by a return to normal platelet levels, in healthy volunteers who received plasma from patients with idiopathic thrombocytopenic purpura



Porpora da Sedormid

- Farmaco ipnotico che agisce da aptene
- Produzione di anticorpi
- Aumentata emocateresi

Porpore da malattie diffuse del connettivo

- Lupus Eritematoso Sistemico, Artrite reumatoide, Sclerodermia
- Diffuso movimento anticorpale
- Autoanticorpi contro le piastrine

Platelet factor-4 (CXCL4) is a 70-amino acid protein that is released from the α-granules of activated platelets and binds with high affinity to heparin. Its major physiologic role appears to be neutralization of heparin-like molecules on the endothelial surface of blood vessels, thereby inhibiting local antithrombin activity and **promoting coagulation**. As a strong chemoattractant for neutrophils and fibroblasts, PF4 probably has a role in inflammation and wound repair.

Heparin-induced thrombocytopenia (HIT)

Heparin is widely used as anti-coagulant during invasive vascular surgery and to treat thrombo-embolic pathology. HIT is a rare (1-5%), paradoxical complication of anticoagulant heparin therapy in which **patients having developed antibodies against CXCL4/heparin complexes, are at risk for venous as well as arterial thrombosis, despite low platelet counts** (Rauova et al., 2010). Heparin is thought to act as an adjuvant integral to immunogenesis, whereas the HIT antibody recognizes antigenic epitopes within CXCL4 and thus the presence of CXCL4 is essential to the clinical manifestations caused by circulating antibodies (Prechel and Walenga, 2013).

Emphasis on the Role of PF4 in the Incidence, Pathophysiology and Treatment of Heparin Induced Thrombocytopenia

M Margaret Prechel and Jeanine M Walenga*

to thrombocytopenia and/or thrombosis. Thus the HIT syndrome depends not only on the presence of HIT antibodies of sufficient titer and specificity but also on the presence of the antigenic PF4 target [37]. Many of the conditions that increase the risk of antibody formation by causing platelet activation and release of PF4 (as described above) similarly increase the risk of clinical consequences due to HIT antibody immune complex-mediated platelet activation [51,70].

Prechel and Walenga *Thrombosis Journal* 2013, **11**:7
http://www.thrombosisjournal.com/content/11/1/7

Monocyte-bound PF4 in the pathogenesis of heparin-induced thrombocytopenia

Lubica Rauova,[1-3] Jessica D. Hirsch,[1] Teshell K. Greene,[1] Li Zhai,[1] Vincent M. Hayes,[1] M. Anna Kowalska,[1,4] Douglas B. Cines,[5,6] and Mortimer Poncz[1,2]

[1]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; [2]National Institute for Rheumatic Diseases, Piestany, Slovakia; [3]Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA; [4]Polish Academy of Science, Lodz, Poland; [5]Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA; and [6]Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

Heparin-induced thrombocytopenia (HIT) is a life- and limb-threatening thrombotic disorder that develops after exposure to heparin, often in the setting of inflammation. We have shown previously that HIT is associated with antibodies to complexes that form between platelet factor 4 and glycosaminoglycan (GAG) side chains on the surface of platelets. However, thrombosis can occur in the absence of thrombocytopenia. We now show that platelet factor 4 binds to monocytes and forms antigenic complexes with their surface GAG side chains more efficiently than on platelets likely due to differences in GAG composition. Binding to monocytes is enhanced when the cells are activated by endotoxin. Monocyte accumulation within developing arteriolar thrombi was visualized by situ microscopy. Monocyte depletion or inactivation in vivo attenuates thrombus formation induced by photochemical injury of the carotid artery in a modified murine model of HIT while paradoxically exacerbating thrombocytopenia. These studies demonstrate a previously unappreciated role for monocytes in the pathogenesis of arterial thrombosis in HIT and suggest that therapies targeting these cells might provide an alternative approach to help limit thrombosis in this and possibly other thrombotic disorders that occur in the setting of inflammation. (*Blood.* 2010;116(23):5021-5031)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

This article was published on April 9, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2104840

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination (AstraZeneca)

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

RESULTS

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4 or PF4–heparin affinity purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

CONCLUSIONS

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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DOI: 10.1056/NEJMoa2104882

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

Nearly all healthy adults have a reservoir of B cells specific for PF4–heparin complexes; production of "heparin-induced thrombocytopenia–like" antibodies by these B cells is kept in check by immune regulatory mechanisms.[9,10]

SUMMARY

We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia. **(VITT)**

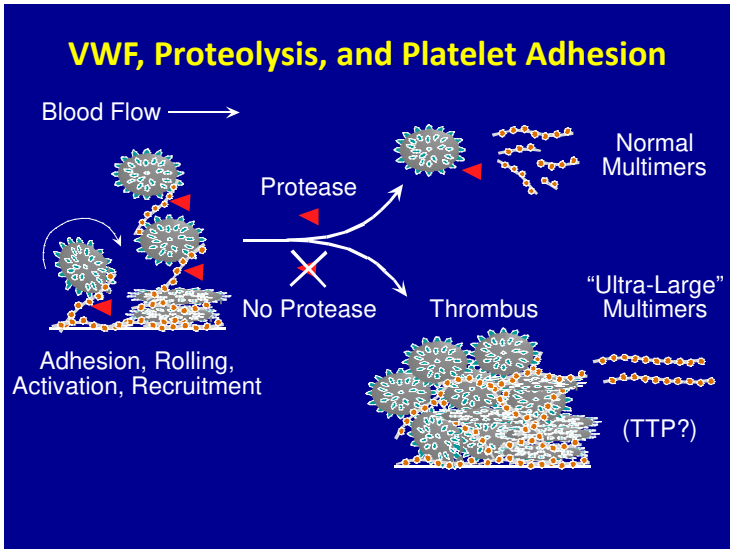
- **↑ consumo**

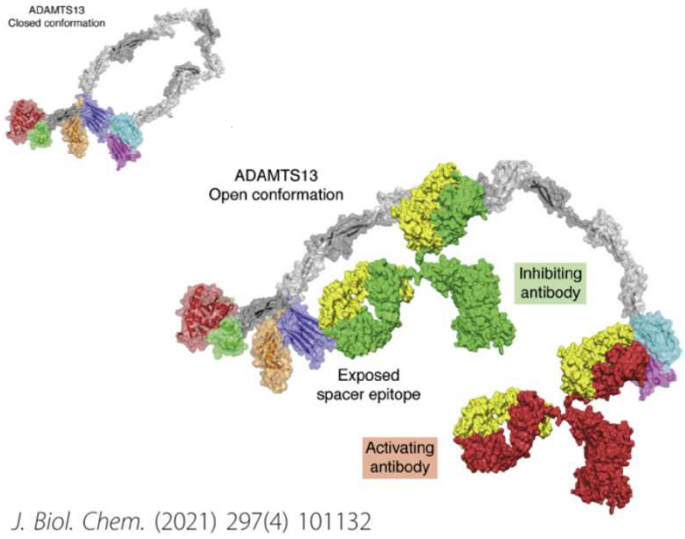
Malattia di Moschowitz
(porpora trombotica trombocitopenica)

- Carenza di ADAMTS13, genetica o acquisita (autoanticorpi)
- ADAMTS 13 proteolizza VWF
- In sua assenza si verifica eccesso di attività aggregante piastrinica con formazione di **trombi capillari**
- Questo causa **trombocitopenia secondaria da consumo**

Sindrome uremico-emolitica di Gasser

- Forma idiopatica o genetica
- Infezione da alimenti contaminati con ceppi di *E. coli* produttori di Shiga toxin
- Danno endoteliale con formazione di **trombi**
- Anemia emolitica microangiopatica con **emoglobinuria**
- **Insufficienza renale**





J. Biol. Chem. (2021) 297(4) 101132

- **Trombocitopatiche**

Sindrome di Bernard-Soullier

- Autosomica recessiva
- Mancanza complesso recettoriale [(GP)Ib-V-IX] per VWF
- «Piastrine giganti» con trombocitopenia
- Aumento del tempo di sanguinamento con tendenza al sanguinamento eccessivo (epistassi, flusso mestruale elevato)

Iatrogene

- Cardioaspirina

Tromboastenia di Glanzmann

- Autosomica recessiva
- Manca il recettore per il fibrinogeno (integrina IIb/IIIa)
- Difettosa aggregazione piastrinica
- Difettosa retrazione del coagulo

Test diagnostici per le porpore

- Tempo di sanguinamento allungato
- Tempo di coagulazione normale
- Conta piastrinica ridotta nelle porpore trombocitopeniche
- Retrazione del coagulo alterata nella malattia di Glanzmann

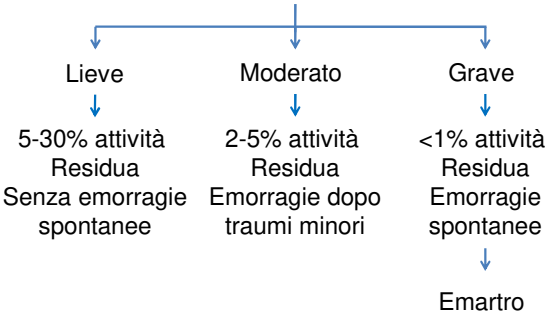
Patologia dell'emostasi: coagulazione

- Emofilia A
- Emofilia B (malattia di Christmas)
- Emofilia C (malattia di Rosenthal)
- Malattia di von Willebrand
- Altre: Fattore X, XIII
- Vitamina K
- Ipofibrinogenemia
  - Genetica
  - Acquisita
    - Consumo: CID
    - Epatopatia
- Coagulopatia da Ac anti fosfolipidi

Emofilia A

- **Carenza di fattore VIII**
- Recessiva legata al cromosoma X
- Femmine portatrici
- Maschi malati
- Sindrome di Turner X0

Fenotipi clinici



Test diagnostici

- Tempo di sanguinamento normale
- Tempo di coagulazione allungato
- TTP allungato
- Tempo di protrombina normale
- Dosaggio fattore VIII

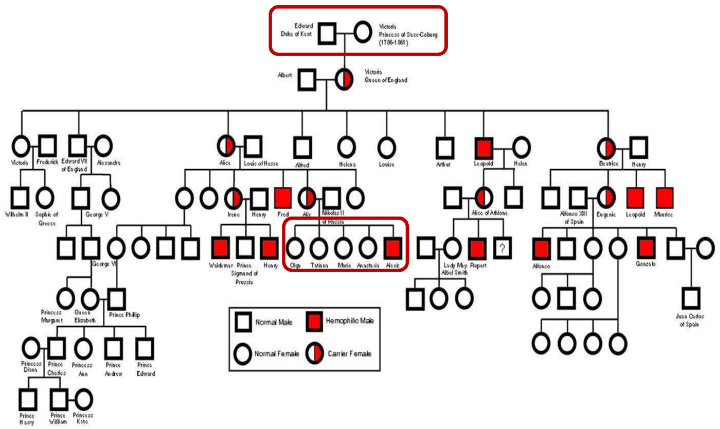
Emofilia B (malattia di Christmas)

- **Carenza di fattore IX**
- Recessiva legata al cromosoma X
- Più rara dell'emofilia A
- Meno grave, necessaria carenza >99%

Emofilia C (malattia di Rosenthal)

- **Carenza fattore XI**
- Recessiva, gene sul cromosoma 4
- Rara (1/1.000.000, ma deficit parziale in 8% degli ebrei Ashkenazi)

Ereditarietà dell'emofilia nella genealogia dell'imperatrice Vittoria



Alexei Nikolaevich, Tsarevich di Russia

Empress Alexandra at the Tsarevich's bedside during a haemophiliac crisis in 1912. (Radio Times Hulton Picture Library.)

Haemophilia (2010), 16, 843–847 DOI: 10.1111/j.1365-2516.2010.02327.x

REVIEW ARTICLE

The 'royal disease'– haemophilia A or B? A haematological mystery is finally solved

N. LANNOY* and C. HERMANS†
*Centre de Génétique humaine; and †Service d'hématologie, Cliniques universitaires Saint-Luc, Brussels, Belgium

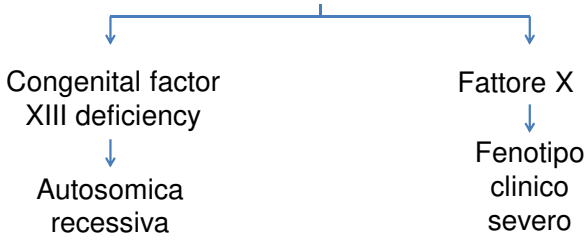
Summary. 'History can change blood. And blood can change the course of history'. Haemophilia is an illustration of this, as this congenital hereditary coagulation disorder, passed through the majority of royal European families at the beginning of the 20th century by Queen Victoria of England and Empress of the Indies, had indisputable political consequences, which led to one of the most defining moments of contemporary history: the Bolshevik Revolution. Today, none of Queen Victoria's living descendents carry haemophilia. Because of this, the characterization of haemophilia (deficit of either factor VIII or XI) and the identification of the causal mutation are rendered impossible. In 1991, a tomb containing the remains of Czar Nicolas II's entire family was discovered. A second tomb was discovered in 2007, allowing Russian and American scientists to fill in this gap in medical history. Following a scientific approach combining current genetic experimentation tools and the development of biological information technology, researchers were able to identify each body, allowing them to obtain precious genetic material from the young Czar Alexis, who was stricken by the disease, which revealed a causal substitution in the splice acceptor site of exon 4 in the F9 gene. This mutation that is responsible for haemophilia B had traumatized European royal families throughout the 20th century!

Keywords: Czar Nicolas II, F9 gene, haemophilia, Queen Victoria, Romanov, splice acceptor site

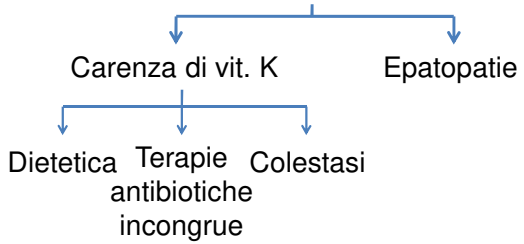
Malattia di von Willebrand

- Carenza del fattore di von Willebrand (VWF), autosomica dominante
- Alterazioni quantitative: Tipo 1, livelli diminuiti; Tipo 3, assenza
- causa **porpore** + **difetti coagulativi simil-emofilici** per carenza del fattore VIII causata da proteolisi da proteina C
- Alterazioni qualitative: Tipo 2, isoforme anomale, causa porpore

Altre patologie genetiche con difetti coagulativi



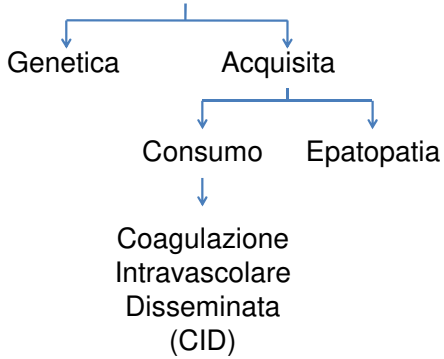
Ridotta sintesi di fattori vit.K-dipendenti



Vitamin K-dependent clotting factors deficiency

- Autosomiche recessive
- Mutazioni γ-glutamil carbossilasi
- Mutazioni vitamina K 2,3-epossido reduttasi

Ipofibrinogenemia



The Elusive Diagnosis of Disseminated Intravascular Coagulation: Does a Diagnosis of DIC Exist Anymore?

Jecko Thachil, MD, FRCPath[1]

[1] Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom

Address for correspondence Jecko Thachil, MD, FRCPath, Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9WL, United Kingdom (e-mail: jecko.thachil@cmft.nhs.uk).

Semin Thromb Hemost (2019) 45, 100-107

Abstract

Disseminated intravascular coagulation (DIC) is an intermediary mechanism of disease known to develop as a complication in other conditions like sepsis, trauma, cancer, or obstetrical disorders. Patients with DIC may present to different specialists depending on symptomology and as such a good understanding of the pathophysiological process is necessary to ensure best management. However, more recently, controversy has risen where experts doubt whether DIC really exists in many of the historically well-established diagnoses. This has led to confusion among both basic science researchers and clinical practitioners about when to consider DIC diagnosis. In this review, the various issues which have led to this uncertainty are addressed, including the problem with different terminologies, simpler explanation of current DIC diagnostic criteria, and reasons behind why the diagnosis may be overlooked or not considered at all, along with their possible solutions. It is hoped that the diagnostic aspects of DIC will come full circle, wherein the recent research can build up on what history had taught us and not refute its existence.

Keywords

- disseminated intravascular coagulation
- coagulopathy
- thrombocytopenia
- sepsis
- trauma

The Problem with Different Terminologies

Disseminated intravascular coagulation terminology has been a kind of "Tower of Babel" leading to an associated "disseminated international confusion" (Satoshi Gando, MD, FRCPath, 2010, personal communication). The different terms used in history that may have been aimed to signify DIC include "consumption coagulopathy," "defibrination syndrome," "diffuse intravascular thrombosis," and even an attempt at describing the condition as a "generalized Shwartzman reaction."[1–4] More recently, some respective experts have decided that DIC does not really exist within their specialty, as they believe that the underlying pathophysiological process they see is completely different. The best example for this is trauma surgeons, who within the last decade have avoided the terminology of DIC in their patients, and alternately chosen "trauma-induced coagulopathy" as their preferred concept.[5]

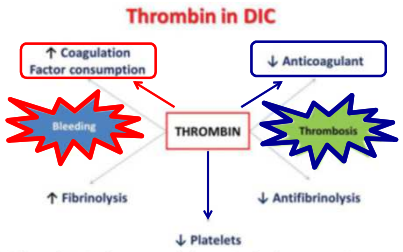


Fig. 1 Thrombin is the central player in the hemostatic process and can activate the procoagulant and anticoagulant pathways and also directly or indirectly impact on the profibrinolytic and antifibrinolytic pathways. In DIC, where there is unregulated thrombin generation, the procoagulant process that consumes the clotting factors and the fibrinolytic pathway activation can cause bleeding while the reduction in anticoagulant proteins and stimulation of the antifibrinolytic pathway can cause thrombosis. These clinical symptoms can vary depending on the predominance of each pathway and thus are dependent on the inciting stimuli (i.e., they will be different in sepsis, trauma, cancer, etc.). Platelets are also activated by thrombin which can cause thrombosis if they are hyperactivated, or bleeding when they are consumed or exhausted. DIC, disseminated intravascular coagulation.

The Scientific and Standardization Committee (SSC) on DIC of the ISTH has previously defined DIC as "*an acquired syndrome characterized by the intravascular activation of coagulation with a 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.*"[9] It is useful to examine this definition in detail, to try and understand why it may be open to different interpretations.

First, it needs to be understood that DIC represents a *pathological* activation of blood coagulation. This is different from normal physiological hemostasis, wherein activation of clotting from vascular damage requires conservation of the important nutrient, blood, within the blood vessels, by forming the clot. The important consideration here is that the clotting process is location limited to the site of vascular injury. However, in the pathological activation of coagulation which occurs in DIC, coagulation activation occurs at different sites to the original site of endothelial perturbation, reflecting the term "disseminated" or "loss of localization" as per the ISTH SSC definition. This dissemination can occur in a different part of the same organ (e.g., placental vessels in obstetric DIC) or a different organ entirely (e.g., pulmonary microthrombi in sepsis and cancer).[10]

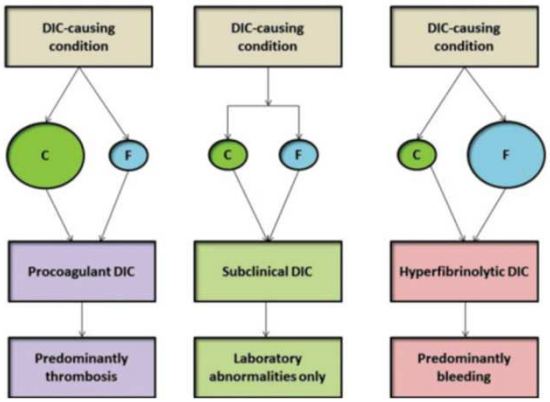


Fig. 2 This figure explains the different types of DIC. If there is predominance of coagulation pathway activation (denoted as C), in comparison with the fibrinolytic pathways (denoted as F), procoagulant DIC is the result. While the reverse leads to hyperfibrinolytic DIC. If there is only low-grade activation of both pathways, clinical manifestation may not occur and only laboratory abnormalities are detected (typically in solid cancers, used to be called chronic DIC). DIC, disseminated intravascular coagulation.

Second, the thrombotic process in DIC arises from, and causes damage to, the microvasculature, which may then lead to organ dysfunction. The problem here is how to identify damage to the microvasculature as there are no readily observable clinical features that would raise the suspicion of thrombi in the microvasculature.[11] Based on the pathophysiology of similar situations, it may be surmised that in the appropriate setting, development of organ impairment may be representative of these microthrombi.[11]

In summary, DIC is indeed a thrombo-hemorrhagic disorder, where bleeding or thrombosis can occur in the same patient at the "same" or at different times.

Conclusion

Disseminated intravascular coagulation has probably always existed and it still does. It is important, however, to understand the reasons why controversy exists in the recent literature in this regard.

the ISTH has worked hard to set up registries which the author would encourage all readers to actively participate. This will surely widen our knowledge of DIC and change it from the sobering "Death Is Coming" to "Death Is Conquered."

PLOS | PATHOGENS

RESEARCH ARTICLE

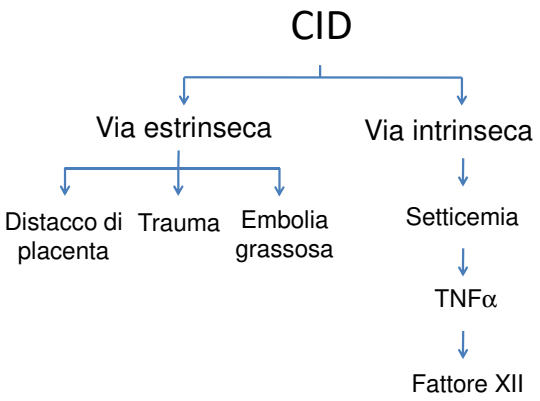
An ADAM-10 dependent EPCR shedding links meningococcal interaction with endothelial cells to purpura fulminans

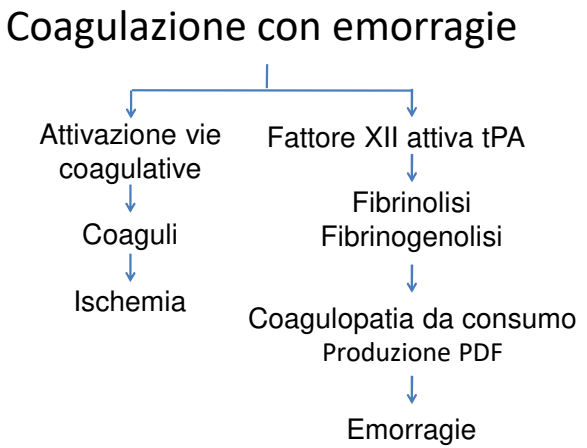
Hervé Lécuyer[1,2,3]*, Zoé Virion[1,2], Jean-Philippe Barnier[1,2,3], Soraya Matczak[1,2], Sandrine Bourdoulous[2,4], Elsa Bianchini[5], François Saller[5], Delphine Borgel[5,6], Xavier Nassif[1,2,3], Mathieu Coureuil[1,2]

1 Institut Necker Enfants Malades, INSERM U1151, CNRS UMR8253, Paris, France, **2** Université Paris Descartes, Paris, France, **3** Assistance Publique–Hôpitaux de Paris, Hôpital Universitaire Necker Enfants Malades, Service de Microbiologie Clinique, Paris, France, **4** Institut Cochin, INSERM U1016, CNRS UMR8104, Paris, France, **5** INSERM UMR-S1176, Université Paris-Sud, Université Paris Saclay, Le Kremlin-Bicêtre, France, **6** Assistance Publique–Hôpitaux de Paris, Hôpital Universitaire Necker Enfants Malades, Service d'Hématologie Biologique, Paris, France

PLOS Pathogens | https://doi.org/10.1371/journal.ppat.1006981 April 9, 2018

Purpura fulminans is a deadly complication of *Neisseria meningitidis* infections due to extensive thrombosis of microvessels. Although a Disseminated Intra-vascular Coagulation syndrome (DIC) is frequently observed during Gram negative sepsis, it is rarely associated with extensive thrombosis like those observed during meningococcemia, suggesting that the meningococcus induces a specific dysregulation of coagulation. Another specific feature of *N. meningitidis* pathogenesis is its ability to colonize microvessels endothelial cells via type IV pili. Importantly, endothelial cells are key in controlling the coagulation cascade through the activation of the potent anticoagulant Protein C (PC) thanks to two endothelial cell receptors among which the Endothelial Protein C Receptor (EPCR). Considering that congenital or acquired deficiencies of PC are associated with *purpura fulminans*, we hypothesized that a defect in the activation of PC following meningococcal adhesion to microvessels is responsible for the thrombotic events observed during meningococcemia. Here we showed that the adhesion of *N. meningitidis* on endothelial cells results in a rapid and intense decrease of EPCR expression by inducing its cleavage in a process know as shedding. Using siRNA experiments and CRISPR/Cas9 genome edition we identified ADAM10 (A Disintegrin And Metalloproteinase-10) as the protease responsible for this shedding. Surprisingly, ADAM17, the only EPCR sheddase described so far, was not involved in this process. Finally, we showed that this ADAM10-mediated shedding of EPCR induced by the meningococcal interaction with endothelial cells was responsible for an impaired activation of Protein C. This work unveils for the first time a direct link between meningococcal adhesion to endothelial cells and a severe dysregulation of coagulation, and potentially identifies new therapeutic targets for meningococcal *purpura fulminans*.





Fegato e patologia dell'emostasi

Insufficienza epatica

- ↓ sintesi fattori Vit. K-dipendenti
- ↓ sintesi fibrinogeno
- ↓ inattivazione tPA
  - ↑Fibrinolisi
  - ↑Fibrinogenolisi
  - ↑ Coagulopatia da consumo
  - Produzione PDF

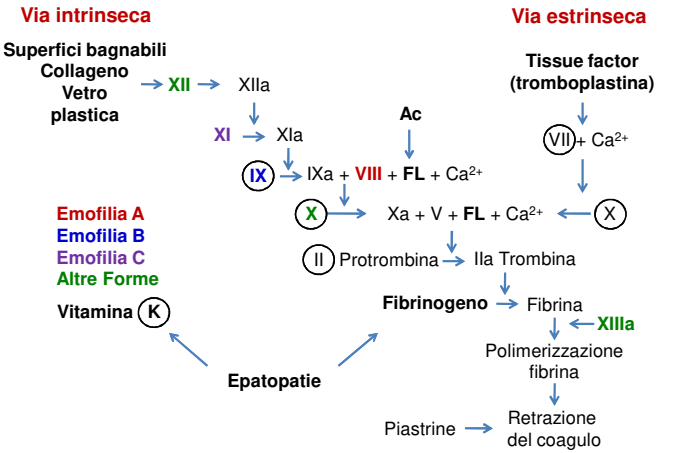
Fegato e patologia dell'emostasi

- Colestasi
  - ↓ assorbimento vit-K liposolubile
- Insufficienza epatica
  - ↓ sintesi trombopoietina
    - Trombocitopenia
- Alcool
  - Inibisce aggregazione piastrinica

Coagulopatie da anticorpi anti-fosfolipidi

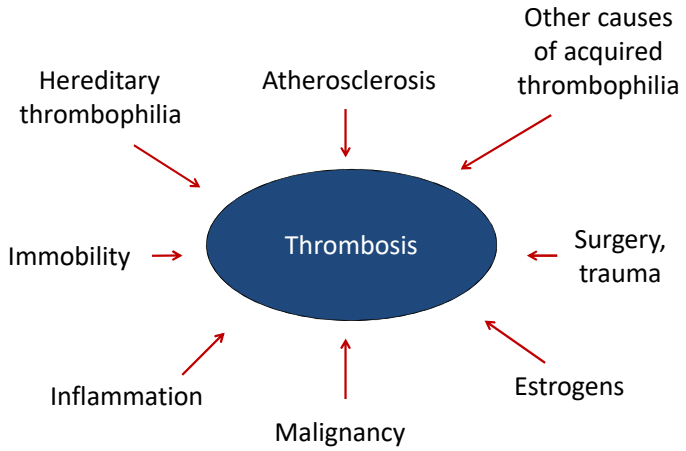
Patologie autoimmuni

3. Fase emocoagulativa

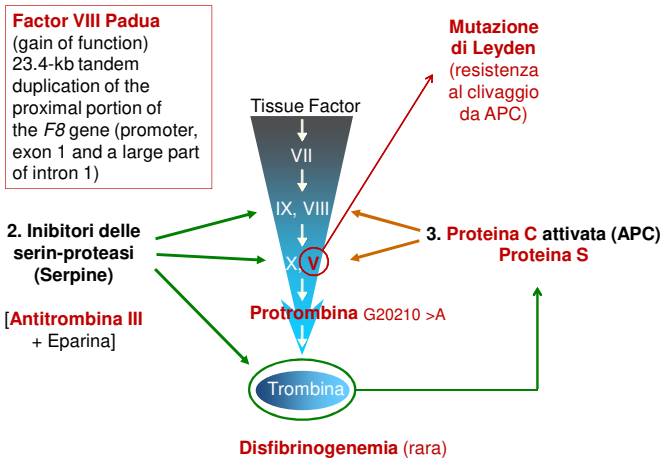


Le trombofilie

Risk Factors for Thrombosis



Le trombofilie ereditarie



Risk vs. Incidence of First Episode of Venous Thrombosis

	Risk	Incidence per year (%)
Normal	1	.008
Oral Cont. Pills	4x	.03
Factor V Leiden (heterozygote)	7x	.06
OCP + Factor V L.	35x	.3
Factor V Leiden (homozygote)	80x	.5-1

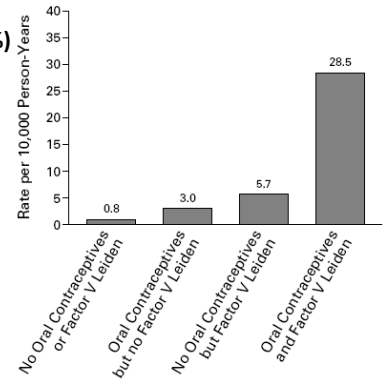
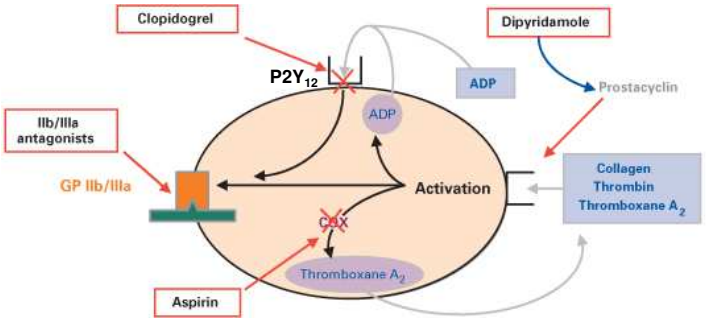


Figure 1. Cases of Deep-Vein Thrombosis per 10,000 Person-Years, According to the Use of Oral Contraceptives and the Presence of Factor V Leiden.



William Turner, Rockets and Blue Lights (close at Hand) to warn Steam-Boats of Shoal-Water, 1840 – © Sterling and Francine Clark Art Institute, Williamstown, Massachusetts, USA