
بسم الله الرحمن الرحیم

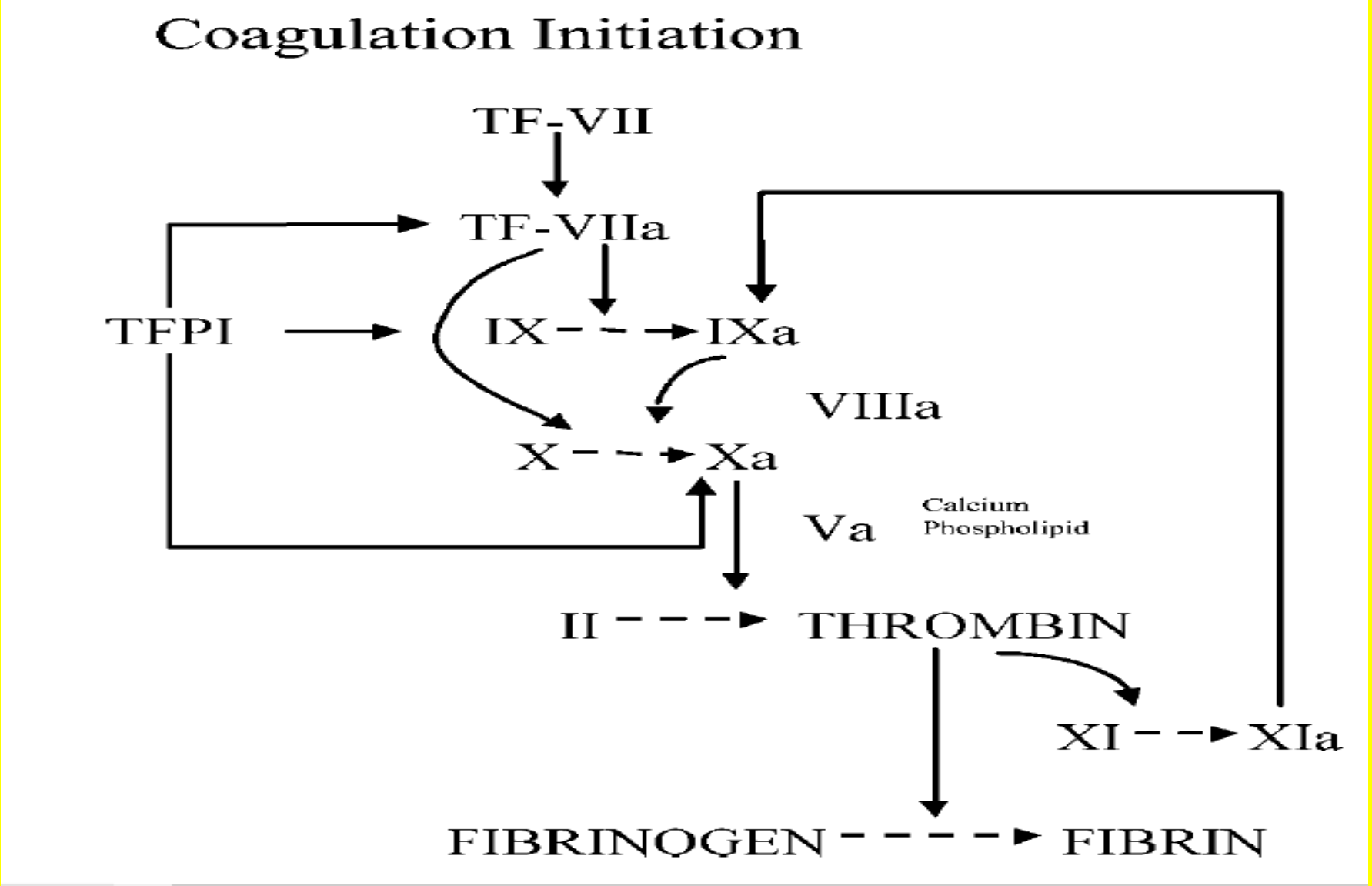
به مناسبت روز جهانی هموستاز - ترومبوز

نقش مهارکننده فاکتور بافتی در انعقاد و رابطه آن با فاکتورهای پنج ؛ هفت و ده

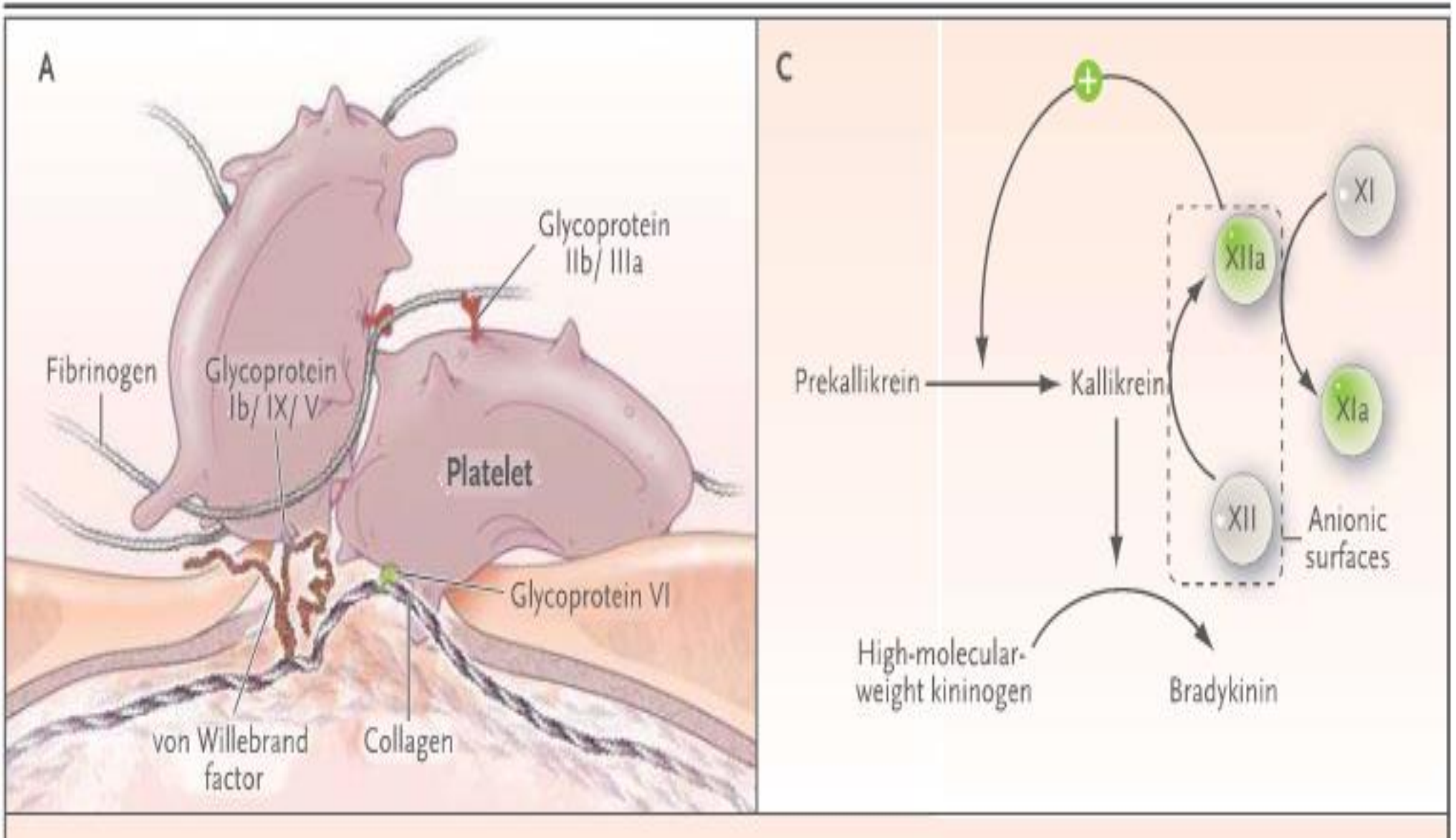
دکتر مهدی شهریاری

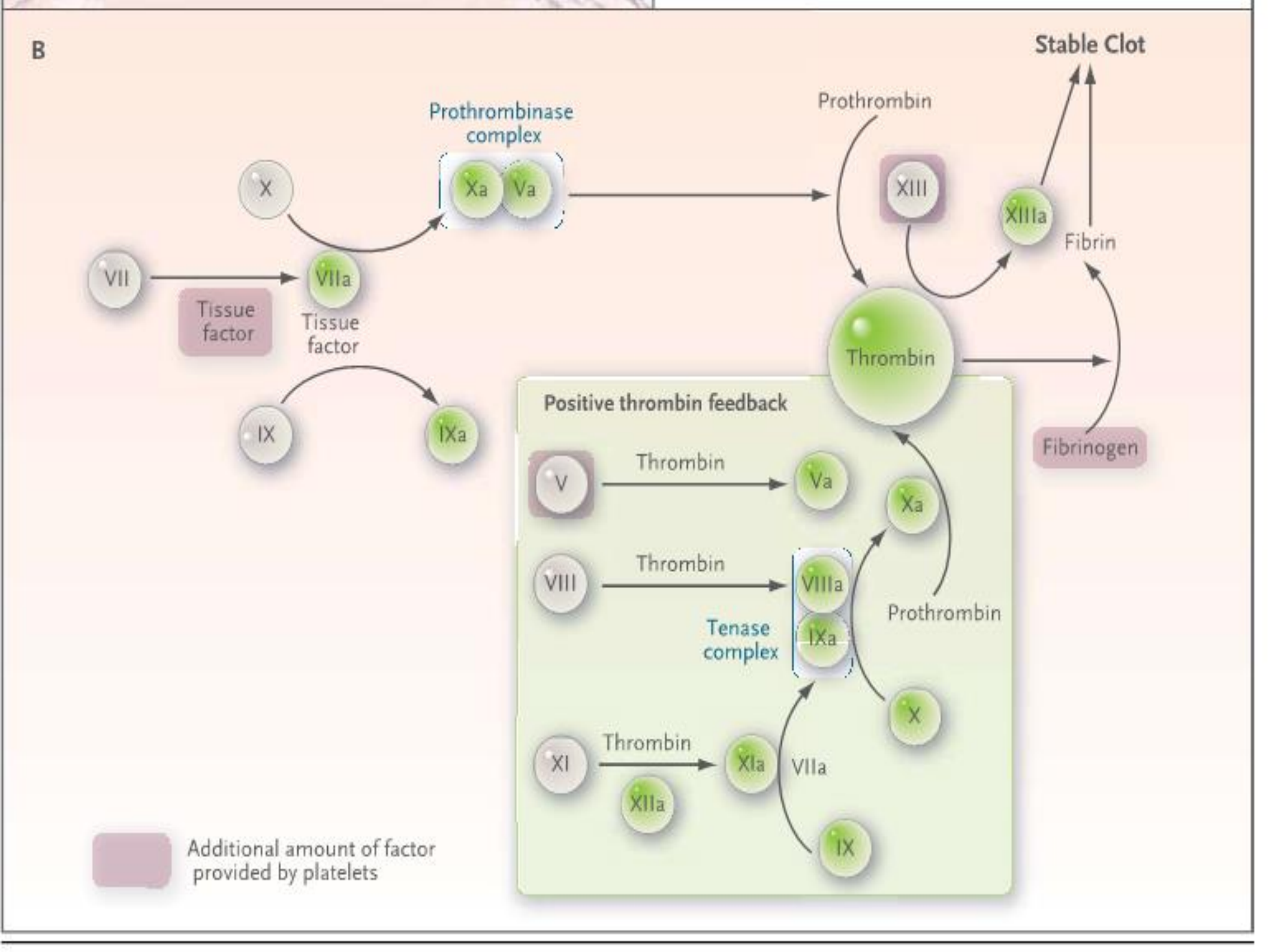
هماتولوژیست انکولوژیست کودکان

Coagulation Cascade

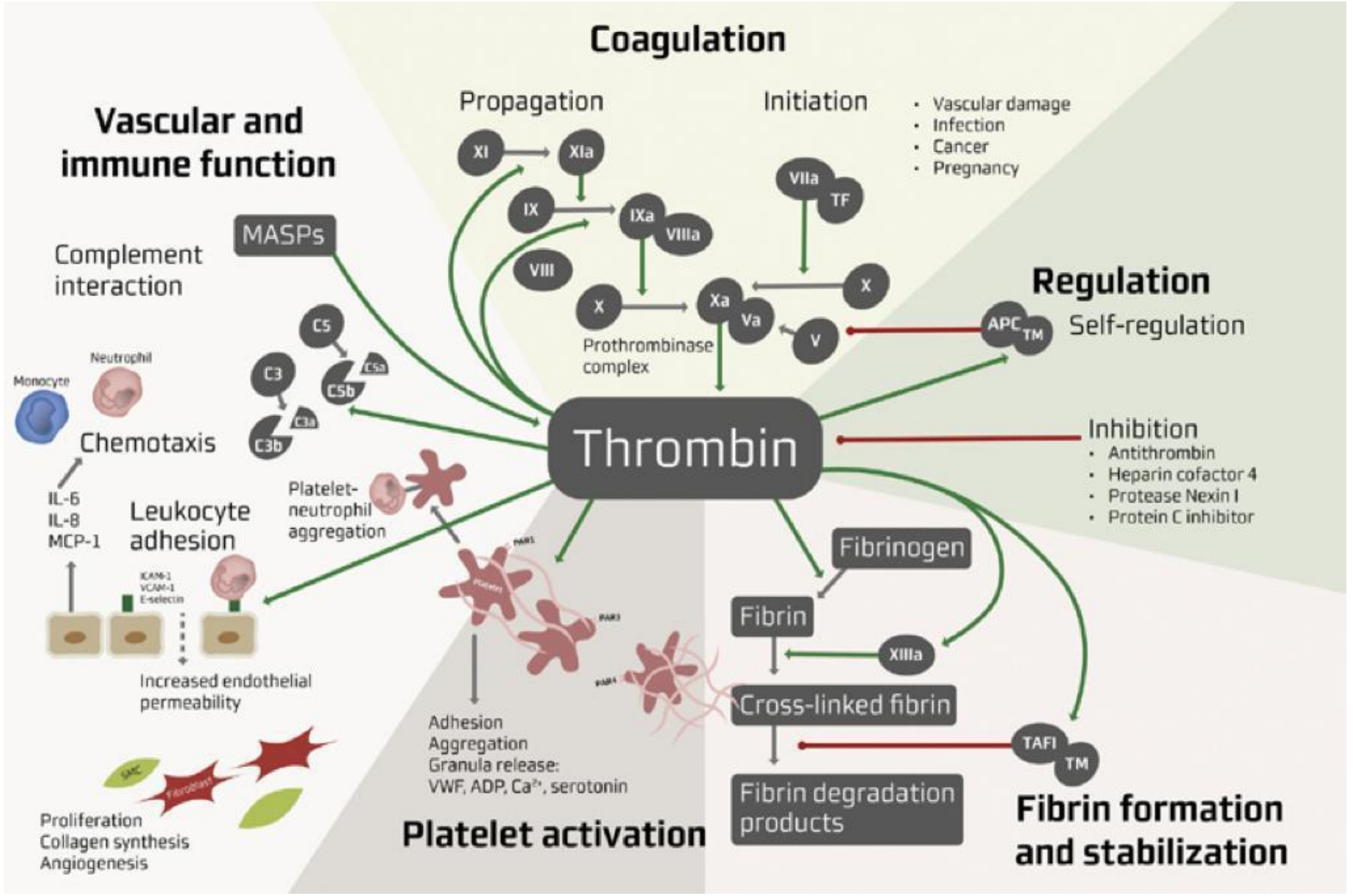


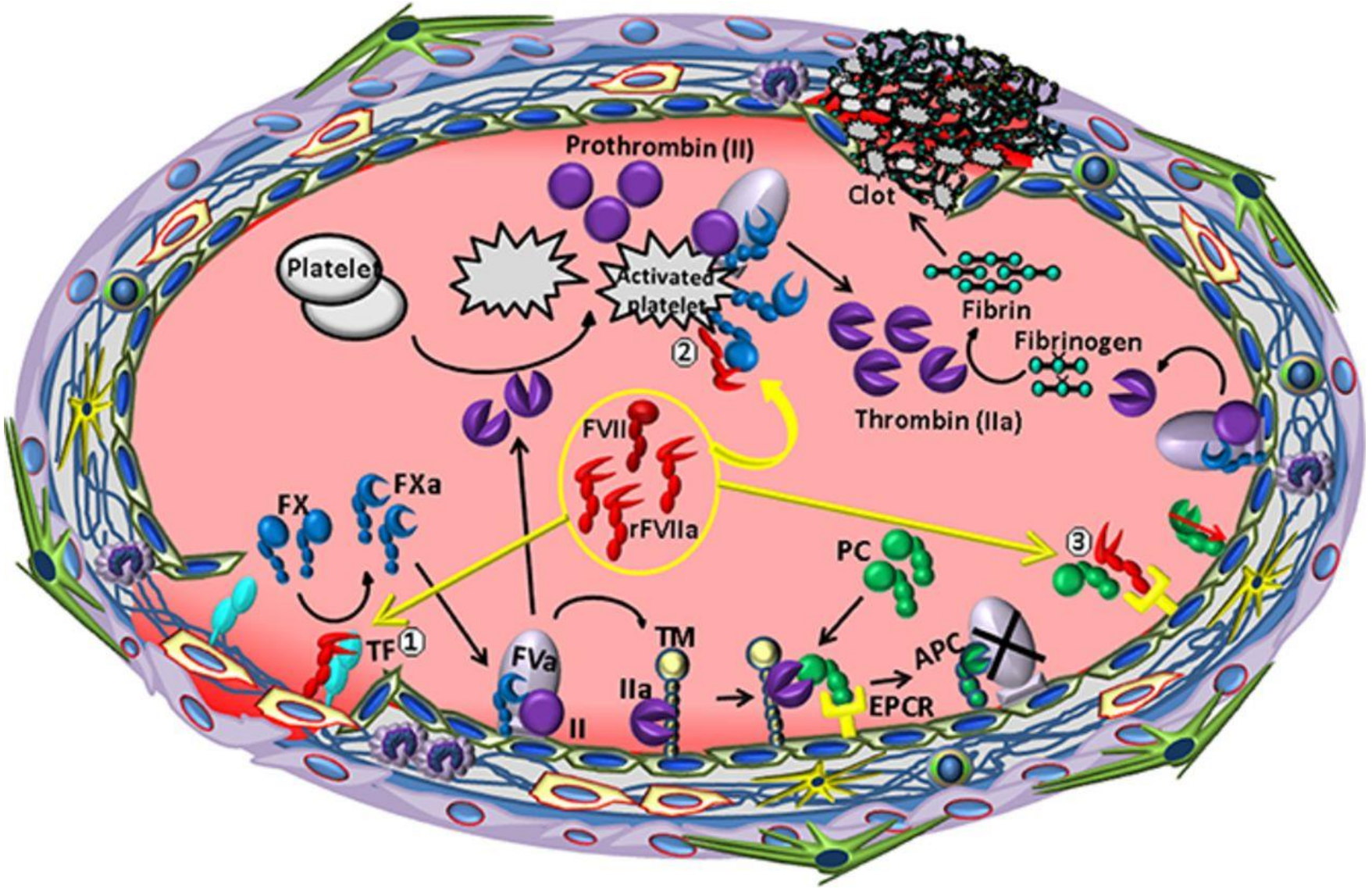
شروع انعقاد


A
Glycoprotein
IIb/ IIIa
Fibrinogen
Glycoprotein
Ib/ IX/ V
Platelet
Glycoprotein VI
von Willebrand
factor
Collagen
C
+
XI
XIIa
Prekallikrein
Kallikrein
XIa
XII
Anionic
surfaces
High-molecular-
weight kininogen
Bradykinin


B
Stable Clot
Prothrombinase complex
Prothrombin
X
Xa
Va
XIII
XIIIa
Fibrin
VII
VIIa
Tissue factor
Tissue factor
Thrombin
IX
IXa
Positive thrombin feedback
Fibrinogen
V
Thrombin
Va
Xa
VIII
Thrombin
VIIIa
Prothrombin
Tenase complex
IXa
X
XI
Thrombin
XIa
VIIa
XIIa
IX
Additional amount of factor provided by platelets

Functions of Thrombin





Shiva Keshava et al. Blood Adv 2017;1:1206-1214

blood advances

TFPI

Tissue factor (TF)-initiated coagulation plays a significant role in the pathophysiology of many diseases, including cancer and inflammation.

TFPI is a plasma Kunitz-type serine protease inhibitor, which modulates initiations of coagulation induced by TF.

In a F Xa-dependent feedback system, TFPI binds directly and inhibits the TF–FVII/FVIIa complex.

TF and TFPI

Deficiencies of either TF or TFPI have not been reported in humans, and a complete absence of either of these two proteins in mice is embryonically lethal.

Normally, TFPI exists in plasma both as a full-length molecule and as variably carboxy-terminal truncated forms.

TFPI

TFPI also circulates in complex with plasma lipoproteins.

***In vivo* administration of recombinant TFPI (rTFPI) in an experimental animal model**

1- prevents thrombosis (and re-thrombosis after thrombolysis),

2- reduces mortality from *E. coli*-induced septic shock,

3- prevents fibrin deposition on subendothelial human matrix and protects against DIC.

TFPI

Thus, TFPI may play an important role in modulating TF-induced thrombogenesis and it may also provide a unique therapeutic approach for prophylaxis and/or treatment of various diseases.

TFPI

- Orlando Piro et al: ***Circulation*. 2004;110:3567-3572.**
- Tissue factor pathway inhibitor (TFPI)-, contains 3 tandem Kunitz-type inhibitory domains.
- Kunitz-1 binds and inhibits factor VIIa in the factor VIIa/tissue factor complex,
- and Kunitz-2 binds and inhibits factor Xa.
- The role of the Kunitz-3 domain of TFPI-, however, is localization of the TFPI α at cell surface.

Protein S as Cofactor for TFPI

Hackeng TM, Rosing J: ***Arterioscler Thromb Vasc Biol.* 2009;29:2015-2020.**

Protein S not only acts as cofactor of activated protein C (APC) in the downregulation of coagulation, but also expresses anticoagulant activity in the absence of APC.

Protein S acts as cofactor of TFPI which stimulates the inhibition of factor Xa by TFPI 10-fold. Therefore, TFPI/protein S system particularly inhibits the TF pathway at low procoagulant stimuli.

Low TFPI plasma level in congenital F V deficiency

Duckers C et al: **Blood. 2008;112:3615-3623.**

Severe factor V (FV) deficiency is associated with mild to moderate bleeding diathesis, but many patients with FV levels lower than 1% bleed less than anticipated.

Thrombin generation in FV-deficient plasma was only measurable at high TF concentrations.

Upon reconstitution of FV-deficient plasma with purified FV, thrombin generation increased steeply with FV concentration, reaching a plateau at approximately 10% FV.

FV-deficient plasma reconstituted with 100% FV generated severalfold more thrombin than normal plasma, especially at low tissue factor concentrations, suggesting reduced TFPI levels in FV-deficient plasma.

A FV/TFPI complex, affects TFPI stability/clearance in vivo.

Low TFPI levels decreased the FV requirement for minimal thrombin generation in FV-deficient plasma to less than 1% and might therefore protect FV-deficient patients from severe bleeding.

Role of FVIIa in the control of bleeding

- Ovansov MV et al: **Blood Coagul Fibrinolysis 2008;19:743–755** Supraphysiological concentrations of recombinant activated factor VII (rFVIIa) are used to control bleeding in hemophilia,….

Current experimental evidence suggests that rVIIa may increase thrombin generation via two pathways:

1- tissue factor (TF)-dependent,

2- activated platelet-dependent.

Contribution of TF to the rVIIa action may justify different administration profiles of rVIIa.

Role of rFVIIa in the control of bleeding

Activation of clotting with less than 5 pmol/l of TF facilitates thrombin and fibrin generation at low, but not at Supraphysiological rFVIIa concentrations.

Activation with more than 13 pmol/l of TF saturates thrombin and fibrin generation kinetics, making it insensitive to rFVIIa.

Role of FVIIa in the control of bleeding

- rFVIIa minimally modulates clot growth on the surface of TF-expressing fibroblasts.
- On the contrary, Supraphysiologic rFVIIa produces spontaneous clot formation in nonflowing platelet-free plasma far away from fibroblasts via plasma lipid particles.