Serum vs. plasma

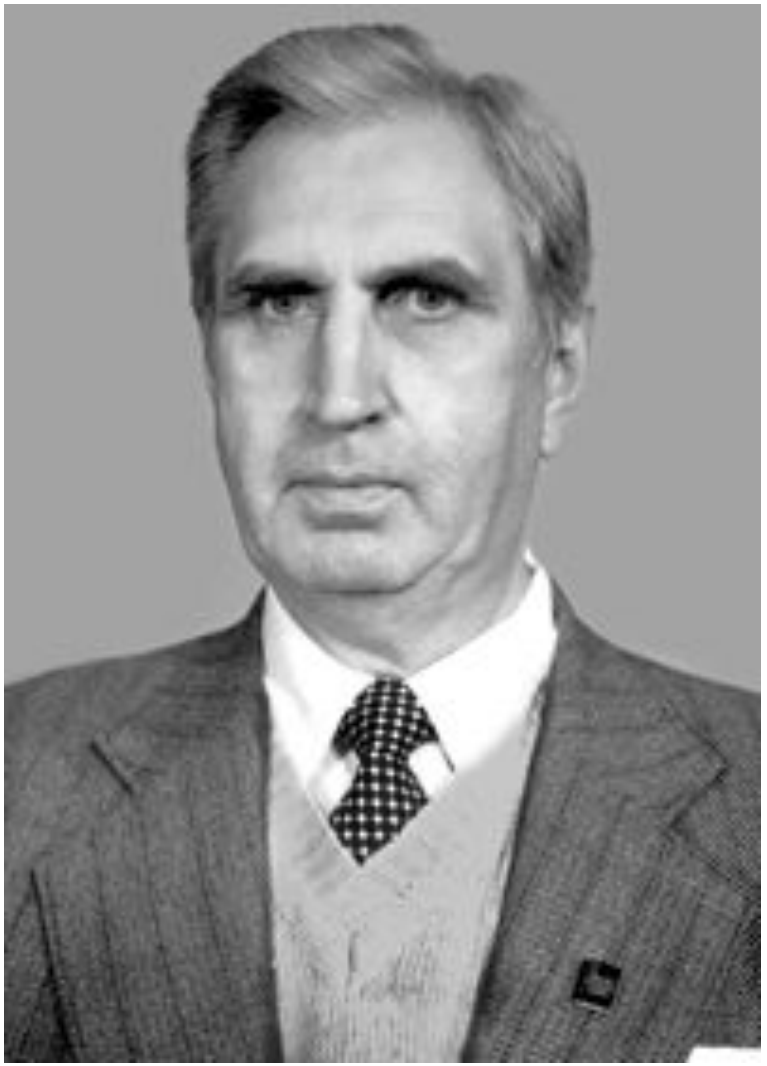
New to pathology? Check out these websites.

My pathology class starts tomorrow – help!

on AUGUST 26, 2016

Tomorrow is the first day of classes for a lot of medical, dental, nursing, physician assistant, medical technology, veterinary, and other allied health students. Most of you will be faced with the beginning of a pathology course tomorrow (or if not tomorrow, soon). And except for a

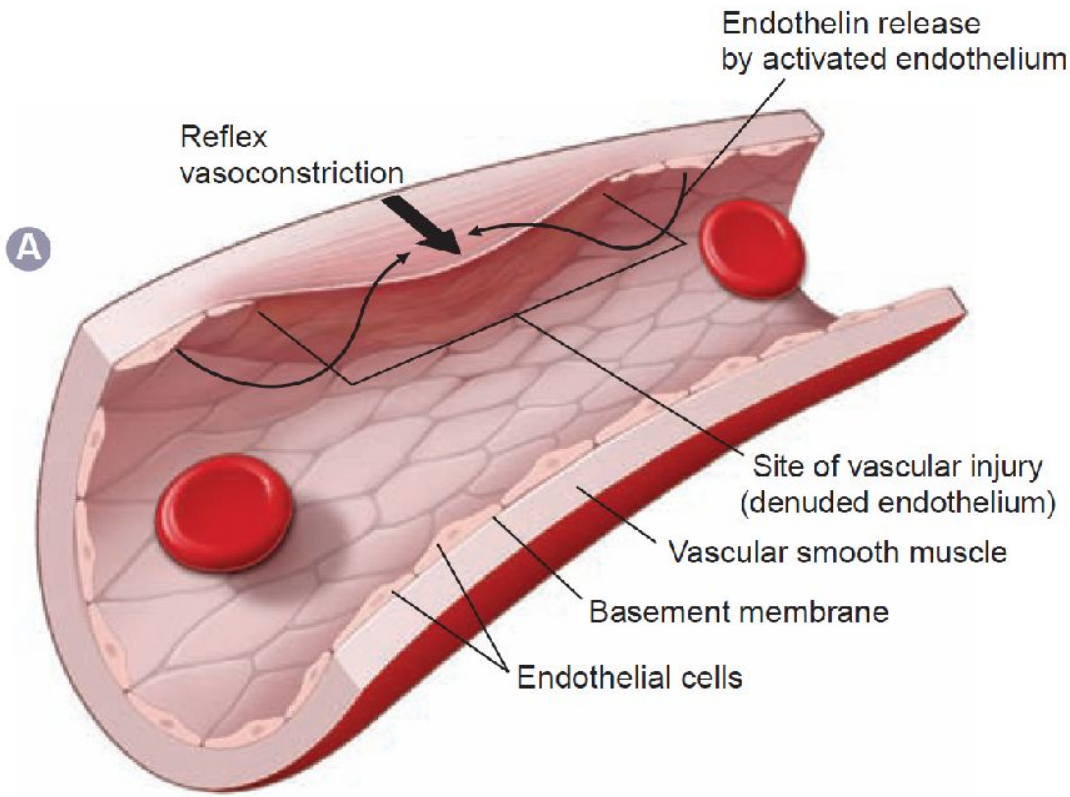
Kristine Krafts, M.D.
University of Minnesota School of Medicine
The story behind Pathology Student



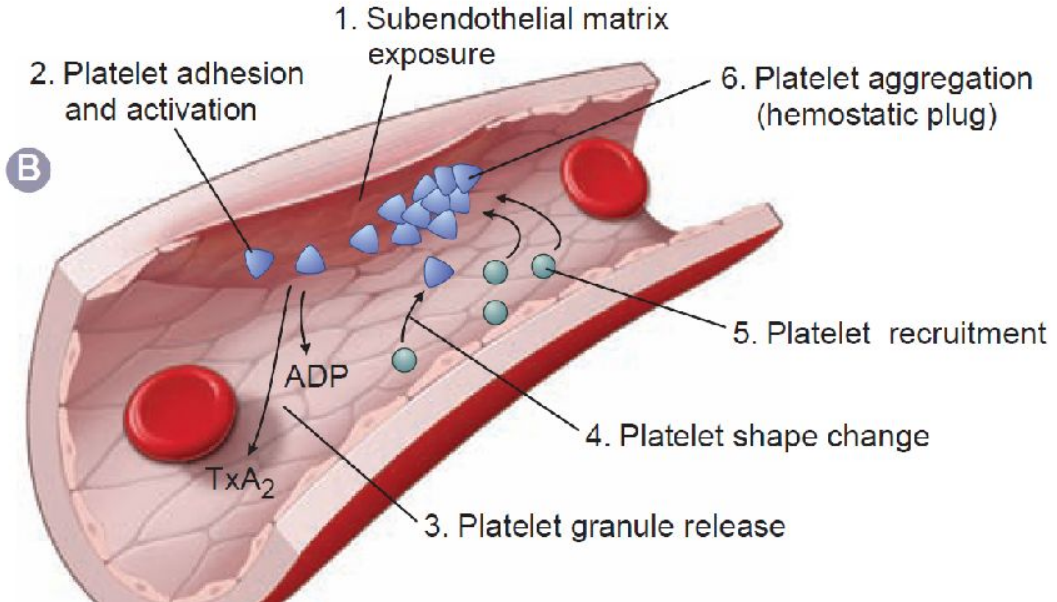
Виктор Петрович Ба́луда (1924 — 2002)

Зиновий Соломонович Баркаган
(1925— 2006)

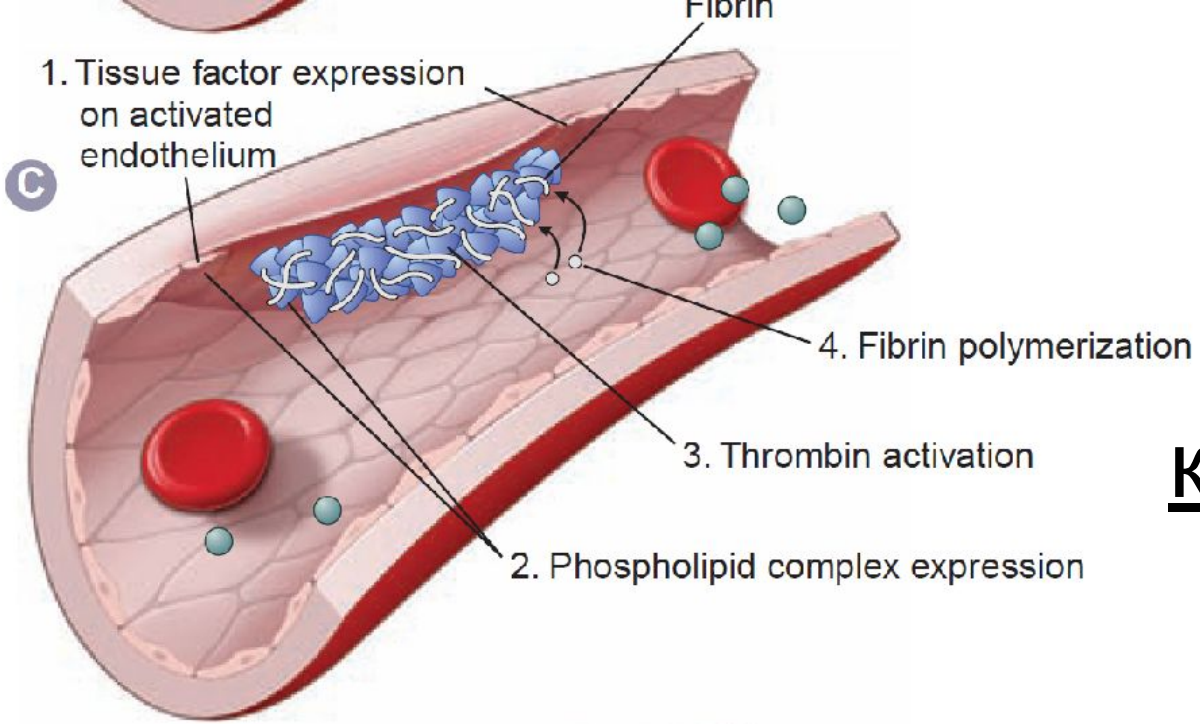
Исидор Абрамович Ойвин (1909 — 1972)



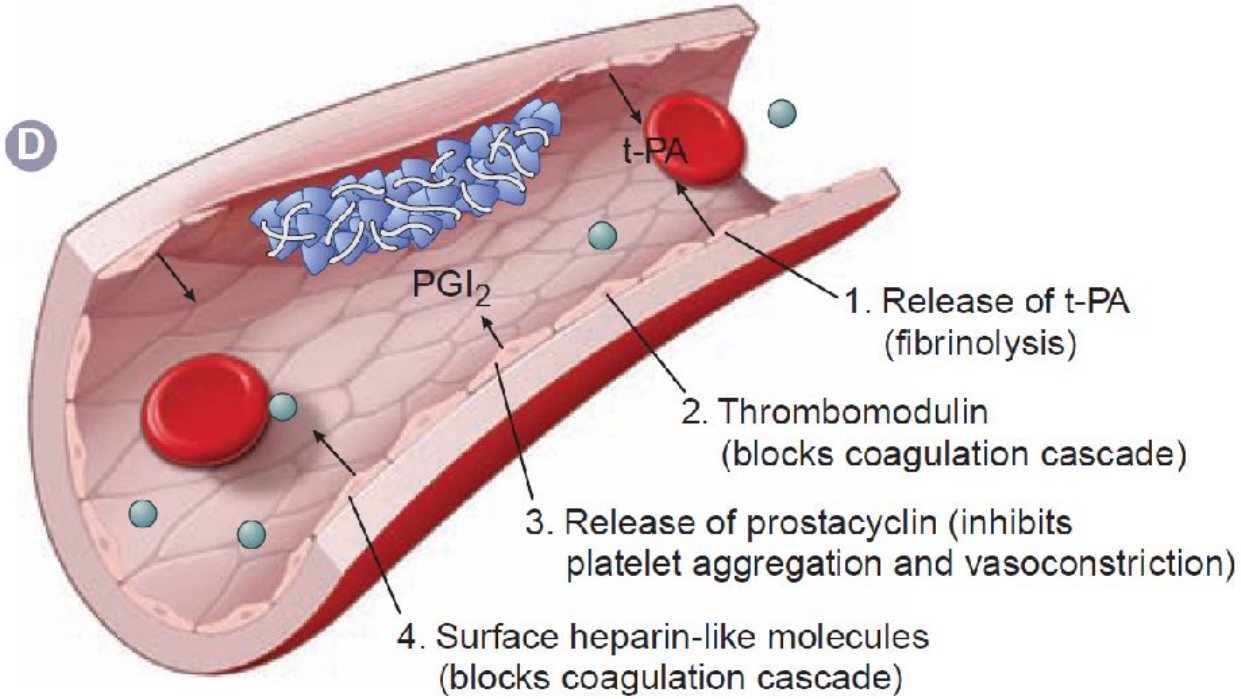
сосудистая фаза



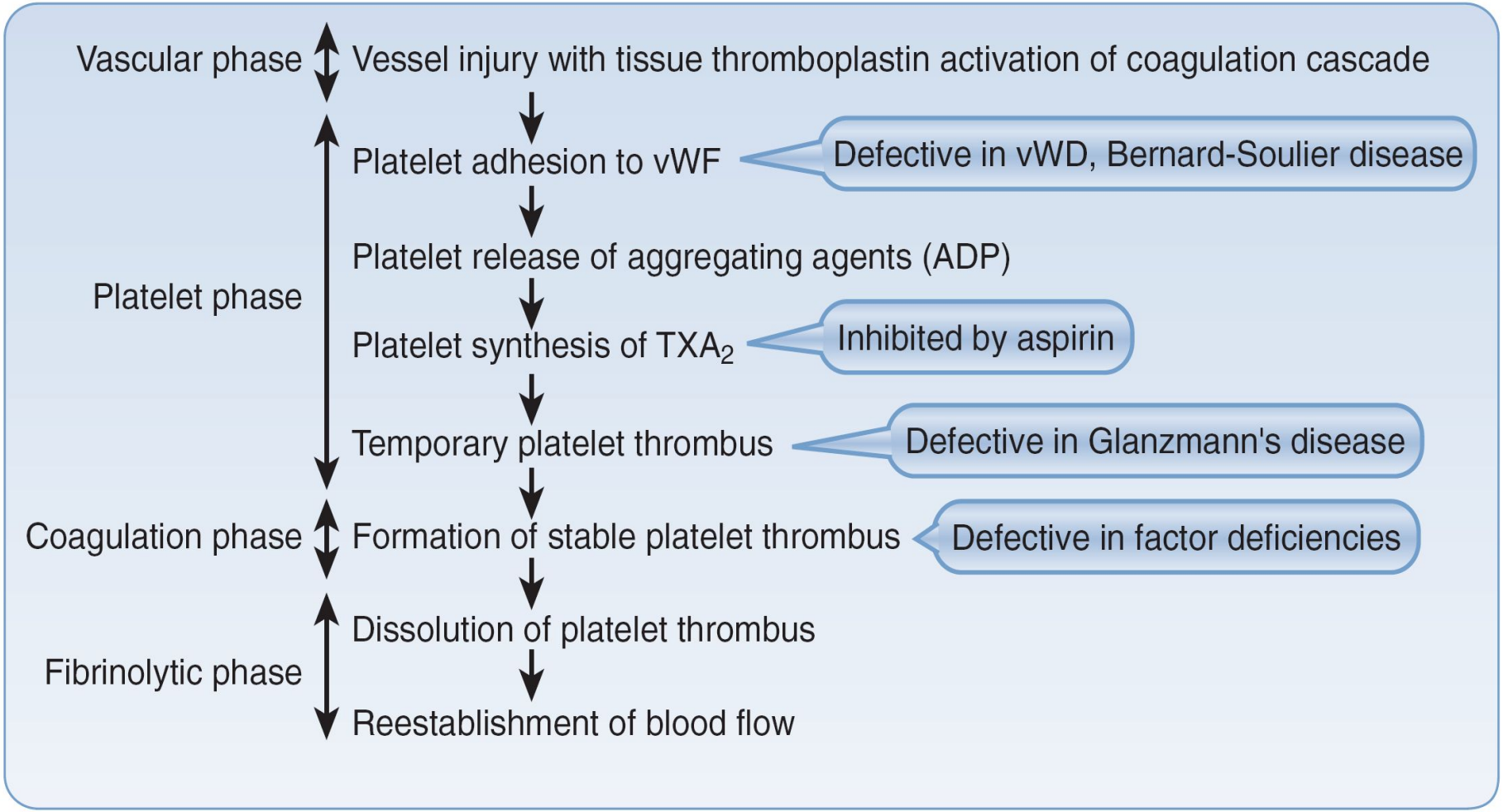
тромбоцитарная фаза



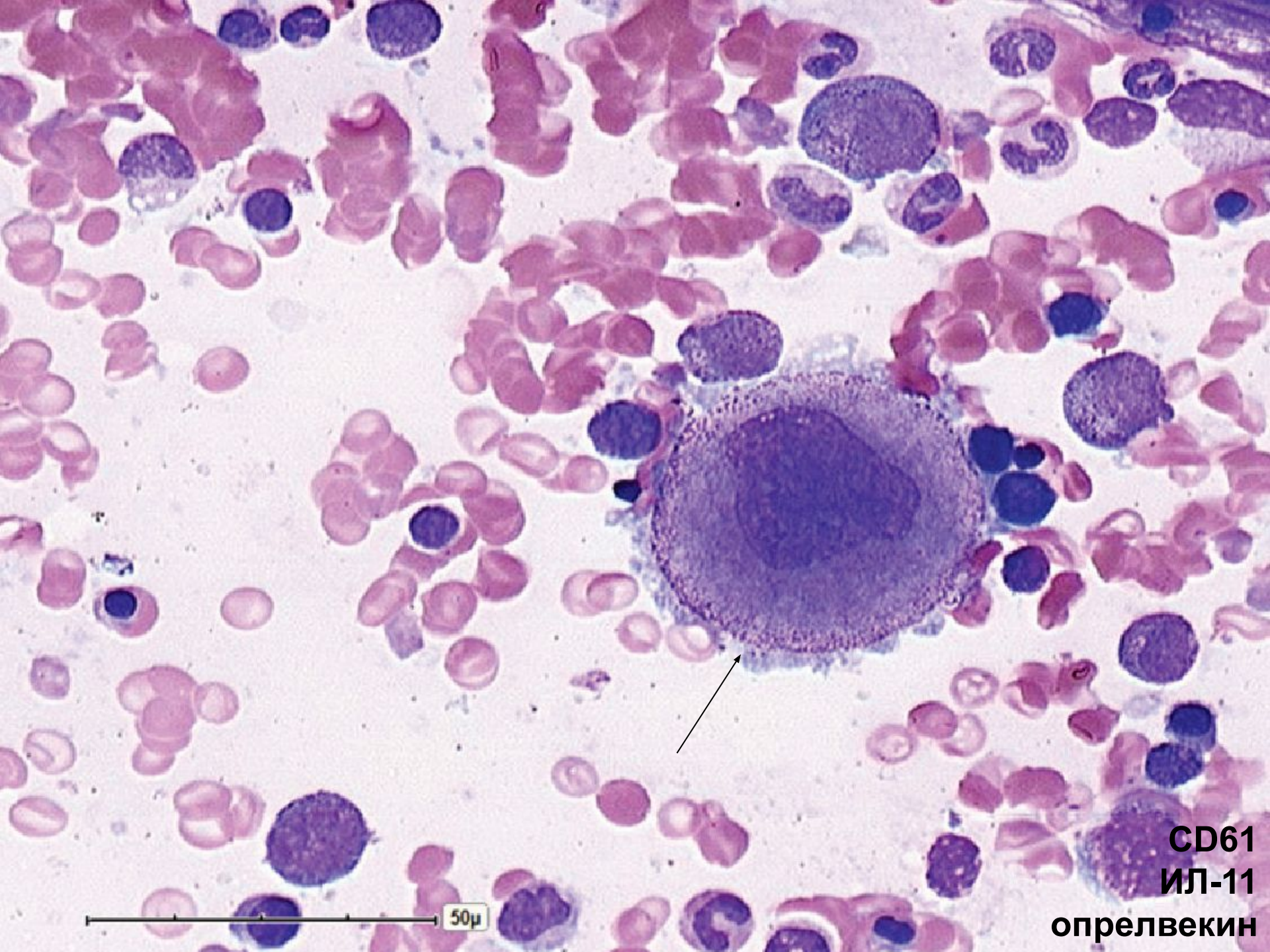
коагуляционная фаза



фибринолиз

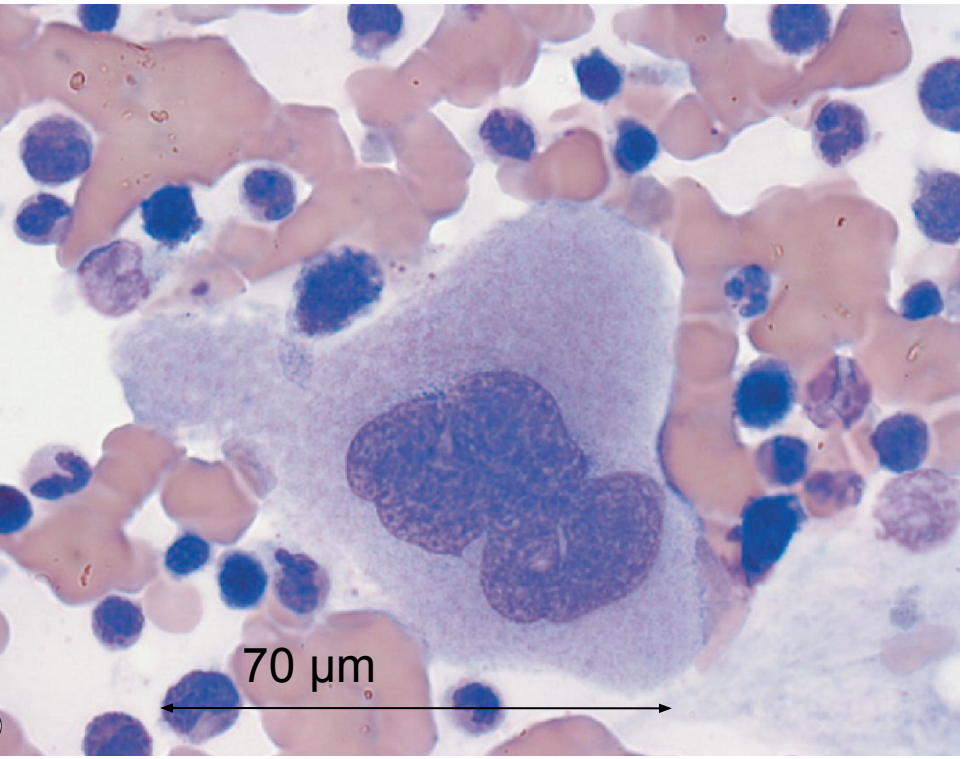

Vascular phase
Vessel injury with tissue thromboplastin activation of coagulation cascade
Platelet phase
Platelet adhesion to vWF
Defective in vWD, Bernard-Soulier disease
Platelet release of aggregating agents (ADP)
Platelet synthesis of TXA2
Inhibited by aspirin
Temporary platelet thrombus
Defective in Glanzmann's disease
Coagulation phase
Formation of stable platelet thrombus
Defective in factor deficiencies
Fibrinolytic phase
Dissolution of platelet thrombus
Reestablishment of blood flow

ТРОМБОЦИТЫ

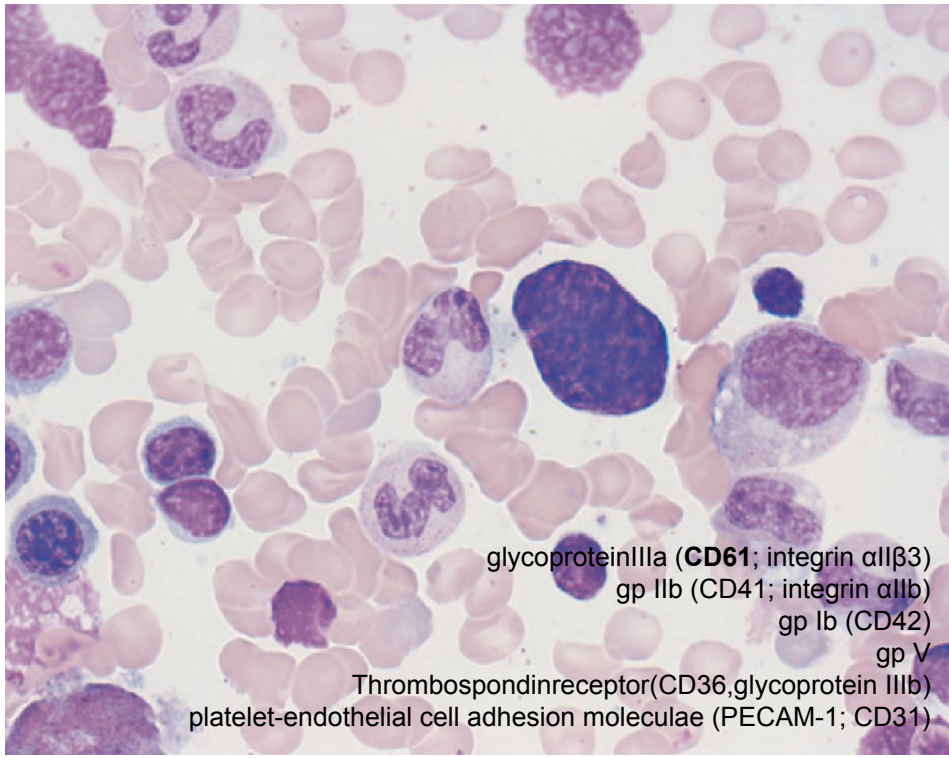


CD61
ИЛ-11
опрелвекин

Мегакариоциты

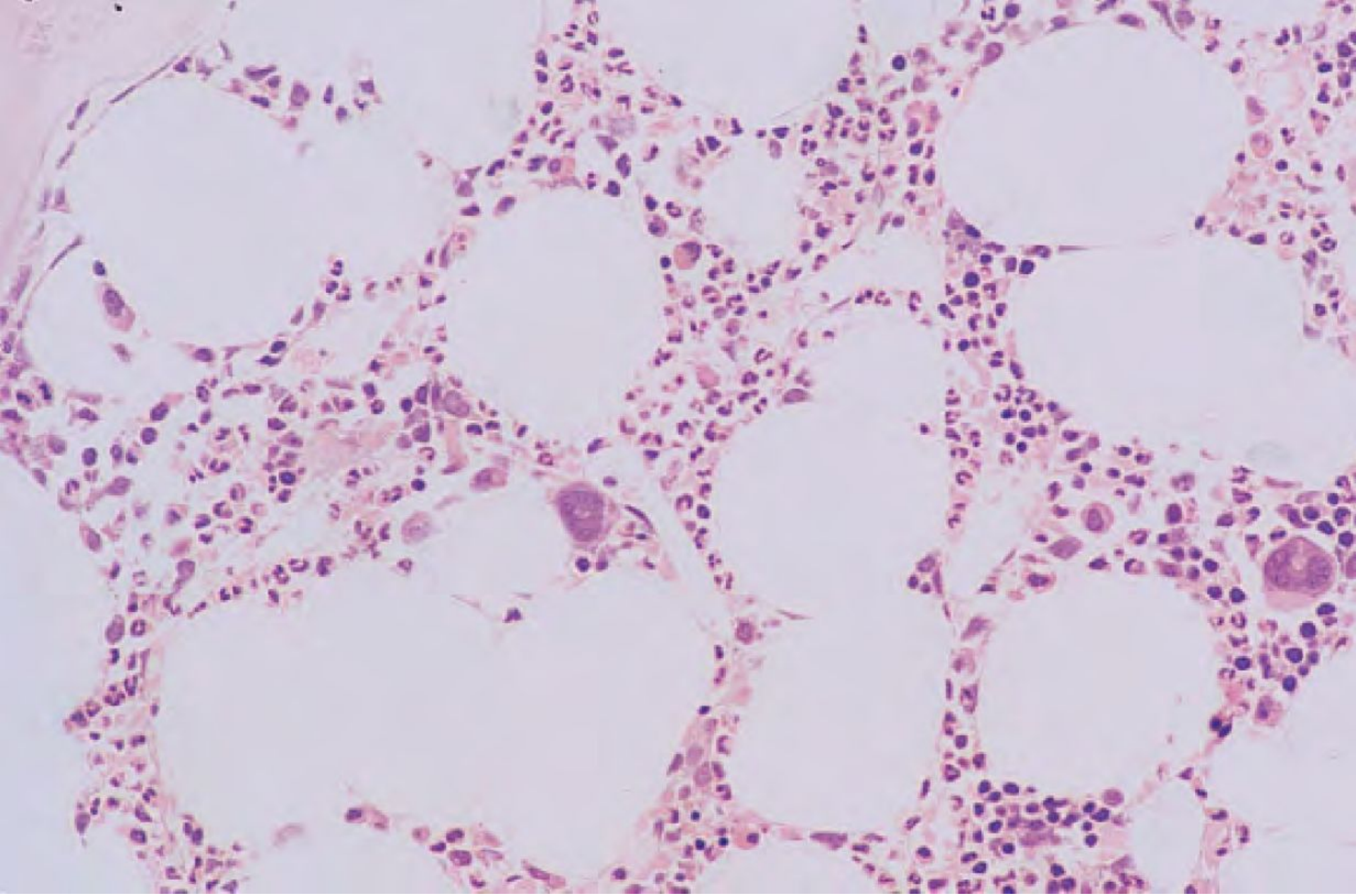


III

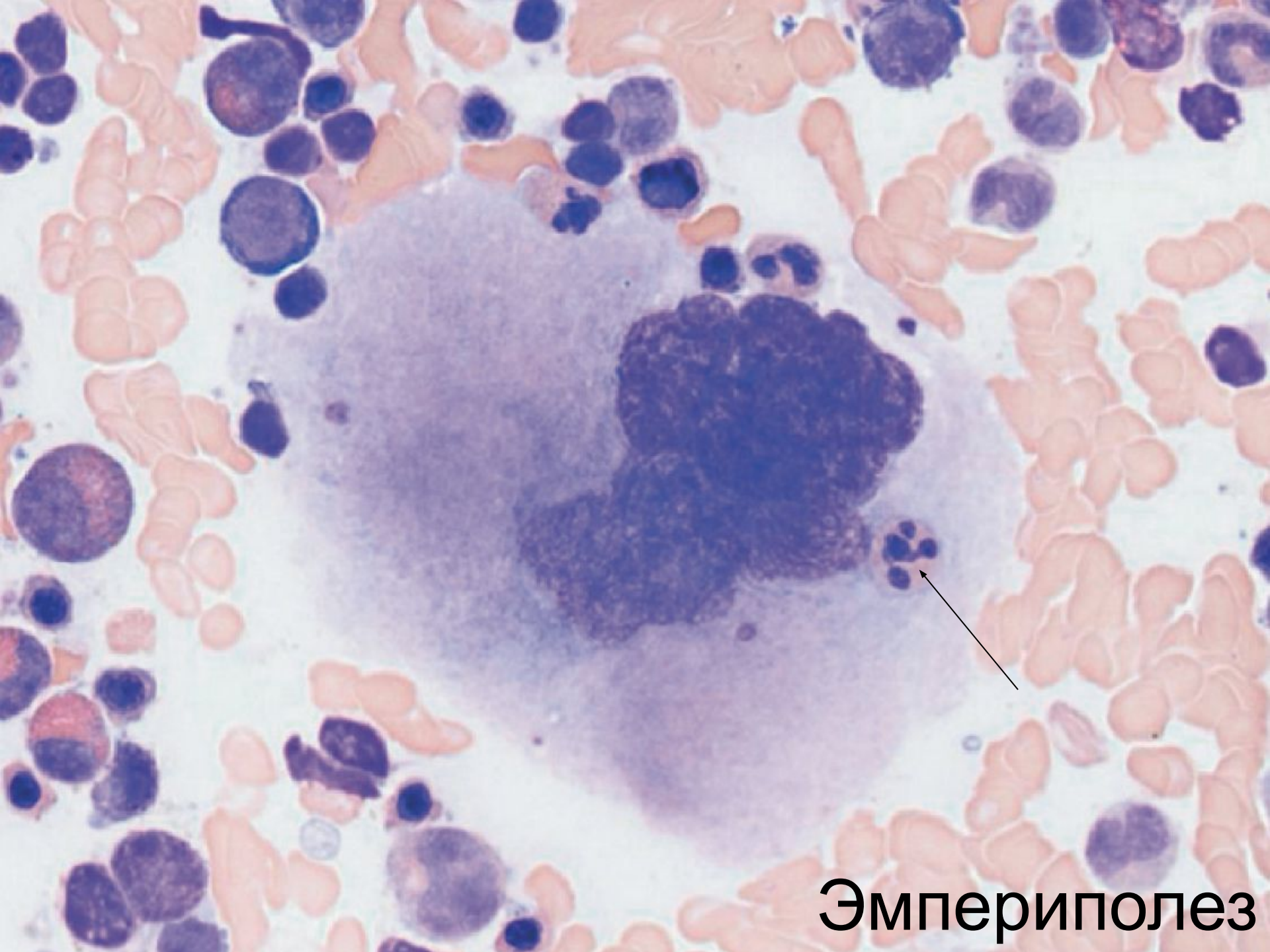


«bare» nuclei

1. megakaryoblasts (group I megakaryocytes)
2. promegakaryocytes (group II megakaryocytes)
3. granular megakaryocytes (group III megakaryocytes) which produce platelets
4. 'bare' nuclei.



normal distribution of all three haemopoietic lineages
megakaryocyte adjacent to a sinusoid
Resin - embedded, H & E × 20



Эмпериполез

ТРОМБОПОЭТИН

- гликопротеин
- источник- печень, почки
- ИЛ-6 стимулирует синтез ТПО
- стимуляция рецептора (CD110, **c-mpl**) активирует JAK-STAT каскад
- связываясь с CD 110 на тромбоцитах, ТПО разрушается (обратная связь)

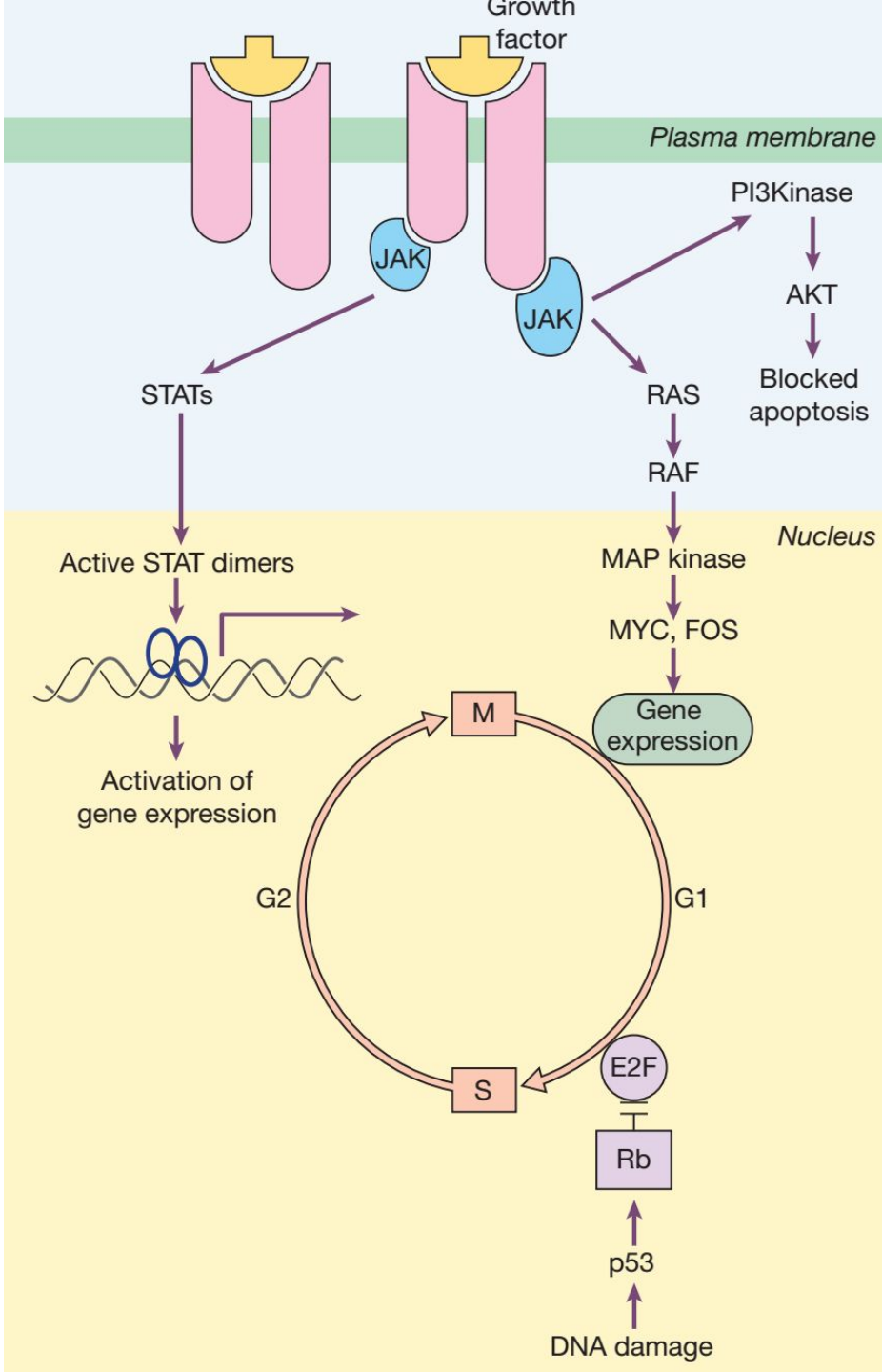
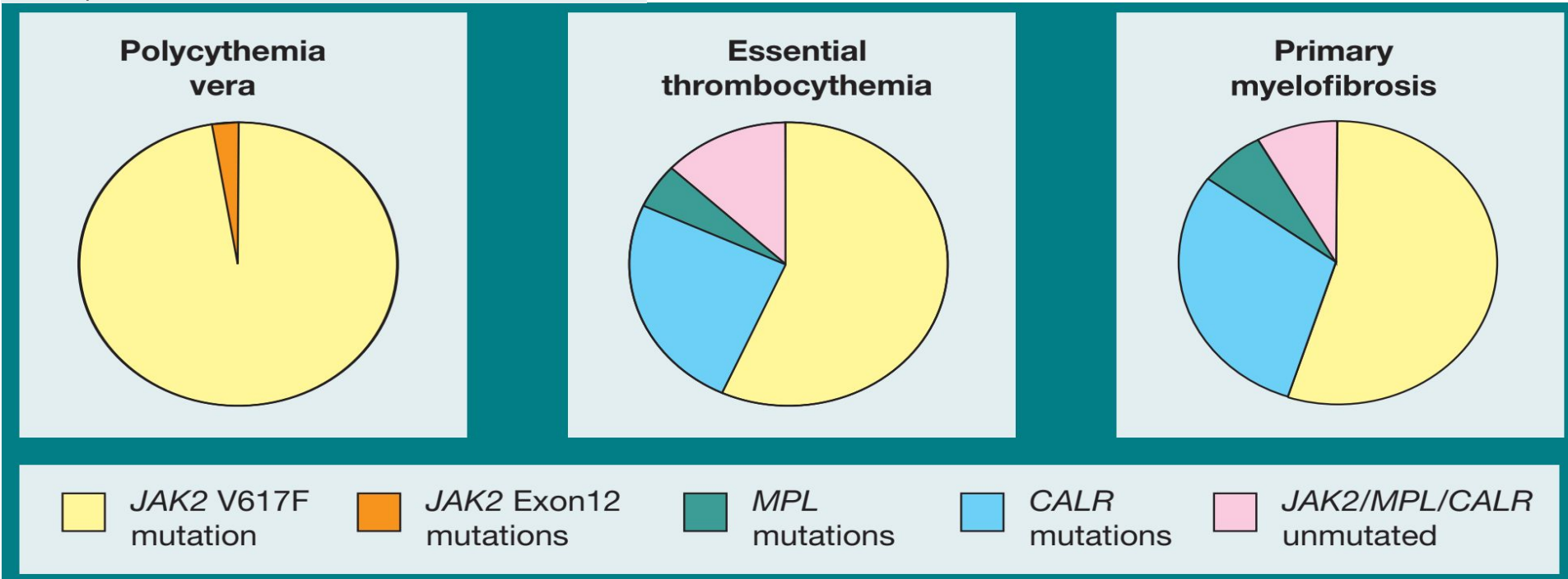


Table 15.1 Genetic mutations in myeloproliferative diseases and other myeloid neoplasms.

Disease	Gene mutations
Chronic myeloid leukaemia	*ABL1*
Polycythaemia vera	*JAK2*
Primary myelofibrosis	*JAK2*, *CALR*, *MPL*
Essential thrombocythaemia	*JAK2*, *CALR*, *MPL*
Mastocytosis	*KIT*
Myeloid neoplasm with eosinophilia	*PDGFRA*, *PDGFRB*, *FGFR1*

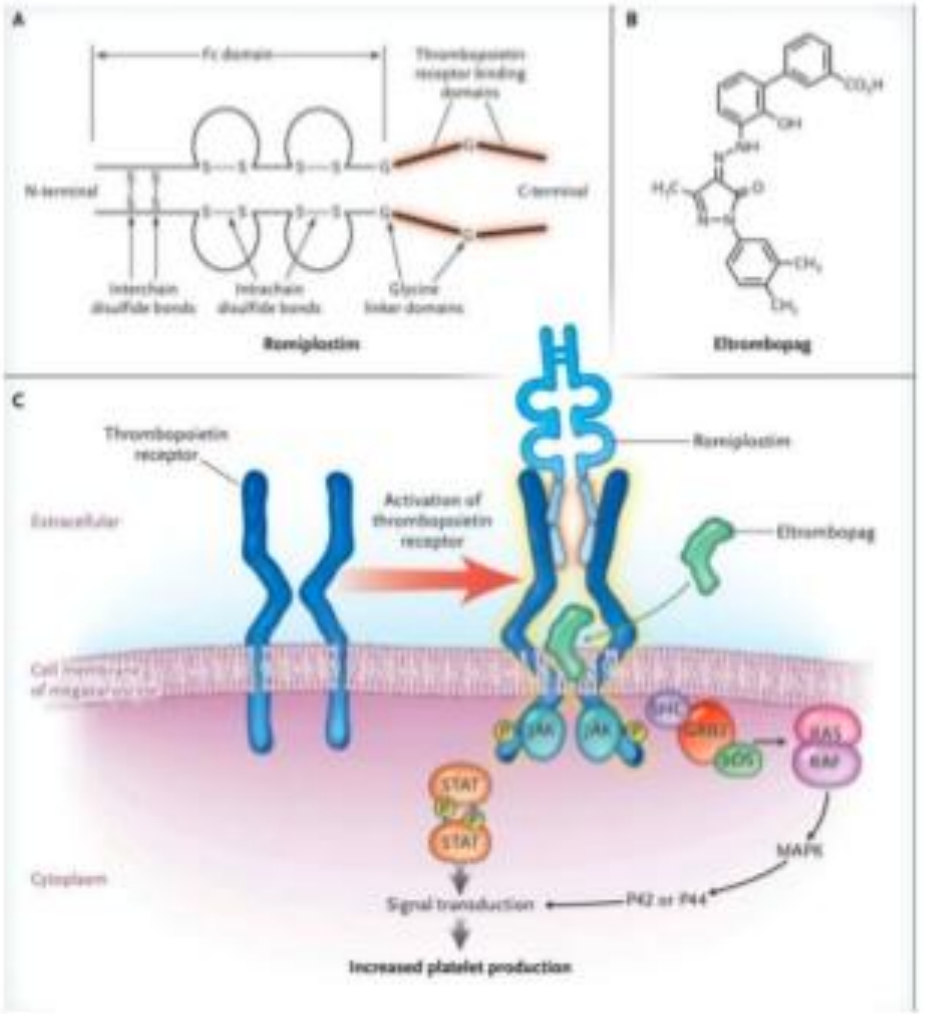


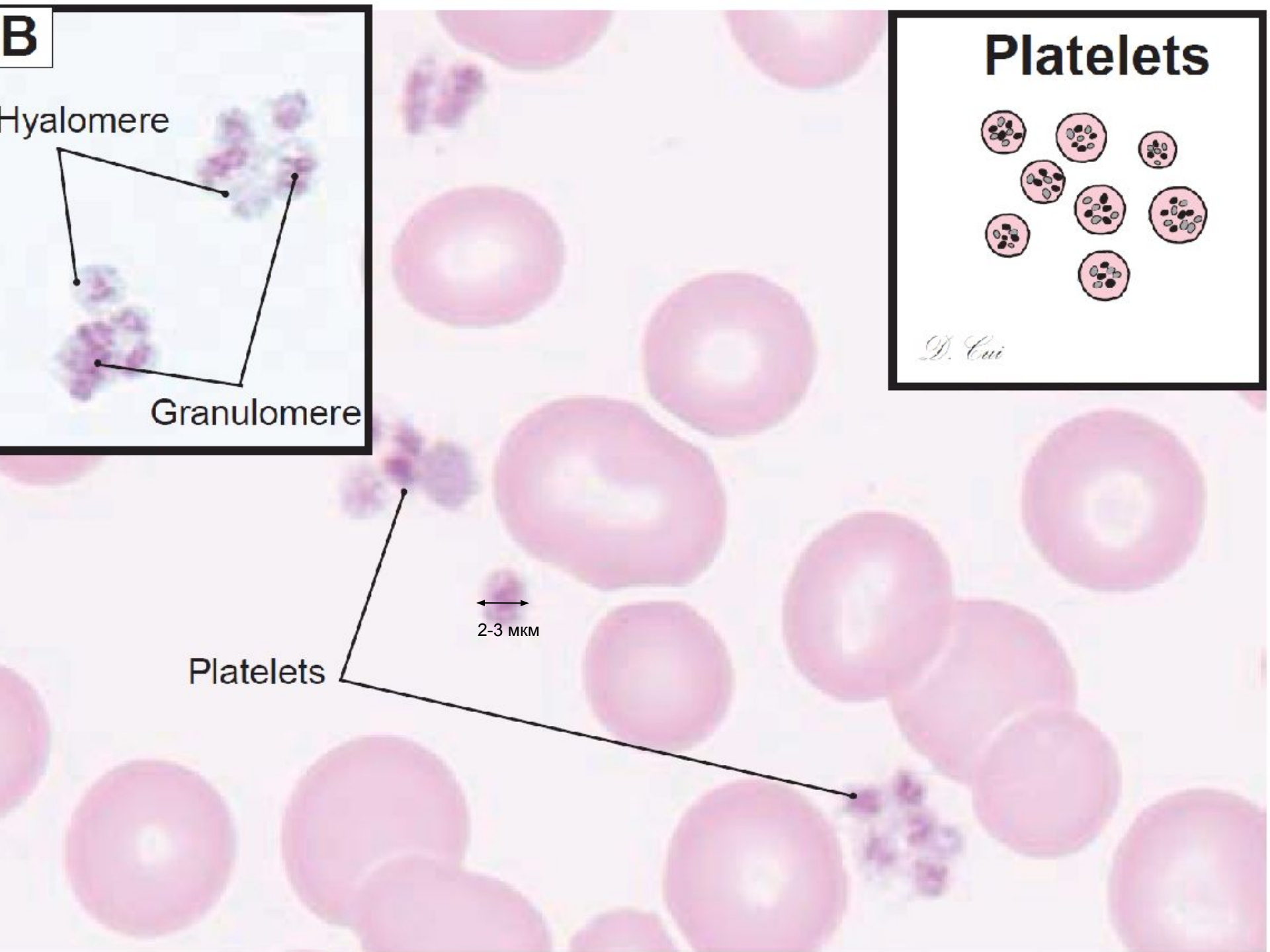
Thrombopoietin-Receptor Agonists for Primary Immune Thrombocytopenia

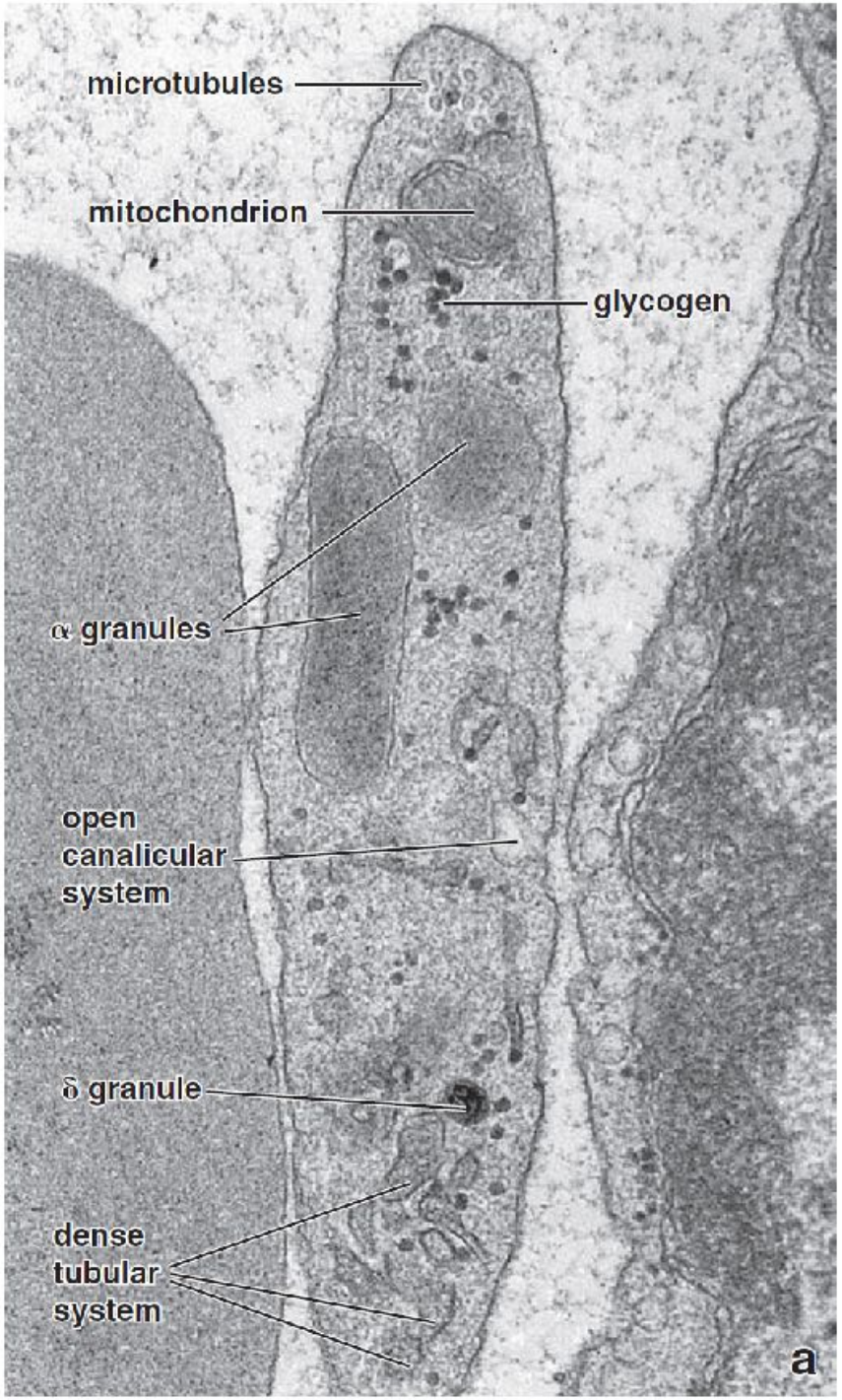
NEJM. 2011

- Eltrombopag
  - Oral thrombopoietin (TPO) receptor agonist
  - Interacts with transmembrane domain of human TPO receptor
  - Induces megakaryocyte proliferation and differentiation from bone marrow progenitor cells

- Romiplostim
  - An Fc-peptide fusion protein (peptibody)
  - Increases platelet production through binding and activation of the thrombopoietin (TPO) receptor – similar mechanism to endogenous TPO



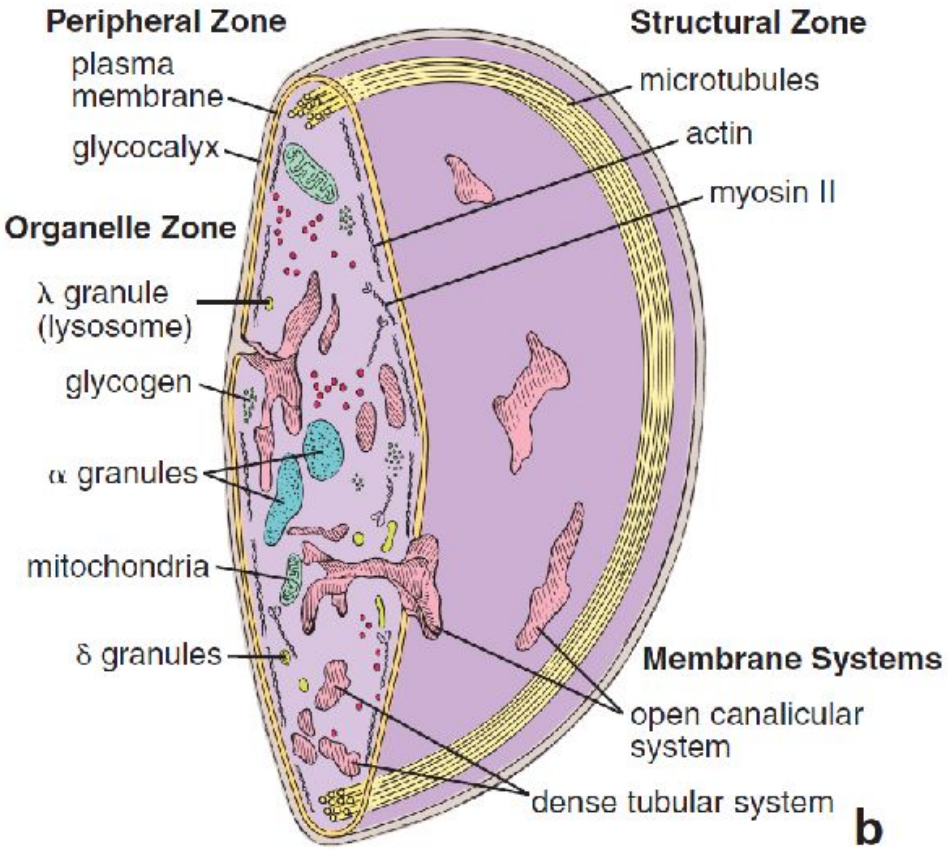

B
Hyalomere
Granulomere
Platelets
D. Cui
2-3 мкм
Platelets

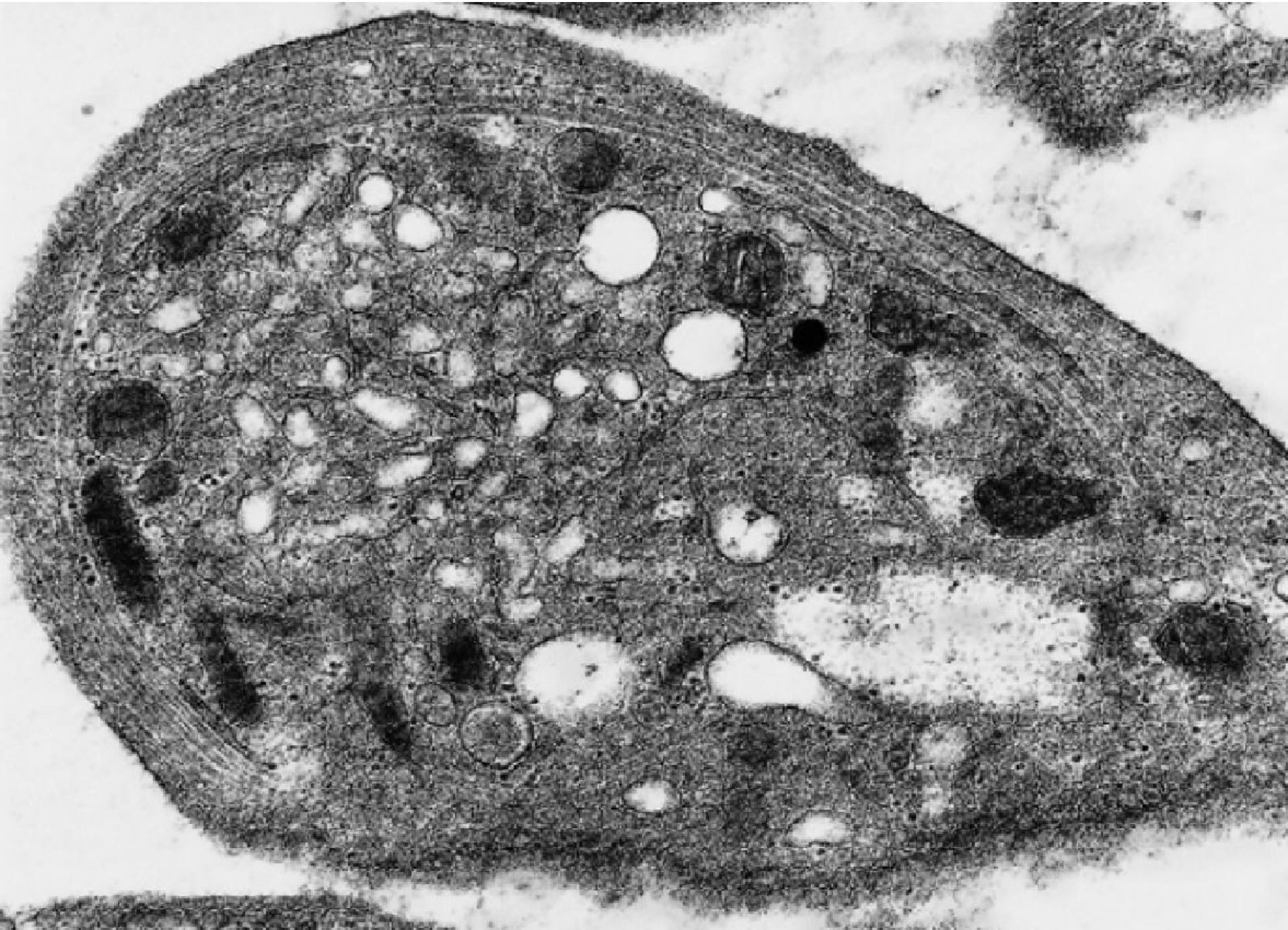


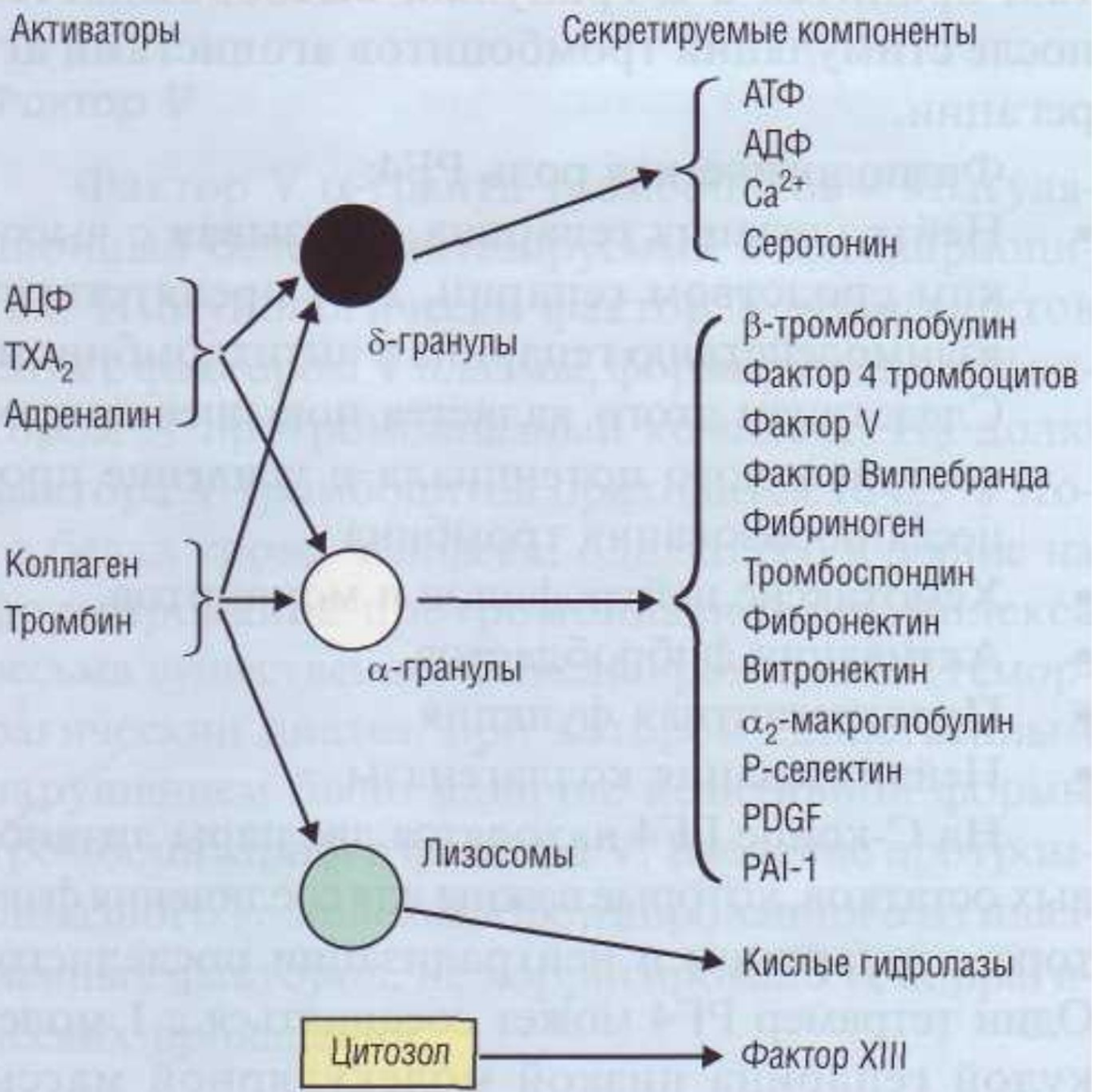
синдром серых тромбоцитов – отсутствие α гранул

Квебекский синдром – деградация α гранул

синдром Германского-Пудлака – отсутствие плотных гранул (+ альбинизм, лизосомальные дефекты)





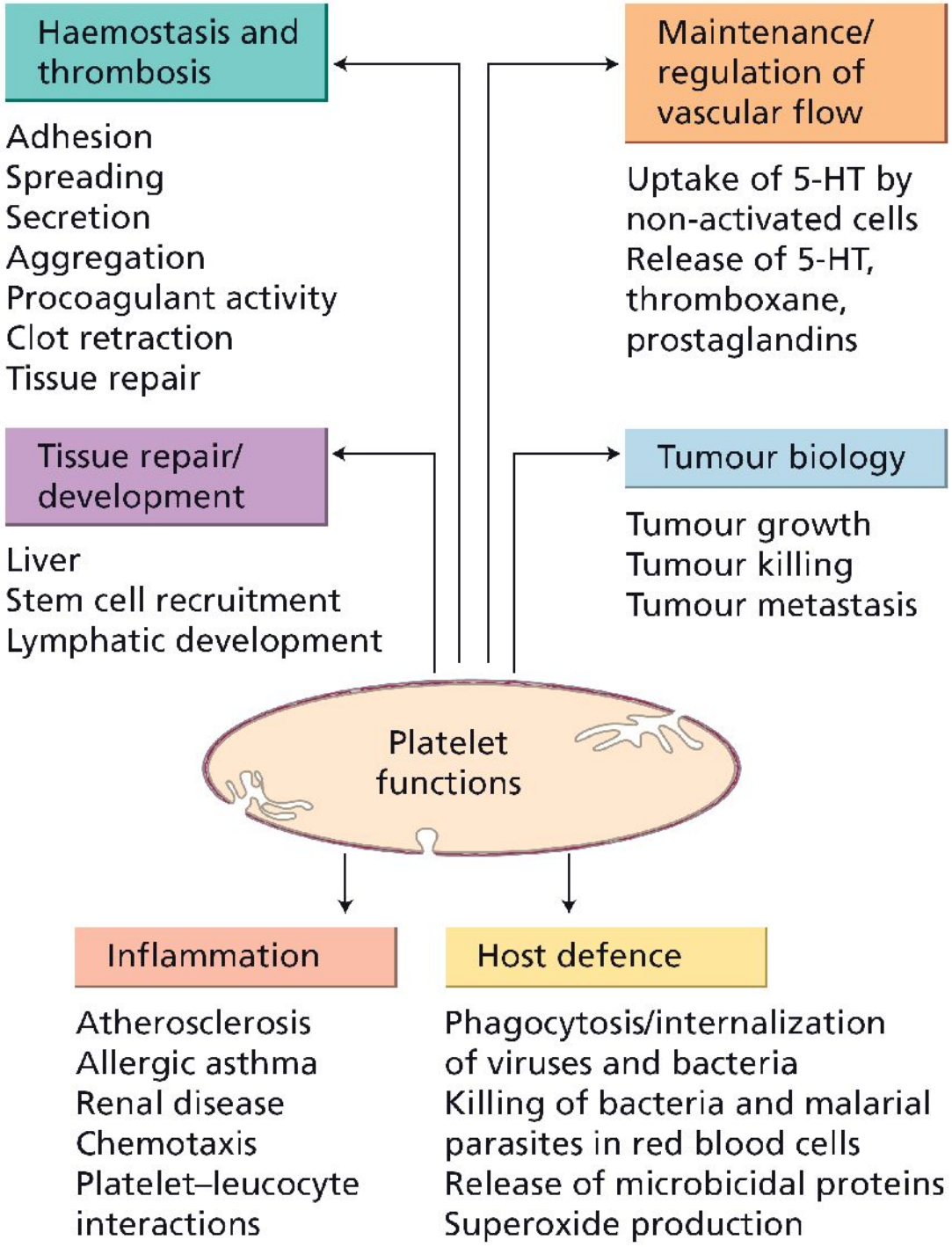

Активаторы
Секретируемые компоненты
АТФ
АДФ
Ca^{2+}
Серотонин
АДФ
$ТХА_2$
Адреналин
δ-гранулы
β-тромбоглобулин
Фактор 4 тромбоцитов
Фактор V
Фактор Виллебранда
Фибриноген
Тромбоспондин
Фибронектин
Витронектин
α_2-макроглобулин
P-селектин
PDGF
PAI-1
Коллаген
Тромбин
α-гранулы
Лизосомы
Кислые гидролазы
Цитозол
Фактор XIII

Platelet functions

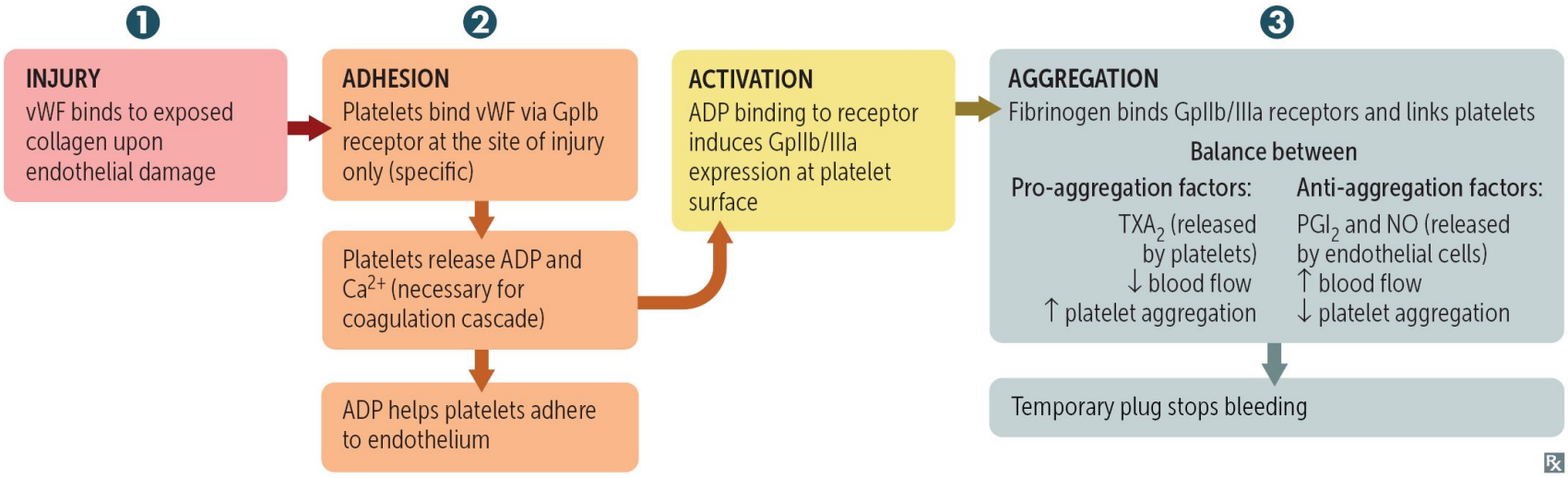
a. Stabilize the vascular endothelial–cadherin complex at intercellular adherens junctions, particularly in postcapillary venules
   (1) The process is accomplished by platelet release of cytokines and growth factors stored within the platelet granules.
   (2) Stabilizing these junctions prevents the leakage of RBCs into the interstitium.
   (3) If the platelet count falls below critical levels, these junctions disassemble, causing extravasation of RBCs into the interstitium.
      - This induces formation of petechiae, a hallmark of thrombocytopenia.
b. Important in the formation of the hemostatic plug (fibrin thrombus) in small vessel injury
c. PDGF stimulates smooth muscle hyperplasia.
   - Important in the pathogenesis of atherosclerosis (refer to Chapter 10)

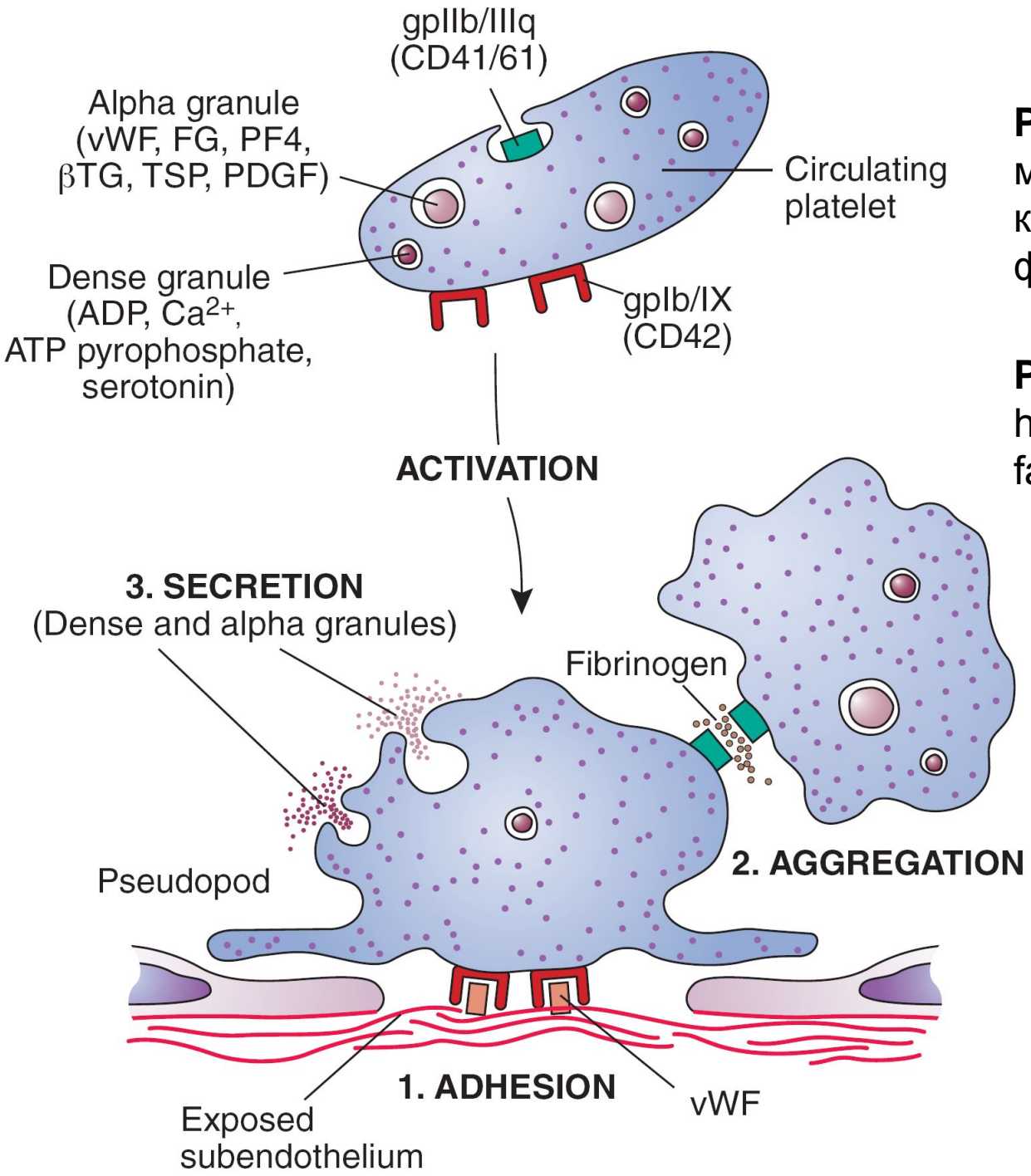
Агонист	Рецепторы
Тромбин	Активируемые протеазами рецепторы PAR1, PAR4; ГП Ib-V-IX
Коллаген	ГП VI, ГП Ia-IIa
АДФ	P2Y12, P2Y2
Тромбоксан А2	TP рецептор
Адреналин	α2-адренорецептор
фактор Виллебранда	ГП Ib-V-IX

А также: 5-HT2A, CD 39, CD 110, FcγRIIA ,C - type lectin receptor (CLEC – 2) и пр.


Haemostasis and thrombosis
Adhesion
Spreading
Secretion
Aggregation
Procoagulant activity
Clot retraction
Tissue repair
Maintenance/ regulation of vascular flow
Uptake of 5-HT by non-activated cells
Release of 5-HT, thromboxane, prostaglandins
Tissue repair/ development
Liver
Stem cell recruitment
Lymphatic development
Tumour biology
Tumour growth
Tumour killing
Tumour metastasis
Platelet functions
Inflammation
Atherosclerosis
Allergic asthma
Renal disease
Chemotaxis
Platelet–leucocyte interactions
Host defence
Phagocytosis/internalization of viruses and bacteria
Killing of bacteria and malarial parasites in red blood cells
Release of microbicidal proteins
Superoxide production

Участие тромбоцитов в гемостазе

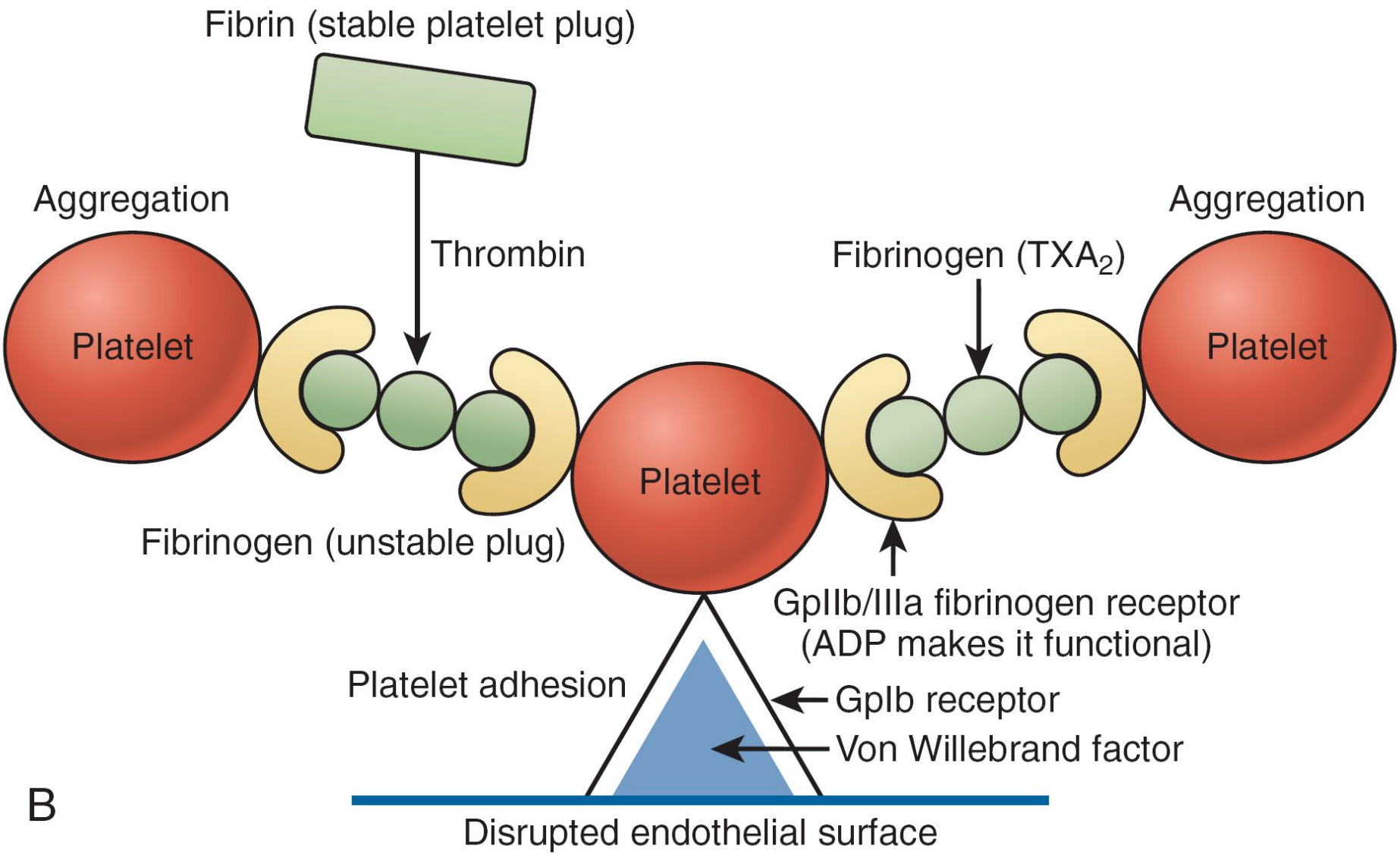


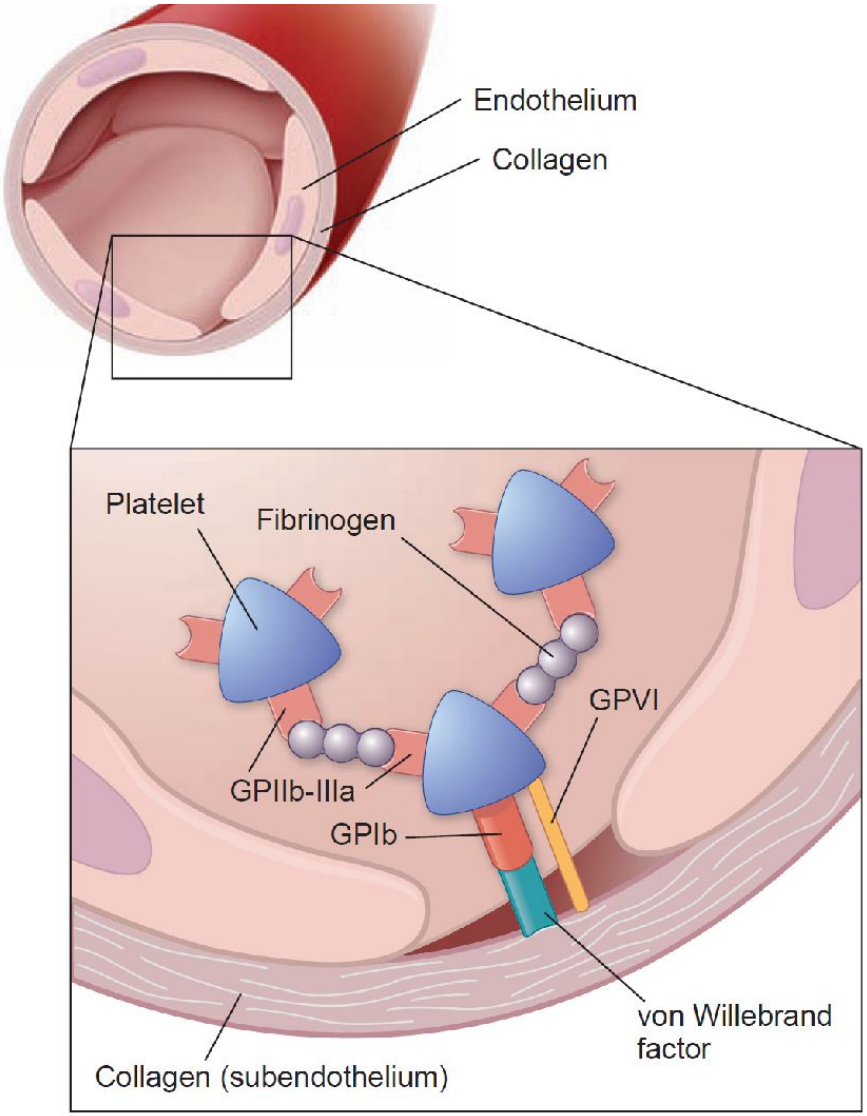


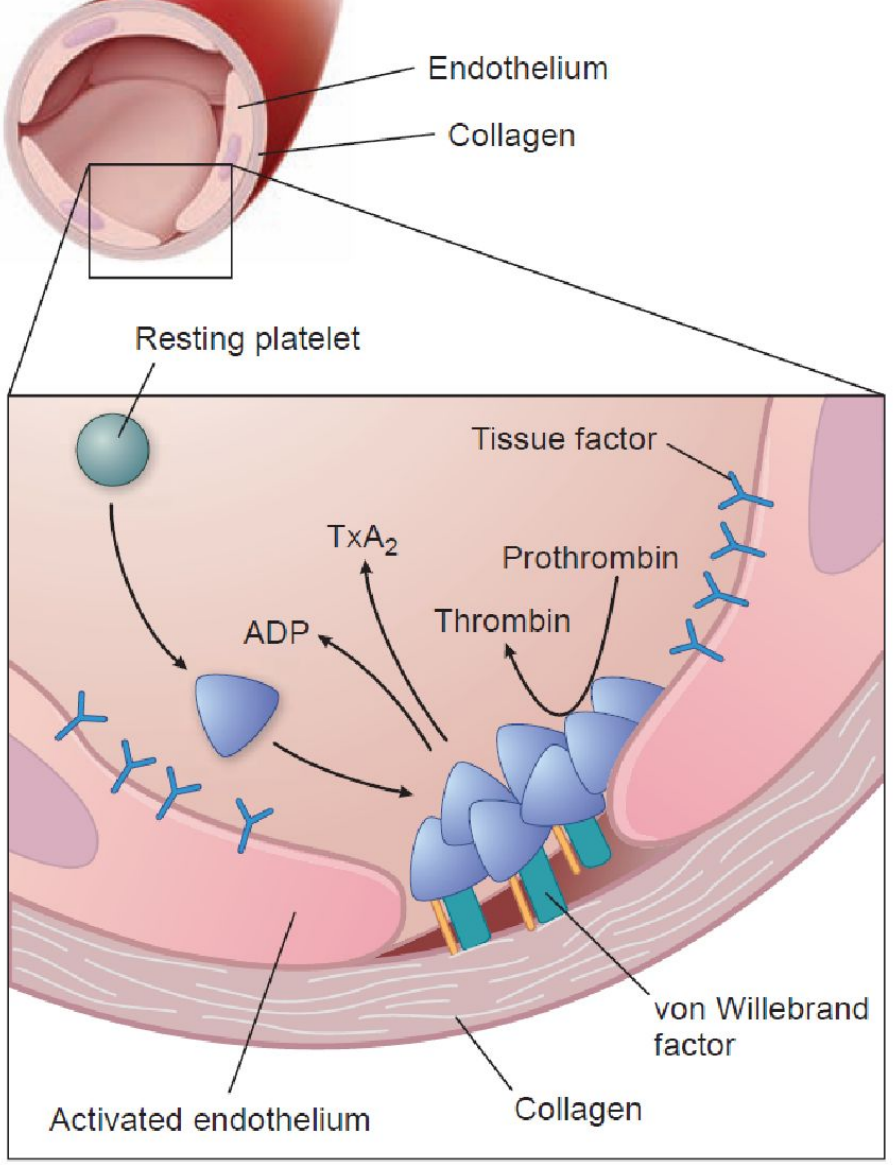
PF3 (фосфолипиды мембраны) - связывает карбоксилированные факторы свертывания

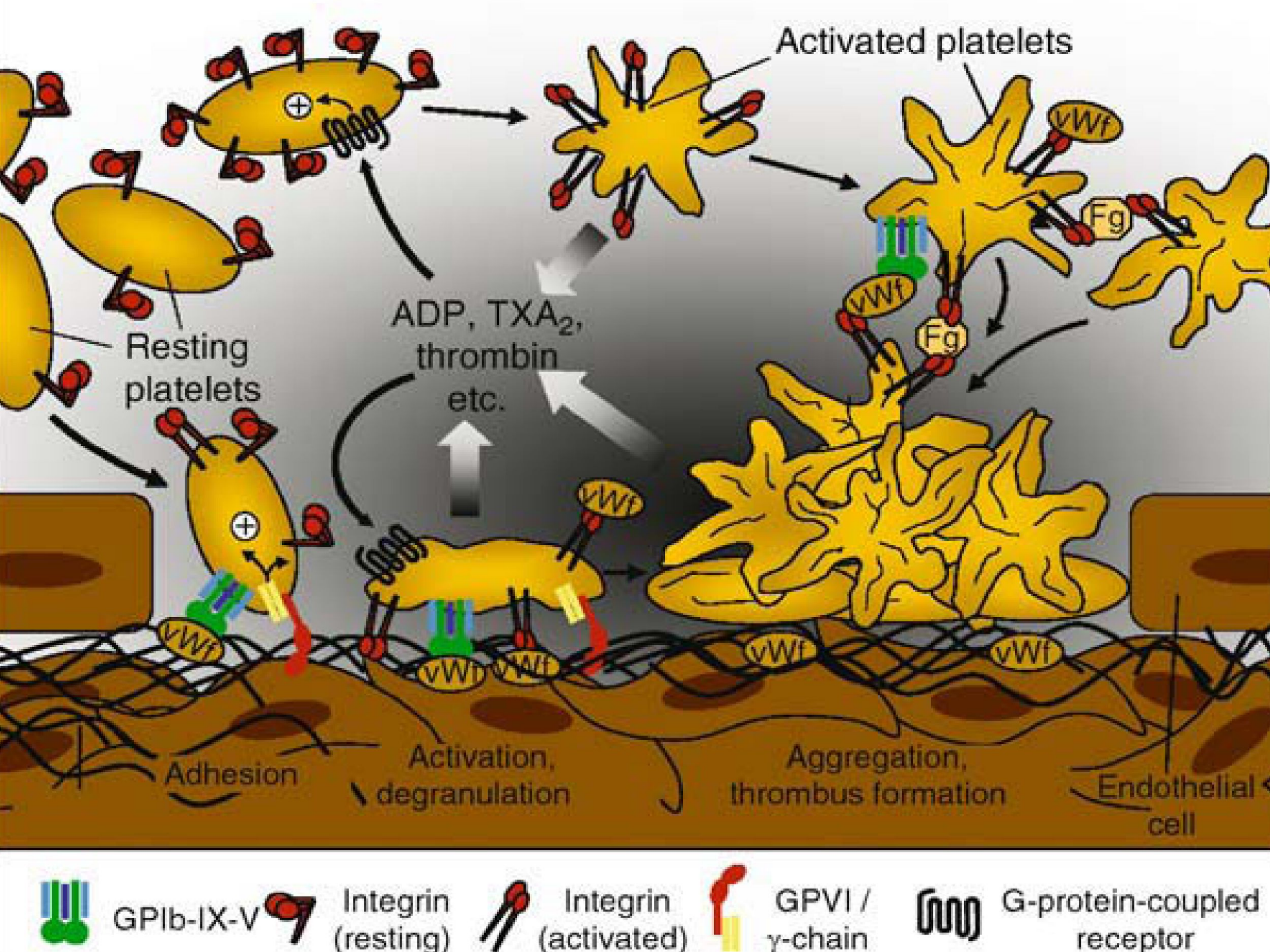
PF4 (CXCL4**)** - heparin-neutralizing factor

эндотелиальная экто-ADPаза (CD39)


Fibrin (stable platelet plug)
Aggregation
Thrombin
Fibrinogen (TXA_2)
Aggregation
Platelet
Platelet
Platelet
Fibrinogen (unstable plug)
GpIIb/IIIa fibrinogen receptor
(ADP makes it functional)
Platelet adhesion
GpIb receptor
Von Willebrand factor
Disrupted endothelial surface
B


Endothelium
Collagen
Platelet
Fibrinogen
GPVI
GPIIb-IIIa
GPIb
von Willebrand factor
Collagen (subendothelium)


Endothelium
Collagen
Resting platelet
Tissue factor
TxA_2
Prothrombin
ADP
Thrombin
von Willebrand factor
Activated endothelium
Collagen


Activated platelets
vWf
Fg
Resting platelets
ADP, TXA2, thrombin etc.
Adhesion
Activation, degranulation
Aggregation, thrombus formation
Endothelial cell
GPIb-IX-V
Integrin (resting)
Integrin (activated)
GPVI / γ-chain
G-protein-coupled receptor

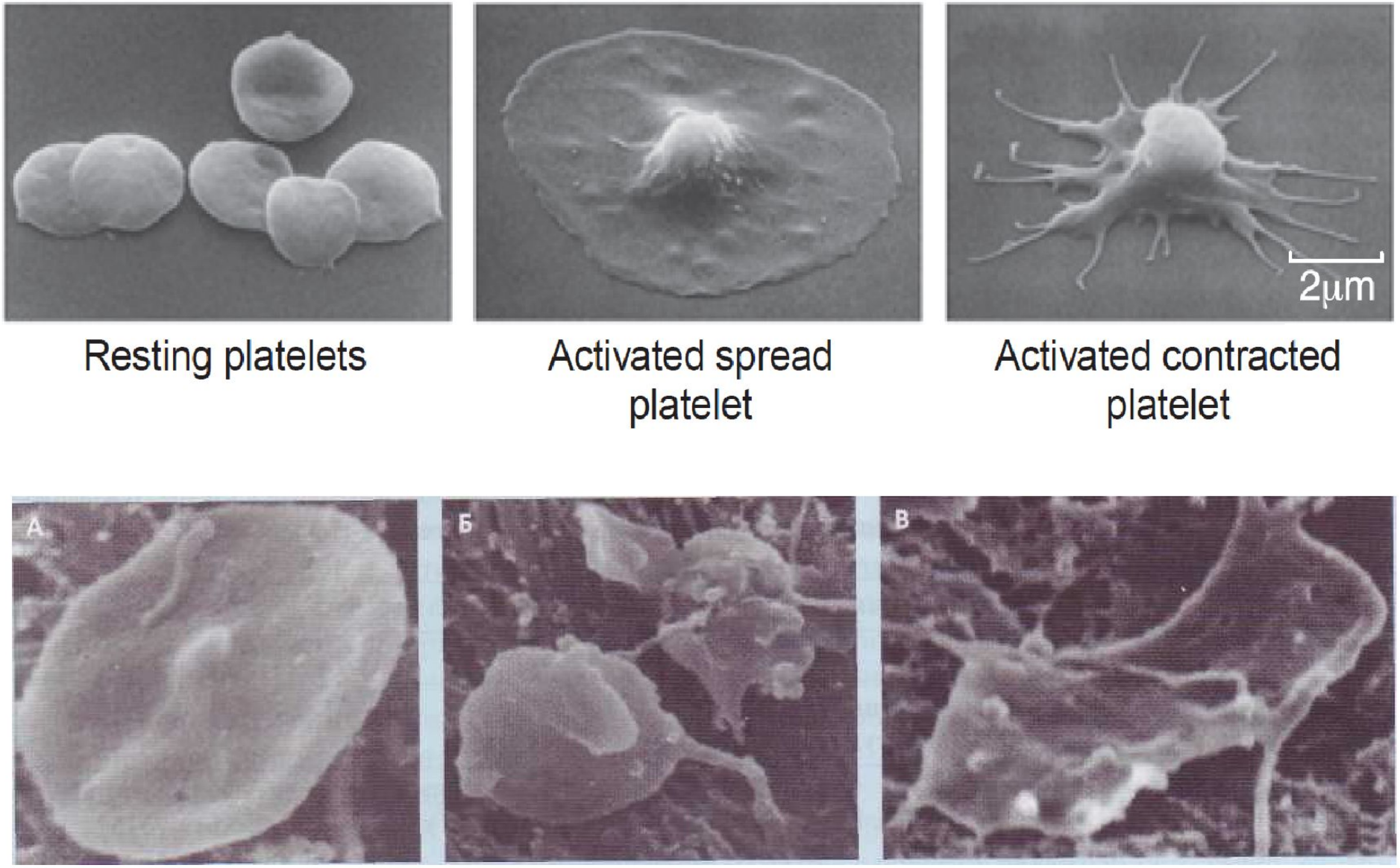
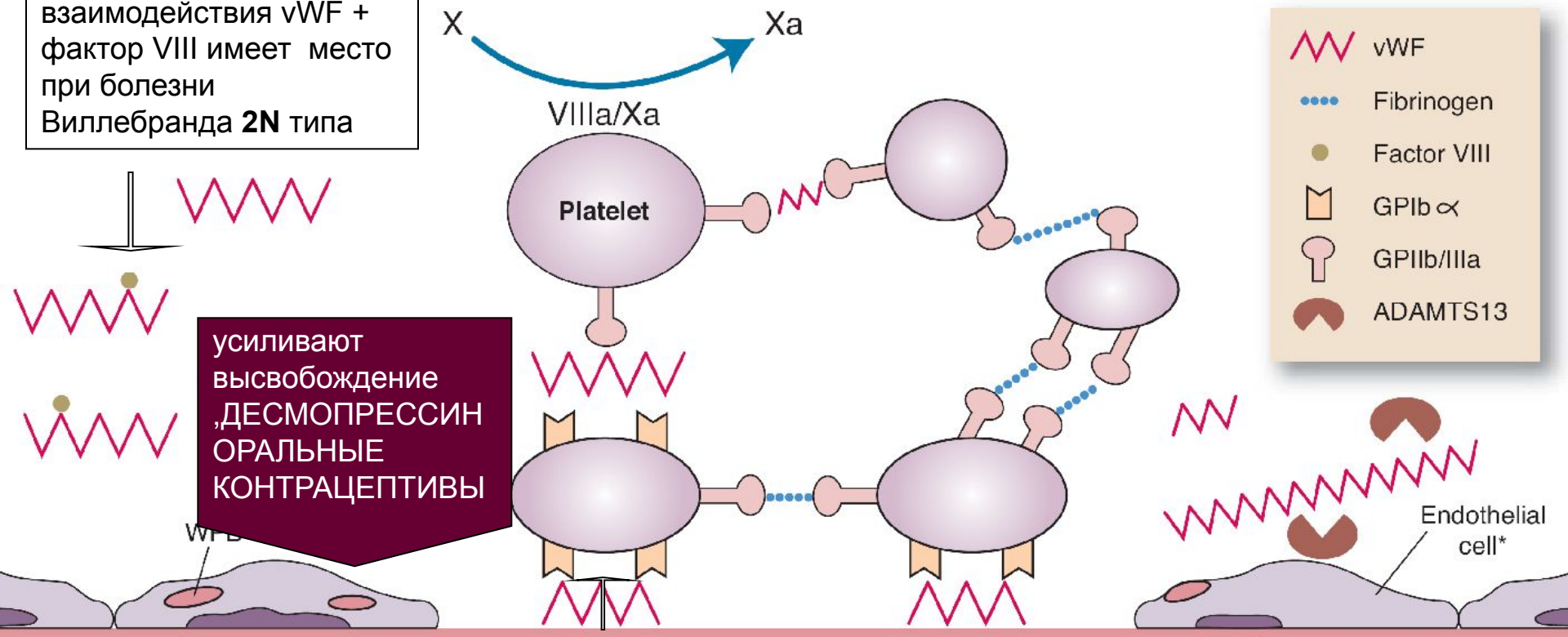


Рис. 27. Стадии контактной активации тромбоцитов: А - неактивный тромбоцит (дискоцит, пластинка); Б - тромбоциты в обратимой стадии контактной активации (шаровидные формы с псевдоподиями); В - тромбоцит в необратимой стадии адгезии (распластанная форма без внутреннего содержимого - «тень тромбоцита»)

Функции vWF:

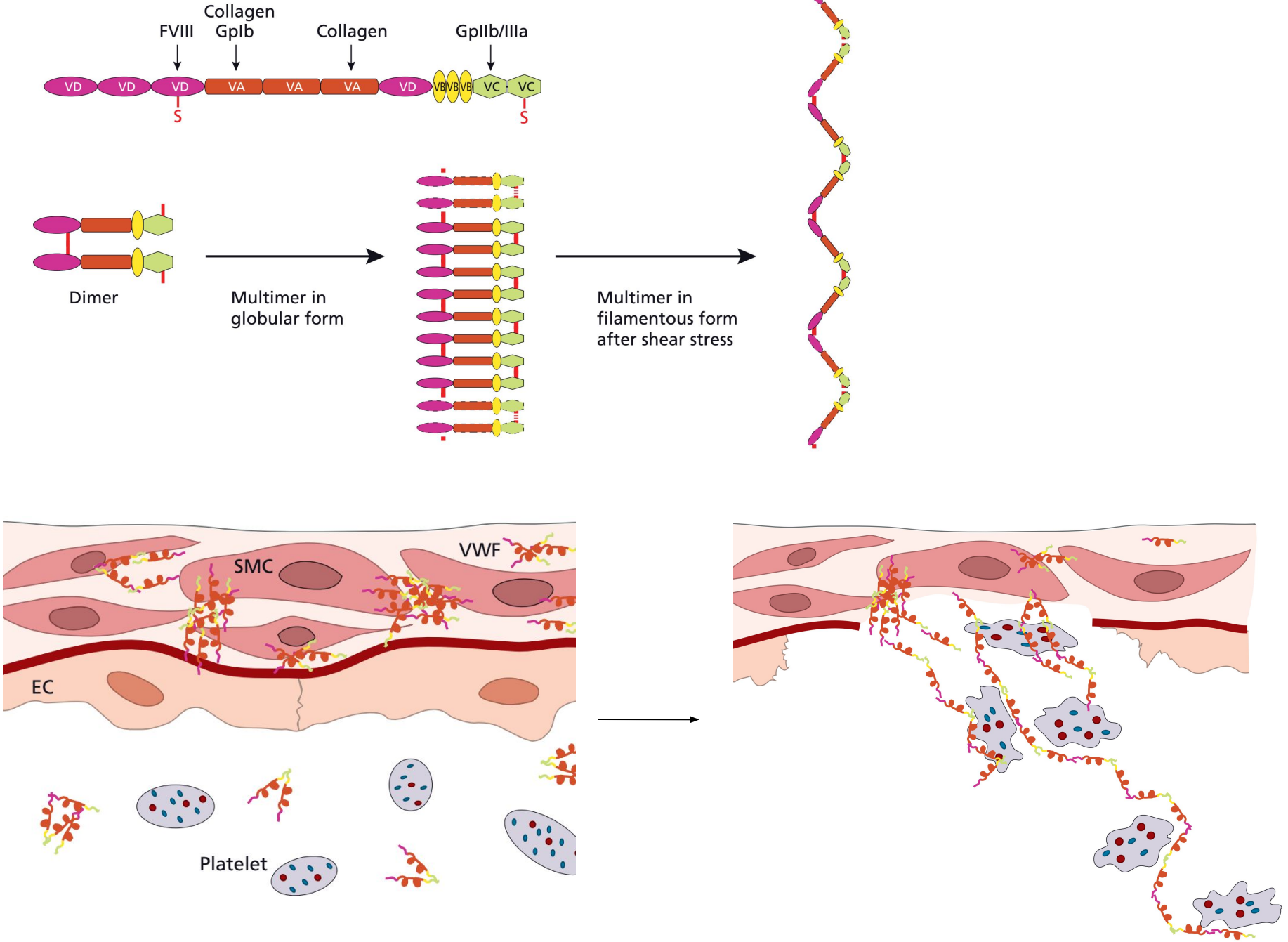
1. помогает тромбоцитам: **адгезия** (домен A vWF + GPIb-V-IX), в меньшей степени, **агрегация** (домен C vWF + GPIIb/IIIa)
2. помогает фактору VIII

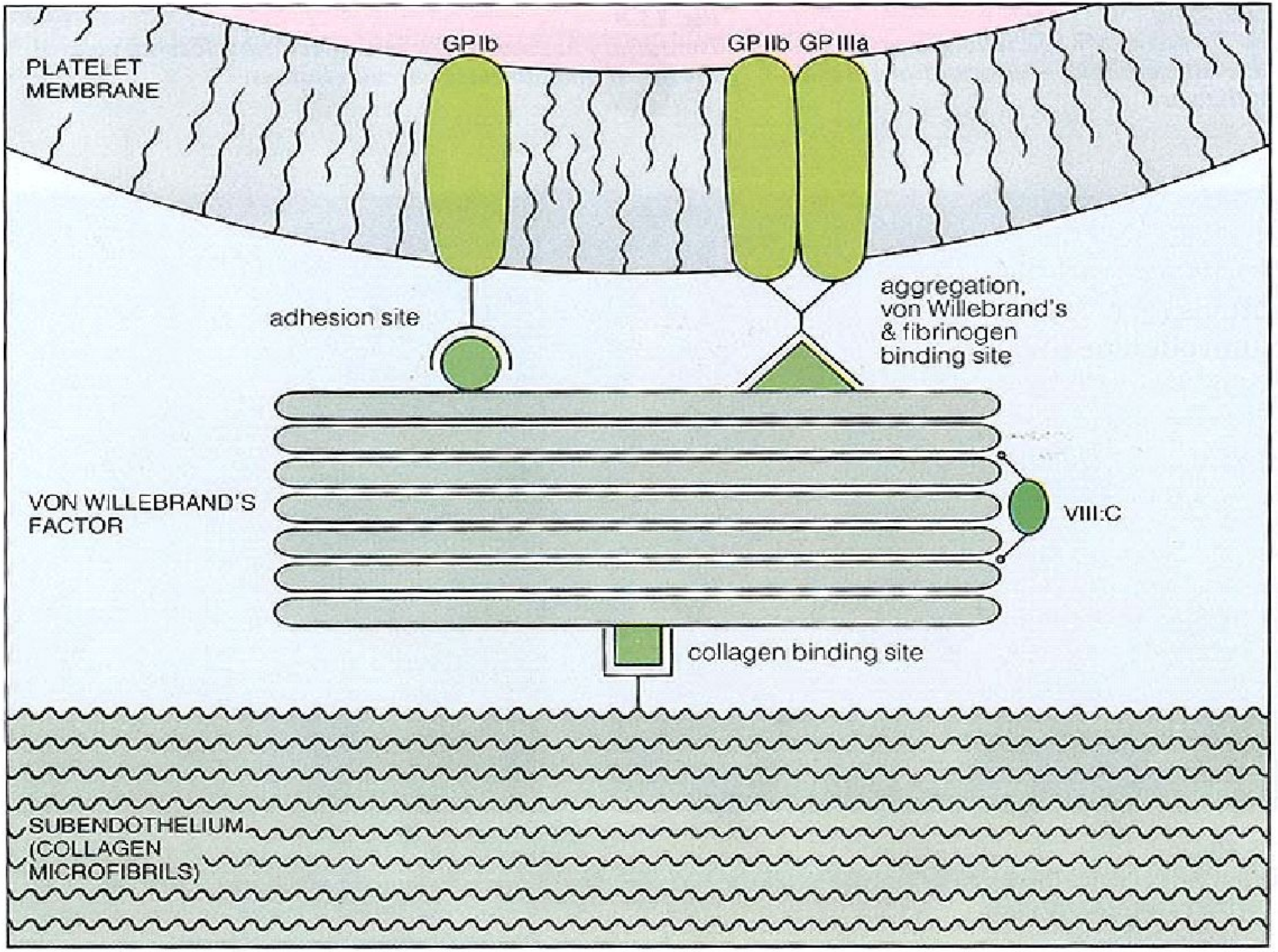
ослабление взаимодействия vWF + фактор VIII имеет место при болезни Виллебранда **2N** типа



усиливают высвобождение ,ДЕСМОПРЕССИН ОРАЛЬНЫЕ КОНТРАЦЕПТИВЫ

стимулятор vWF + GPIb-V-IX - РИСТОЦЕТИН
ослабление vWF + GPIb-V-IX имеет место при болезни Виллебранда **2A** типа, усиление при - **2B** типе


FVIII
Collagen GpIb
Collagen
GpIIb/IIIa
VD
VD
VD
VA
VA
VA
VD
VB
VB
VB
VC
VC
S
S
Dimer
Multimer in globular form
Multimer in filamentous form after shear stress
SMC
VWF
EC
Platelet


PLATELET MEMBRANE
GPIb
GPIIb GPIIIa
adhesion site
aggregation, von Willebrand's & fibrinogen binding site
VON WILLEBRAND'S FACTOR
VIII:C
collagen binding site
SUBENDOTHELIUM (COLLAGEN MICROFIBRILS)

КОАГУЛЯЦИЯ

transglutaminase

сериновые протеазы

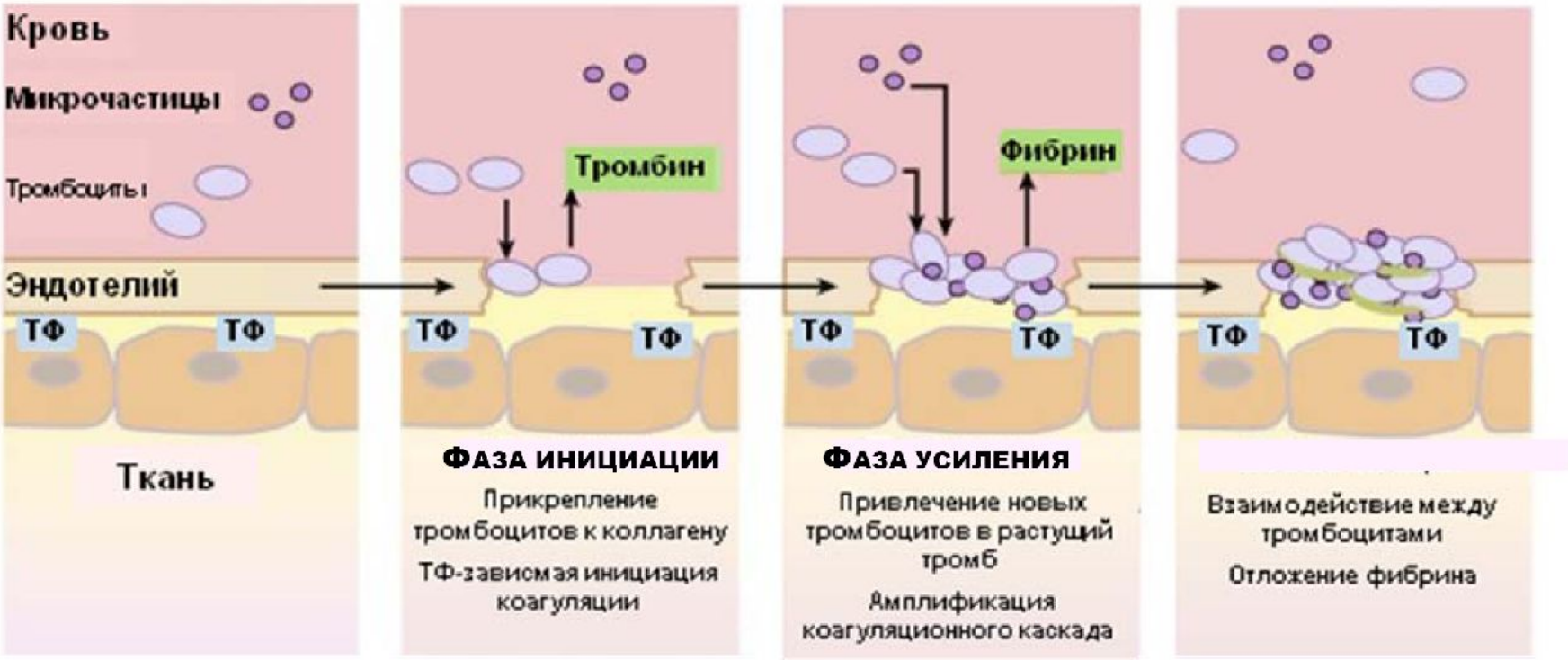
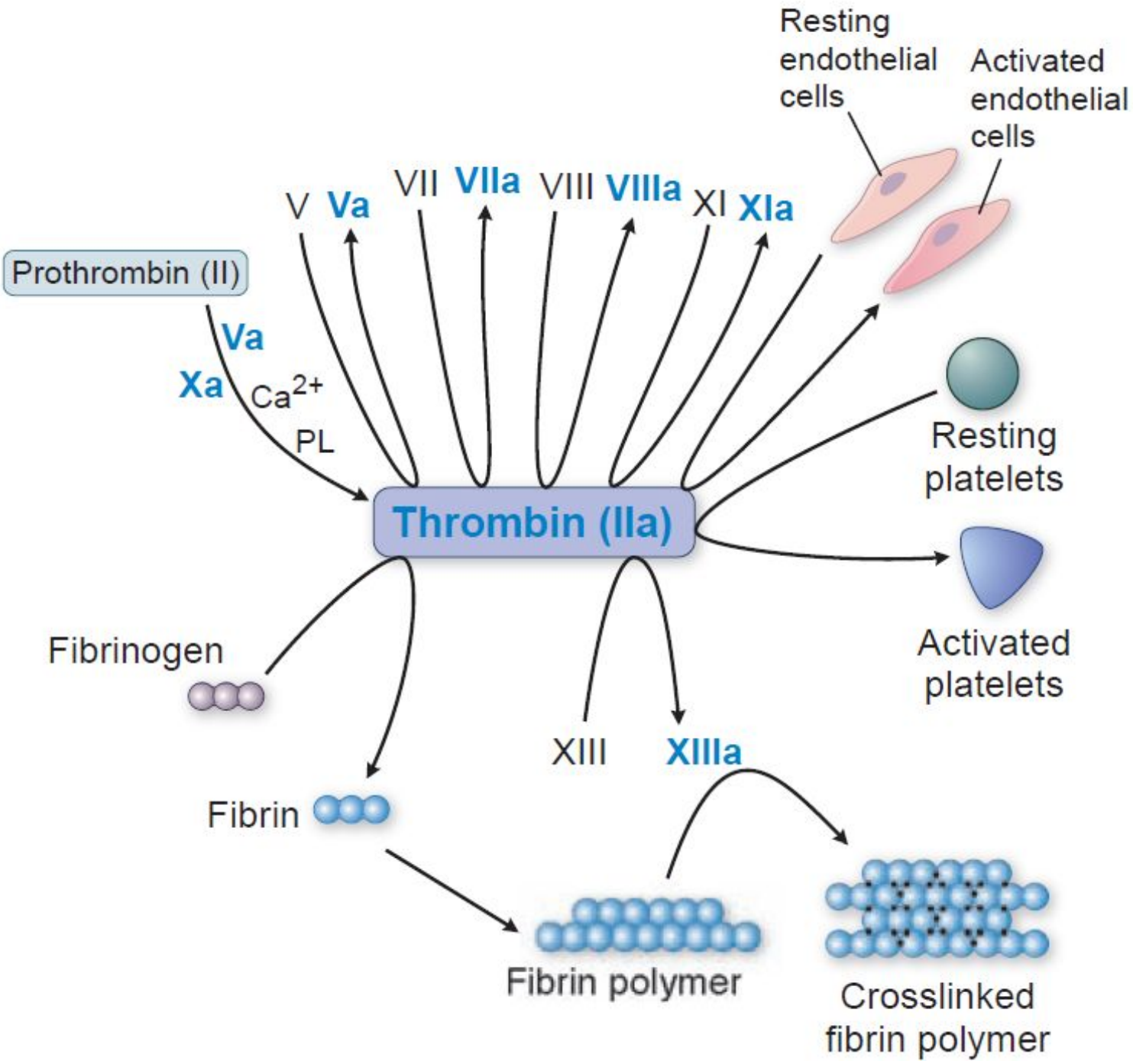
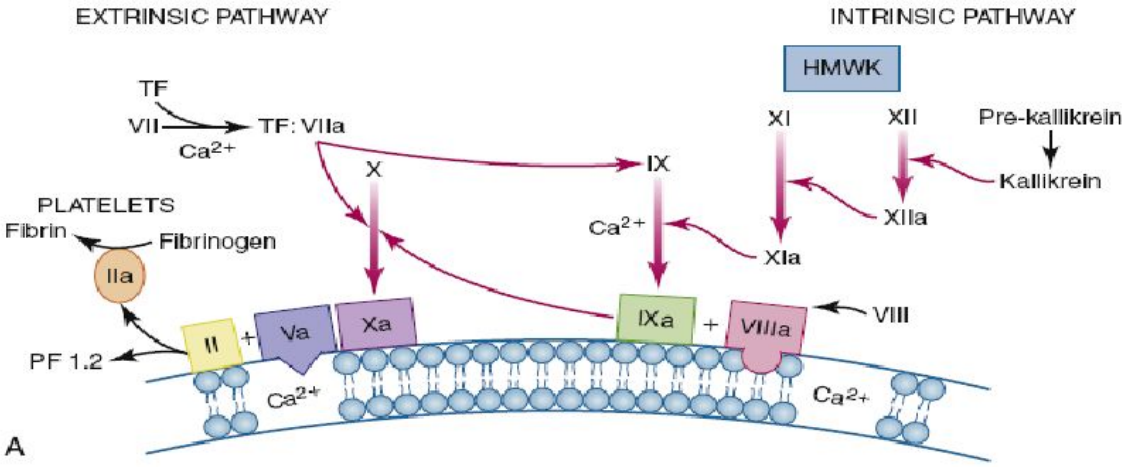
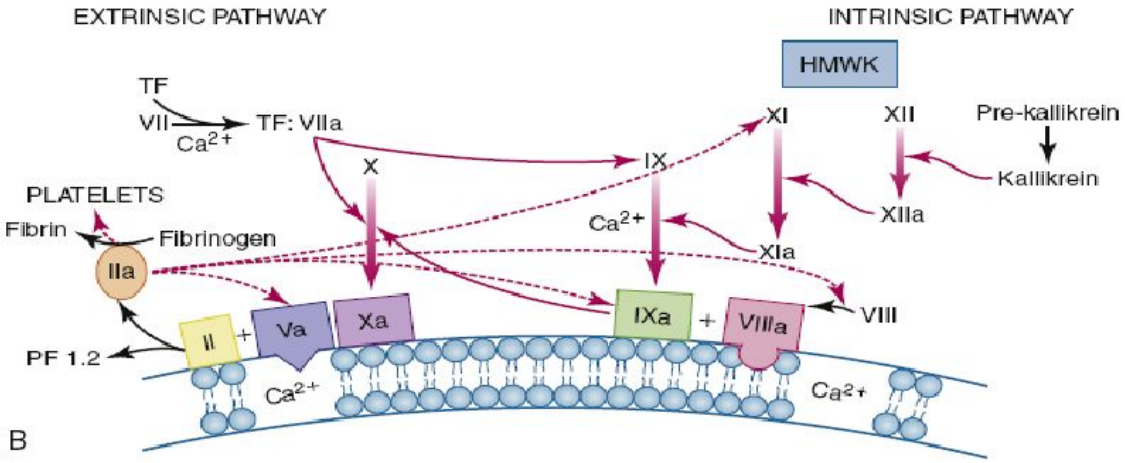


Рисунок 1. Современная схема свертывания крови *(из Mackman N, Tilley RE, Key NS: Role of extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscleros Thromb Vasc Biol 27:1688, 2007).*


Resting endothelial cells
Activated endothelial cells
V Va
VII VIIa
VIII VIIIa
XI XIa
Prothrombin (II)
Va
Xa
Ca2+
PL
Thrombin (IIa)
Resting platelets
Activated platelets
Fibrinogen
XIII XIIIa
Fibrin
Fibrin polymer
Crosslinked fibrin polymer


EXTRINSIC PATHWAY
INTRINSIC PATHWAY
HMWK
TF
VII
TF: VIIa
Ca2+
X
IX
XI
XII
Pre-kallikrein
Kallikrein
XIIa
XIa
Ca2+
PLATELETS
Fibrin
Fibrinogen
IIa
II
Va
Xa
IXa
VIIIa
VIII
PF 1.2
Ca2+
Ca2+
A


EXTRINSIC PATHWAY
INTRINSIC PATHWAY
HMWK
TF
VII
TF: VIIa
Ca2+
X
IX
XI
XII
Pre-kallikrein
Kallikrein
XIIa
XIa
Ca2+
PLATELETS
Fibrin
Fibrinogen
IIa
II
Va
Xa
IXa
VIIIa
VIII
PF 1.2
Ca2+
Ca2+
B

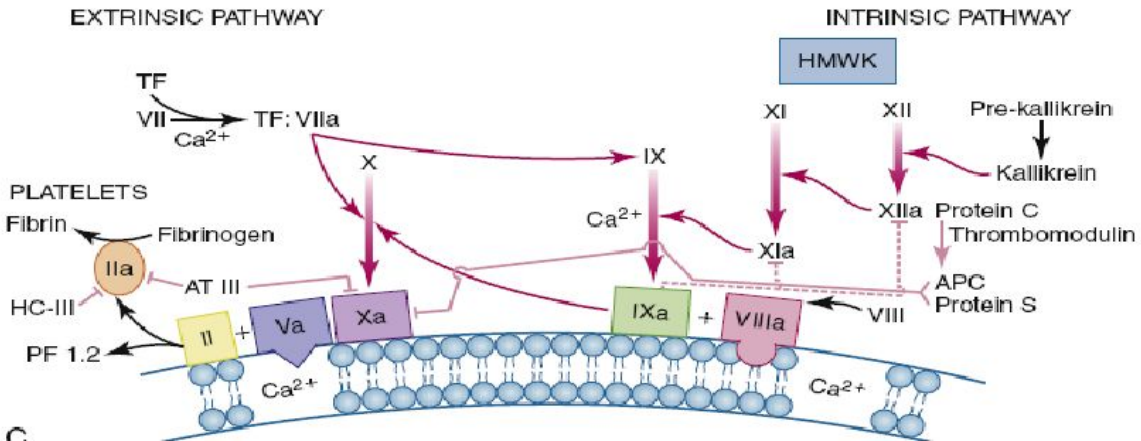

EXTRINSIC PATHWAY
INTRINSIC PATHWAY
HMWK
TF
VII
TF: VIIa
Ca2+
X
IX
XI
XII
Pre-kallikrein
Kallikrein
XIIa
Protein C
Thrombomodulin
XIa
Ca2+
APC
Protein S
PLATELETS
Fibrin
Fibrinogen
IIa
AT III
HC-III
II
Va
Xa
IXa
VIIIa
VIII
PF 1.2
Ca2+
Ca2+
C

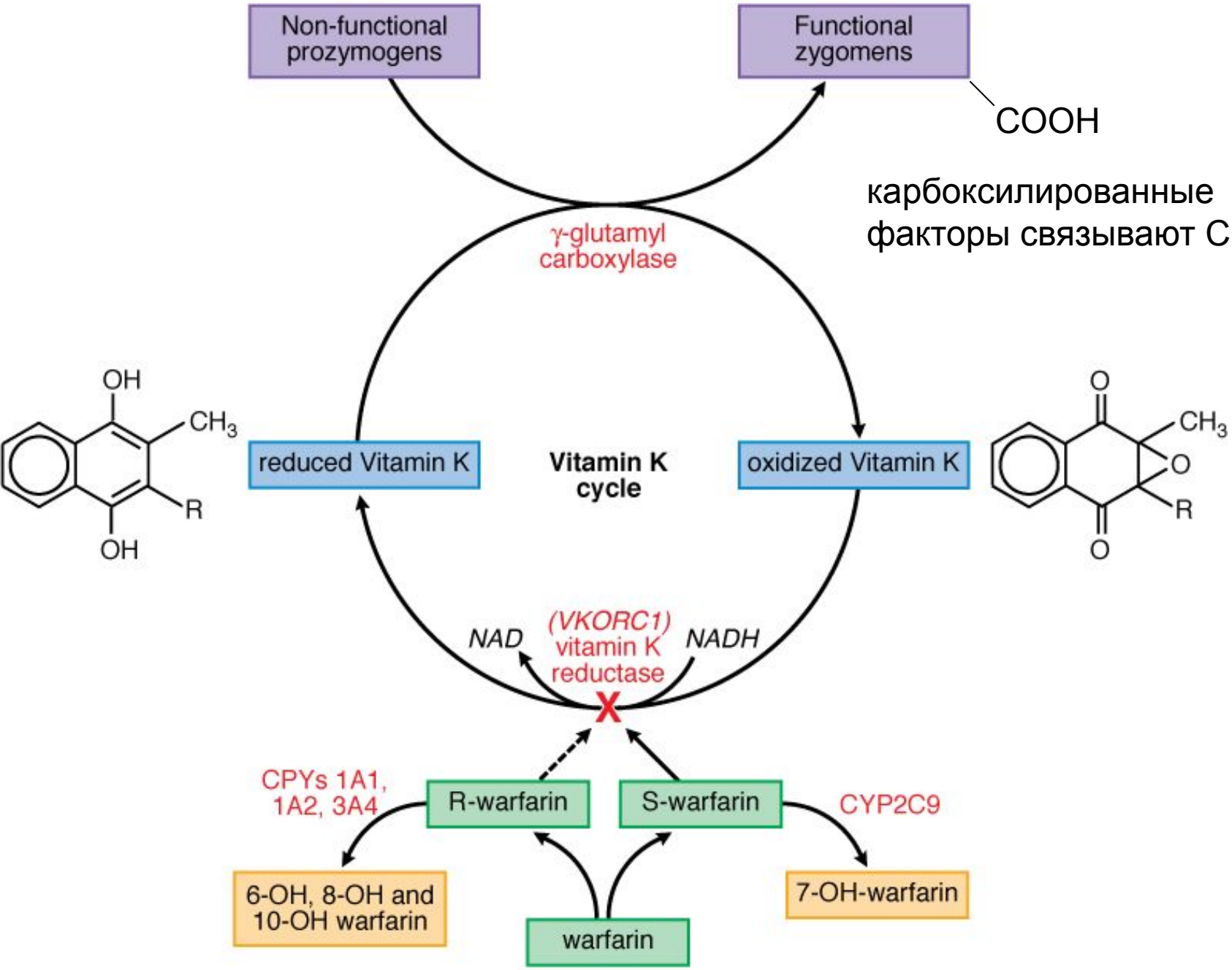
Таблица 1 (по Долгову В.В. и Свирину П.В., 2005)

Плазменные факторы свертывания крови

Сим-вол фак-тора	Название	Время полу-жизни, ч	Концентрация в плазме	Гемостати-ческий минимум	Зависи-мость от витамина К
1	2	3	4	5	6
I	Фибриноген	64-96	2-4 г/л	0,5-1,0 г/л	-
II	Протромбин	48	100-150 мг/л	40%	+
V	Проакцелерин	12	7-10 мг/л	10-15%	-
VII	Проконвертин	4-6	0,4 мг/л	5-10%	+
VIII	Антигемофильный глобулин А	15-20	0,7	30-35%	-
IX	Антигемофильный фактор В	24	3-5 мг/л	20-30%	+
X	Фактор Стюарта-Прауэра	32	8-10 мг/л	10-20%	+
XI	Антигемофильный глобулин С, фактор Розенталя	60-80	3-6 мг/л	10-20%	_
XII	Фактор Хагемана	50-70	25-35 мг/л	<1%	-
XIII	Фибрин-стабилизирующий фактор, трансглютаминаза	40-50	25-35 мг/л	<1%	-
ПК	Прекалликреин, фактор Флетчера		30-50 мг/л	<1%	-
ВМК	Высокомолекулярный кининоген, фактор Фитцжеральда		60-80 мг/л	<1%	-

NO.	FACTOR	RMM (DALTONS)	HALF-LIFE	CONCENTRATION IN PLASMA	
				µg/ml	nmol/l
I	Fibrinogen	340 000	90 h	1.5–4 × 10	–
II	Prothrombin	70 000	60 h	100–150	1400
V	–	330 000	12–36 h	5–10	20
VII	–	48 000	6 h	0.5	10
VIII	–	200 000	12 h	0.2	0.7
VWF	–	800 000–140 000 000	10–24 h[a]	10	–
IX	–	57 000	24 h	4	90
X	–	58 000	40 h	10	170
XI	–	158 000	60 h	6	30
XII	–	80 000	48–52 h	30	375
Prekallikein	–	85 000	48 h	40	450
HMWK	–	120 000	6.5 days	80	700
XIII	–	32 000	3–5 days	30 (A+B)	900 (tetramer)

RMM, relative molecular mass (molecular weight); h, hours; HMWK, high molecular weight kininogen; VWF, von Willebrand factor.
[a]The half-life of VWF varies according the ABO blood group, being shortest in O, longest in AB and intermediate in A and B.



карбоксилированные факторы связывают Ca и PF3

Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

European Heart Journal
doi:10.1093/eurheartj/ehw210

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

9.5.6 Genetic testing

In addition to food and drug interactions, multiple genetic variations affect the metabolism of VKAs.[497] The systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled clinical studies.[498–500] Genetic testing has little effect on TTR or bleeding risk on warfarin, and is not recommended for clinical use at present.[501]

TABLE 4-3 Some Pharmacologic Substrates, Inhibitors, and Inducers of Cytochrome P450 Enzymes (continu

P450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
P450 2C19	Antidepressants Clomipramine Imipramine Proton pump inhibitors Lansoprazole Omeprazole Pantoprazole Others Clopidogrel Propranolol R-Warfarin	Proton pump inhibitors Omeprazole Others Fluoxetine Ritonavir Sertraline	Norethindrone Prednisone Rifampin
P450 2C9	Angiotensin II receptor antagonists Irbesartan Losartan Nonsteroidal anti-inflammatory drugs (NSAIDs) Ibuprofen Suprofen Others S-Warfarin Tamoxifen	Antifungal agents (azoles) Fluconazole Miconazole Others Amiodarone Phenylbutazone	Rifampin Secobarbital
P450 1A2	Antidepressants Amitriptyline Clomipramine Clozapine Imipramine Others R-Warfarin Tacrine	Quinolones Ciprofloxacin Enoxacin Norfloxacin Ofloxacin Others Fluvoxamine	Char-grilled meat Cruciferous vegetables Insulin Omeprazole Tobacco smoke

1972

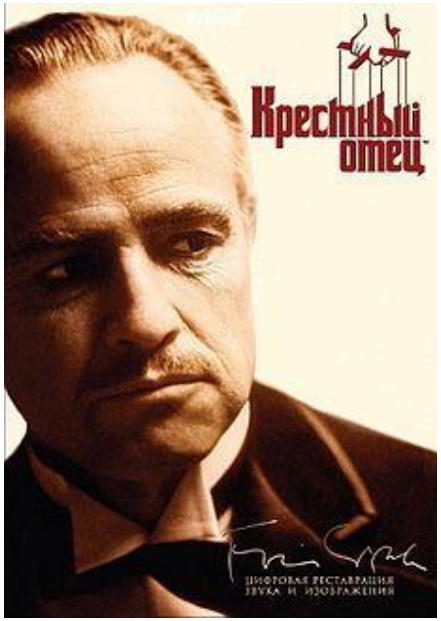


Image from the New York Times.

NB

К-зависимыми являются также синтезируемые печенью антикоагулянты:

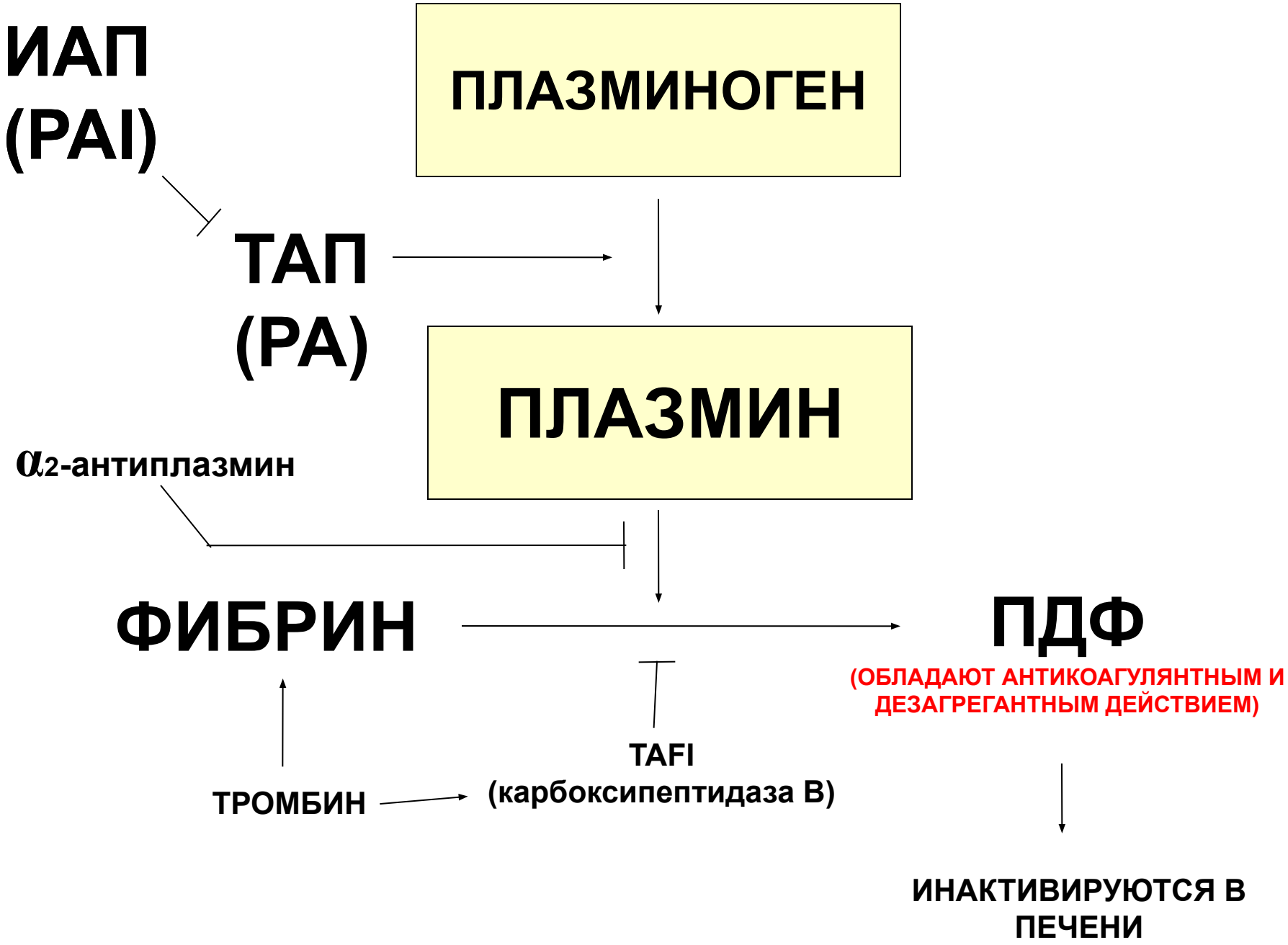
протеин С,

протеин S,

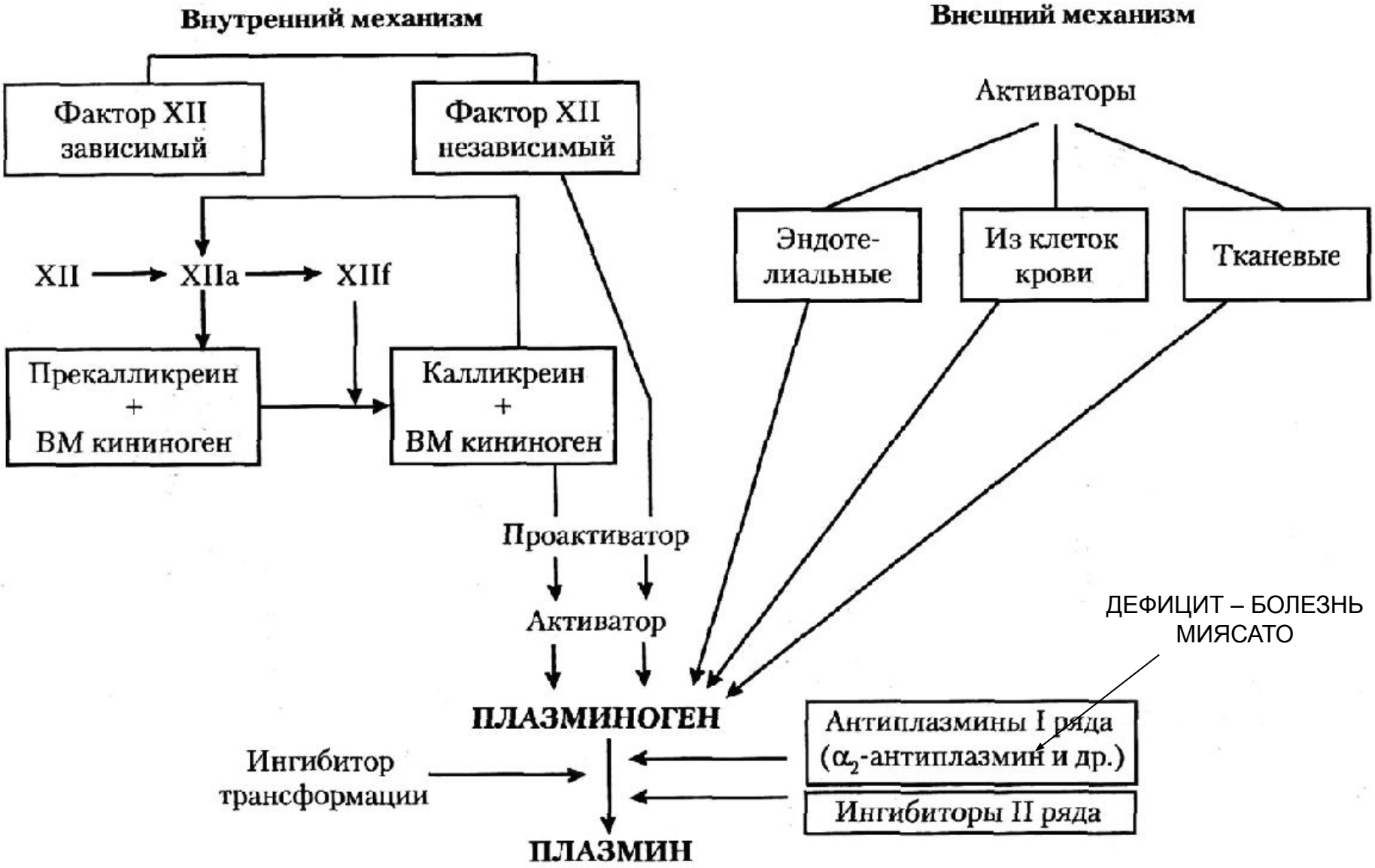
антитромбин (АТ)

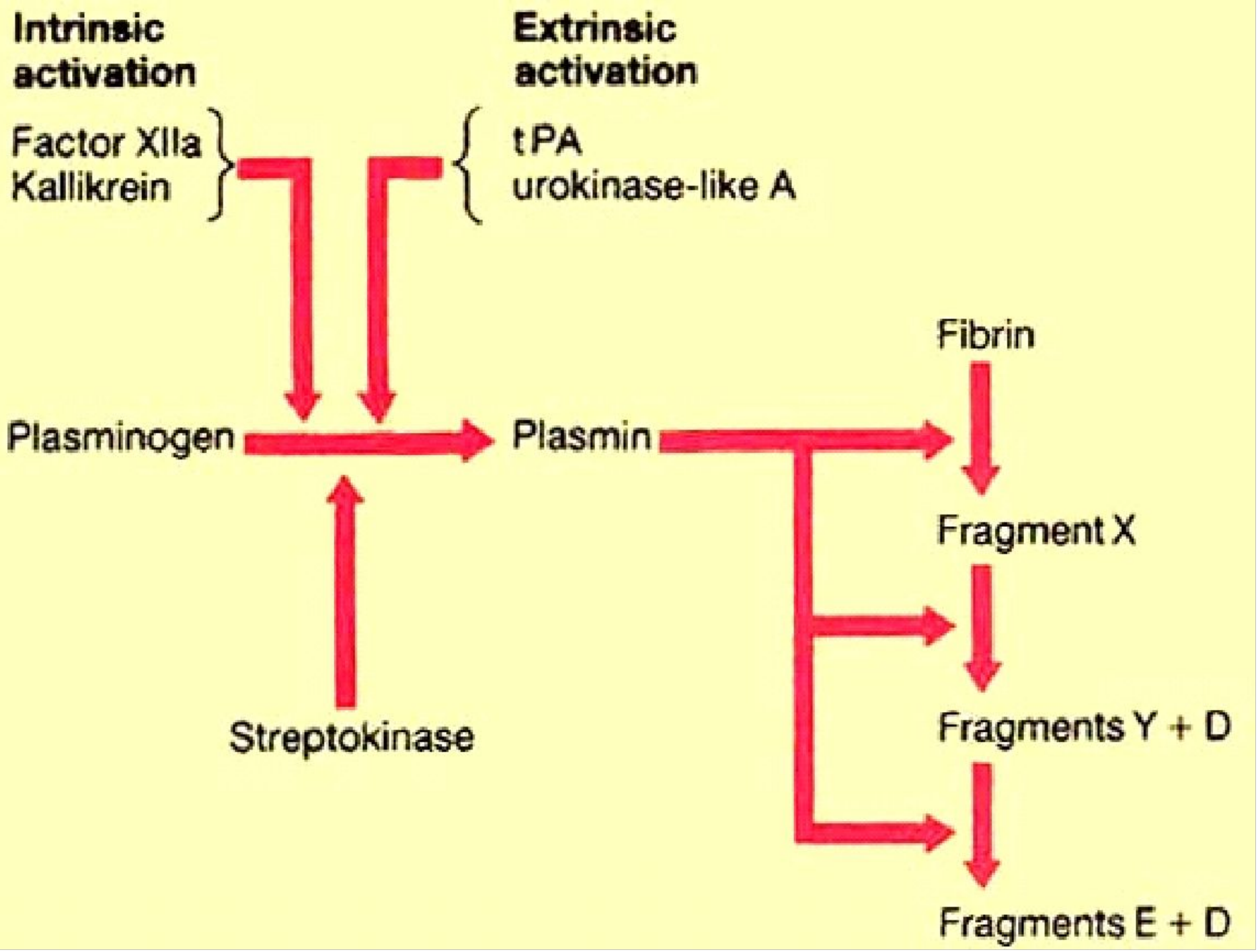
FIGURE 22-14 **ACDR-related cutaneous necrosis: warfarin** Bilateral areas of cutaneous infarction with purple-to-black coloration of the breast surrounded by an area of erythema occurred on the fifth day of warfarin therapy.

ФИБРИНОЛИЗ


ИАП
(PAI)
ПЛАЗМИНОГЕН
ТАП
(PA)
ПЛАЗМИН
α2-антиплазмин
ФИБРИН
ПДФ
(ОБЛАДАЮТ АНТИКОАГУЛЯНТНЫМ И ДЕЗАГРЕГАНТНЫМ ДЕЙСТВИЕМ)
TAFI
(карбоксипептидаза В)
ТРОМБИН
ИНАКТИВИРУЮТСЯ В ПЕЧЕНИ

Основные механизмы фибринолитической системы (А.А.Кишкун, 2007)



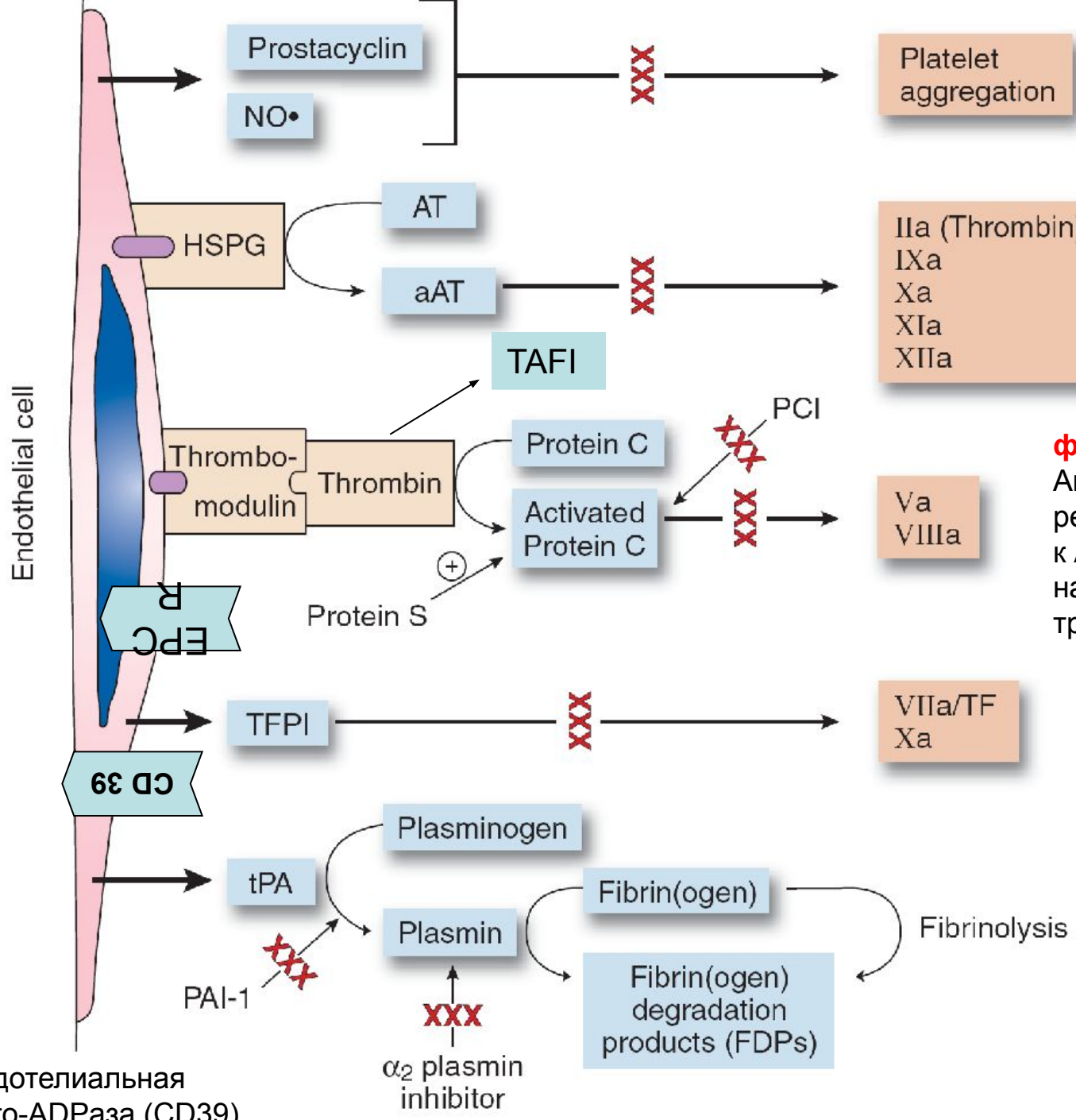

Intrinsic activation
Extrinsic activation
Factor XIIa
Kallikrein
tPA
urokinase-like A
Plasminogen
Plasmin
Fibrin
Fragment X
Fragments Y + D
Fragments E + D
Streptokinase

Plasminogen Activators	Molecular Weight (kd)	Chains	Plasma Concentration (mg/dL)	Plasma Concentration Half-Life ($t_{1/2}$)	Substrates
Endogenous					
Plasminogen	92	2	20	2.2 days	(Fibrin)
Tissue-type PA (t-PA)	68 (59)	1→2	5×10^{-4}	5-8 min	Fibrin/plasminogen
Single-chain urokinase-type PA (scu-PA)	54 (46)	1→2	$2–20 \times 10^{-4}$	8 min	Fibrin/plasmin(ogen)
Urokinase-type PA (u-PA)	54 (46)	2	8×10^{-4}	9-12 min	Plasminogen
Exogenous					
Streptokinase	47	1	0	41 and 30 min	Plasminogen, fibrin(ogen)
Anisoylated plasminogen-streptokinase activator complex (APSAC)	131	Complex	0	70-90 min	Fibrin(ogen)
Staphylokinase	16.5		0		Plasminogen

Inhibitor	Molecular Weight (kd)	Chains	Plasma Concentration (mg/dL^{-1})	Plasma Concentration Half-Life ($t_{1/2}$)	Inhibitor Substrates
Plasmin inhibitors					
α_2-Antiplasmin	65	1	7	3.3 min	Plasmin
α_2-Macroglobulin	740	4	250		Plasmin (excess)
Plasminogen activator inhibitors (PAIs)					
PAI-1	48-52	1	5×10^{-2}	7 min	t-PA, u-PA
PAI-2	47, 70	1	$<5 \times 10^{-4}$	24 hr	t-PA, u-PA
PAI-3	50				u-PA, t-PA

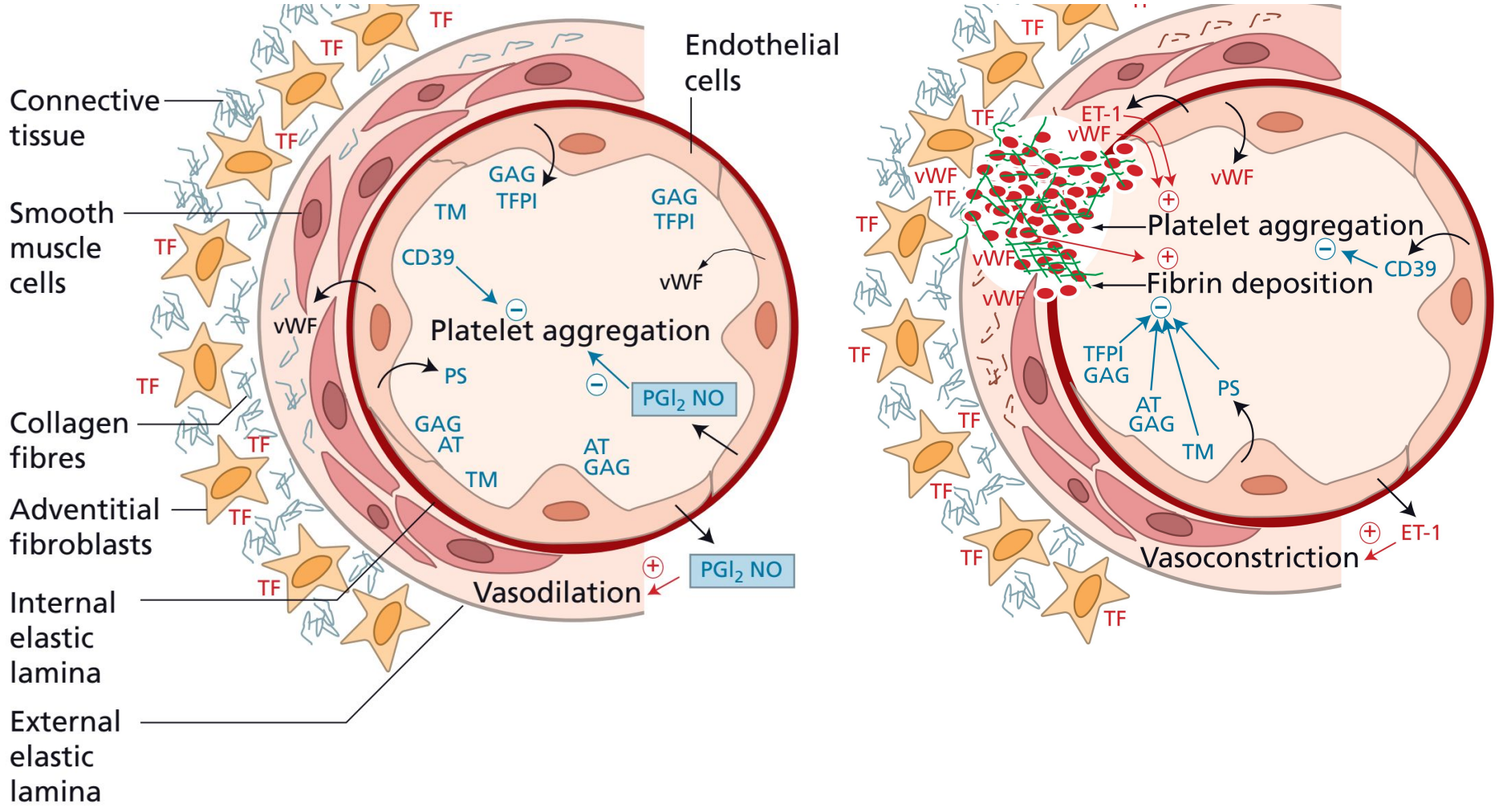
t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator.

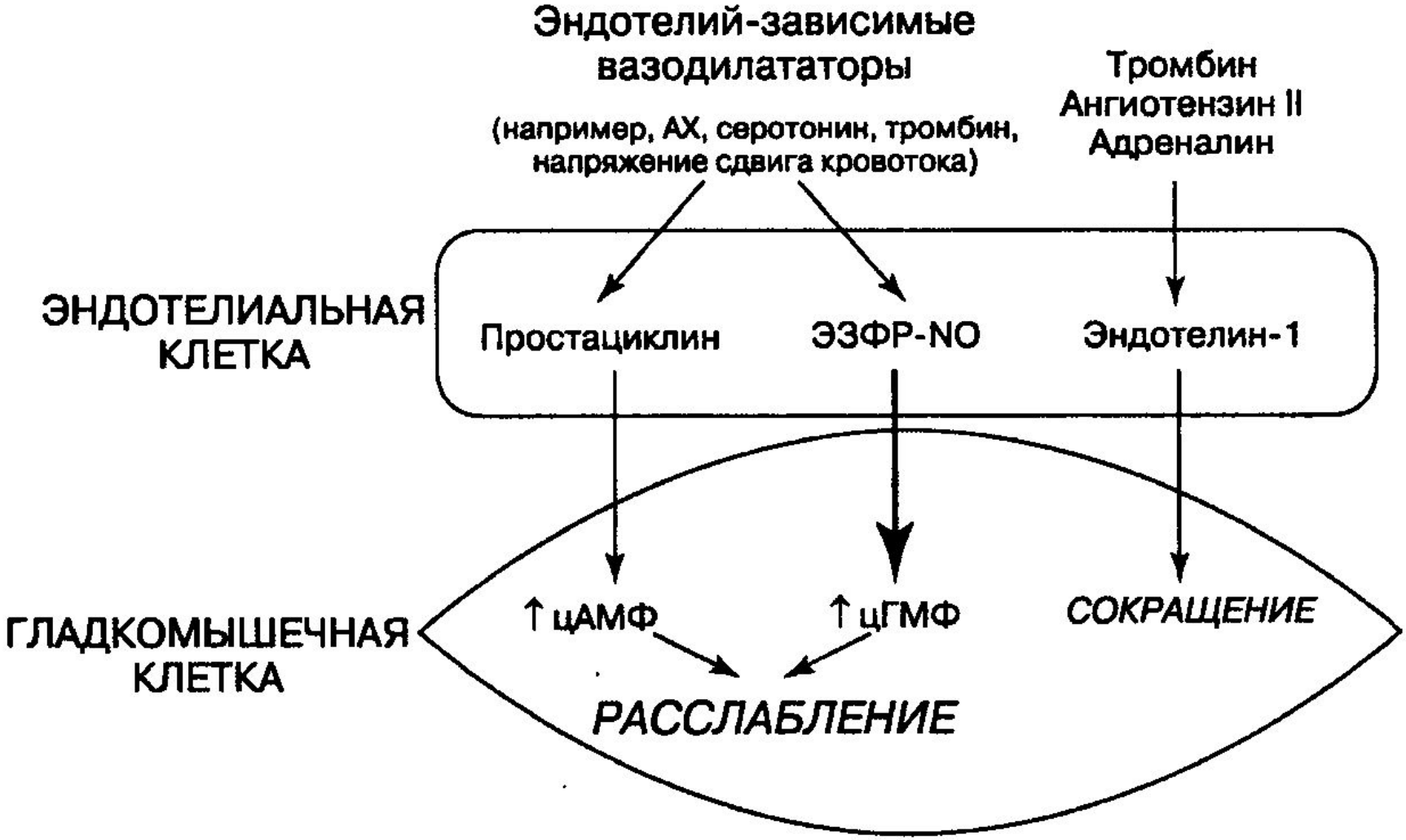
РОЛЬ ЭНДОТЕЛИЯ



эндотелиальная экто-ADPаза (CD39)

фV Лейден (мутация Arg506Gln) – резистентность V фактора к АПС, самая частая наследственная тромбофилия (2-8%)


Connective tissue
Smooth muscle cells
Collagen fibres
Adventitial fibroblasts
Internal elastic lamina
External elastic lamina
Endothelial cells
TF
GAG
TFPI
TM
CD39
vWF
Platelet aggregation
PS
PGI2 NO
GAG
AT
AT
GAG
Vasodilation
ET-1
Fibrin deposition
TFPI
GAG
AT
GAG
TM
PS
Vasoconstriction


Эндотелий-зависимые вазодилататоры
(например, АХ, серотонин, тромбин, напряжение сдвига кровотока)
Тромбин
Ангиотензин II
Адреналин
ЭНДОТЕЛИАЛЬНАЯ КЛЕТКА
Простациклин
ЭЗФР-NO
Эндотелин-1
ГЛАДКОМЫШЕЧНАЯ КЛЕТКА
↑ цАМФ
↑ цГМФ
СОКРАЩЕНИЕ
РАССЛАБЛЕНИЕ

К противосвертывающим факторам плазмы крови относятся: антитромбин (АТ), гепариновый кофактор II (ГК II), протеин С (ПС), протеин S (ПS), ингибитор тканевого фактора (ИТФ), протеаза нексин 2 (ПН-2), протеин Z (ПZ) и ПZ-зависимый ингибитор, С1-ингибитор, а1-антитрипсин (а1-АТ), а2-макроглобулин (а2-М).

По механизму действия ингибиторы свертывания крови относятся к групам :
1- **серпины** - АТ, ГК II, ПZ, С1-ингибитор , а1-АТ (блокируется субстратсвязывающий центр сериновой протеазы и фактор свертывания не вступает в протеолитическую реакцию) ;
2- **кунины** – ИТФ, ПН2, лекарство апротинин (панкреатический ингибитор трипсина);
3- другие: ПС, ПS, а2-макроглобулин, ингибитор “мусорщик” (не связывается со специфическим активным центром протеазы)

Common name	*Abbreviation*	*Subunit*	*Gene symbol*	*Gene location*	*No. of exons*	*Amino acids (mature)*	*M_r of monomer (kDa)*	*Plasma level (μg/mL)*	*Plasma level (nmol/L)*	*$t_{½}$ (hours)*	*Main action*
Tissue factor	TF		*F3*	1p22–p21	6	263	44	NA	NA	NA	Cofactor for FVII/FVIIa
Prothrombin	FII		*F2*	11p11.1	14	579	72	90	1400	65	Clots FBG, activates PC, FXI, TAFI
Factor V	FV		*F5*	1q23	25	2196	330	10	30	15	Cofactor for FXa
Factor VII	FVII		*F7*	13q34	8	416	50	0.5	10	3	Activates FIX and FX
Factor VIII	FVIII		*F8*	Xq28	26	2332	330	0.1	0.3	10	Cofactor for FIXa
Factor IX	FIX		*F9*	Xq27	8	415	56	5	90	25	Activates FX
Factor X	FX		*F10*	13q34	8	445	59	8	135	40	Activates prothrombin
Factor XI	FXI		*F11*	4q35	15	607	80*	5	30	45	Activates FIX
Prekallikrein	PK		*KLKB1*	4q35	15	638	86	50	580	35	Anti-angiogenic, profibrinolytic
Factor XIII† (A chain)	FXIII	A	*F13A1*	6p25.3–p24.3	15	731	75†	10	30	200	Cross-links fibrin
Factor XIII† (B chain)	FXIII	B	*F13B*	1q31	12	641	80†	10	30	200	Cross-links fibrin
Fibrinogen (α-chain)‡	FGN	α	*FGA*	4q28	6	866	68‡	3000	9000	90	Mechanical stabilization of clot
Fibrinogen (β-chain)‡	FGN	β	*FGB*	4q28	8	491	52‡	3000	9000	90	Mechanical stabilization of clot
Fibrinogen (γ-chain)‡	FGN	γ	*FGG*	4q28	10	453	49‡	3000	9000	90	Mechanical stabilization of clot
von Willebrand factor	VWF		*VWF*	12p13.3	52	2050	255	10	40	12	Cell adhesion and FVIII carrier
Thrombomodulin	TM		*THBD*	20p11.2	1	557	60	NA	NA	NA	Cofactor in PC/TAFI activation

*FXI circulates as a 160-kDa homodimer of two 80-kDa monomers.

†FXIII circulates as a 326-kDa tetramer of two A- and two B-chains.

‡Fibrinogen circulates as a 340-kDa complex of two each of A-, B- and C-chains.

Endothelial protein C receptor	EPCR	*PROCR*	20q11.2	7	220	27	NA	NA	NA	Cofactor in PC activation
Protein C	PC	*PROC*	2q13–14	9	419	62	4	65	6	Inactivation of FVa and FVIIIa
Protein S	PS	*PROS1*	3q11.2	15	676	69	10 (free)	145	?	Inactivation of FVa and FVIIIa
Tissue factor pathway inhibitor	TFPI	*TFPI*	2q32	12	304	42	0.08	2.5	?	Inhibition of coagulation initiation
Antithrombin	AT	*SERPINC1*	1q23–q25.1	9	464	58	140	2400	5	Inhibits thrombin, FIX, FX, FXI
Heparin cofactor II	HCII	*SERPIND1*	22q11.21	5	499	66	90	1200	60	Prevention of arterial thrombosis?
Plasminogen	PLG	*PLG*	6q26	14	791	92	200	2000	50	Dissolution of clot in wound repair
Tissue plasminogen activator	tPA	*PLAT*	8p12	14	562	69	0.005	0.07	0.03	Plasma activator of plasminogen
Prourokinase	UK	*PLAU*	10q24	11	431	54	0.0015	0.04	0.03	Tissue activator of plasminogen
Plasminogen activator inhibitor 1	PAI-1	*SERPINE1*	7q21.3–q22	9	379	52	10	200	0.1	Inhibition of tPA and uPA
α_2-Antiplasmin	α_2-AP	*SERPINF2*	17p13	9	452	67	70	1000	72	Inhibition of plasmin
Thrombin-activatable fibrinolysis inhibitor	TAFI	*CPB2*	13q14.11	11	401	60	5	75	0.2	Inhibition of fibrinolysis

Изменение параметров гемостаза при беременности

Platelet count	No consistent change but often falls
Platelet aggregation	Progressive enhancement
Fibrinogen	Progressive rise up to 400% basal
Prothrombin	No consistent change
Factor V	No consistent change
Factor VII	Progressive rise up to 300% basal
Factor VIII	Progressive rise up to 200% basal
von Willebrand factor	Progressive rise up to 250% basal
Factor IX	Variable, no consistent change
Factor X	No consistent change
Factor XI	Variable, no consistent change
Factor XIII	Progressive fall to 50% basal

Изменение параметров гемостаза при беременности

Antithrombin	No consistent change
Tissue factor pathway inhibitor	Progressive rise
Protein C	No consistent change, but APC resistance increases
Protein S	Progressive fall to 50% basal
Plasminogen	Progressive rise up to 300% basal
tPA	No consistent change
α_2-Antiplasmin	Progressive rise up to 300% basal
PAI-1	Progressive rise up to 300% basal
PAI-2	Progressive marked rise