



Search

Serum vs. plasma

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Kristine Krafts, M.D.

University of Minnesota School of Medicine  
The story behind Pathology Student

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A short, awesome  
pathology newsletter  
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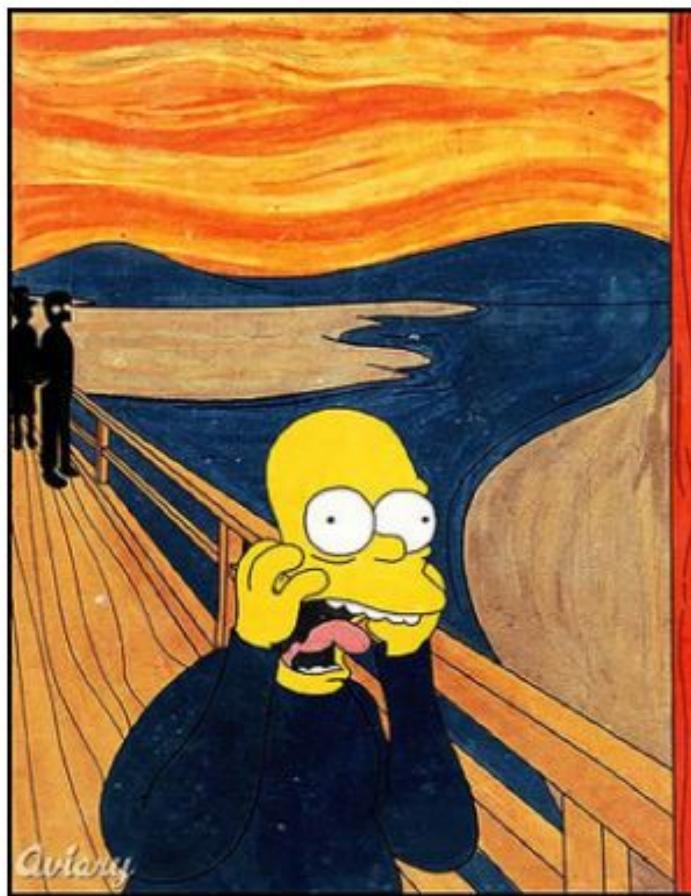
## Blog Posts

Never miss a post!

Name:

## My pathology class starts tomorrow – help!

on AUGUST 26, 2016

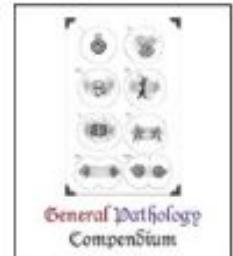
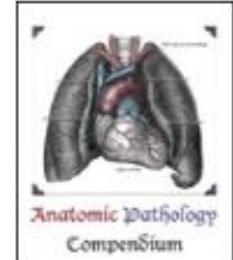
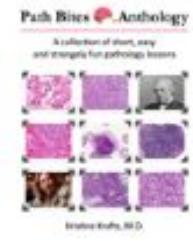
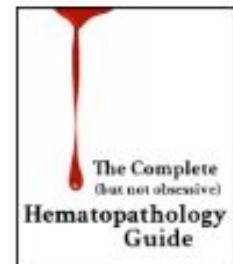
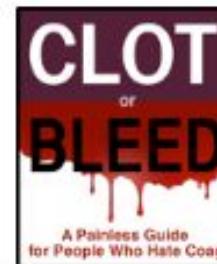


*Cervix*

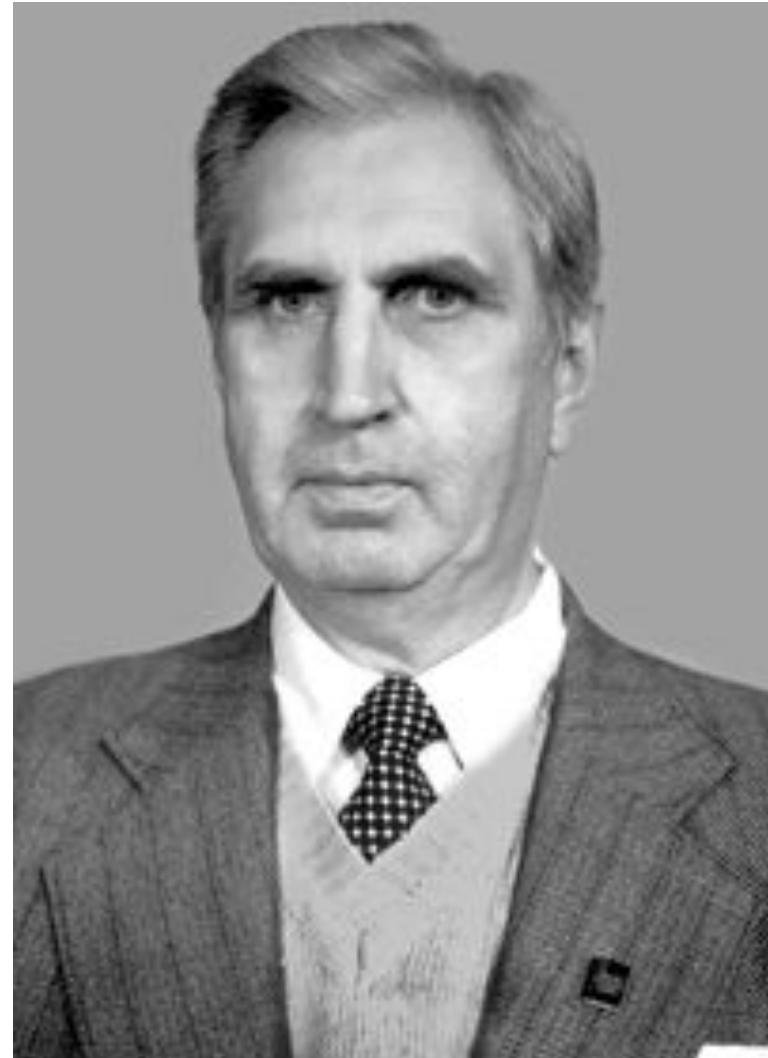
Tomorrow is the first day of classes for a lot of medical, dental, nursing, physician assistant, medical technology, veterinary, and other allied health students. Most of you will be faced with the beginning of a pathology course tomorrow (or if not tomorrow, soon). And except for a

## Need path help?

We've got simple explanations  
for complicated topics.



I feel like I have learned more in 1 hour from



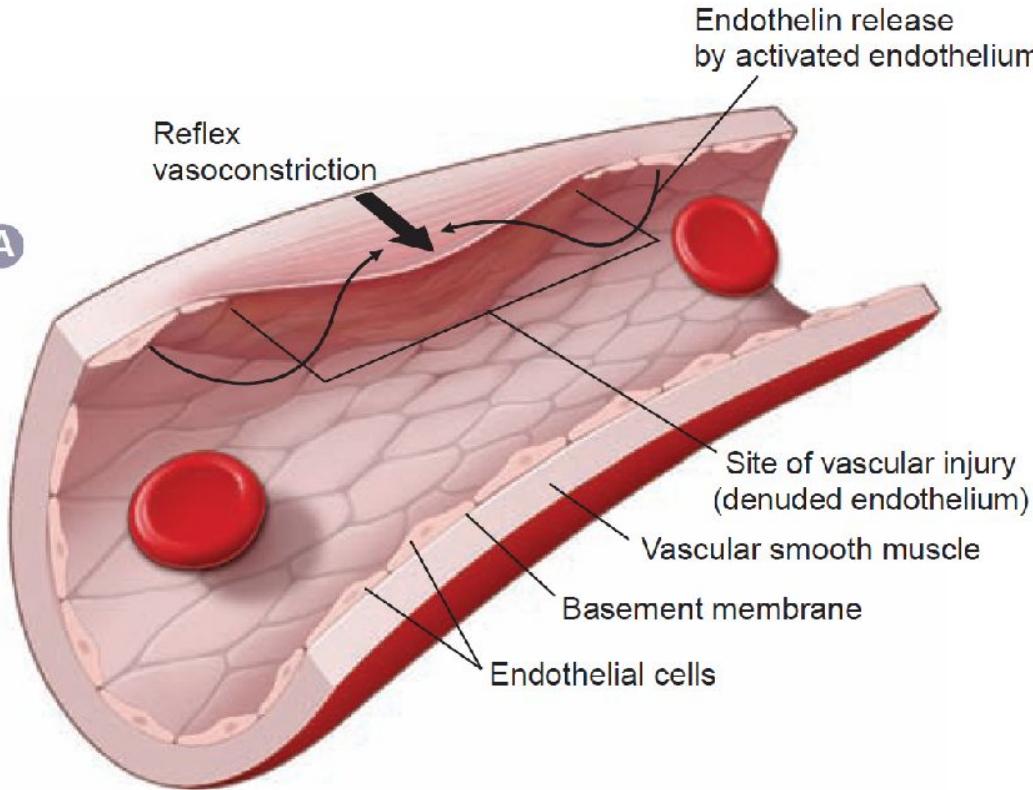
Виктор Петрович Балуда (1924 — 2002)



**Зиновий Соломонович Баркаган**  
**(1925— 2006)**



Исидор Абрамович Ойвин (1909 — 1972)

**A**

Reflex  
vasoconstriction

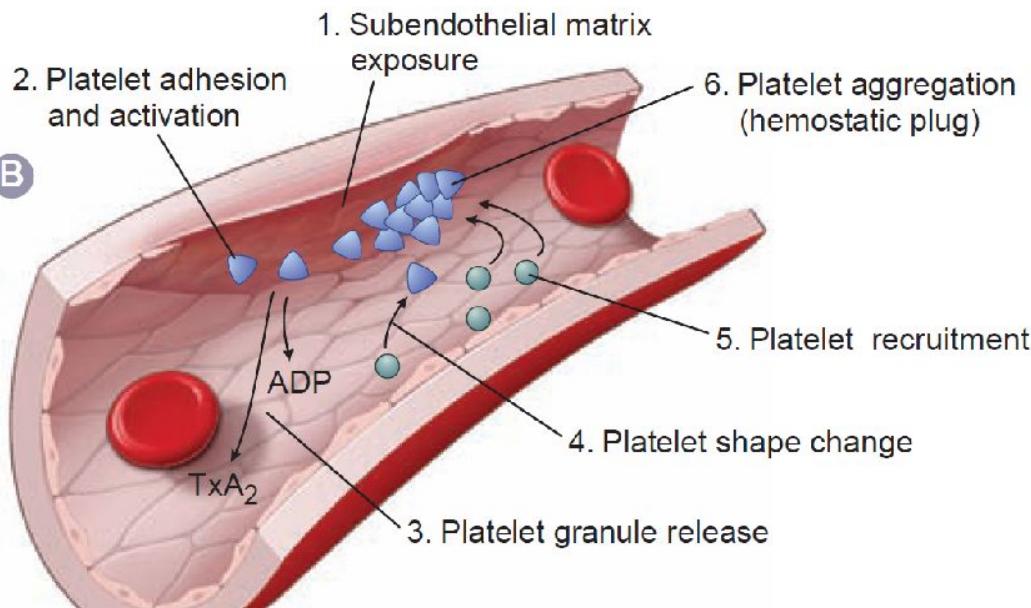
Endothelin release  
by activated endothelium

Site of vascular injury  
(denuded endothelium)

Vascular smooth muscle

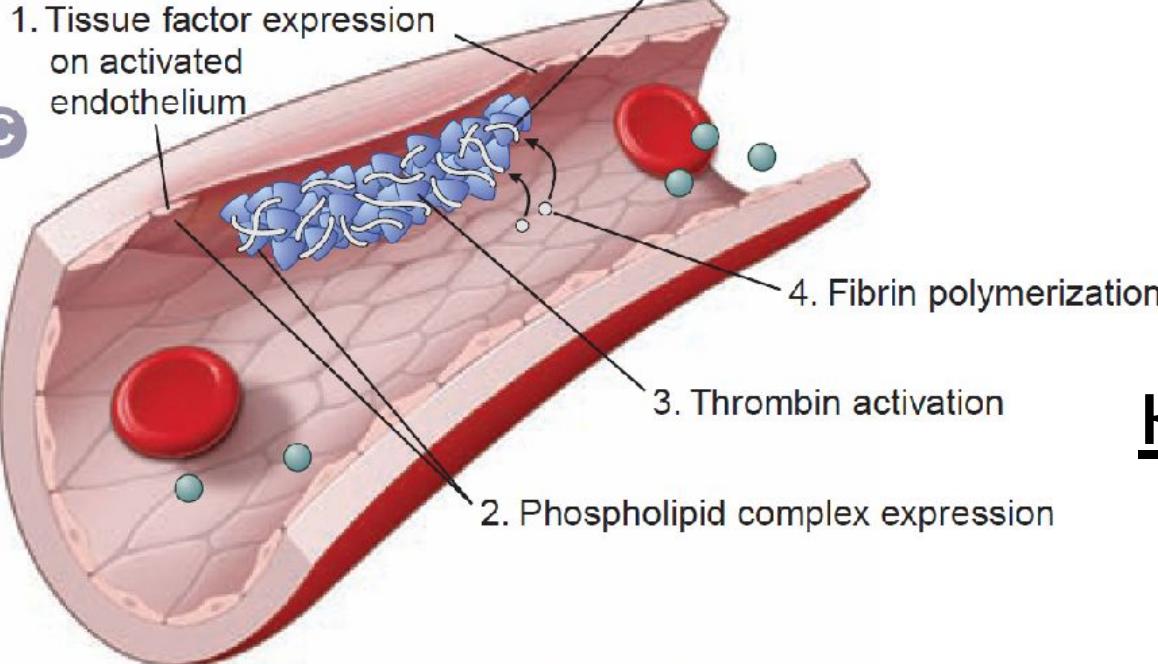
Basement membrane

Endothelial cells

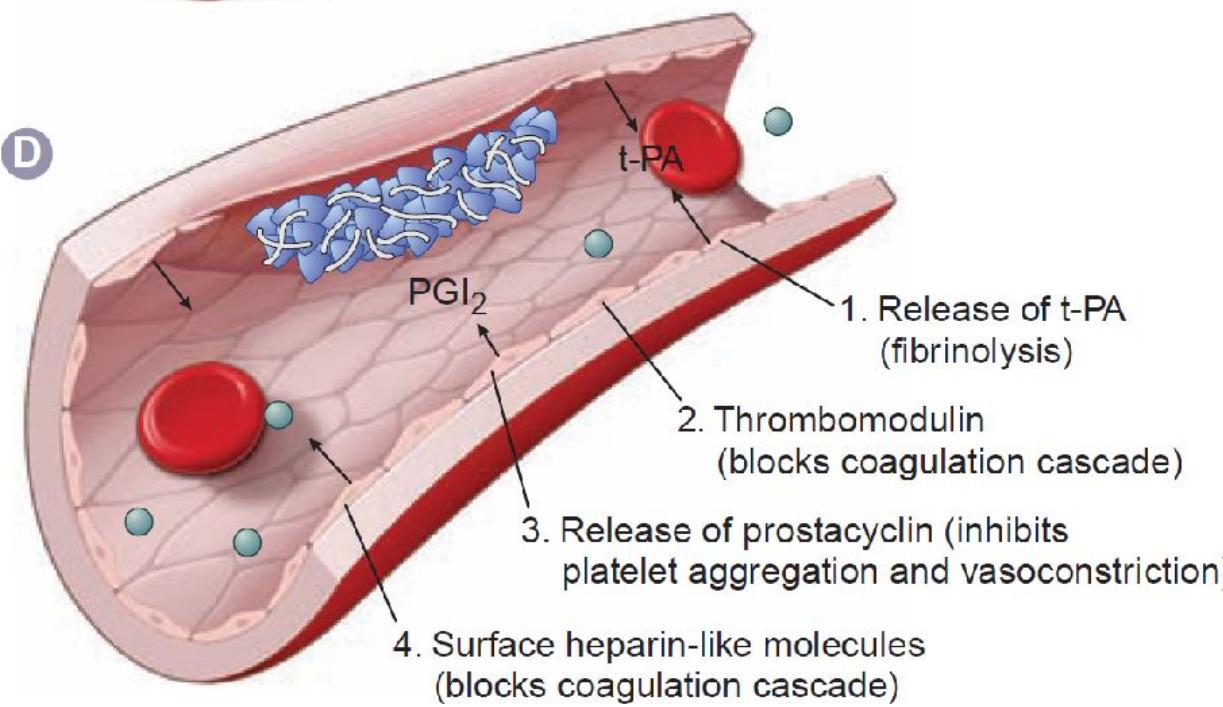
**B**

# сосудистая фаза

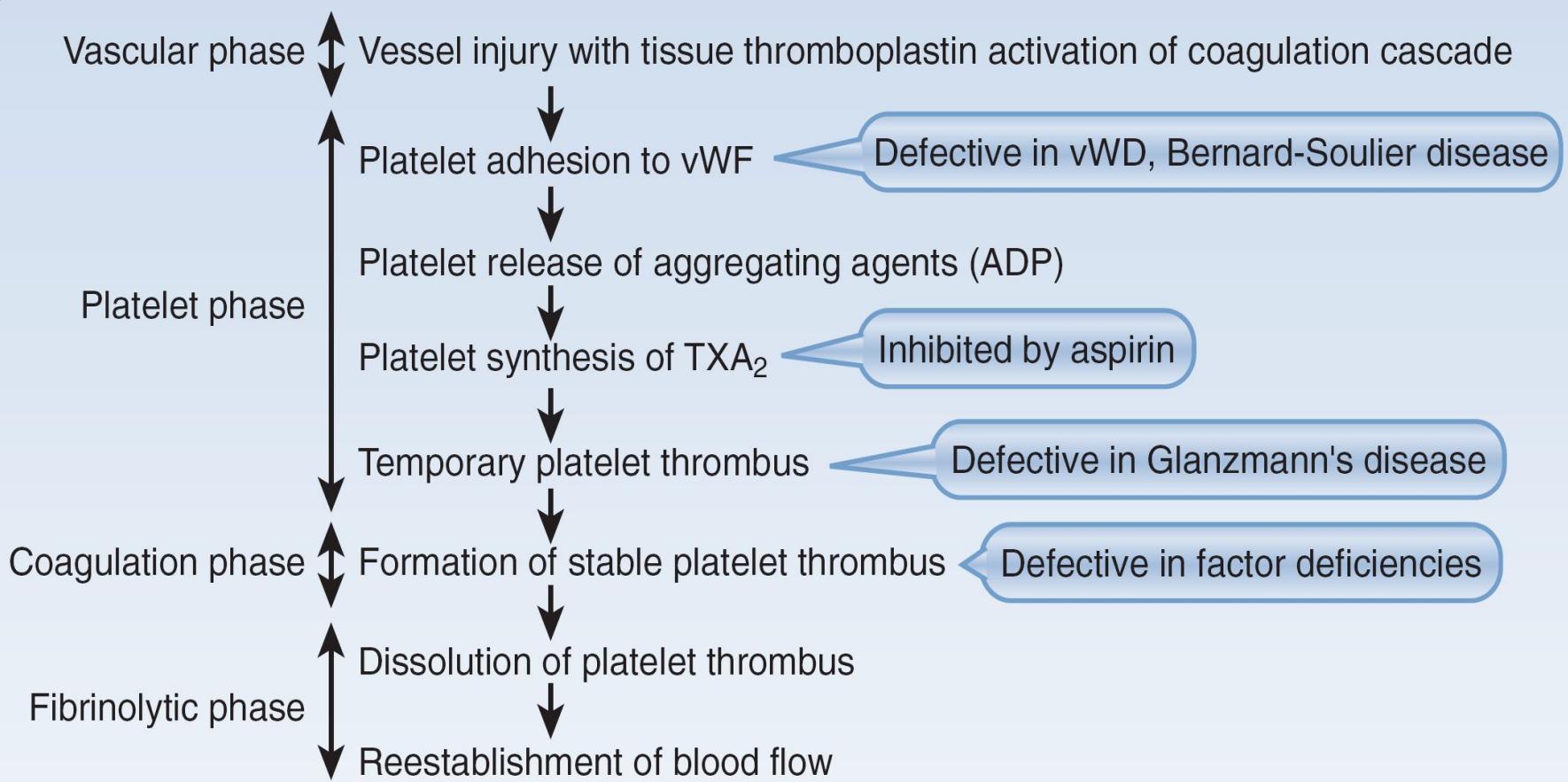
# тромбоцитарная фаза



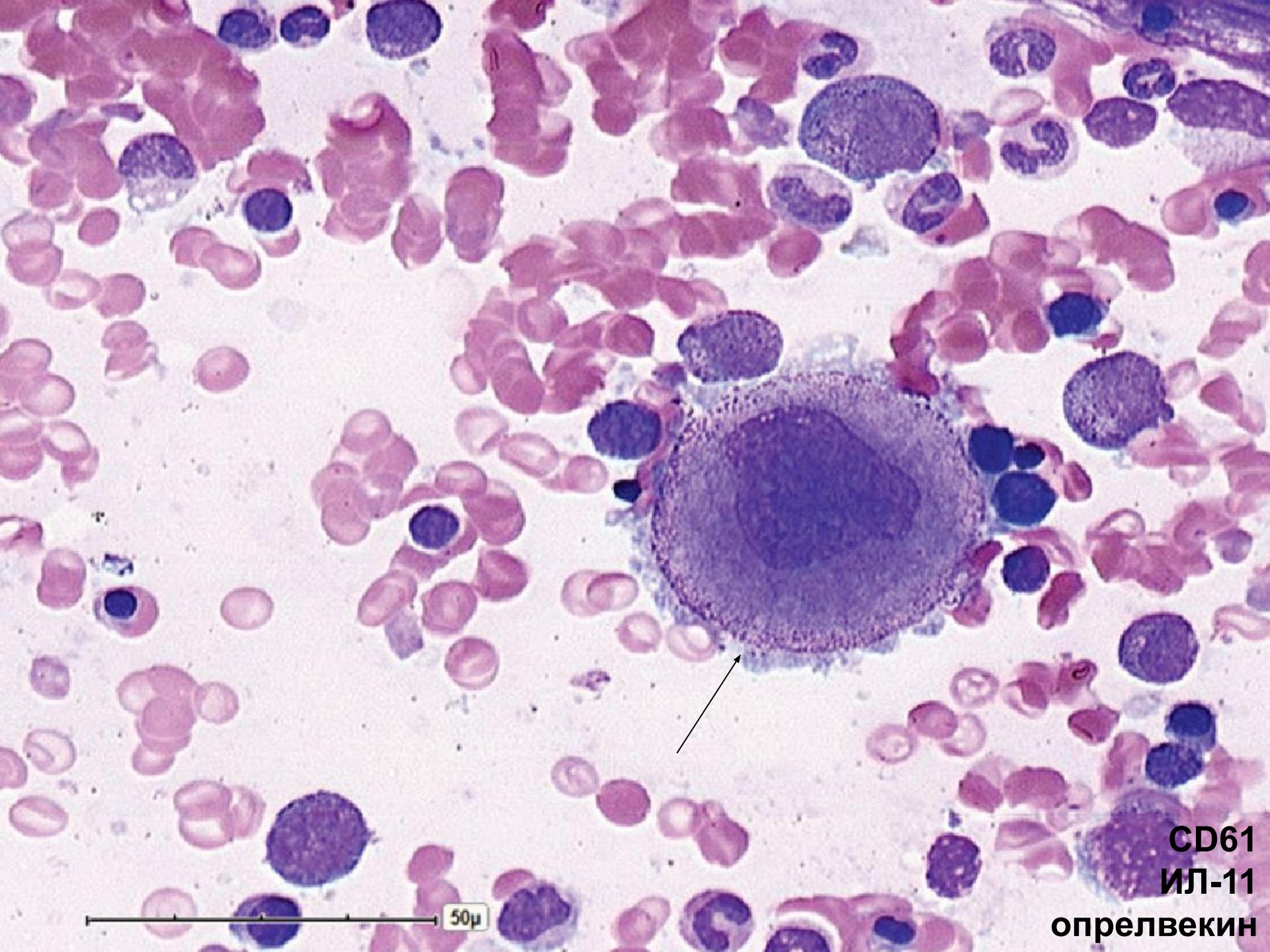
## коагуляционная фаза



## фибринолиз



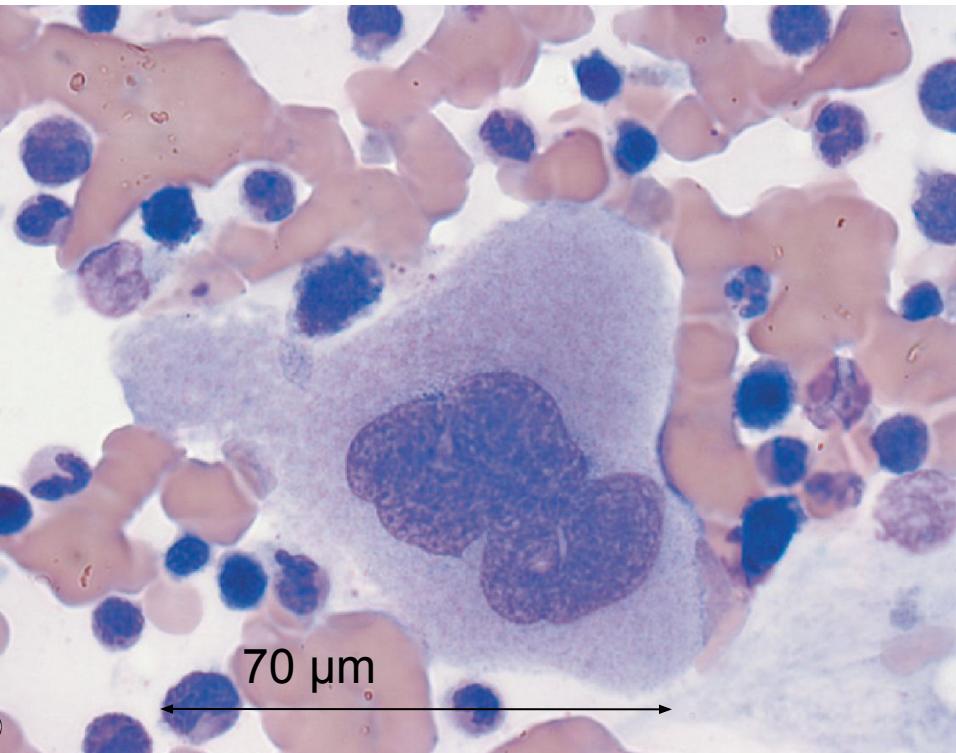
# ТРОМБОЦИТЫ



CD61  
ИЛ-11  
опрелвекин

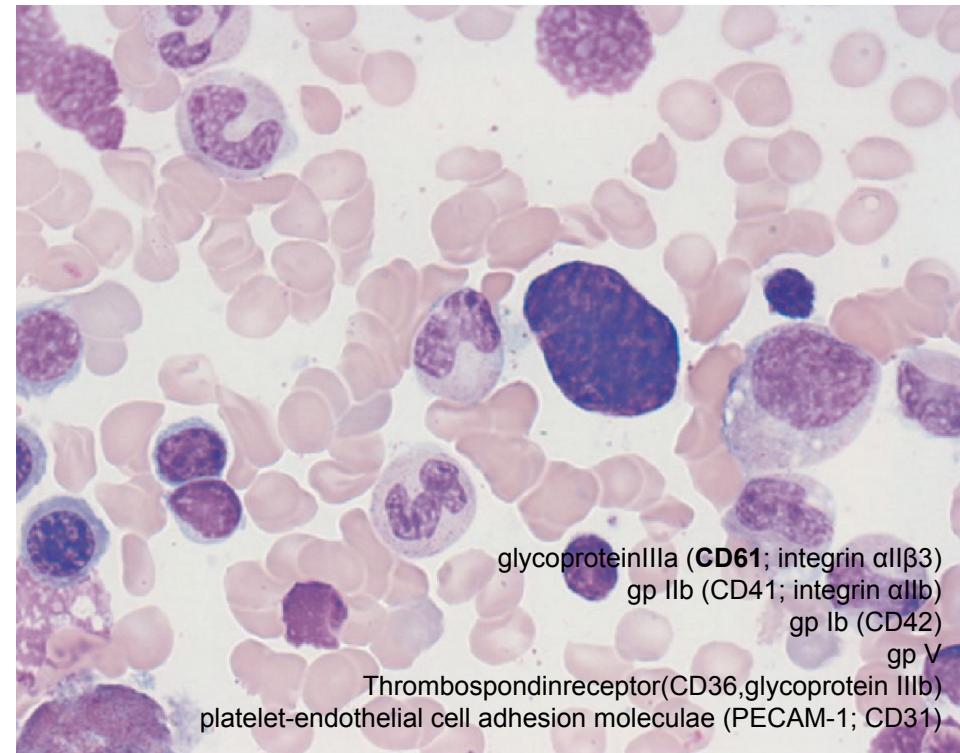
50 $\mu$

# Мегакариоциты

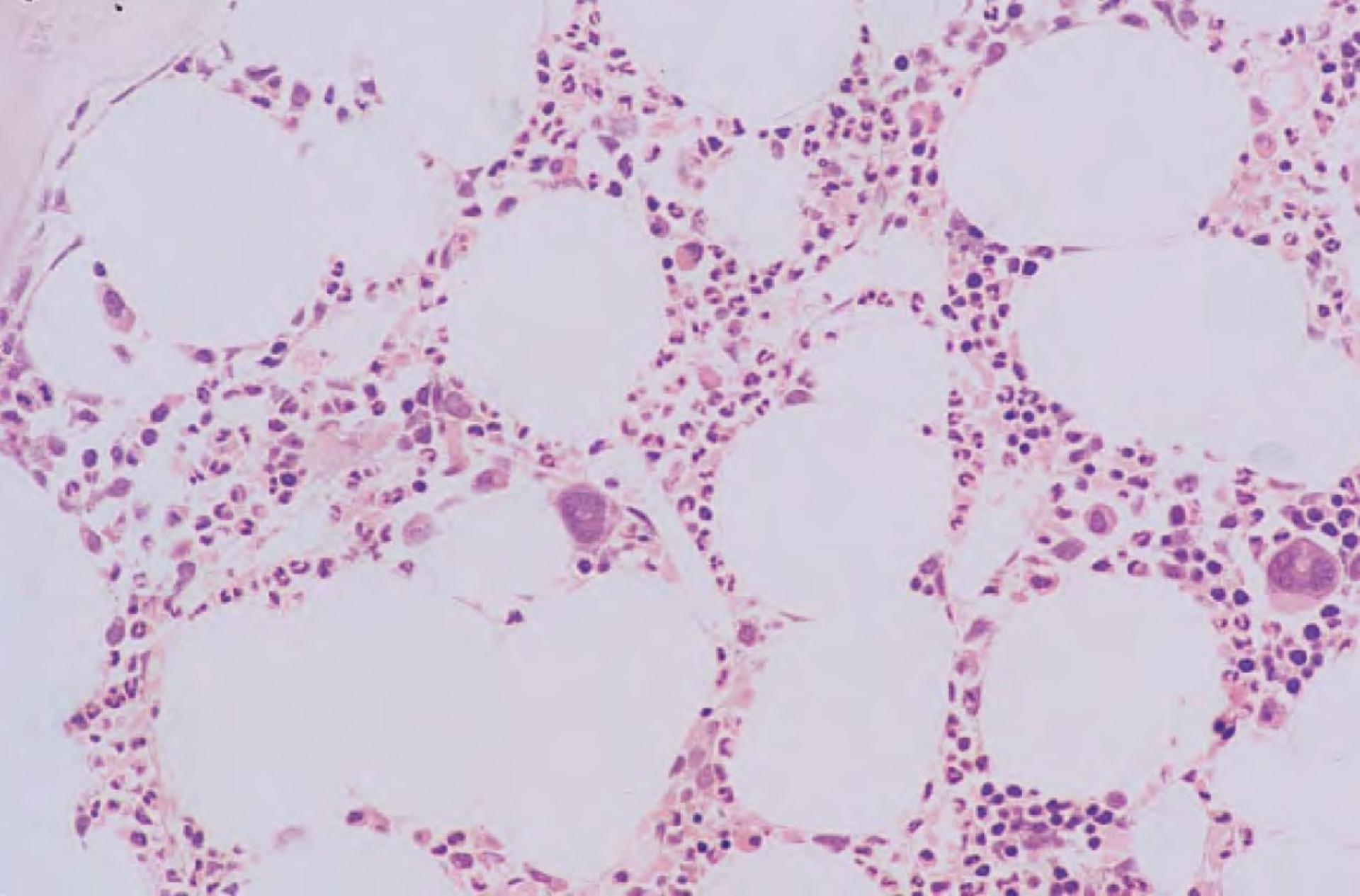


III

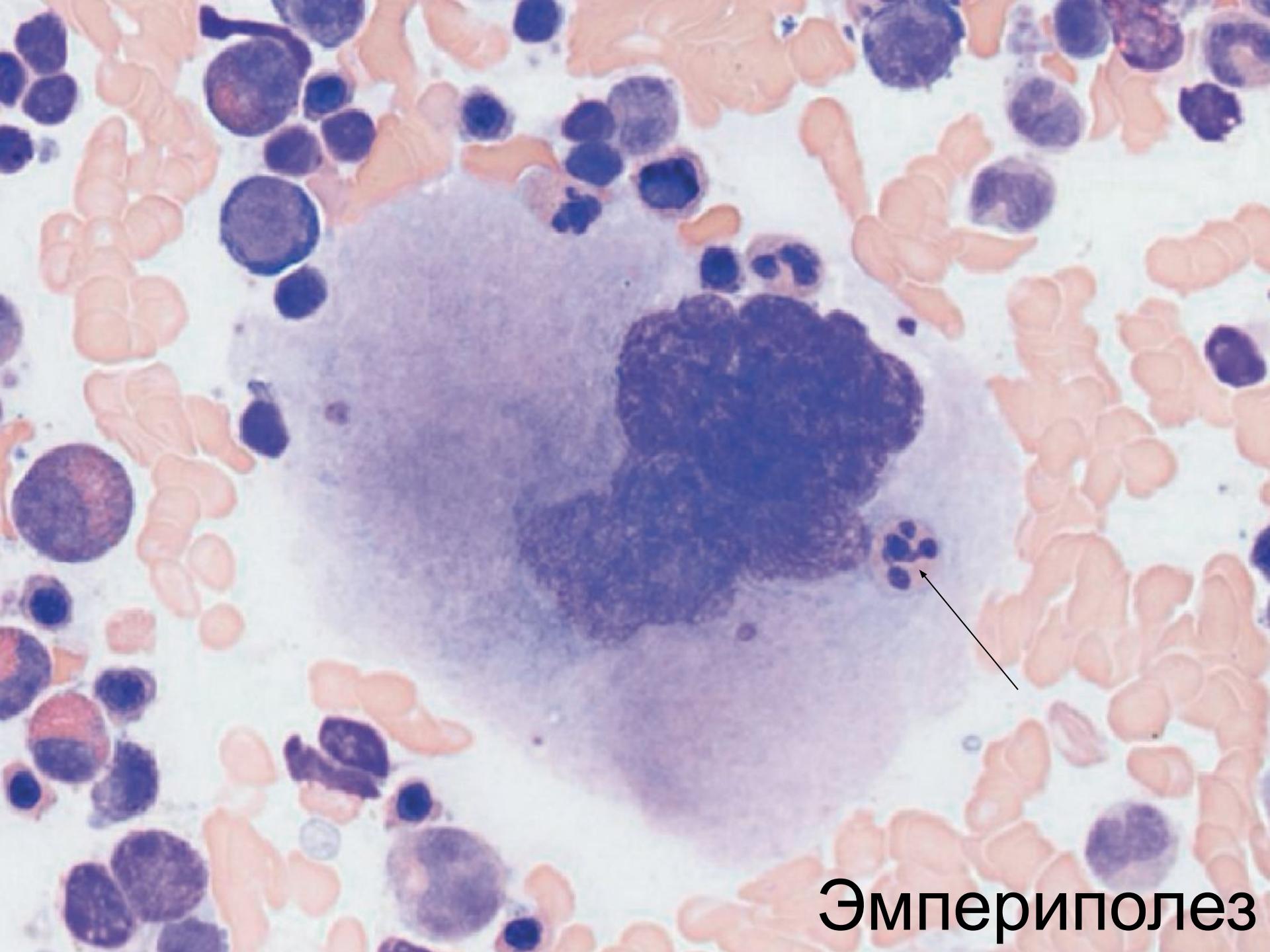
1. megakaryoblasts (group I megakaryocytes)
2. promegakaryocytes (group II megakaryocytes)
3. granular megakaryocytes (group III megakaryocytes)  
which produce platelets
4. 'bare' nuclei.



«bare» nuclei



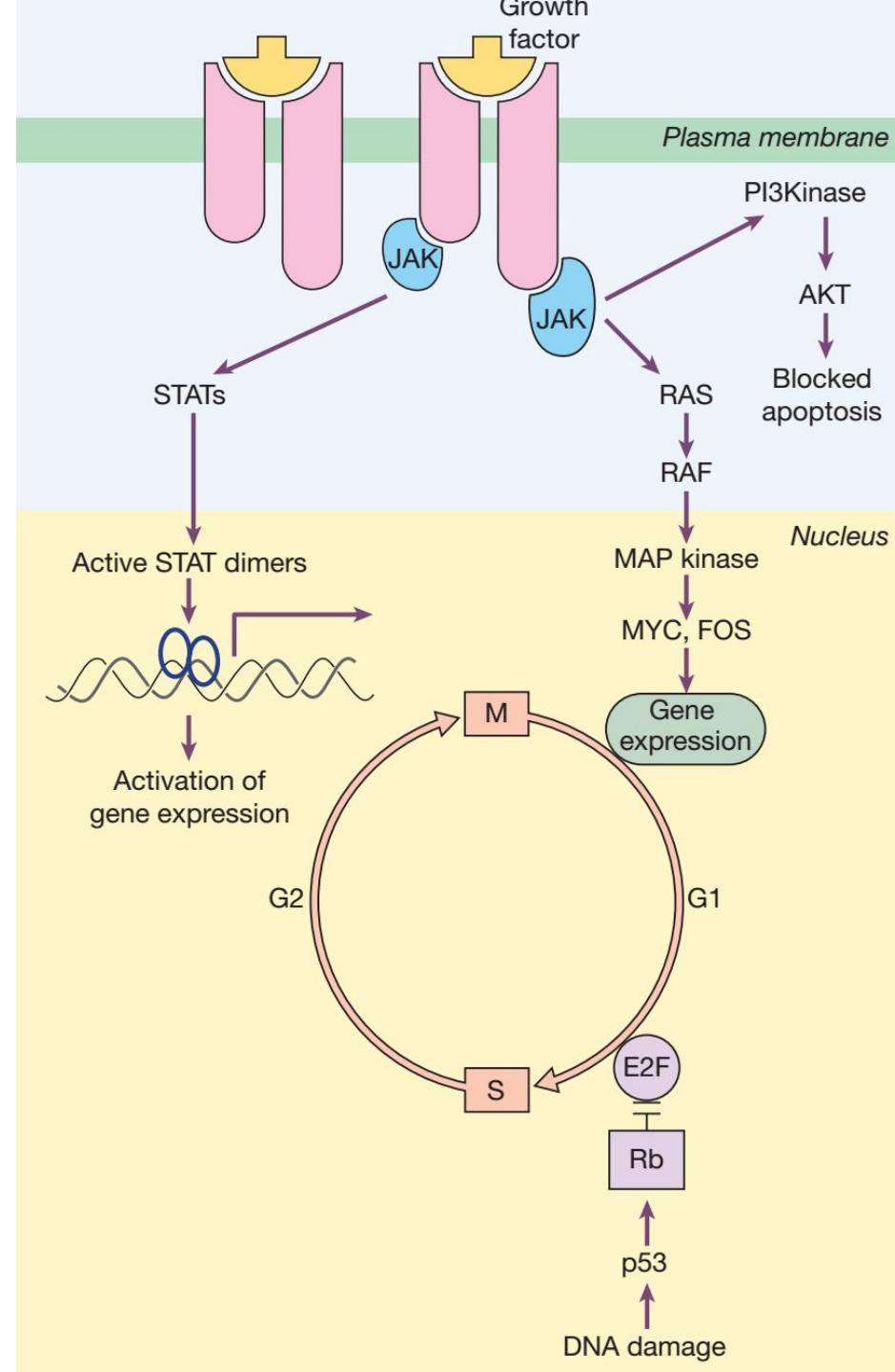
normal distribution of all three haemopoietic lineages  
megakaryocyte adjacent to a sinusoid  
Resin - embedded, H & E  $\times 20$



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.

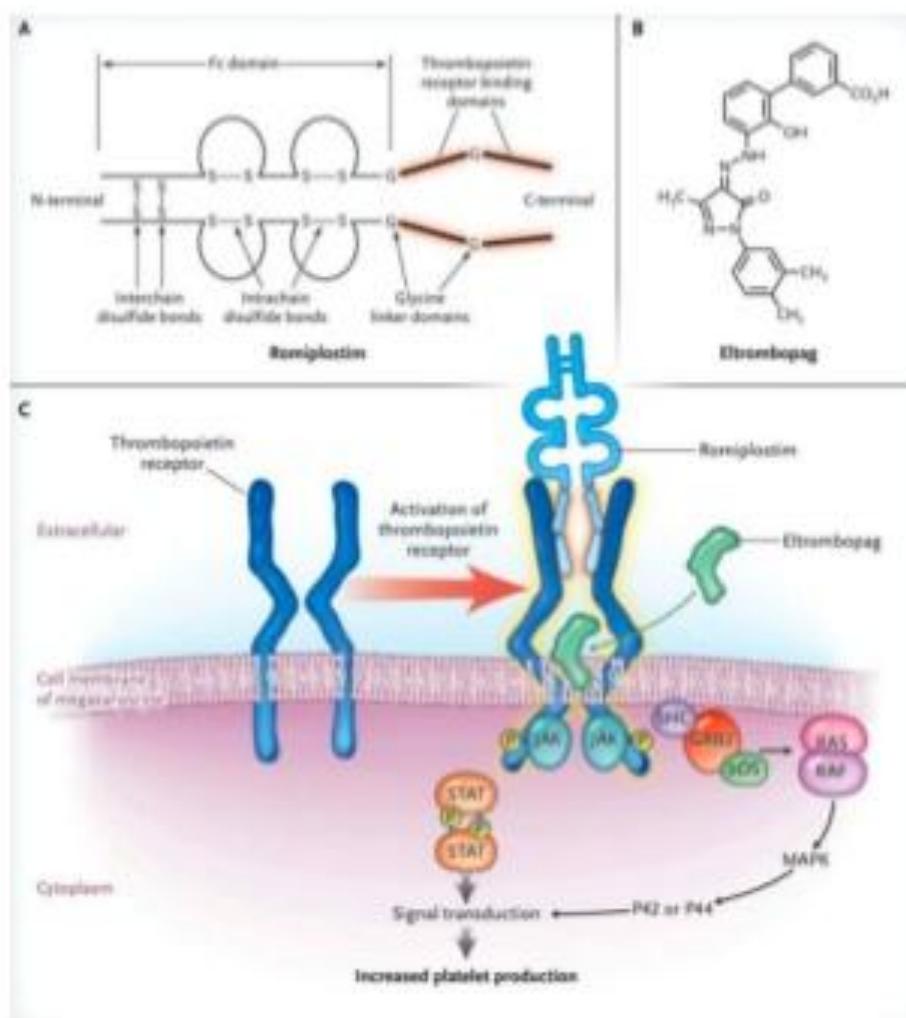


# Thrombopoietin-Receptor Agonists for Primary Immune Thrombocytopenia

NEJM. 2011

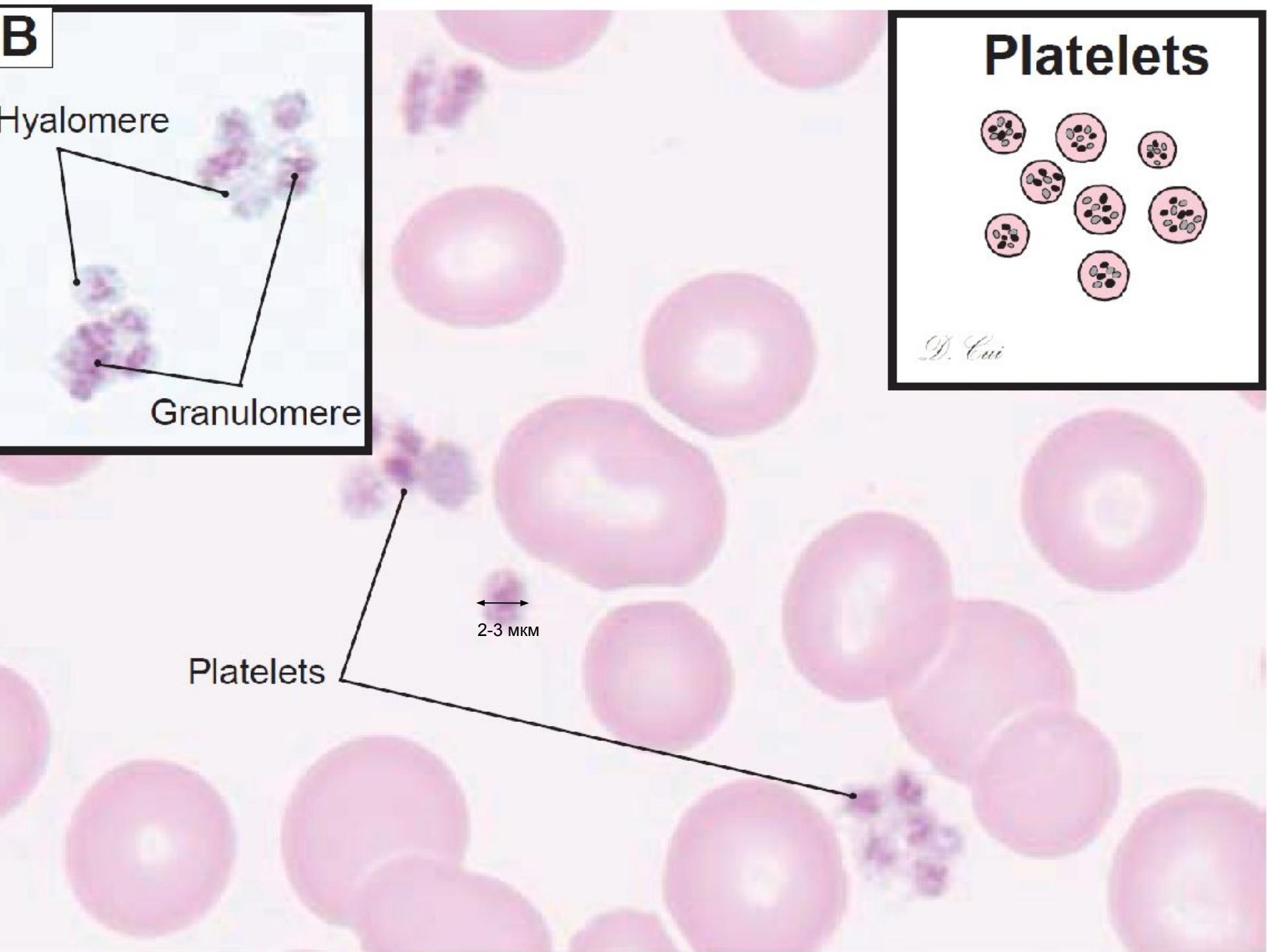
- **Eltrombopag**

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

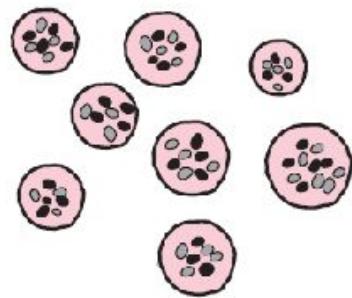


- **Romiplostim**

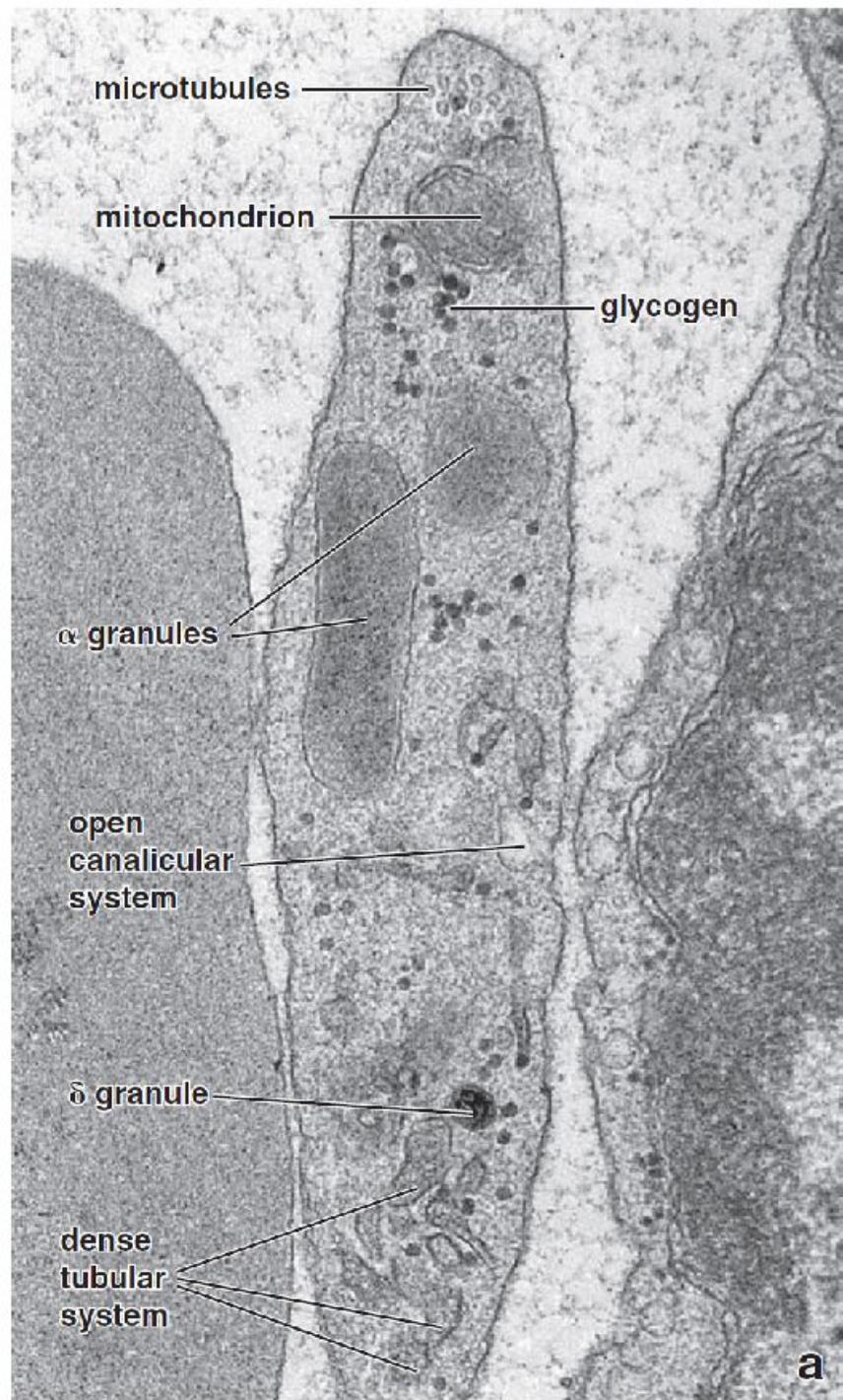
- An Fc-peptide fusion protein (peptibody)
- Increases platelet production through binding and activation of the thrombopoietin (TPO) receptor – similar mechanism to endogenous TPO

**B**

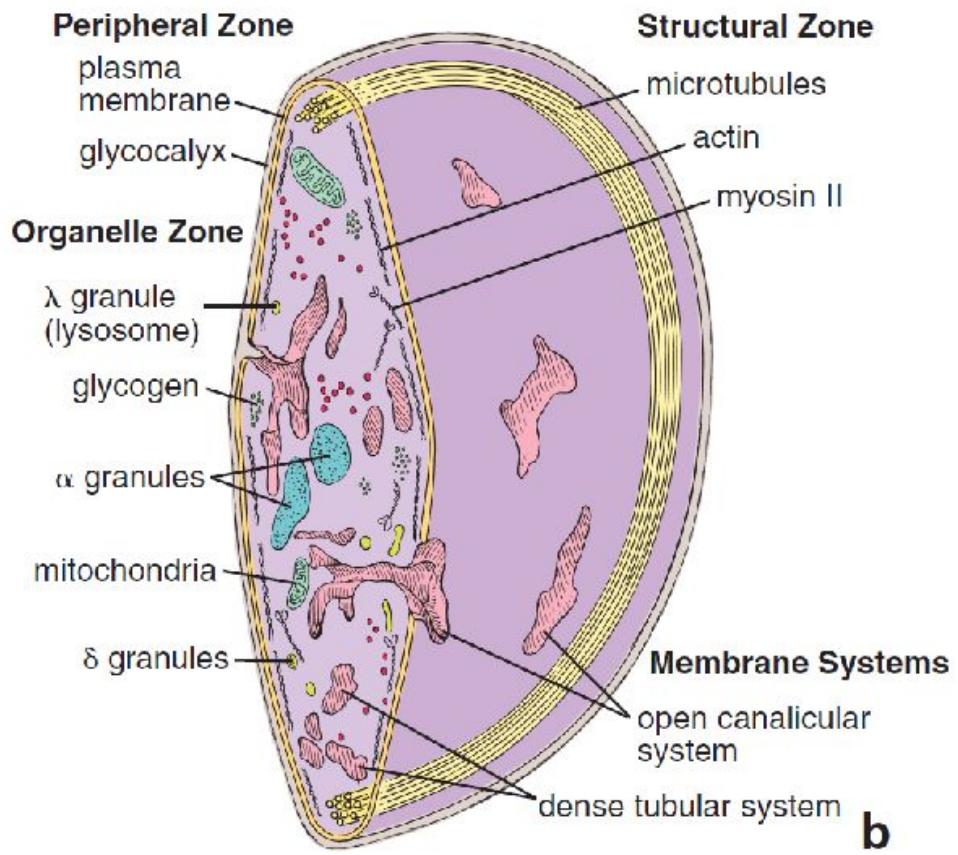
## Platelets

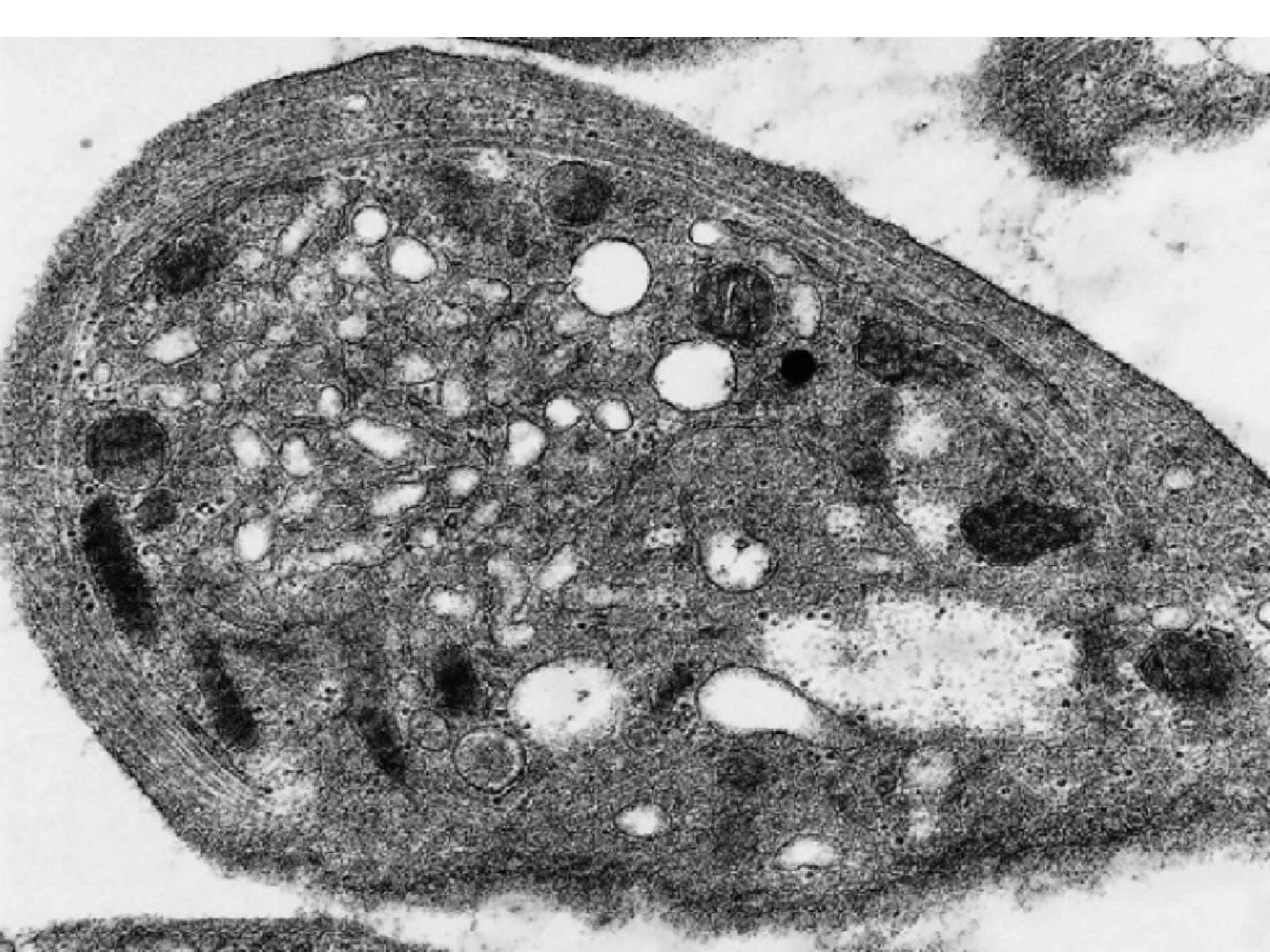


*D. Cui*



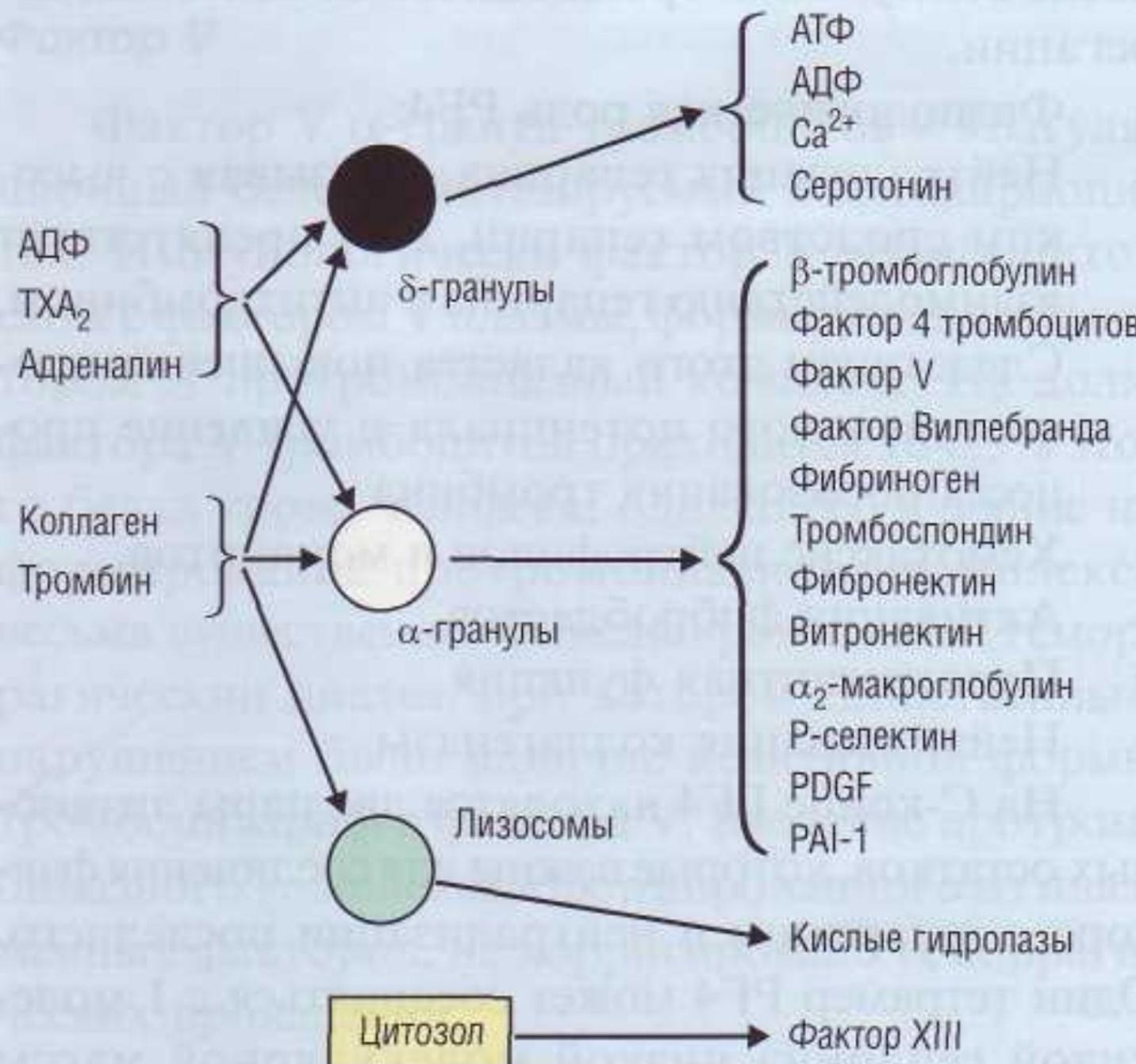
**синдром серых тромбоцитов –**  
отсутствие  $\alpha$  гранул  
**Квебекский синдром –** деградация  $\alpha$  гранул  
**синдром Германского-Пудлака –**  
отсутствие плотных гранул (+ альбинизм, лизосомальные дефекты)





## Активаторы

## Секретируемые компоненты



## 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 I <sub>b</sub> -V-IX
Коллаген	ГП VI, ГП Ia-IIa
АДФ	P2Y12, P2Y2
Тромбоксан А2	TP receptor
Адреналин	α2-адренорецептор
фактор Виллебранда	ГП I <sub>b</sub> -V-IX

А также: 5-HT<sub>2A</sub>, 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

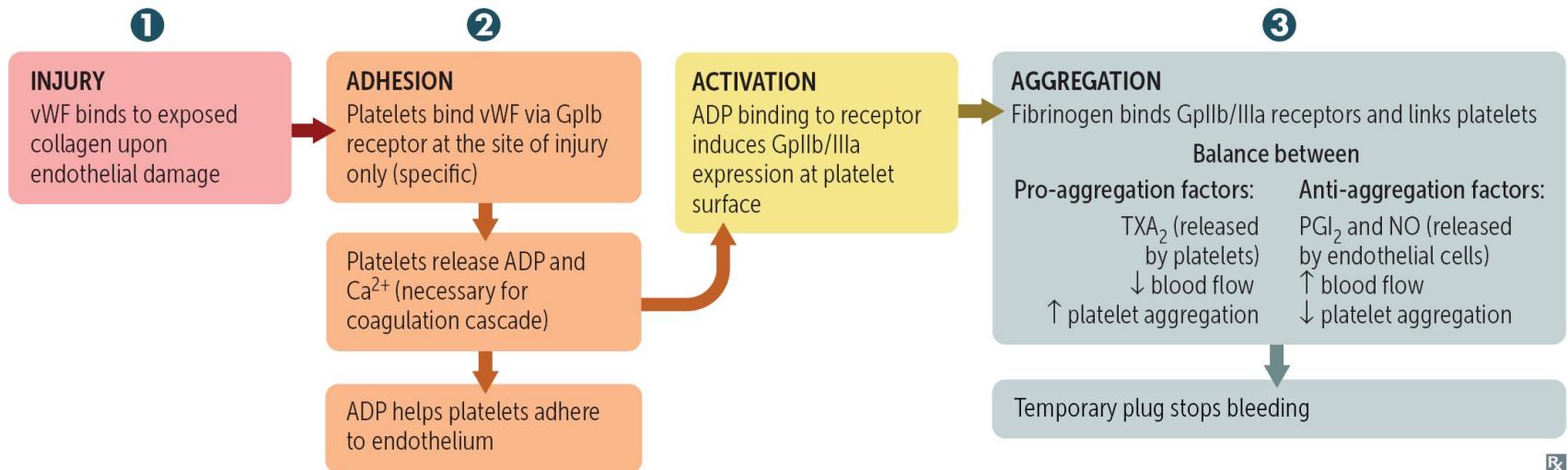
### Inflammation

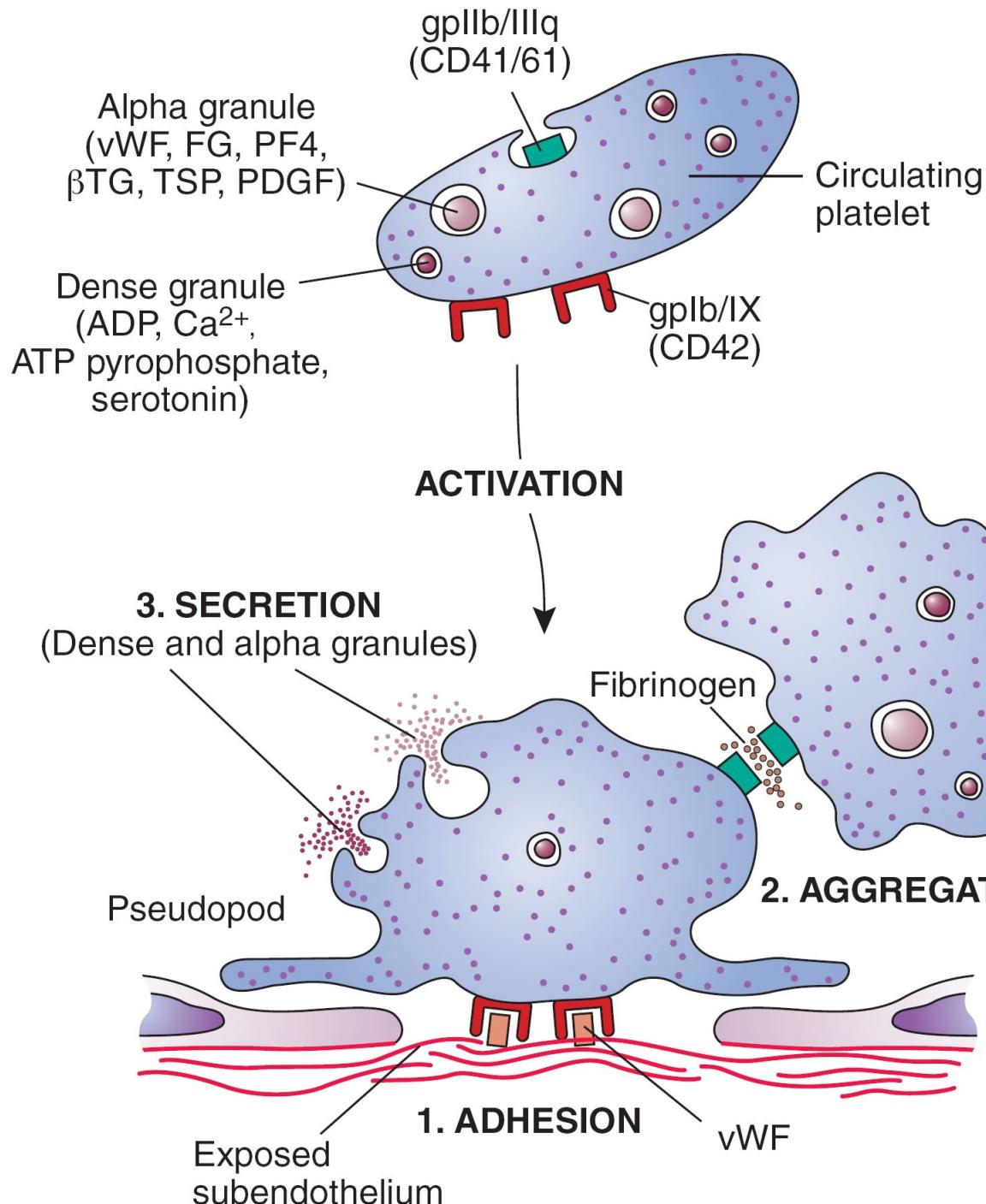
Atherosclerosis  
Allergic asthma  
Renal disease  
Chemotaxis  
Platelet–leucocyte interactions

### Host defence

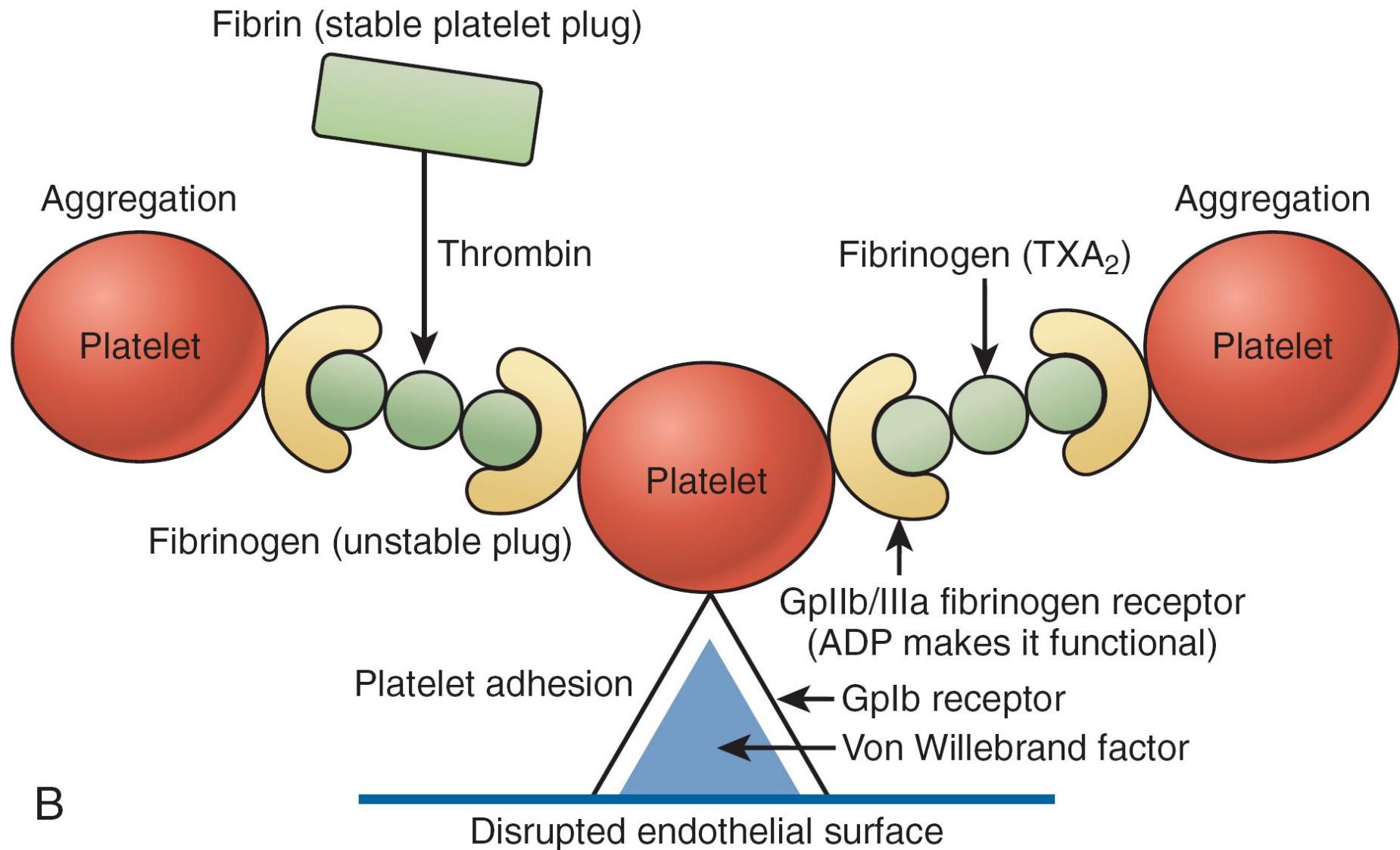
Phagocytosis/internalization of viruses and bacteria  
Killing of bacteria and malarial parasites in red blood cells  
Release of microbicidal proteins  
Superoxide production

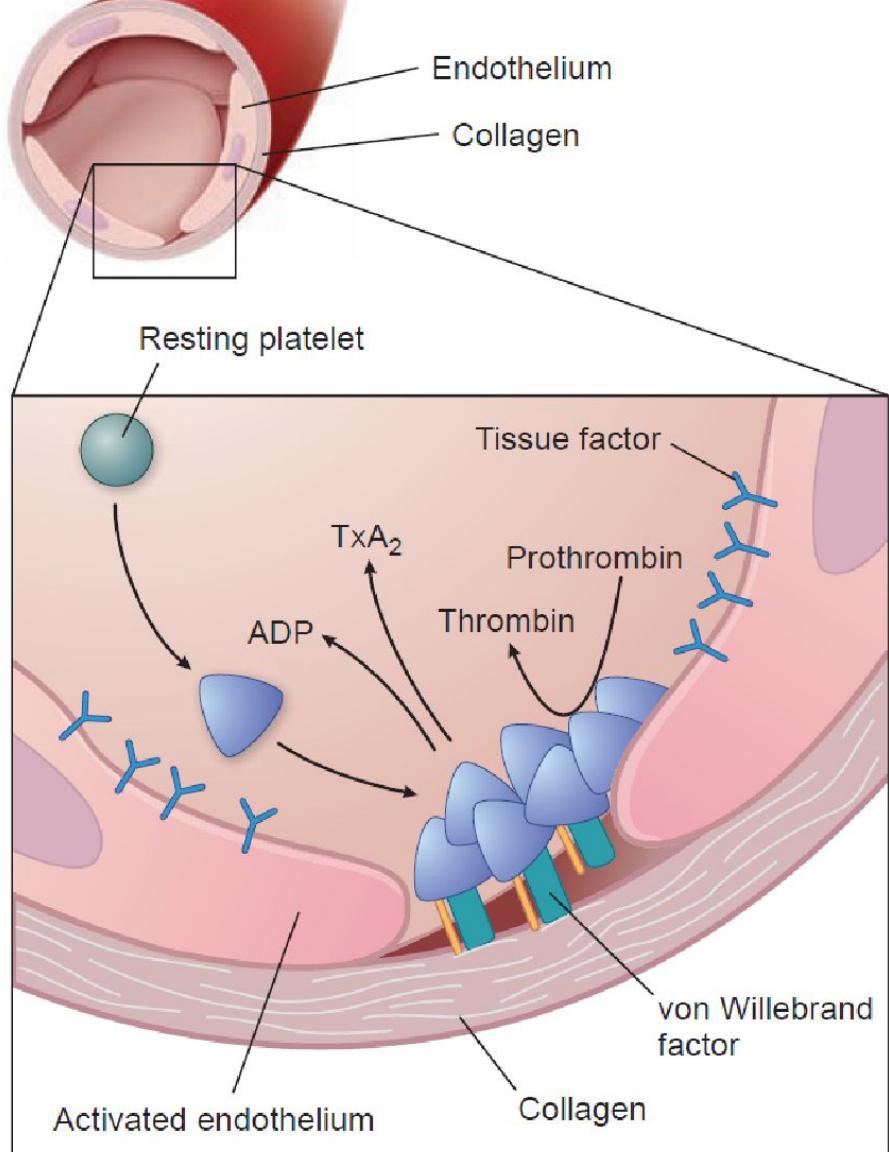
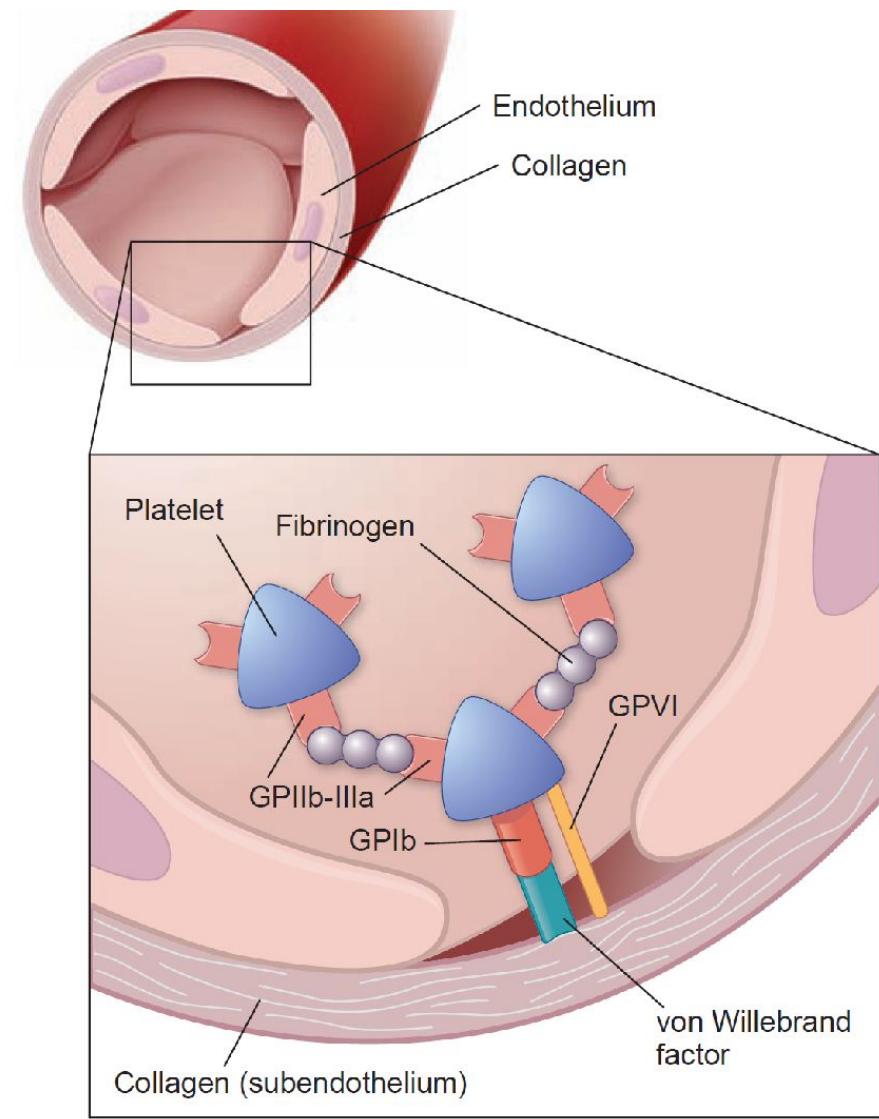
# Участие тромбоцитов в гемостазе

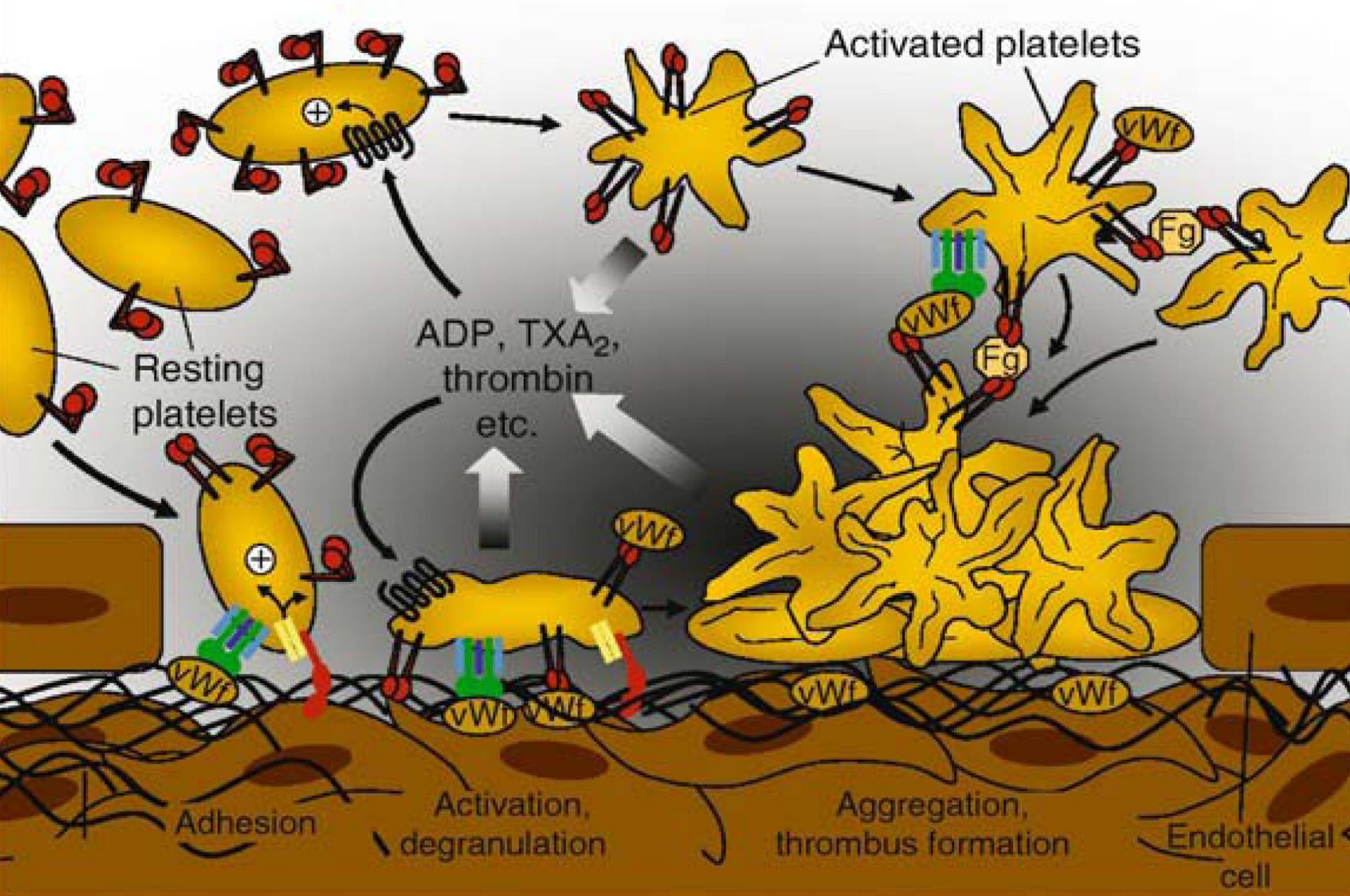




эндотелиальная  
экто-АДРаза (CD39)







GPIb-IX-V

Integrin  
(resting)



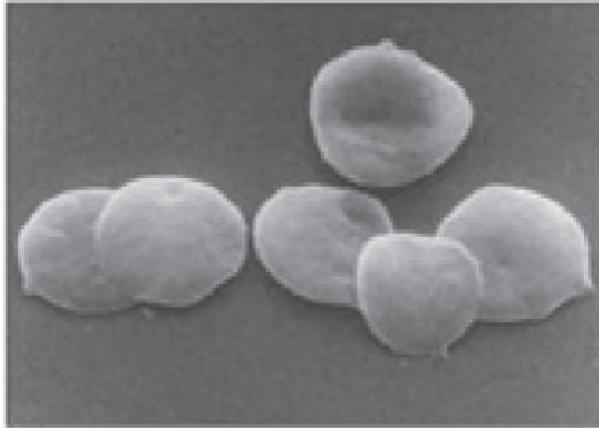
Integrin  
(activated)



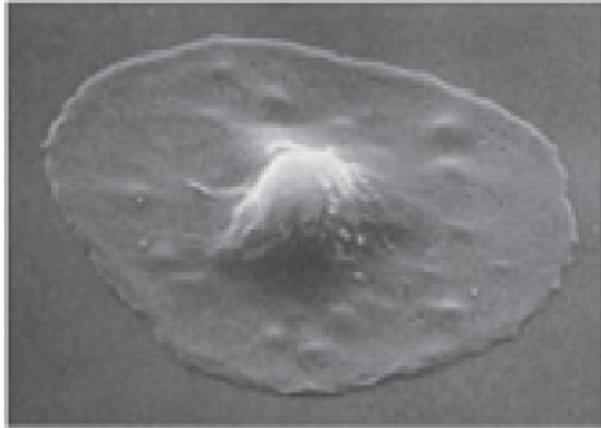
GPVI /  
 $\gamma$ -chain



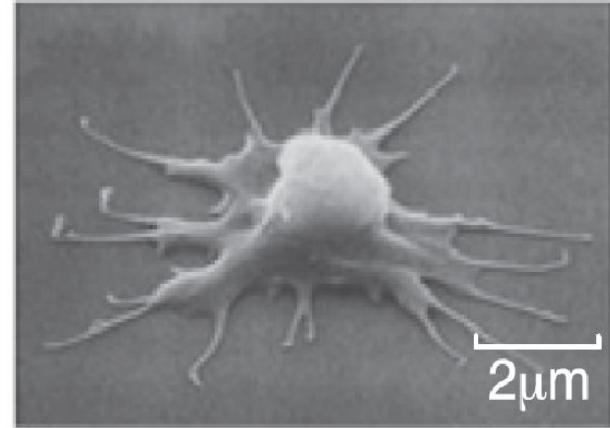
G-protein-coupled  
receptor



Resting platelets



Activated spread platelet



Activated contracted platelet

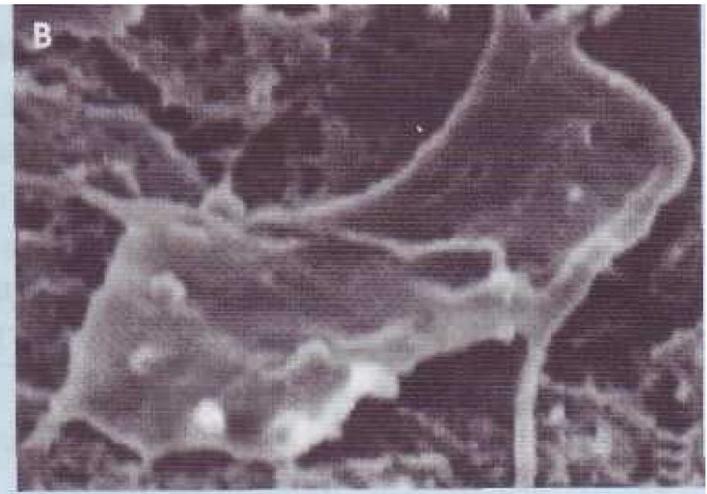
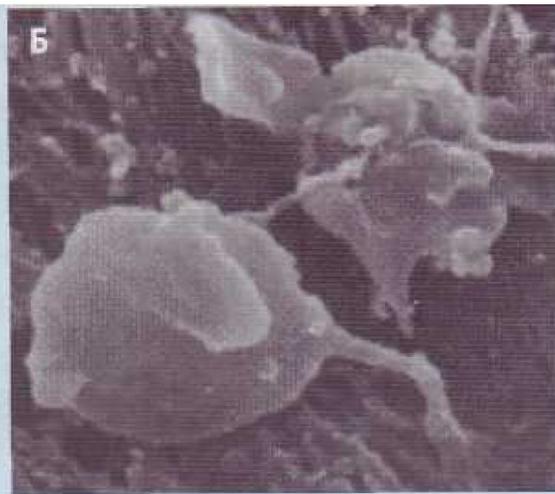
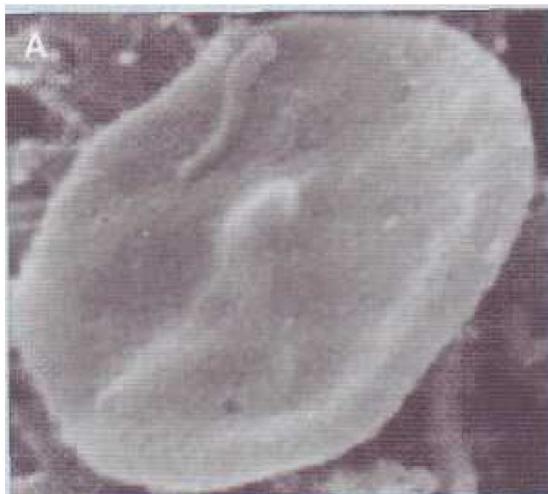
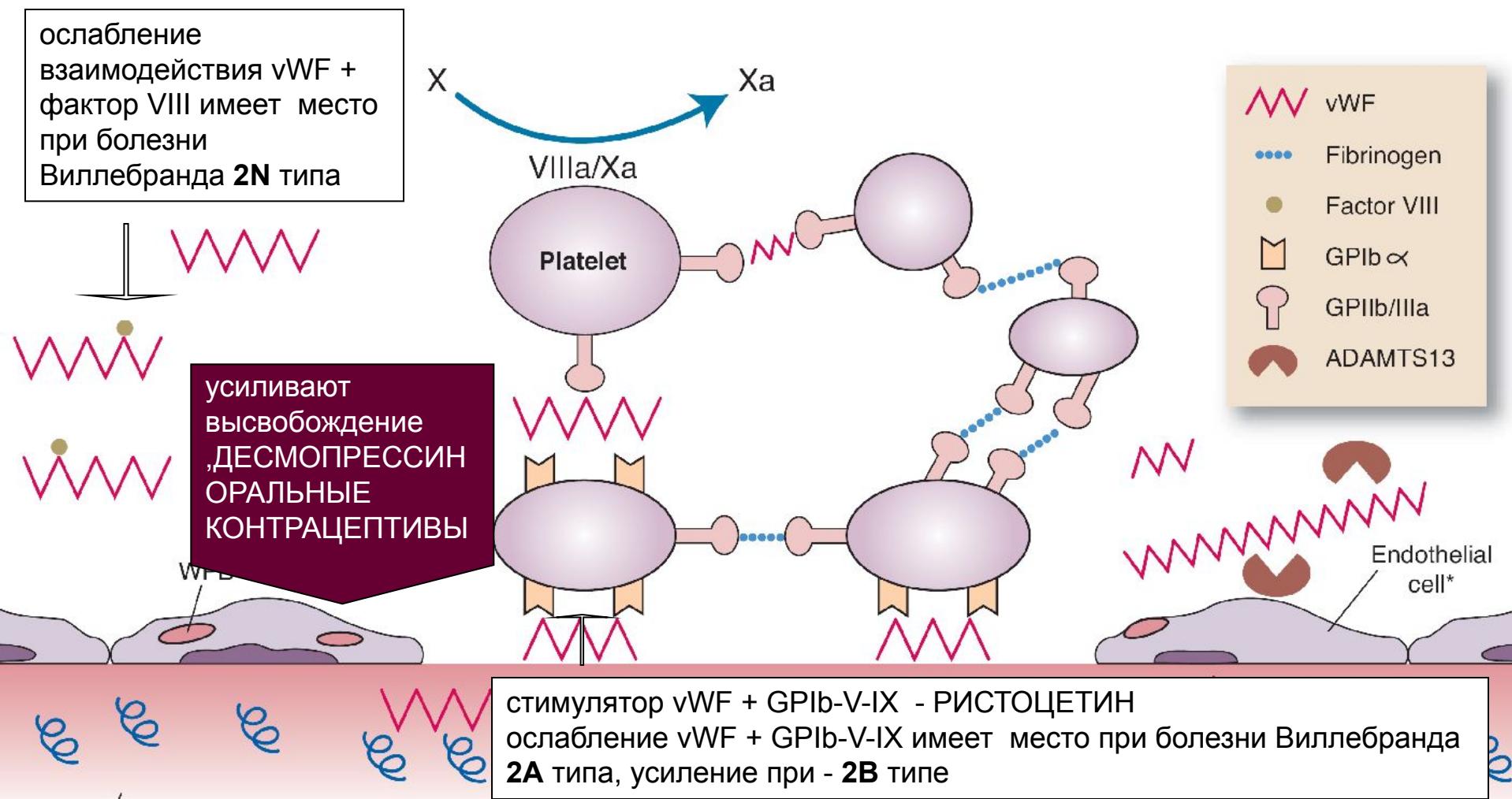
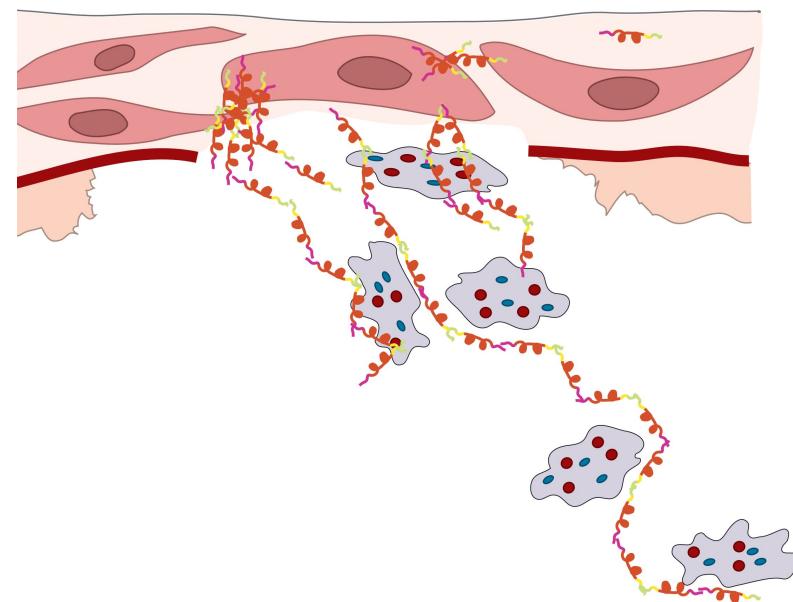
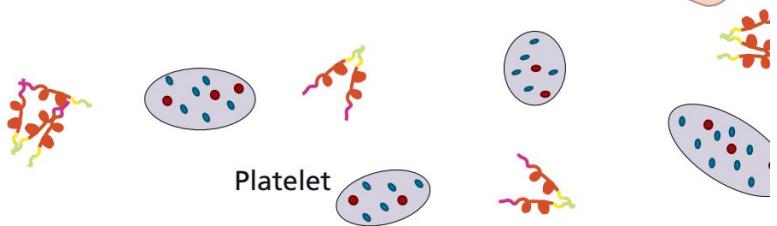
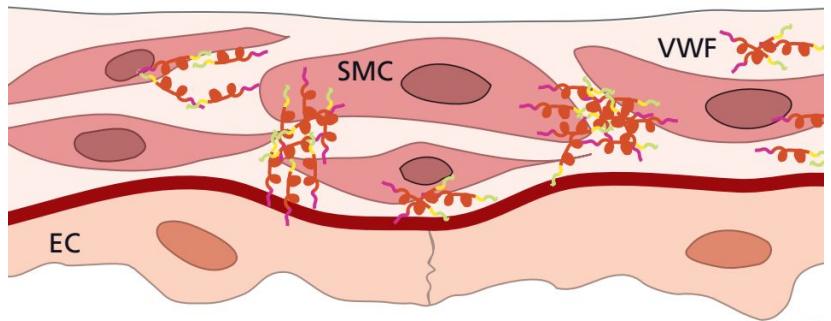
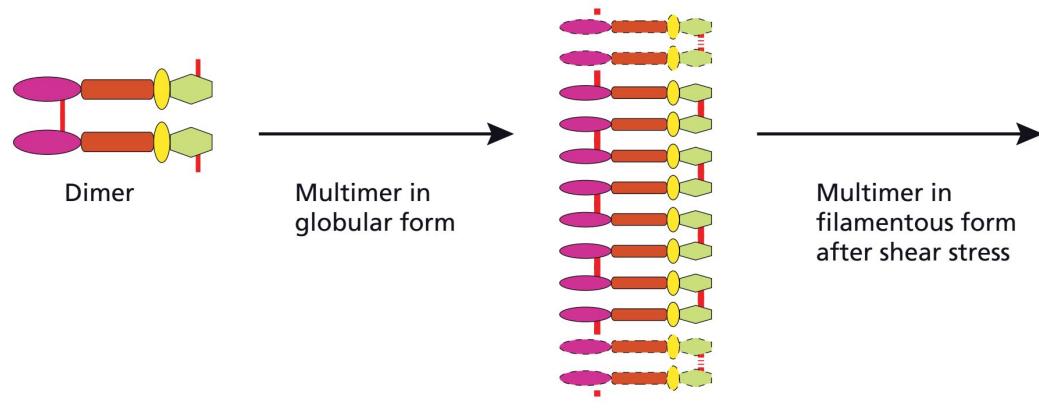
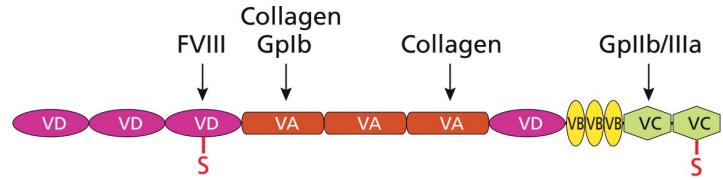


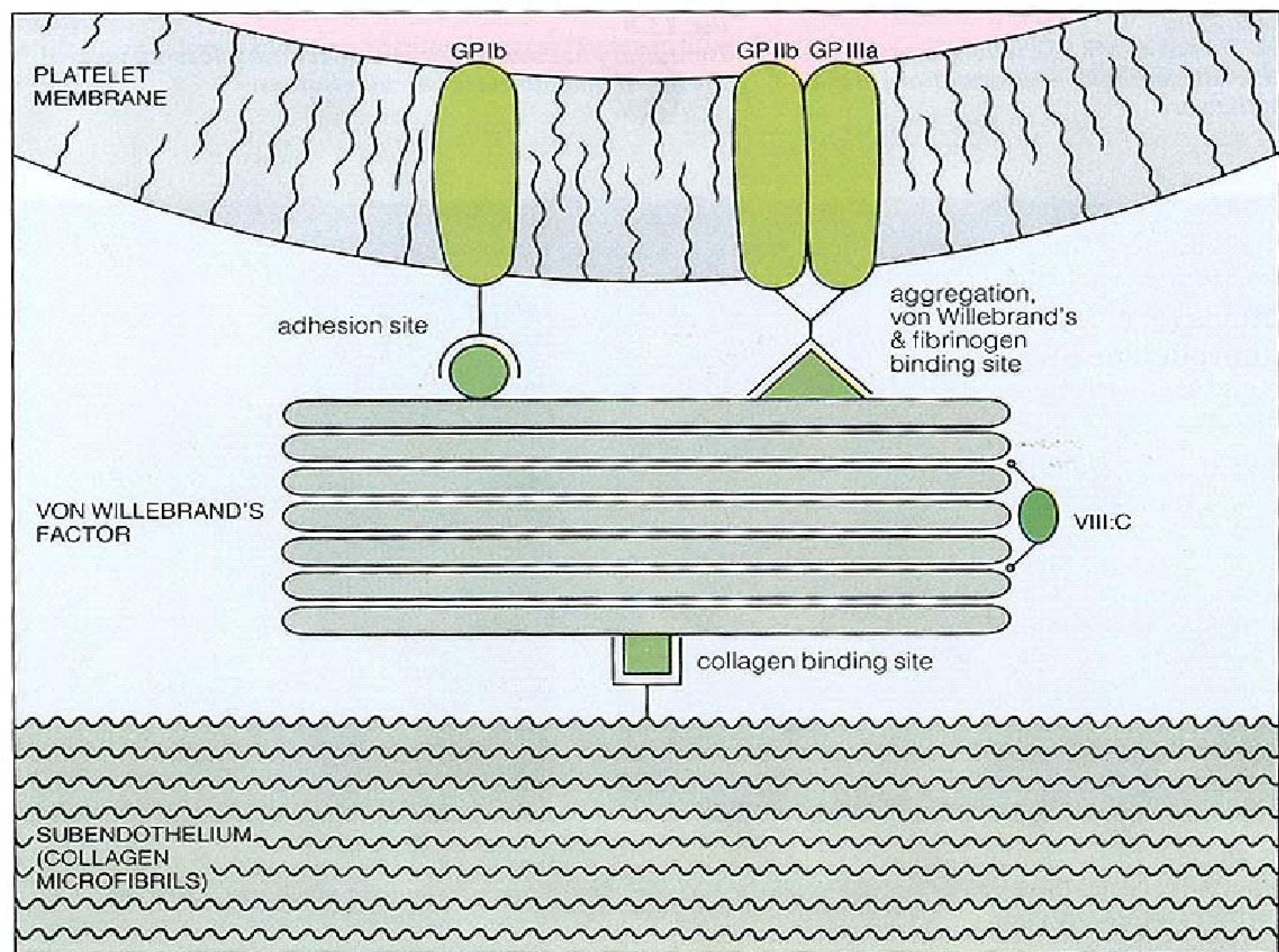
Рис. 27. Стадии контактной активации тромбоцитов: А - неактивный тромбоцит (дискоцит, пластиинка); Б - тромбоциты в обратимой стадии контактной активации (шаровидные формы с псевдоподиями); В - тромбоцит в необратимой стадии адгезии (распластанная форма без внутреннего содержимого - «тень тромбоцита»)

## 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



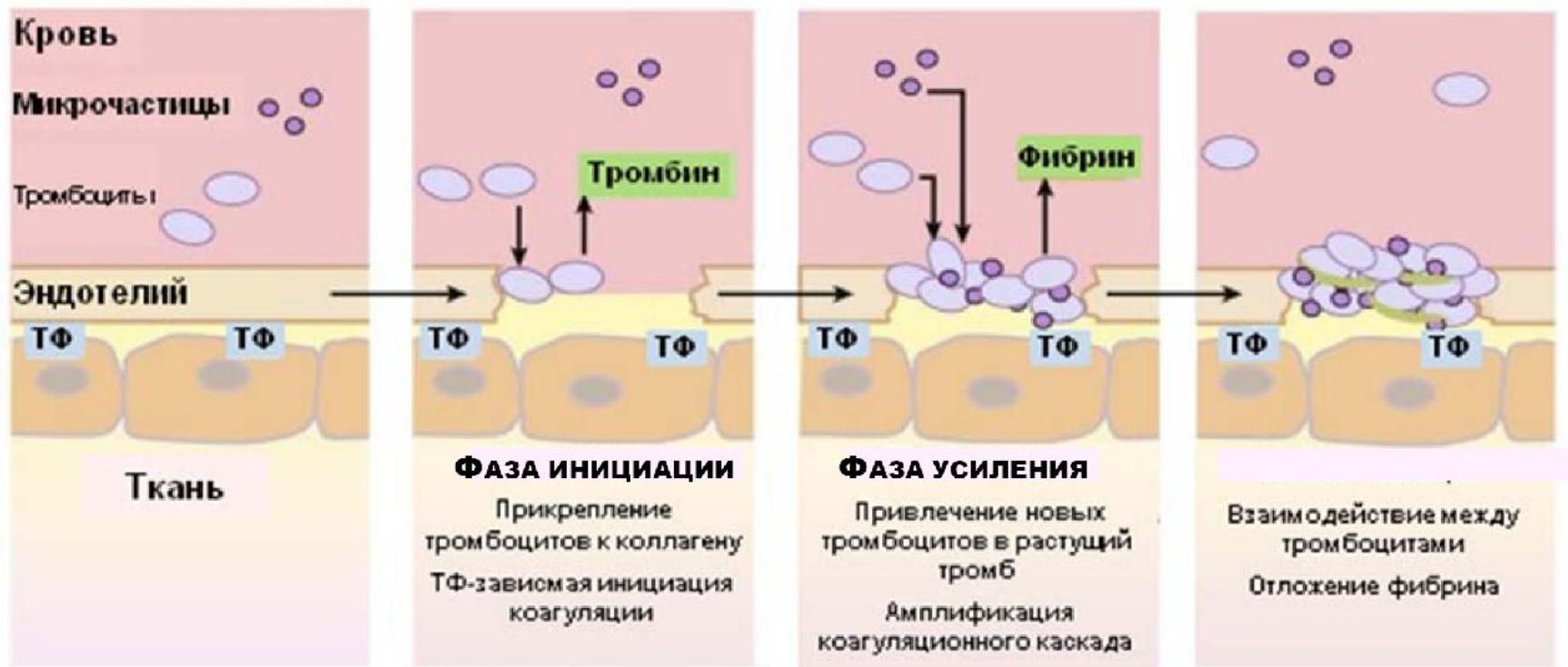




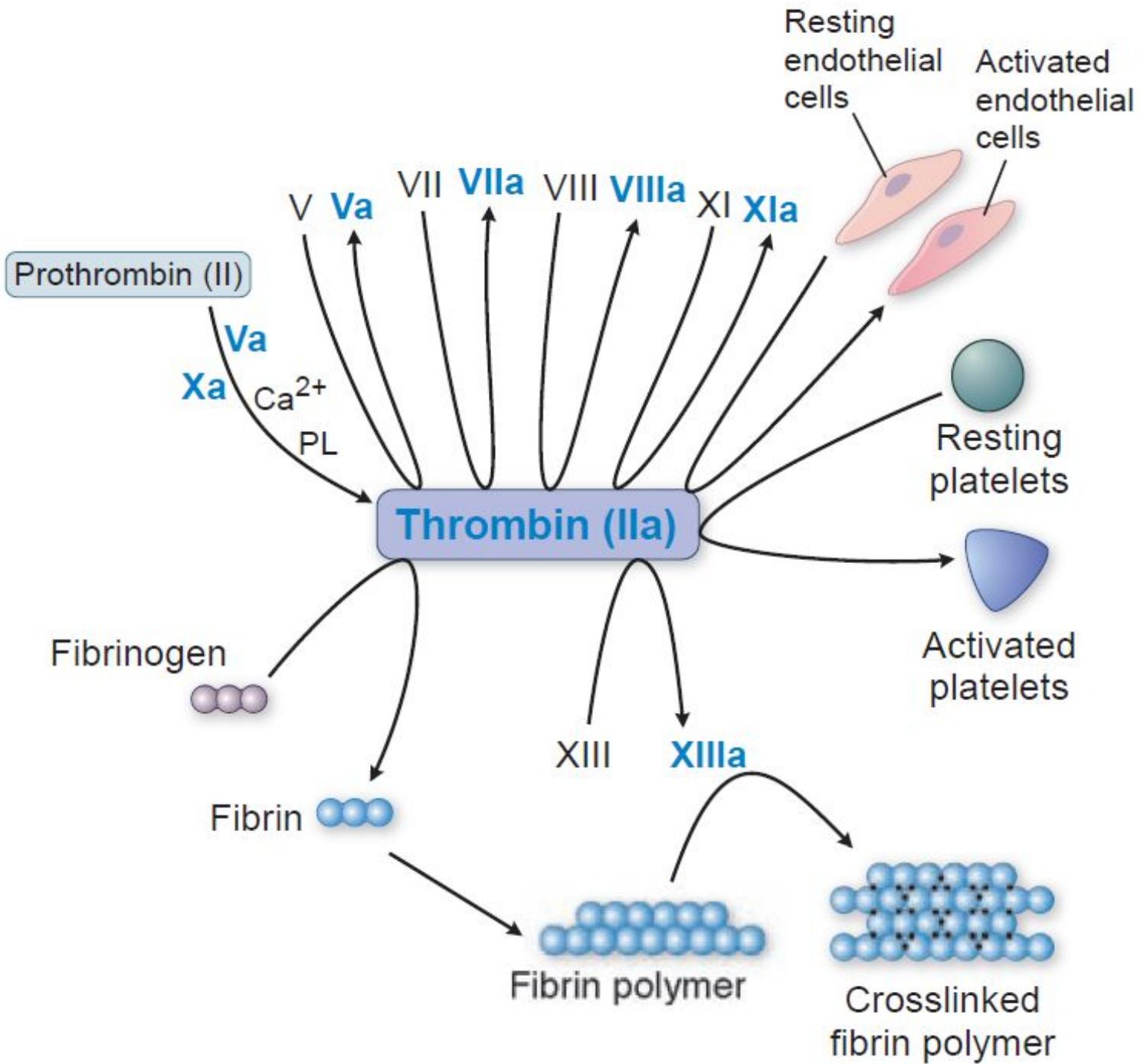
КОАГУЛЯЦИЯ

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*).



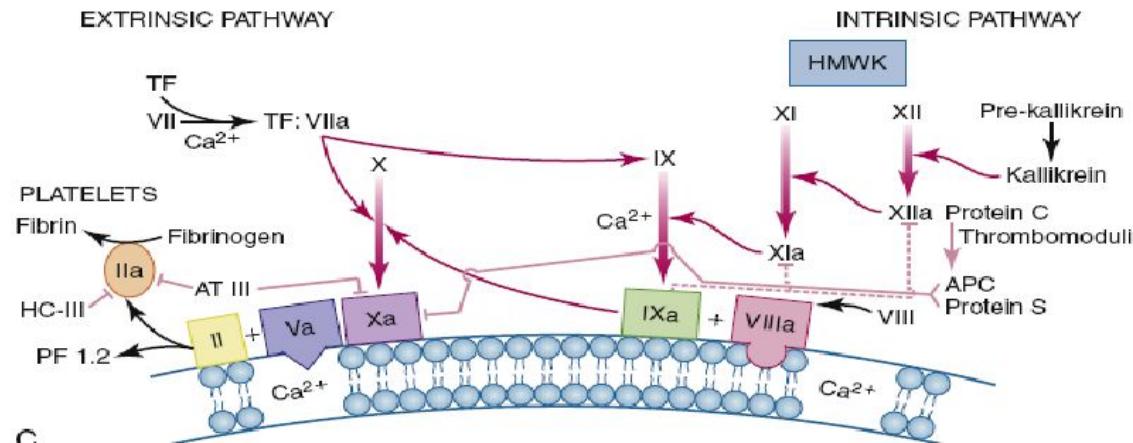
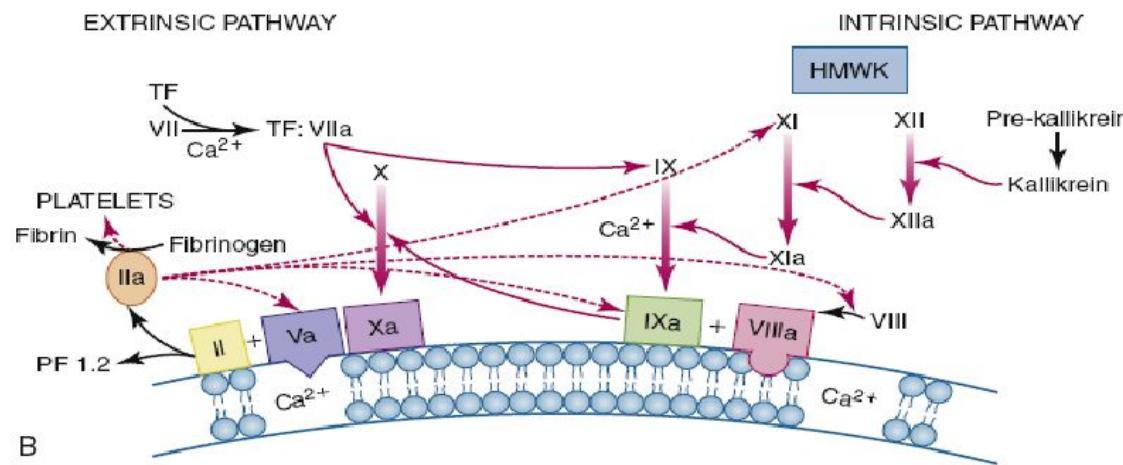
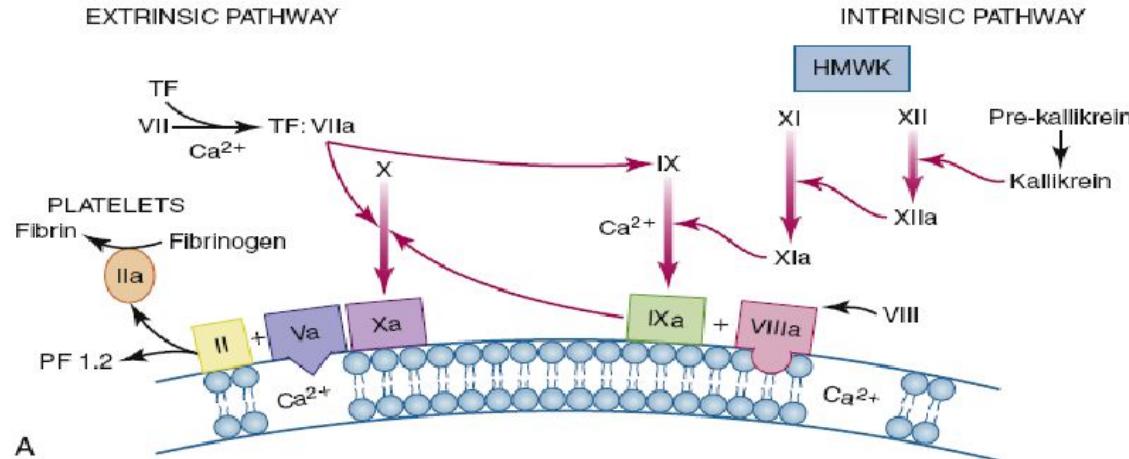


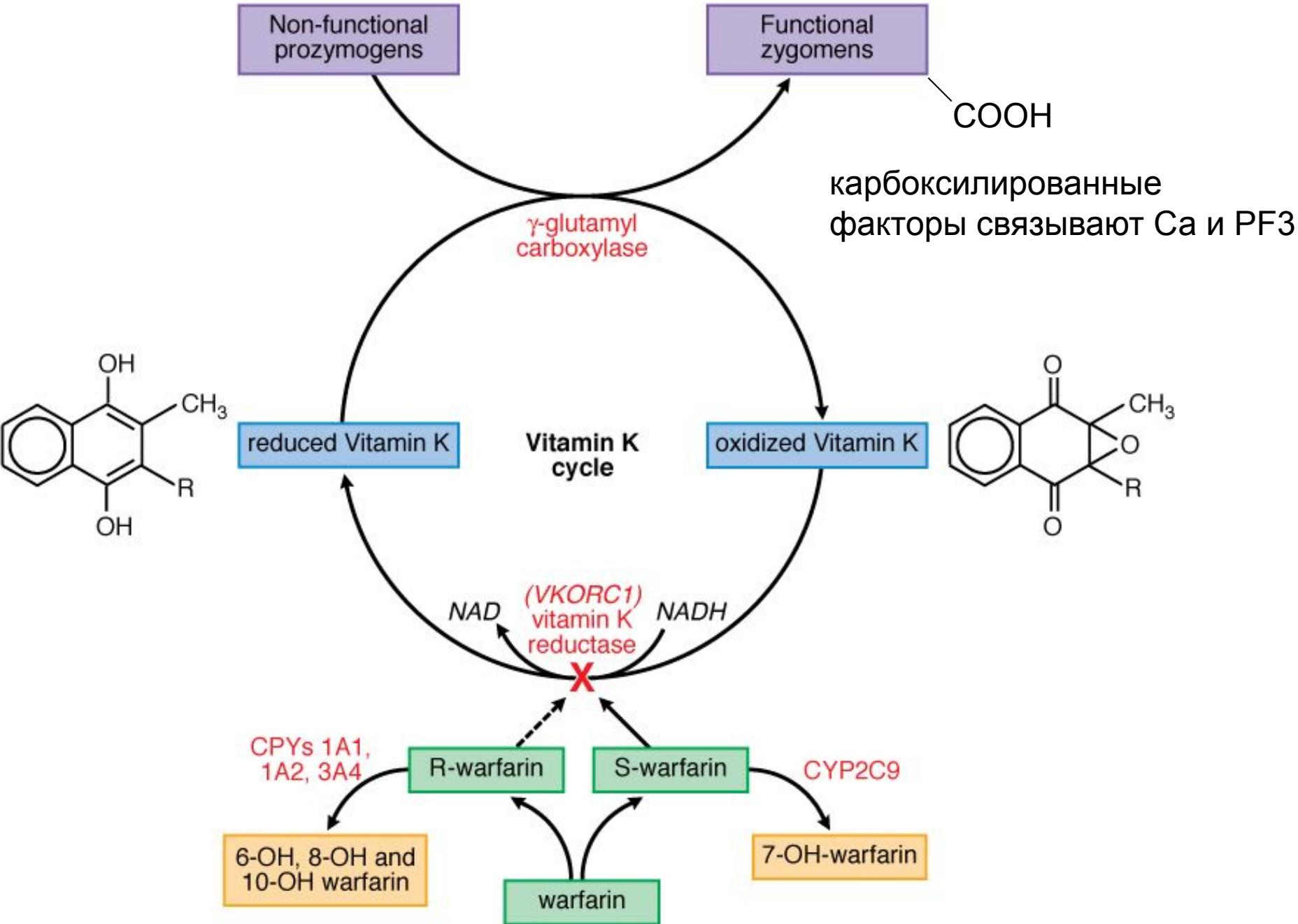
Таблица 1 (по Долгову В.В. и Свирину П.В., 2005)  
**Плазменные факторы свертывания крови**

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 Фитцджеральда		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 <sup>a</sup>	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
Prekallikrein	–	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.

<sup>a</sup>The half-life of VWF varies according the ABO blood group, being shortest in O, longest in AB and intermediate in A and B.



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

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# 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.<sup>497</sup> The systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled clinical studies.<sup>498–500</sup> Genetic testing has little effect on TTR or bleeding risk on warfarin, and is not recommended for clinical use at present.<sup>501</sup>

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

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

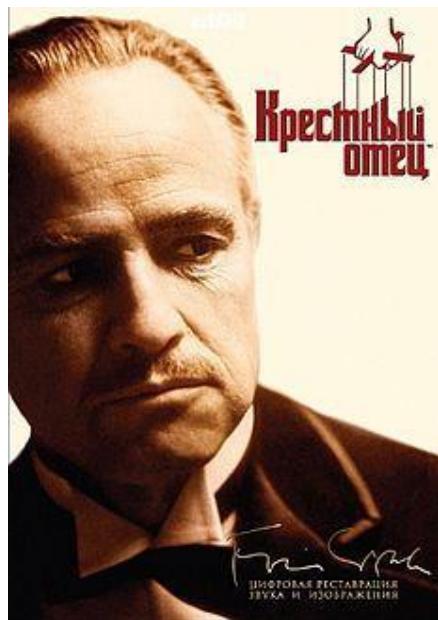
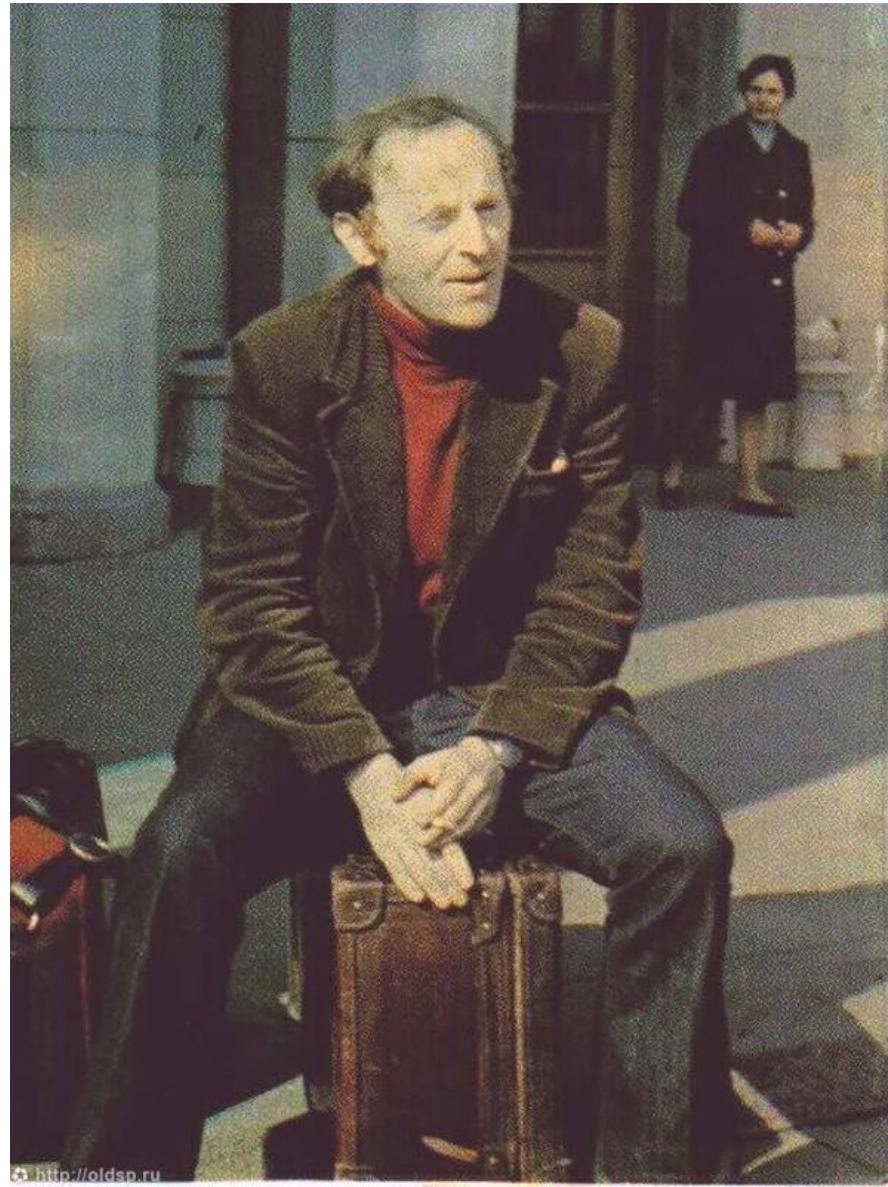


Image from the New York Times



NB

К-зависимыми являются также синтезируемые печенью антикоагулянты:  
протеин C,  
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**

**$\alpha_2$ -антиплазмин**

**ФИБРИН**

**ПДФ**

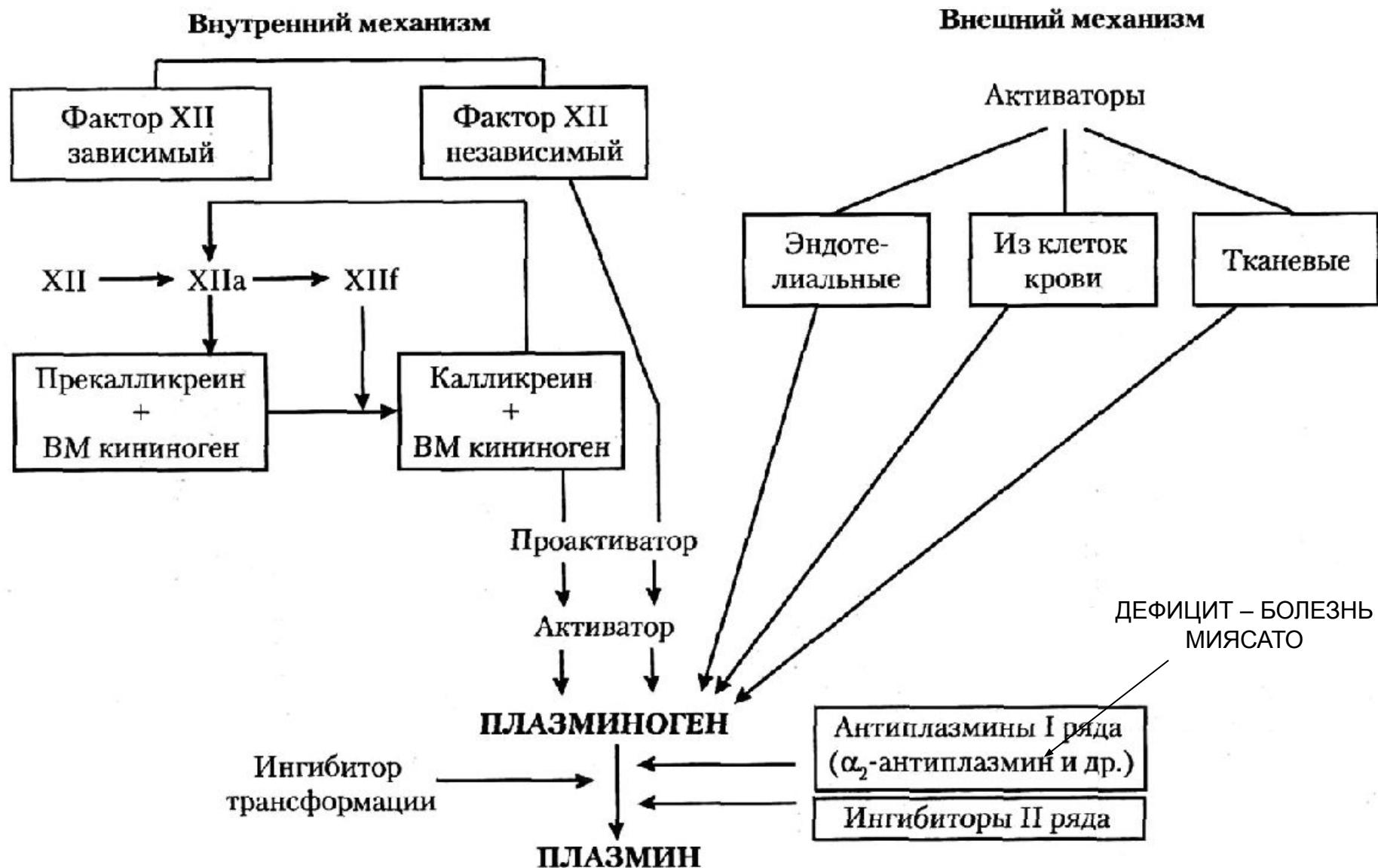
**(ОБЛАДАЮТ АНТИКОАГУЛЯНТНЫМ И  
ДЕЗАГРЕГАНТНЫМ ДЕЙСТВИЕМ)**

**TAFI**

**ТРОМБИН** → **(карбоксипептидаза В)**

**ИНАКТИВИРУЮТСЯ В  
ПЕЧЕНИ**

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

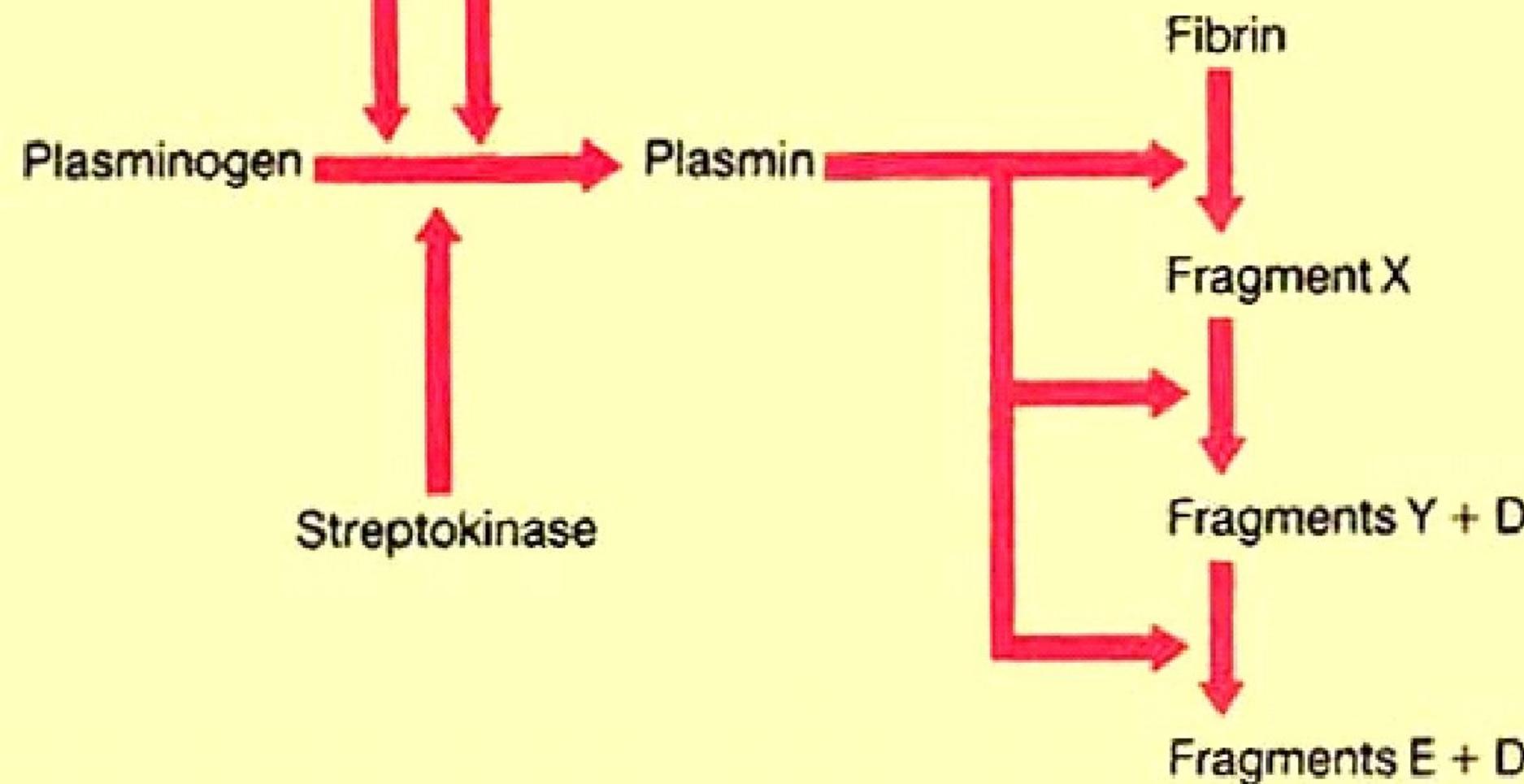


## Intrinsic activation

Factor XIIa  
Kallikrein

## Extrinsic activation

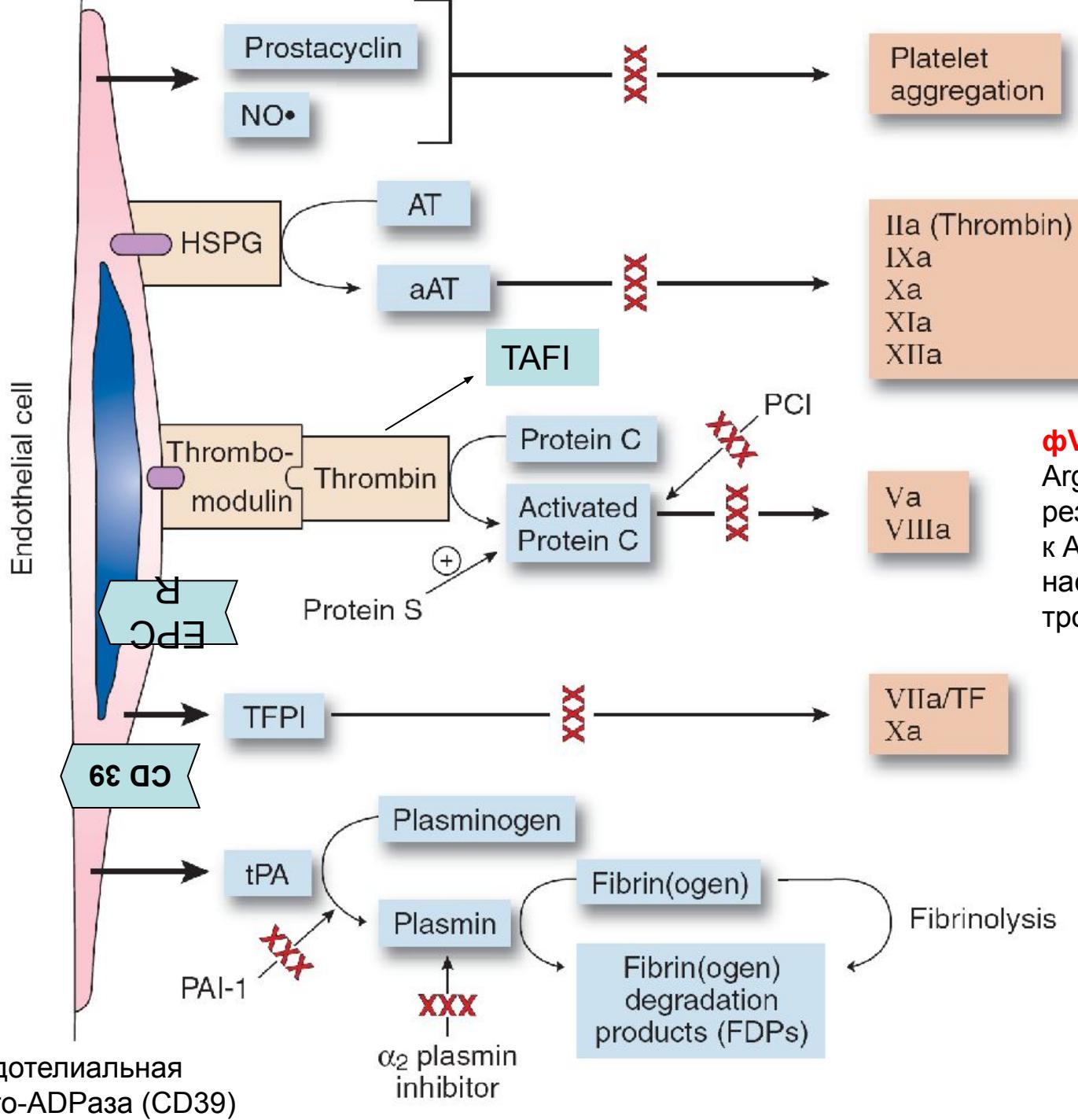
tPA  
urokinase-like A



Plasminogen Activators	Molecular Weight (kd)	Chains	Plasma Concentration (mg/dL)	Plasma Concentration Half-Life ( $t_{1/2}$ )	Substrates
<b>Endogenous</b>					
Plasminogen	92	2	20	2.2 days	(Fibrin)
Tissue-type PA (t-PA)	68 (59)	1-2	$5 \times 10^{-4}$	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	$8 \times 10^{-4}$	9-12 min	Plasminogen
<b>Exogenous</b>					
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 <sup>-1</sup> )	Plasma Concentration Half-Life ( $t_{1/2}$ )	Inhibitor Substrates
<b>Plasmin inhibitors</b>					
$\alpha_2$ -Antiplasmin	65	1	7	3.3 min	Plasmin
$\alpha_2$ -Macroglobulin	740	4	250		Plasmin (excess)
<b>Plasminogen activator inhibitors (PAIs)</b>					
PAI-1	48-52	1	$5 \times 10^{-2}$	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.

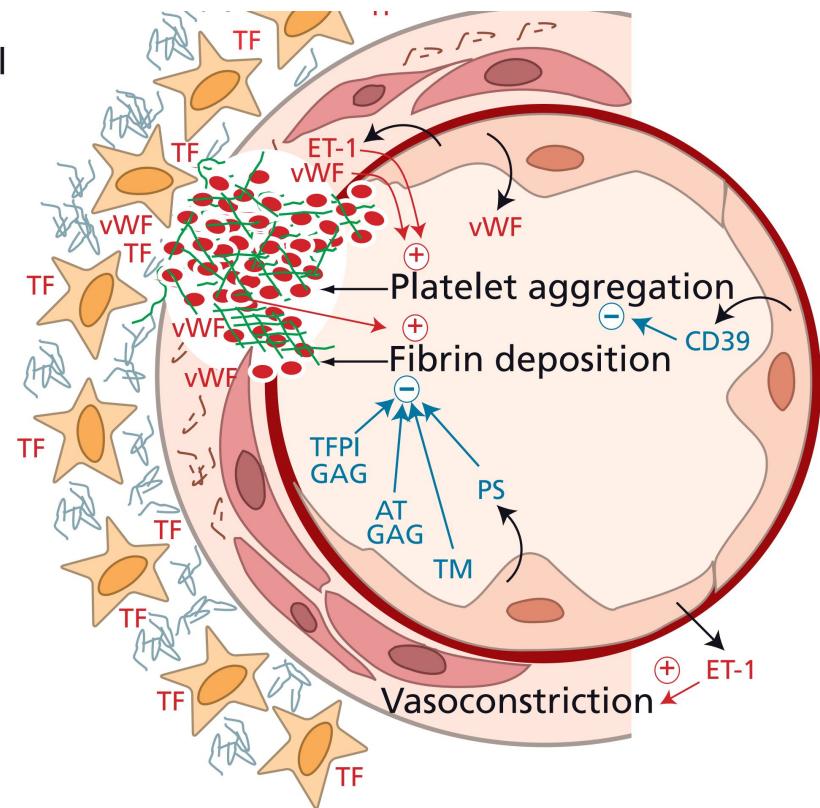
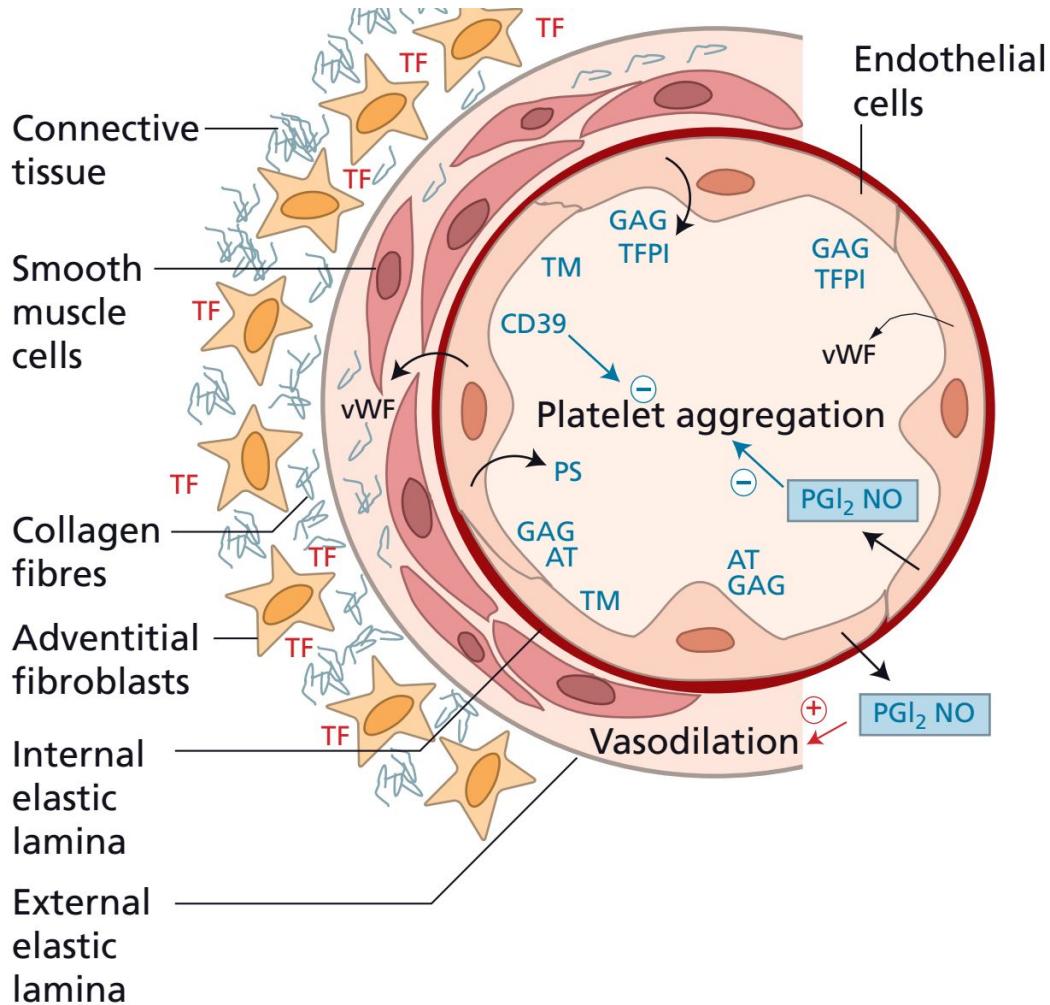
# РОЛЬ ЭНДОТЕЛИЯ



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

эндотелиальная  
экто-ADРаза (CD39)





**Эндотелий-зависимые  
вазодилататоры**

(например, АХ, серотонин, тромбин,  
напряжение сдвига кровотока)

Тромбин  
Ангиотензин II  
Адреналин

**ЭНДОТЕЛИАЛЬНАЯ  
КЛЕТКА**

Простациклин

ЭЗФР-НО

Эндотелин-1

**ГЛАДКОМЫШЕЧНАЯ  
КЛЕТКА**

$\uparrow$  цАМФ

$\uparrow$  цГМФ

**СОКРАЩЕНИЕ**

**РАССЛАБЛЕНИЕ**

К противосвертывающим факторам плазмы крови относятся: антитромбин (АТ), гепариновый кофактор II (ГК II), протеин С (ПС), протеин S (ПС), 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 группам :

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 <sub>r</sub> of monomer (kDa)	Plasma level (μg/mL)	Plasma level (nmol/L)	t <sub>½</sub> (hours)	Main action
Tissue factor	TF		<i>F3</i>	1p22–p21	6	263	44	NA	NA	NA	Cofactor for FVII/FVIIa
Prothrombin	FII		<i>F2</i>	11p11.1	14	579	72	90	1400	65	Clots FBG, activates PC, FXI, TAFI
Factor V	FV		<i>F5</i>	1q23	25	2196	330	10	30	15	Cofactor for FXa
Factor VII	FVII		<i>F7</i>	13q34	8	416	50	0.5	10	3	Activates FIX and FX
Factor VIII	FVIII		<i>F8</i>	Xq28	26	2332	330	0.1	0.3	10	Cofactor for FIXa
Factor IX	FIX		<i>F9</i>	Xq27	8	415	56	5	90	25	Activates FX
Factor X	FX		<i>F10</i>	13q34	8	445	59	8	135	40	Activates prothrombin
Factor XI	FXI		<i>F11</i>	4q35	15	607	80*	5	30	45	Activates FIX
Prekallikrein	PK		<i>KLKB1</i>	4q35	15	638	86	50	580	35	Anti-angiogenic, profibrinolytic
Factor XIII <sup>†</sup> (A chain)	FXIII	A	<i>F13A1</i>	6p25.3–p24.3	15	731	75 <sup>†</sup>	10	30	200	Cross-links fibrin
Factor XIII <sup>†</sup> (B chain)	FXIII	B	<i>F13B</i>	1q31	12	641	80 <sup>†</sup>	10	30	200	Cross-links fibrin
Fibrinogen (α-chain) <sup>‡</sup>	FGN	α	<i>FGA</i>	4q28	6	866	68 <sup>‡</sup>	3000	9000	90	Mechanical stabilization of clot
Fibrinogen (β-chain) <sup>‡</sup>	FGN	β	<i>FGB</i>	4q28	8	491	52 <sup>‡</sup>	3000	9000	90	Mechanical stabilization of clot
Fibrinogen (γ-chain) <sup>‡</sup>	FGN	γ	<i>FGG</i>	4q28	10	453	49 <sup>‡</sup>	3000	9000	90	Mechanical stabilization of clot
von Willebrand factor	VWF		<i>VWF</i>	12p13.3	52	2050	255	10	40	12	Cell adhesion and FVIII carrier
Thrombomodulin	TM		<i>THBD</i>	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.

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

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

Endothelial protein C receptor	EPCR	<i>PROCR</i>	20q11.2	7	220	27	NA	NA	NA	Cofactor in PC activation
Protein C	PC	<i>PROC</i>	2q13–14	9	419	62	4	65	6	Inactivation of FVa and FVIIIa
Protein S	PS	<i>PROS1</i>	3q11.2	15	676	69	10 (free)	145	?	Inactivation of FVa and FVIIIa
Tissue factor pathway inhibitor	TFPI	<i>TFPI</i>	2q32	12	304	42	0.08	2.5	?	Inhibition of coagulation initiation
Antithrombin	AT	<i>SERPINC1</i>	1q23–q25.1	9	464	58	140	2400	5	Inhibits thrombin, FIX, FX, FXI
Heparin cofactor II	HCII	<i>SERPIND1</i>	22q11.21	5	499	66	90	1200	60	Prevention of arterial thrombosis?
Plasminogen	PLG	<i>PLG</i>	6q26	14	791	92	200	2000	50	Dissolution of clot in wound repair
Tissue plasminogen activator	tPA	<i>PLAT</i>	8p12	14	562	69	0.005	0.07	0.03	Plasma activator of plasminogen
Prourokinase	UK	<i>PLAU</i>	10q24	11	431	54	0.0015	0.04	0.03	Tissue activator of plasminogen
Plasminogen activator inhibitor 1	PAI-1	<i>SERPINE1</i>	7q21.3–q22	9	379	52	10	200	0.1	Inhibition of tPA and uPA
$\alpha_2$ -Antiplasmin	$\alpha_2$ -AP	<i>SERPINF2</i>	17p13	9	452	67	70	1000	72	Inhibition of plasmin
Thrombin-activatable fibrinolysis inhibitor	TAFI	<i>CPB2</i>	13q14.11	11	401	60	5	75	0.2	Inhibition of fibrinolysis

# Изменение параметров гемостаза при беременности

Platelet count	No consistent change but often <u>falls</u>
Platelet aggregation	Progressive enhancement
Fibrinogen	<u>Progressive rise up to 400% basal</u>
Prothrombin	No consistent change
Factor V	No consistent change
Factor VII	<u>Progressive rise up to 300% basal</u>
Factor VIII	<u>Progressive rise up to 200% basal</u>
von Willebrand factor	<u>Progressive rise up to 250% basal</u>
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

$\alpha_2$ -Antiplasmin

Progressive rise up to 300% basal

PAI-1

Progressive rise up to 300% basal

PAI-2

Progressive marked rise