Часть 7

Теломераза и рак
Метастазирование
Эпигенетические механизмы
Тератогенез

7.1. Теломера и теломераза

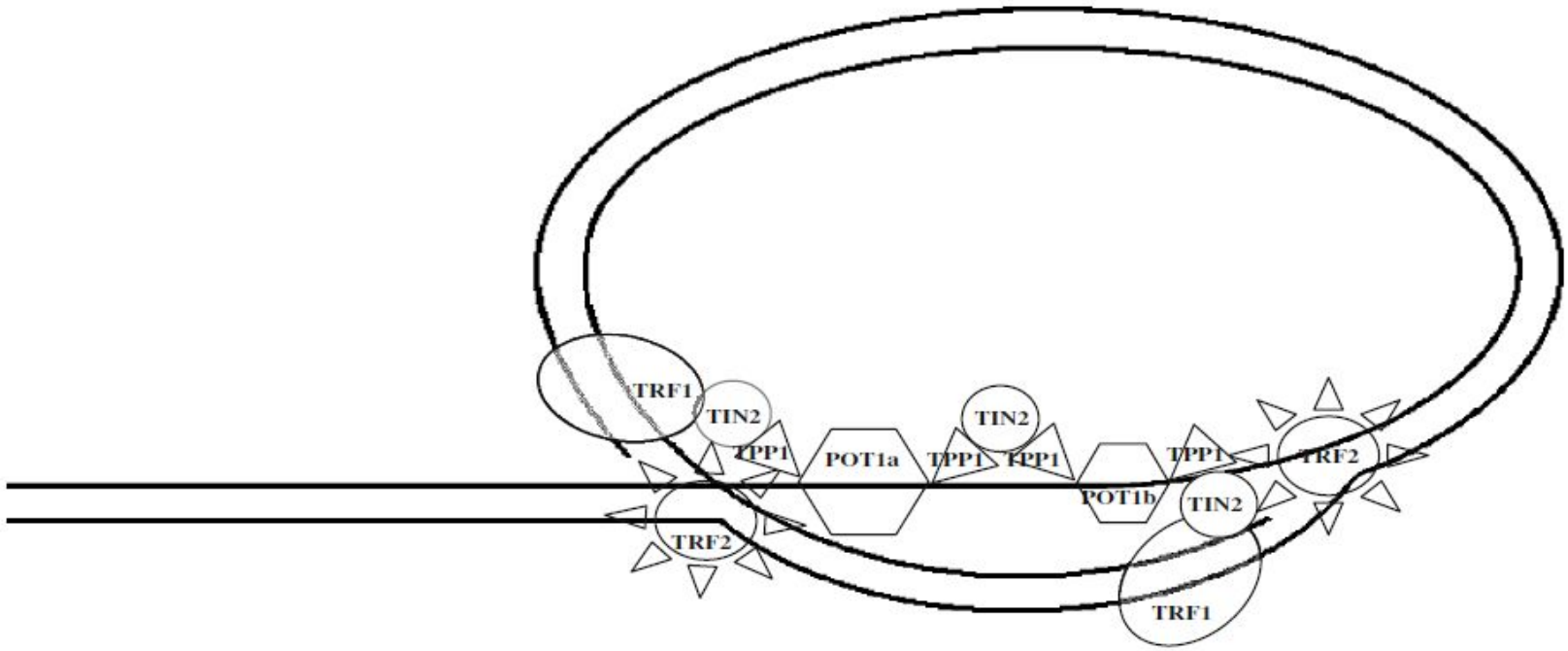
Состоит из:

- **РНК (TER) – матрица для синтеза тел. ДНК**
- **TERT - тел. обратная транскриптаза**

Теломера

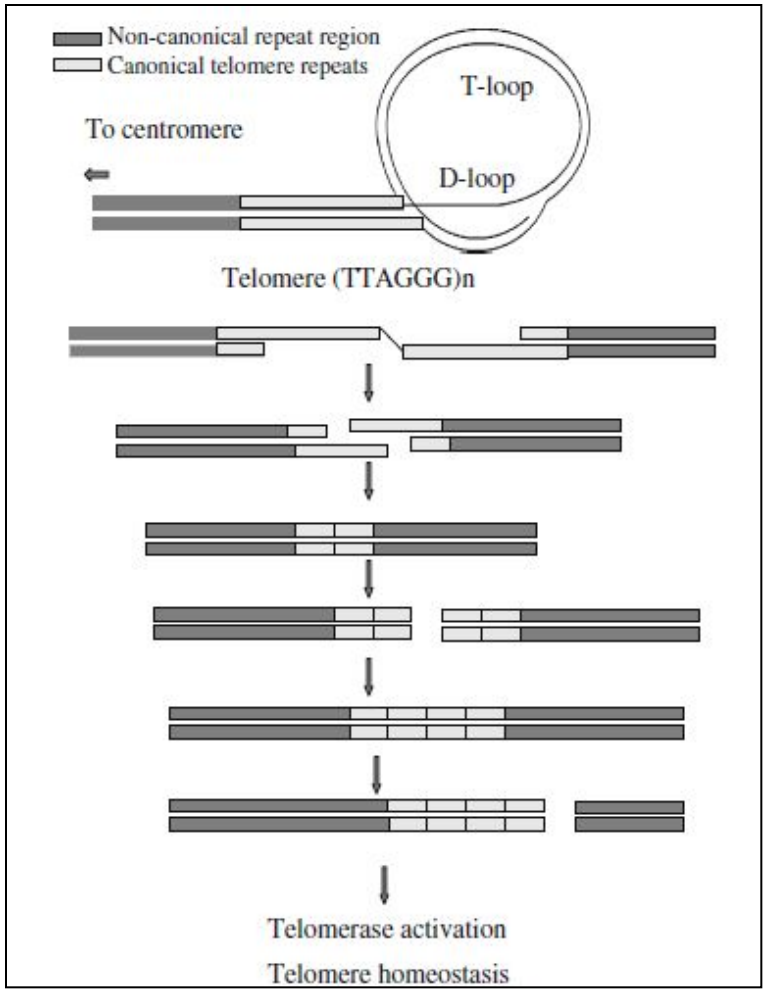
Теломерная ДНК состоит из повторов (TTAGGG)n с выступающими G-концами. В клетках млекопитающих, 2-нитевые теломерные повторы связанны с мультибелковым комплексом (shelterin или telosome), представленным tankyrase, telomeric repeat-binding factor 1 (TRF1), telomeric repeat-binding factor 2 (TRF2), TRF1-interacting protein 2 (TIN2), repressor-activator protein 1 (Rap1), protection of telomeres 1 (POT1), и TPP1(formerly bnamed PTOP/PIP1/TINT1).
Теломерный G-конец связан с Pot1/TPP1 гетеродимером. Теломера сворачивается в двунитевую T-петлю или однонитевую D-петлю.

Белковые взаимодействия в теломере



TRF1 and TRF2 binds to the double-stranded DNA, while POT1 binds to the single-stranded DNA and has two orthologs. These three proteins interact directly or indirectly with TIN2 and TPP1. TRF1 bends, loops, and pairs DNA to form while the TRF2 localized at the two junctions to stabilize the loop structure

Механизм поддержания теломер



Теломера становится незащищенной при критически короткой длине и рекомбирирует с другой теломерой, активируется ответ на повреждение ДНК и клетка вступает в репликативное старение .

При дефиците сверочных точек КЦ клетка со слитой хромосомой продолжается делиться. Теломера продолжает укорачиваться, наступает кризис. Слитая хромосома разрывается в анафазе в другом месте. Сестринские хроматиды проходят через «слитость» после репликации. Слитые хромосомы повреждаются при амплификации ДНК и терминальных деелциях. Теломераза реактивируется и длина теломер поддерживается.

Репликация ДНК эукариотической хромосомы

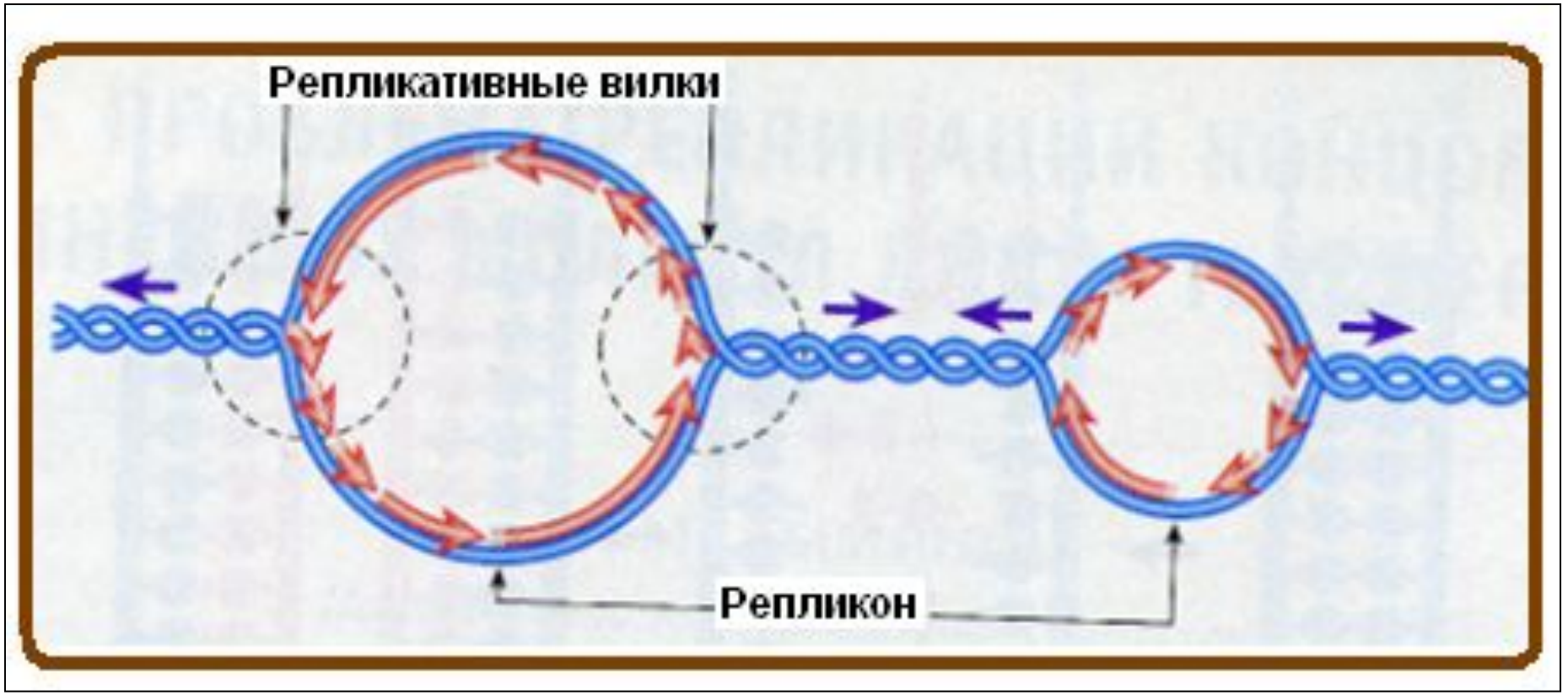


Схема образования дочерних цепей ДНК

Наращивание концов ДНК теломерными повторами

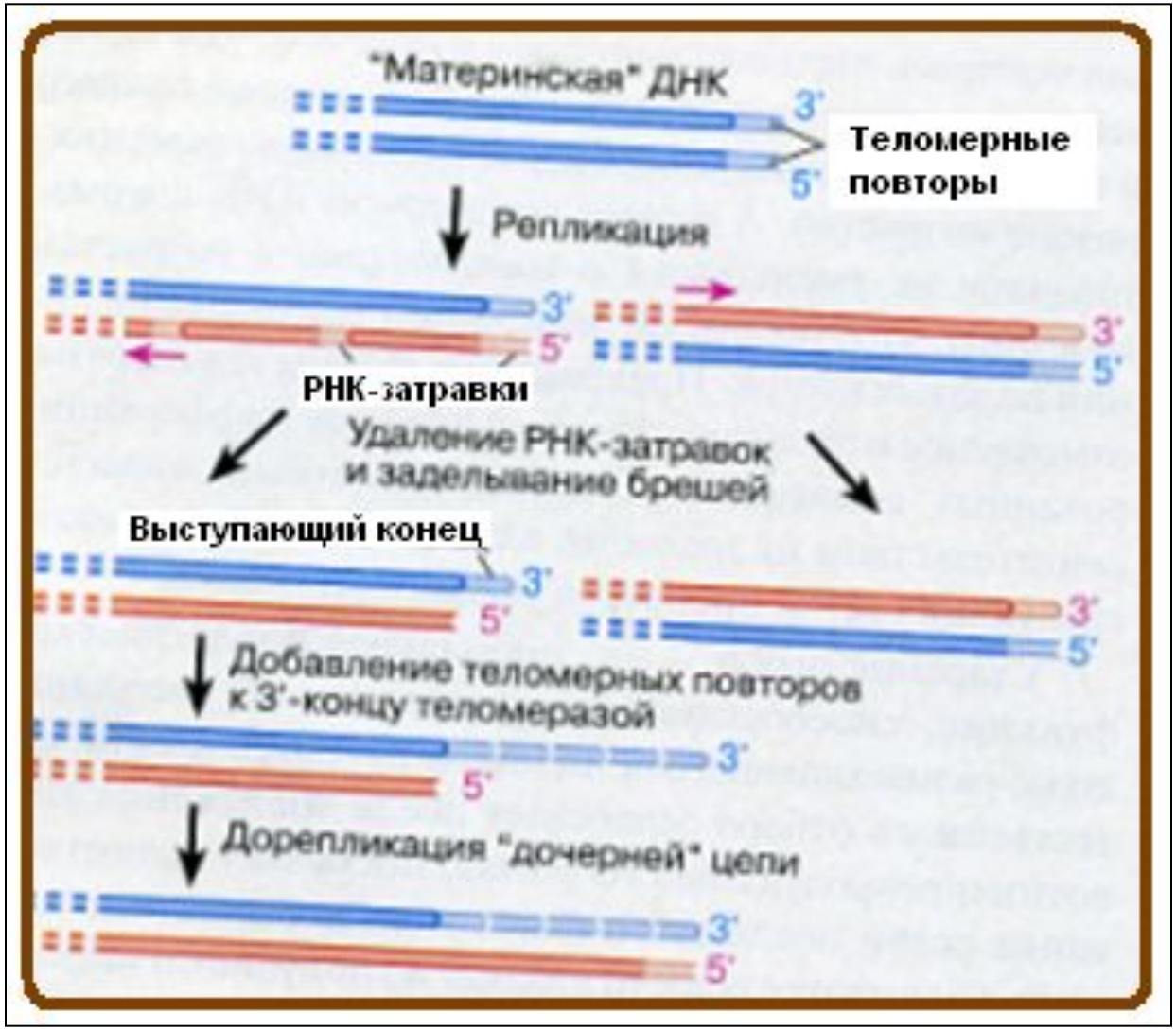
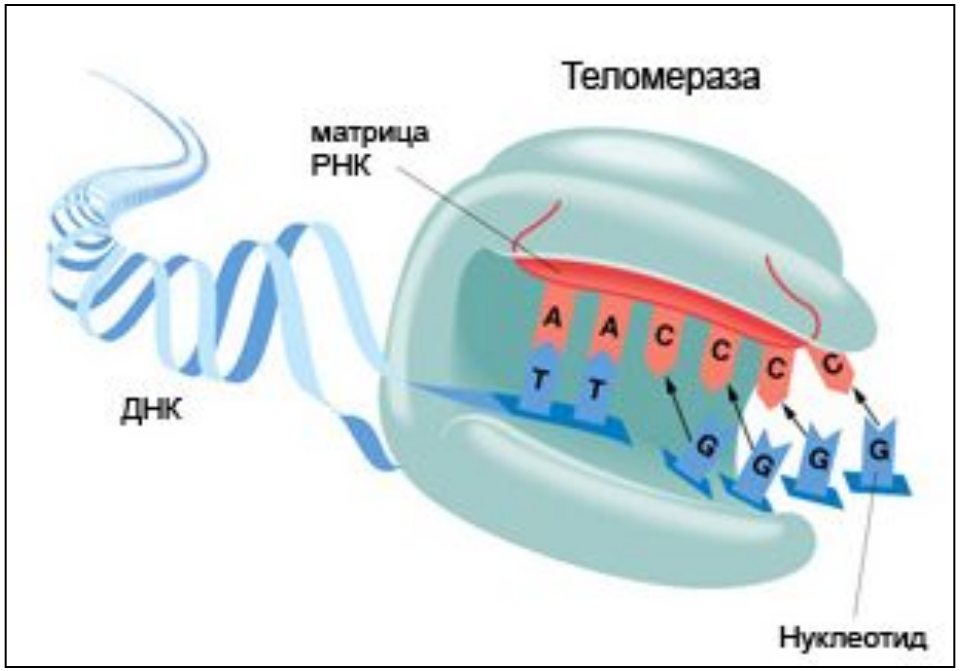
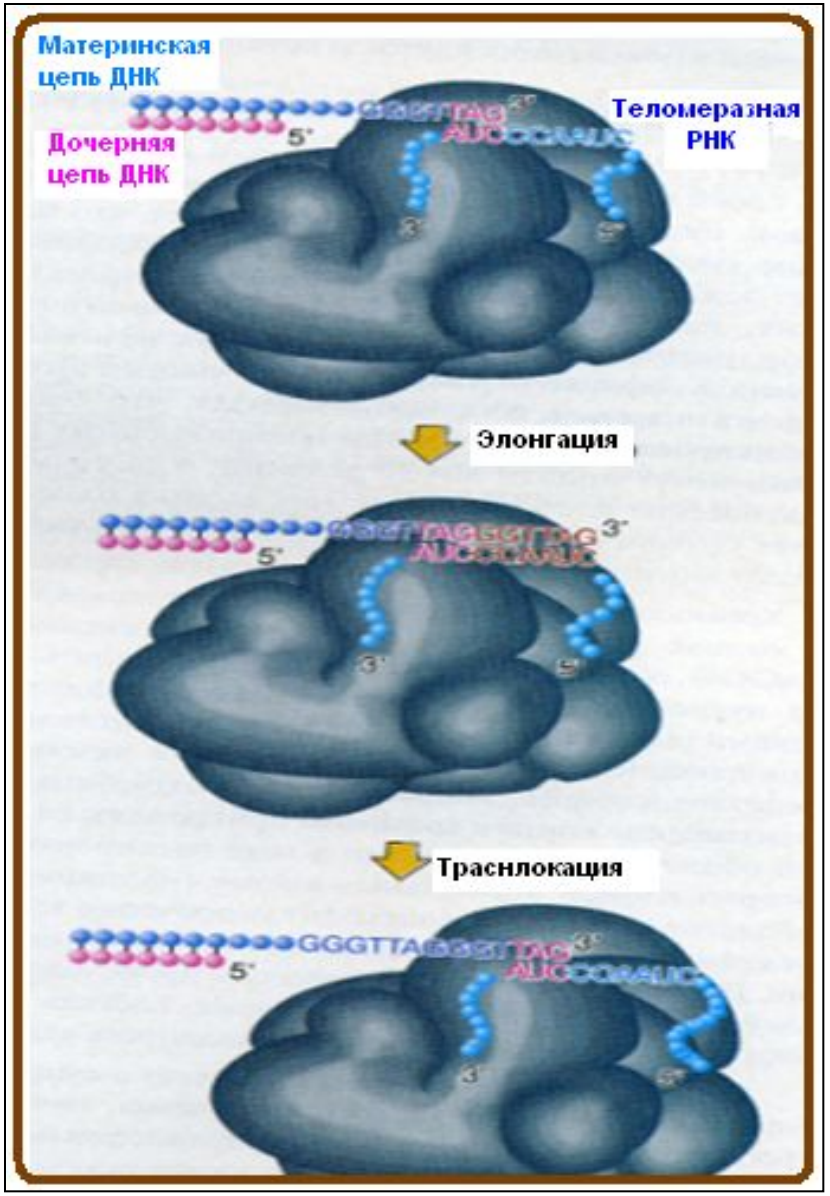


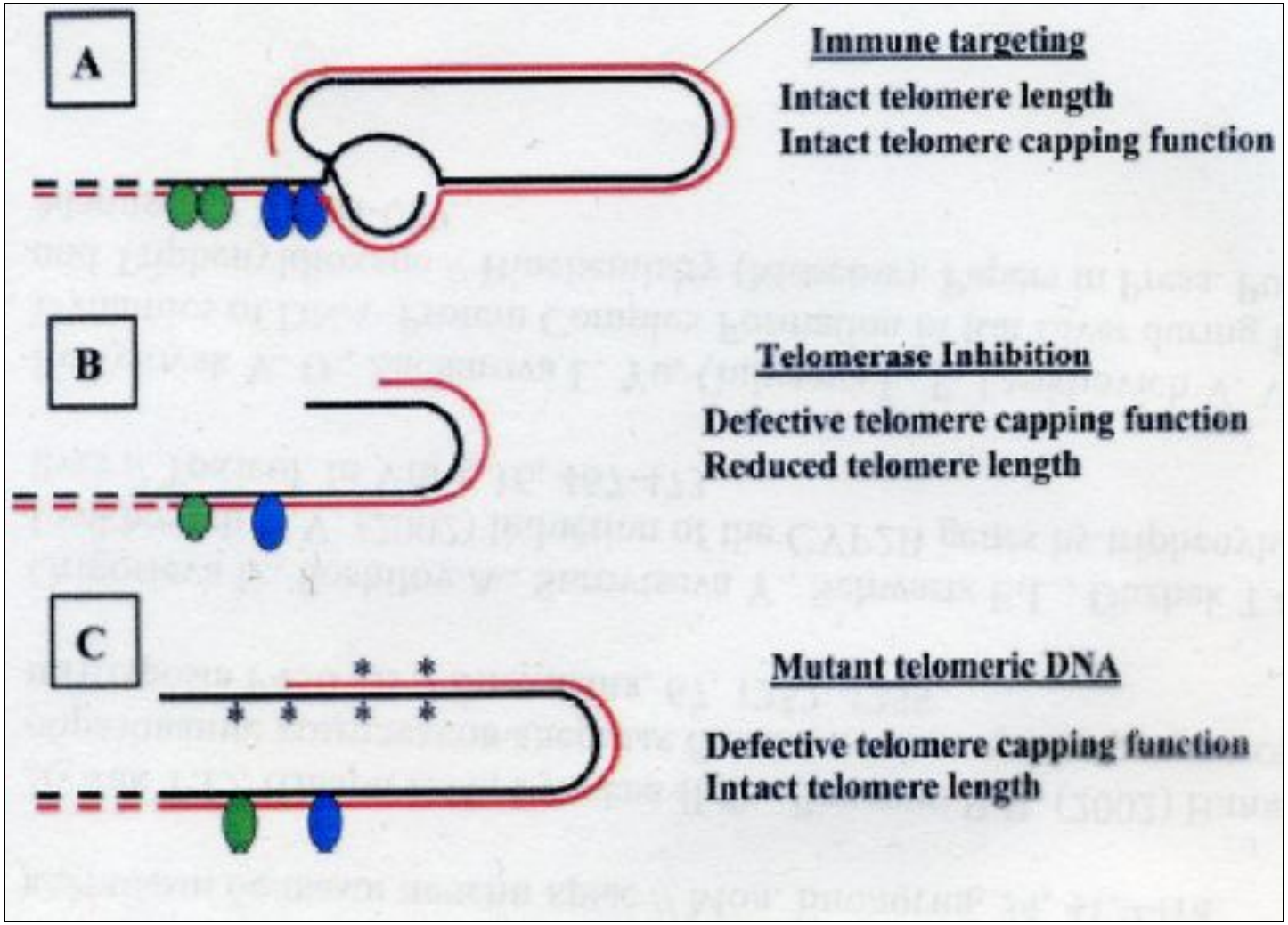
Схема удлинения 3’-конца ДНК

Красный – спаренные комплементарные нуклеотиды выступающего конца и матричного участка теломеразной ДНК





Стратегия лечения рака на основе теломеразы как мишени



Метастазирование

Основные свойства:

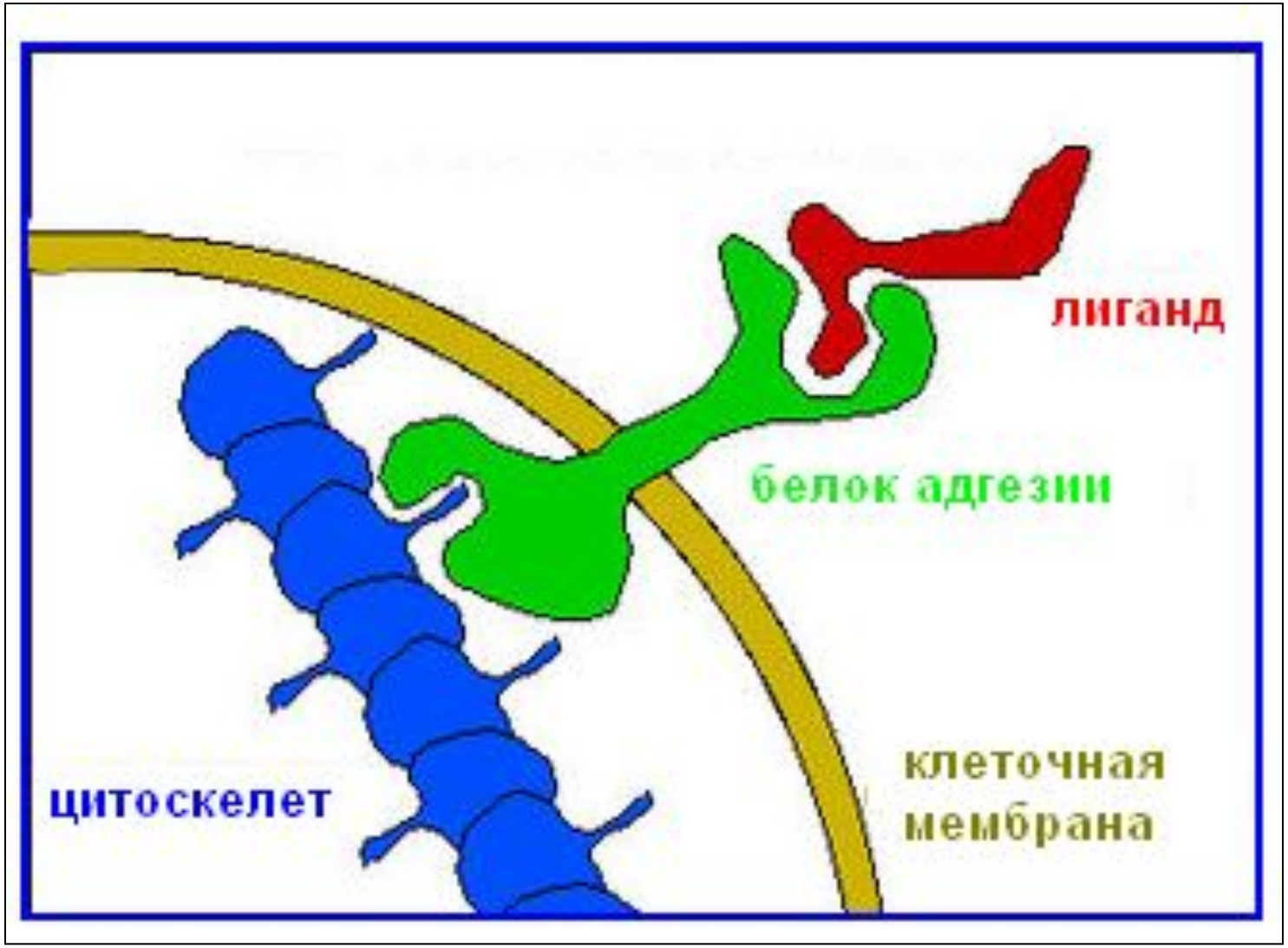
- Нарушение адгезии и межклеточных контактов
- Активация металлопротеиназ
- Активация TF
- Активация ангиогенеза

7.2. Межклеточные контакты, адгезия

3 основных класса молекул:

- Клеточные адгезивные молекулы (CAMs)
- Белки внеклеточного матрикса (ECM) – фибронектин и ламины
- Белки цитоплазматической периферической мембраны (осуществляют связь с цитоскелетом, регулируя адгезию)

Схема адгезии



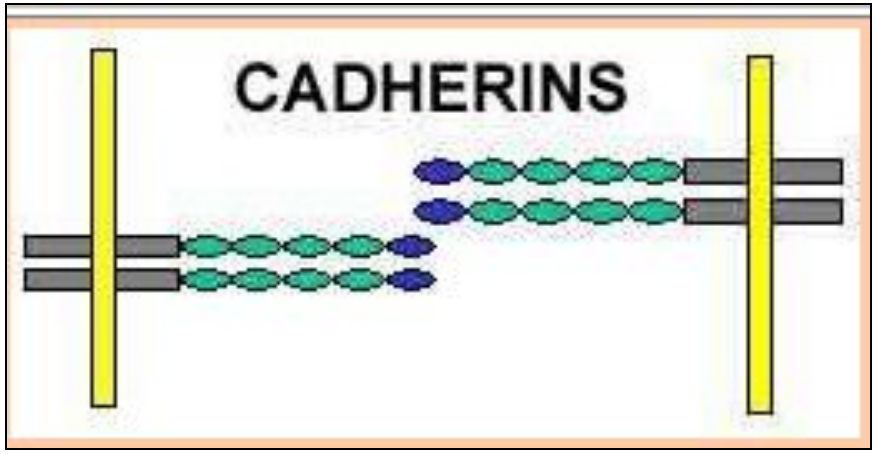
CAM белки

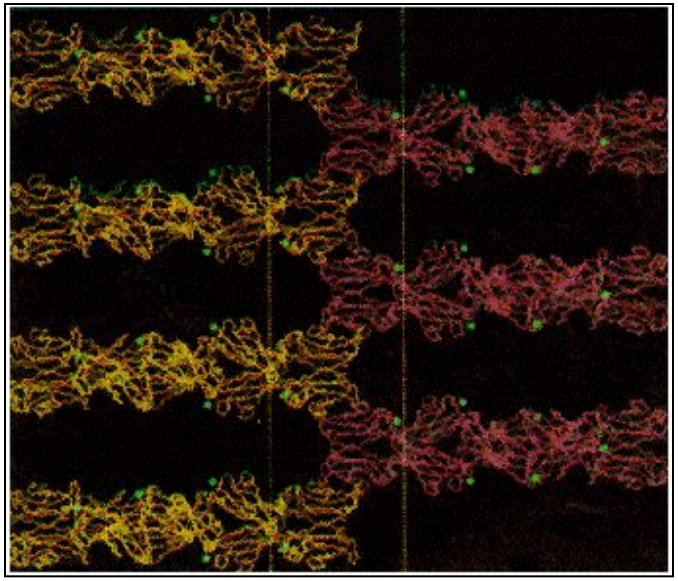
- Кадхерины
- Интегрины
- Селектины
- Ig (immunoglobulin) superfamily (IgSF CAMs)

Это трансмембранные гликопротеины

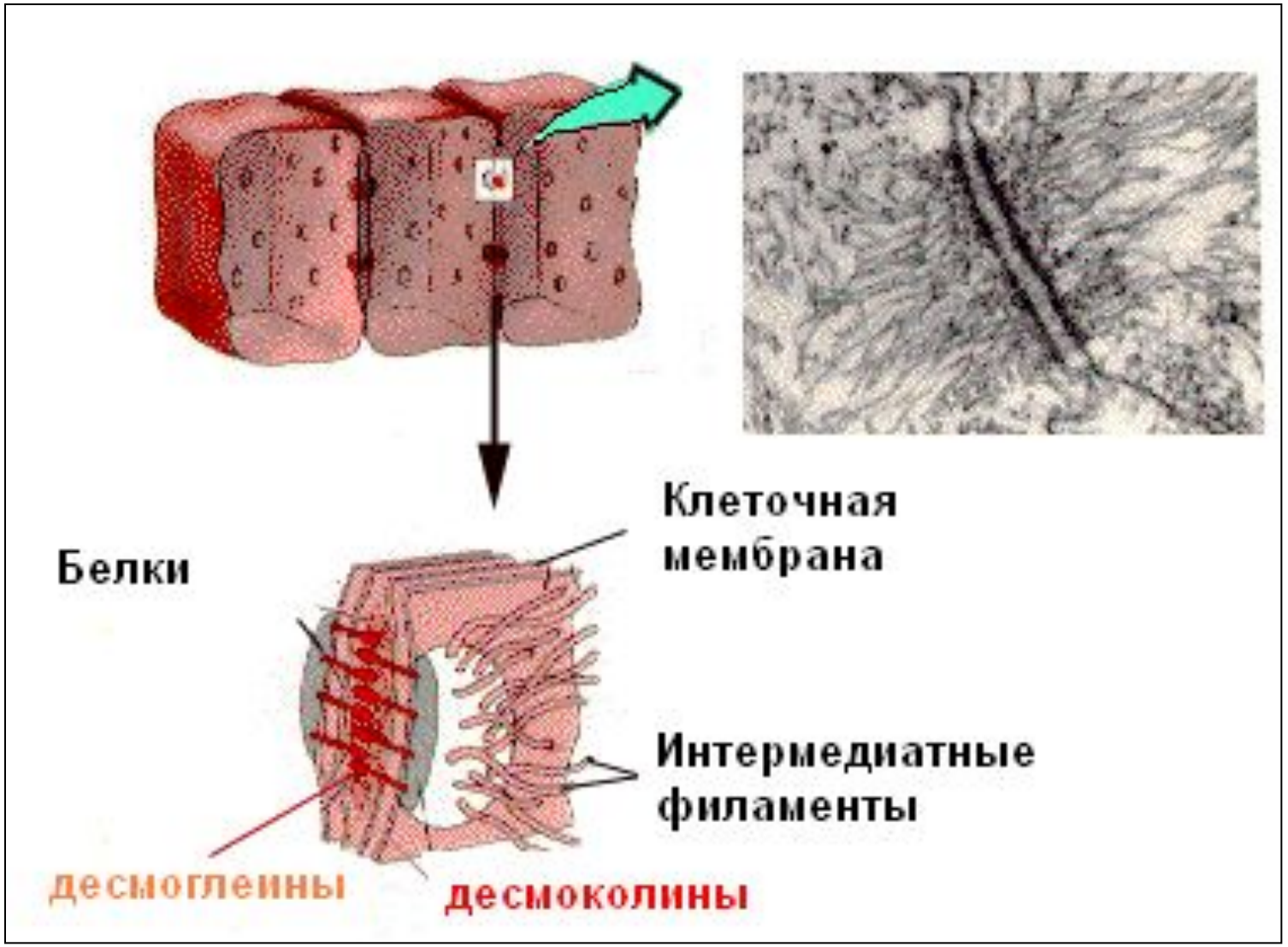
Кадхерины

Взаимодействие с активном цитоскелета: кадхерины N; P; R; B; E
Ассоциированные с десмосомами: Десмоглеины & десмоколины
Взаимодействие с интермедиатными филаментами

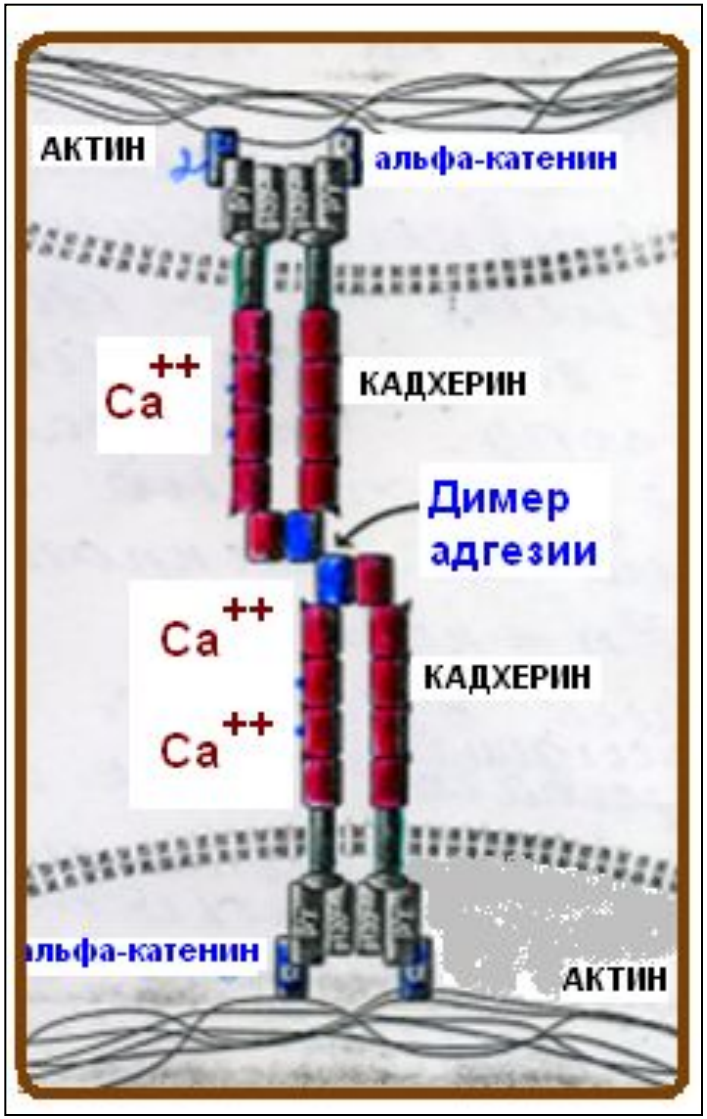




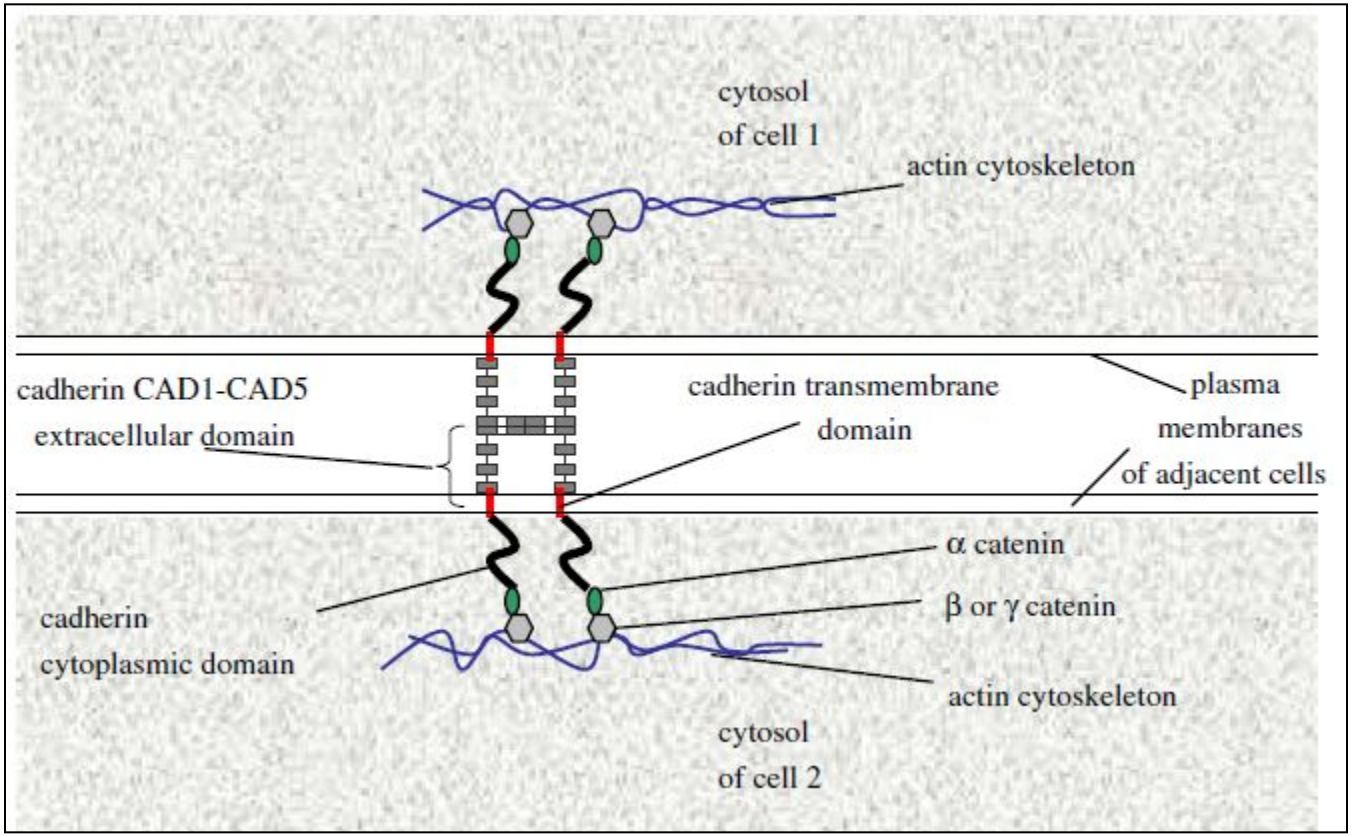
Десмосомы


Белки
Клеточная мембрана
Интермедиатные филаменты
десмоглеины
десмоколины

Взаимодействие кадхерина и катенина (1)



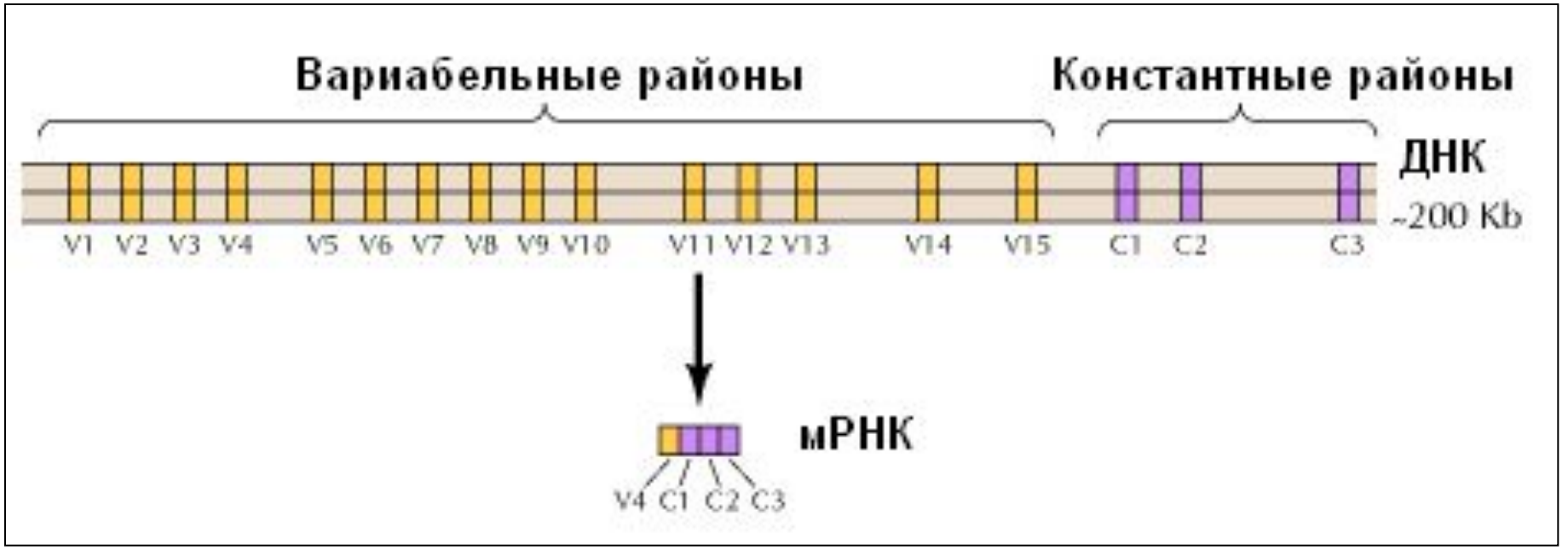
Взаимодействие кадхерина и катенина (2)



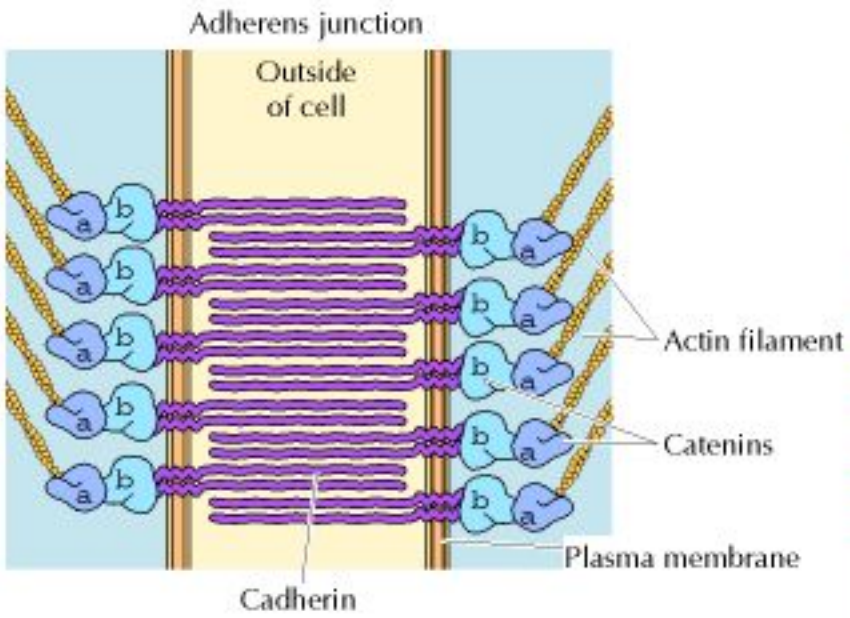
Ca^{2+} - зависимые адгезивные молекулы

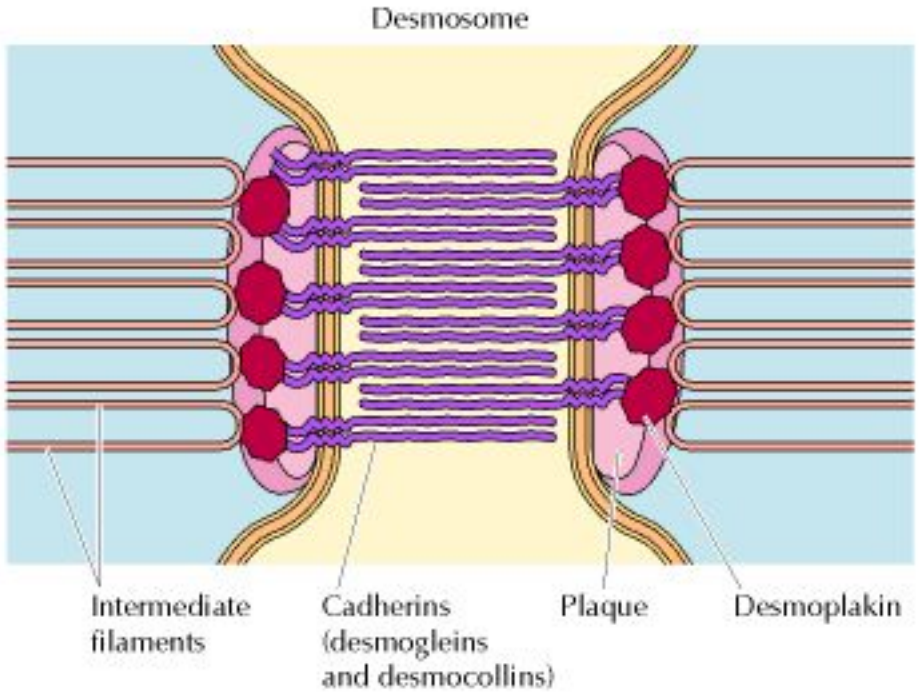
Тип кадхерина	Ткань	Структура	Внутрикл. связ. белки	Цитоплаз. филаменты
E-Cadherin; P-Cadherin	Эпителиальные клетки	adhesion belts	Катенины, альфа-актин	Актин
Desmosomal Cadherin	Эпидермис и плацента	desmosomes	Десмоплакины I, II; Плакоглобулин	Кератин; десмин
N-Cadherin	Нервы, мышцы клетки хрусталика	adhesion belts	Катенины, альфа-актин, винкулин	Актин

Организация генных кластеров кадхеринов



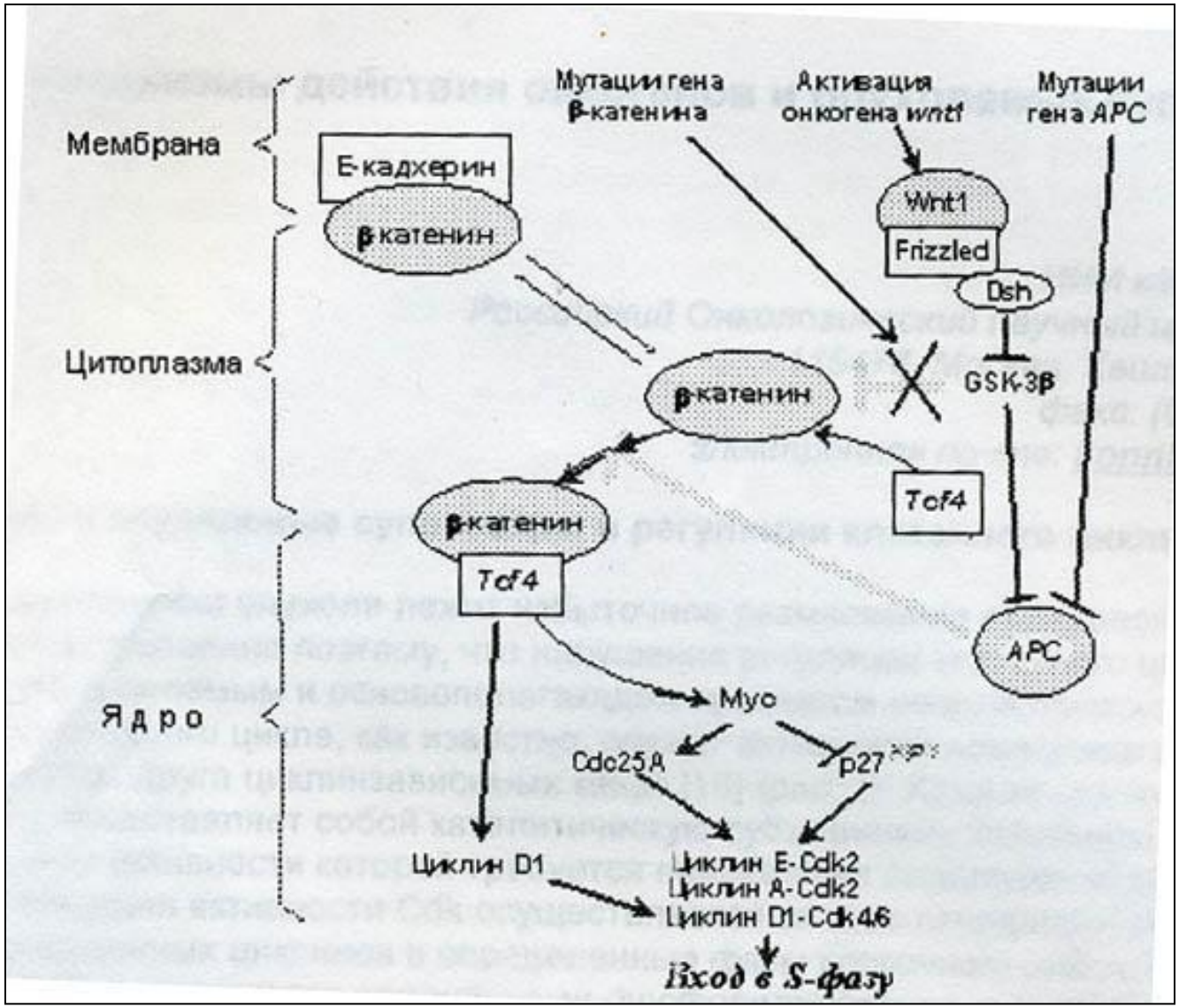
Два типа взаимодействий с участием кадхеринов



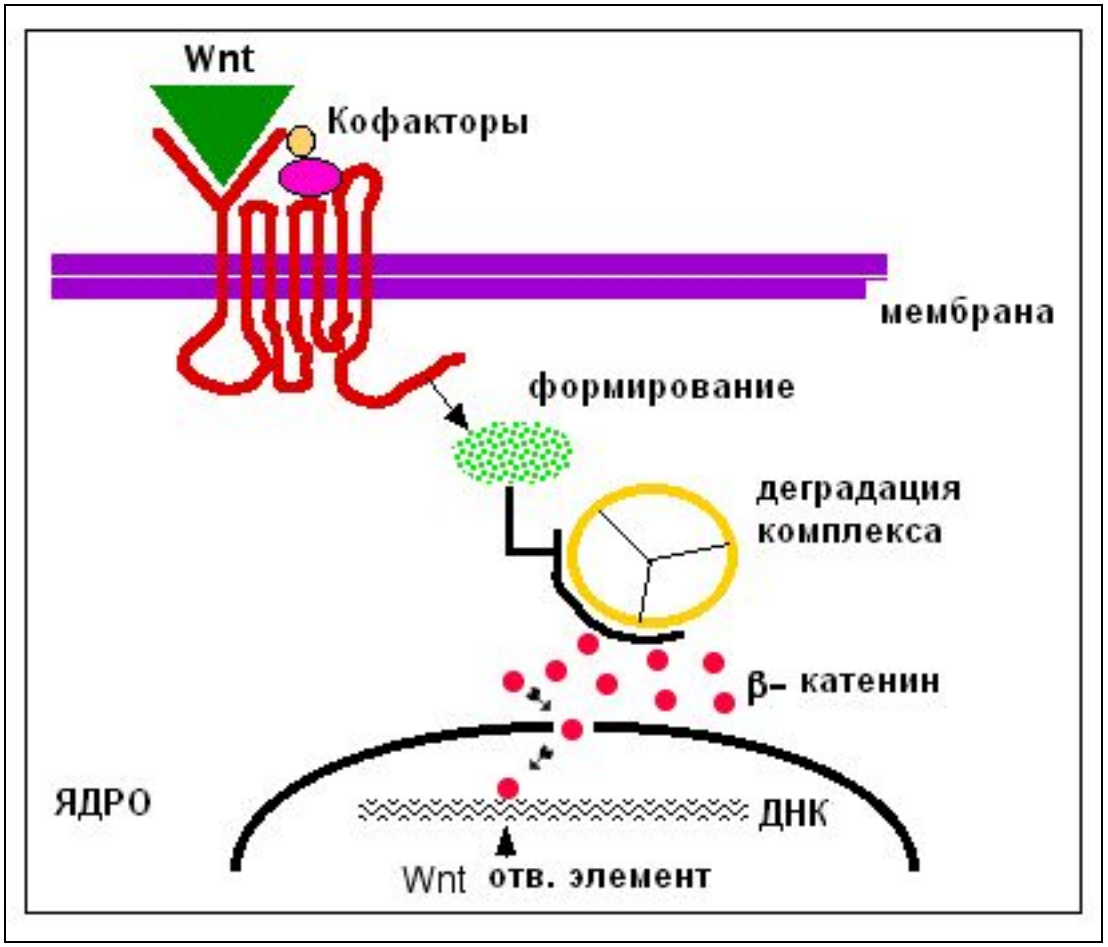


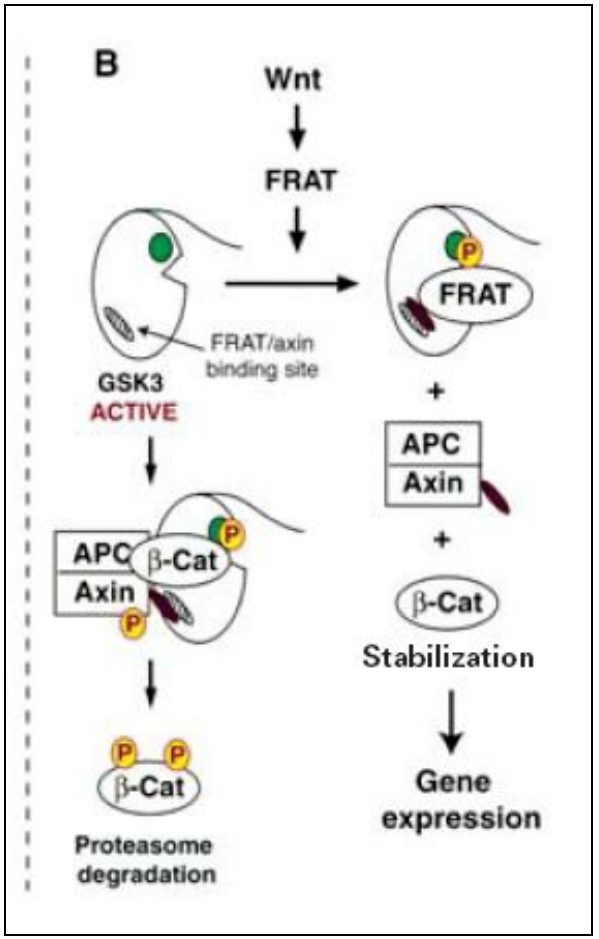
Роль фосфорилирования/ дефосфорилирования в адгезии

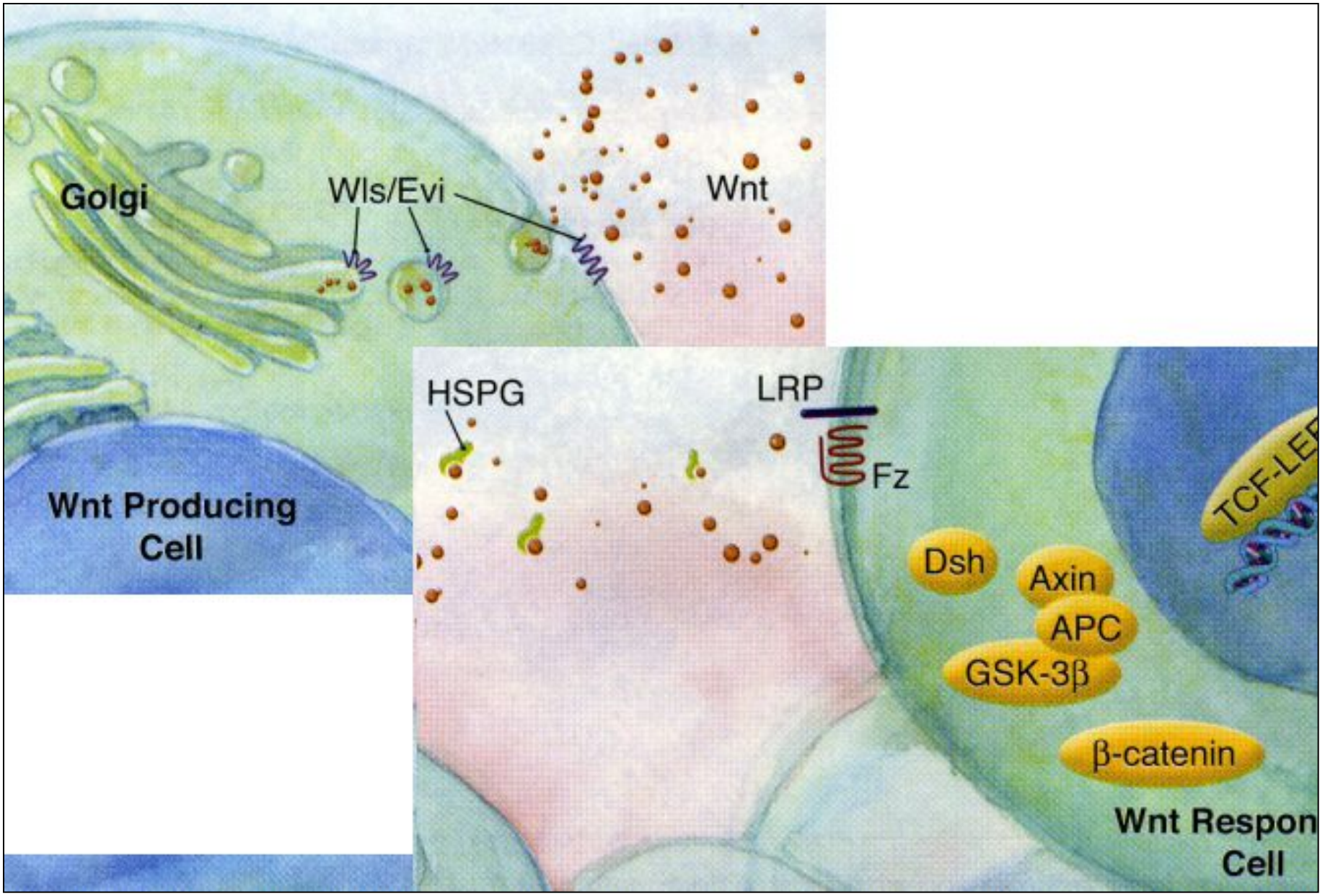
Кадхерины и катенины в СТ



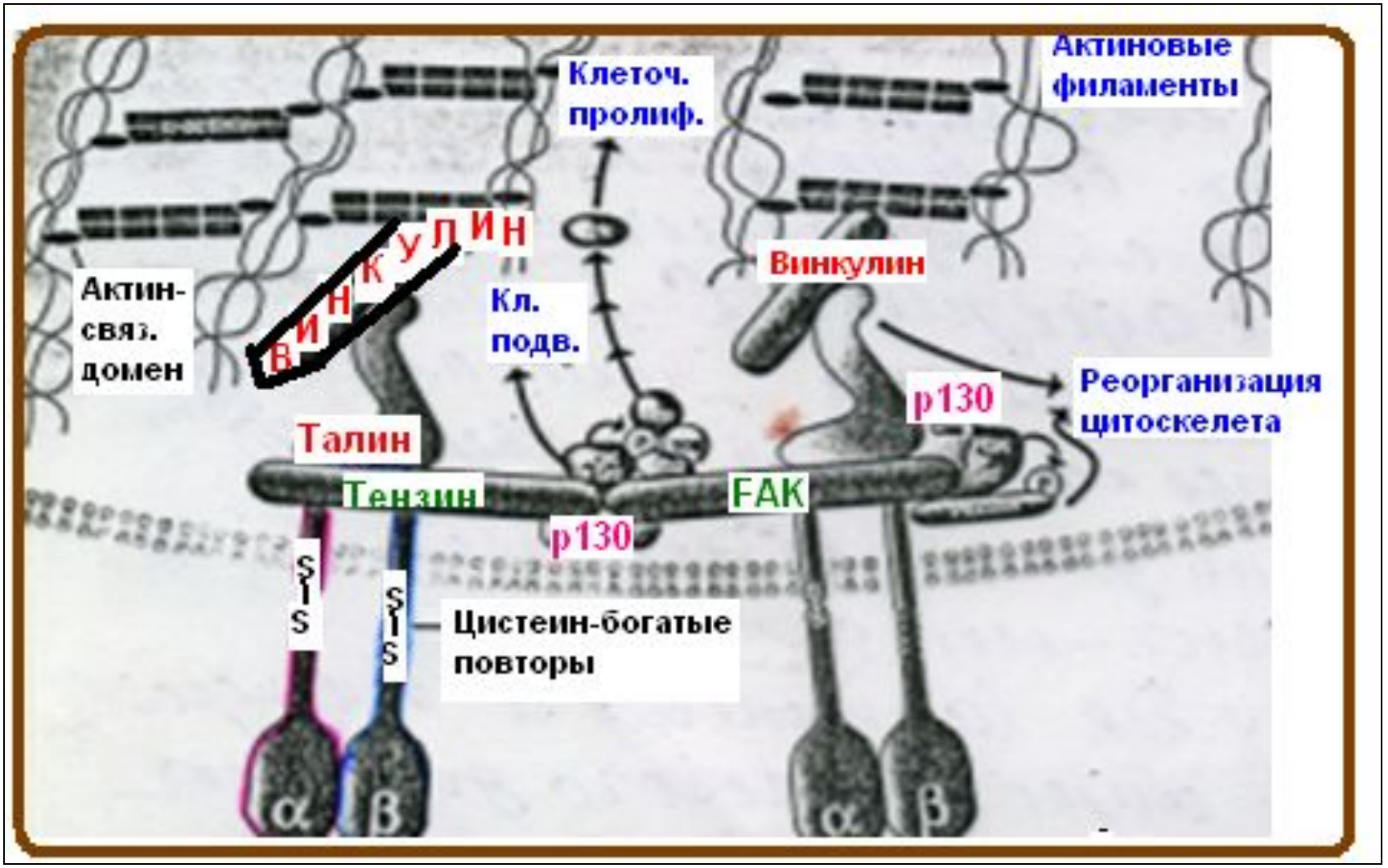
Wnt путь СТ


Wnt
Кофакторы
мембрана
формирование
деградация
комплекса
β– катенин
ЯДРО
ДНК
Wnt отв. элемент

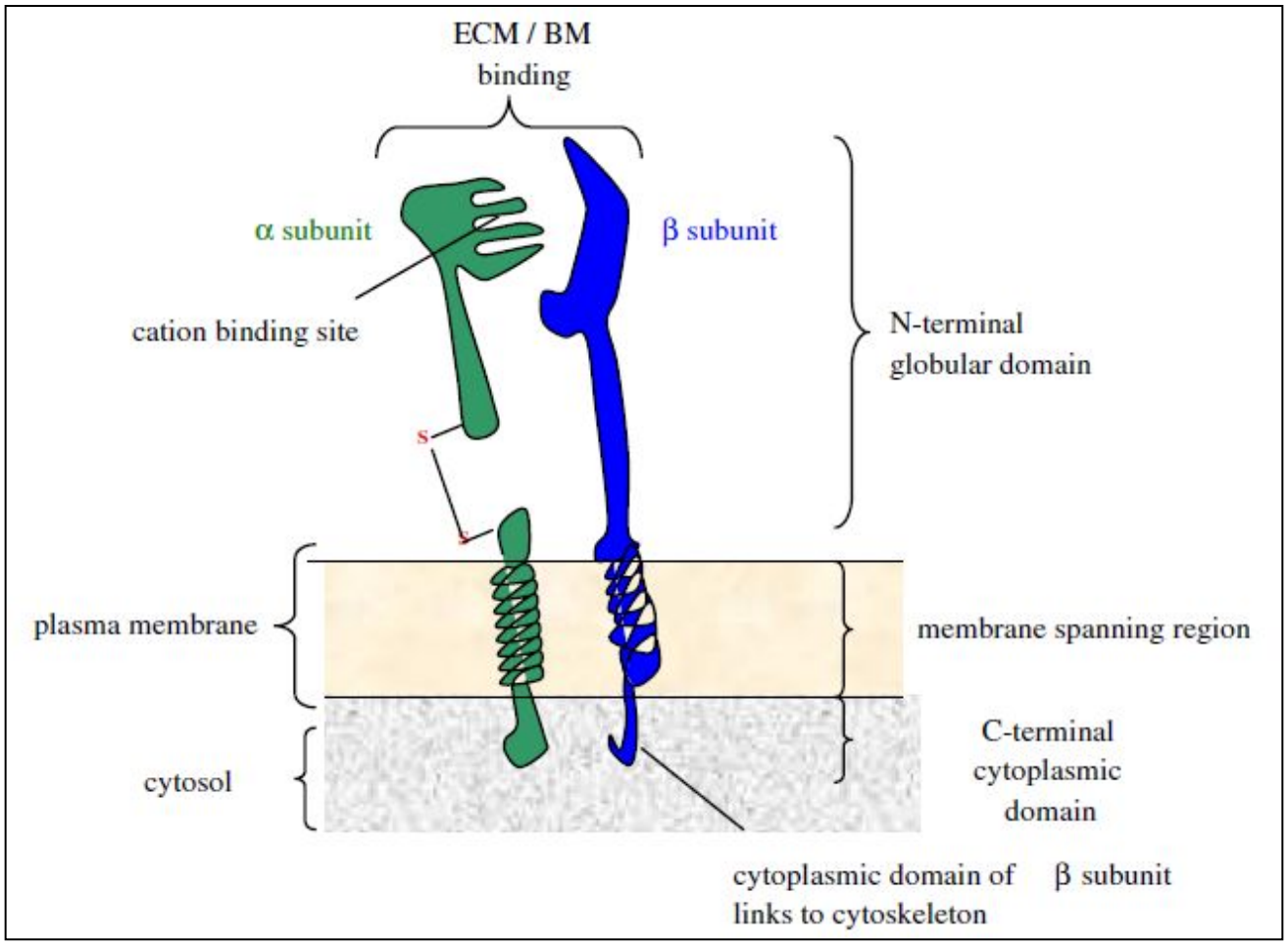

B
Wnt
FRAT
FRAT/axin
binding site
GSK3
ACTIVE
FRAT
+
APC
Axin
+
β-Cat
Stabilization
APC
Axin
β-Cat
β-Cat
Proteasome
degradation
Gene
expression


Golgi
Wls/Evi
Wnt
Wnt Producing Cell
HSPG
LRP
Fz
Dsh
Axin
APC
GSK-3β
β-catenin
Wnt Respon
Cell

Взаимодействие через интегрины



Структура интегринов

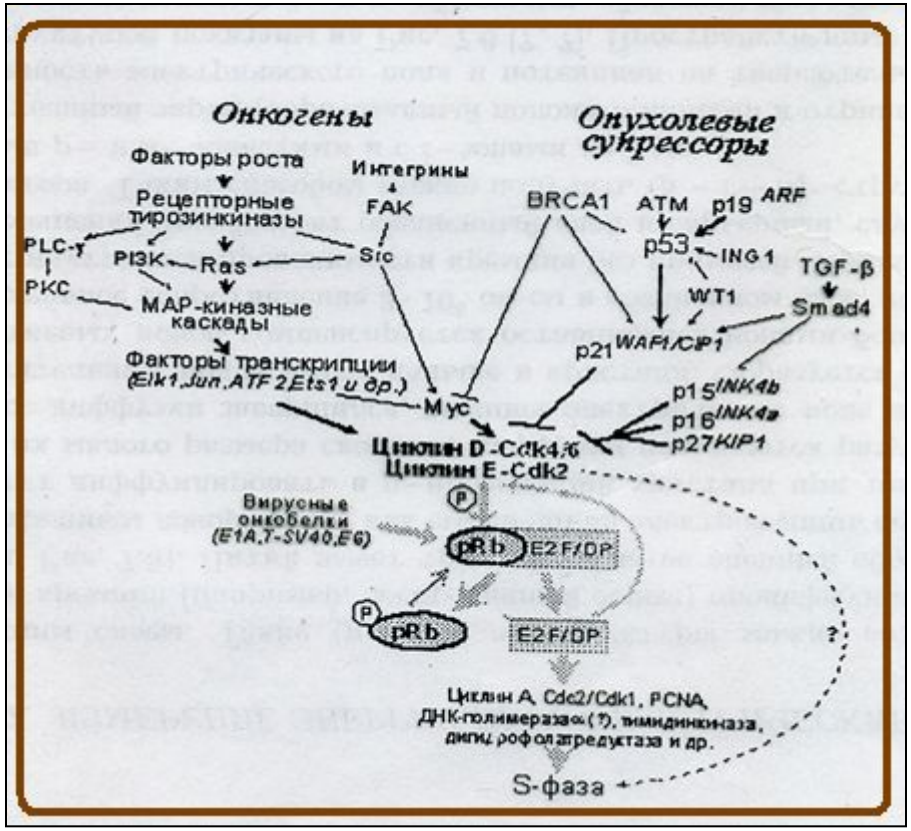


Интегрины и их лиганды

Integrin subunits		Alternative nomenclature	Ligand
$\beta 1$	$\alpha 2$	VLA-2/Cd49b/CD29/	Coll, lam, $\alpha 3\beta 1$
	$\alpha 3$	la-lla	Lam, coll, $\alpha 2\beta 1$,$\alpha 3\beta 1$
	$\alpha 5$	VLA-3/CD49c/CD29/ VLA-5	fn (RGD)
$\beta 3$	αv		fn, fb (RGD)
$\beta 4$	$\alpha 6$	CD49e/CD104	Lam
$\beta 5$	αv		fn (RGD)
$\beta 6$	αv		fn (RGD)

en = entactin, fn = fibronectin, fb = fibrinogen, lam = laminin, vn = vitronectin.

Интегрины в СТ



Примеры интегринов

Молекулы	Лиганды	Распределение
α1β1	Laminin; Collagen Tenascin, common form	NK, B & Activated T cells; Fibroblasts; Glial Perineurium; Schwann cells; Endothelial
α2β1	Laminin; Collagen	NK, B & Activated T cells; Platelets Endothelial; Fibroblasts; Epithelium Astrocytes; Schwann cells; Ependymal
α3β1	Laminin; Collagen; Fibronectin	Activated T cells; Thymocytes; Endothelium; Fibroblasts; Epithelium; Astrocytes
α4β1	α4β1; α4β7; Fibronectin; VCAM-1; MAdCAM-1; TSP-1	NK, B & T cells; Eosinophils; Endothelial; Muscle; Fibroblasts; Neural-crest derived **Function**: T cell Transendothelial migration
α5β1	Fibronectin; murine L1	Activated B & T cells; memory T-cells; Thymocytes; Fibroblasts; Epithelium; Platelets; Endothelial; Astrocytes **α-5 disease**: Myopathy in Chimeric mouse
α6β1	Laminin	Leukocytes; Thymocytes; Epithelial; T cells (Memory & activated) Glial; Fibroblasts; Endothelial **α-6 disease**: Junctional epidermolysis bullosa

Селектины

Молекулы	Лиганды	Распределение
L-selectin (CD62L)	Sulfated: GlyCAM-1 CD34 MAdCAM-1	Leukocytes (Homing receptor)
E-selectin (CD62e)	Tetrasaccharides: Sialyl-Lewis^{X}; Sialyl-Lewis^{a} Cutaneous lymphocyte-associated antigen	Endothelial cells
P-selectin (CD62P)	Tetrasaccharides: Sialyl-Lewis^{X} P-selectin glycoprotein ligand-1	Endothelial cells Platelets

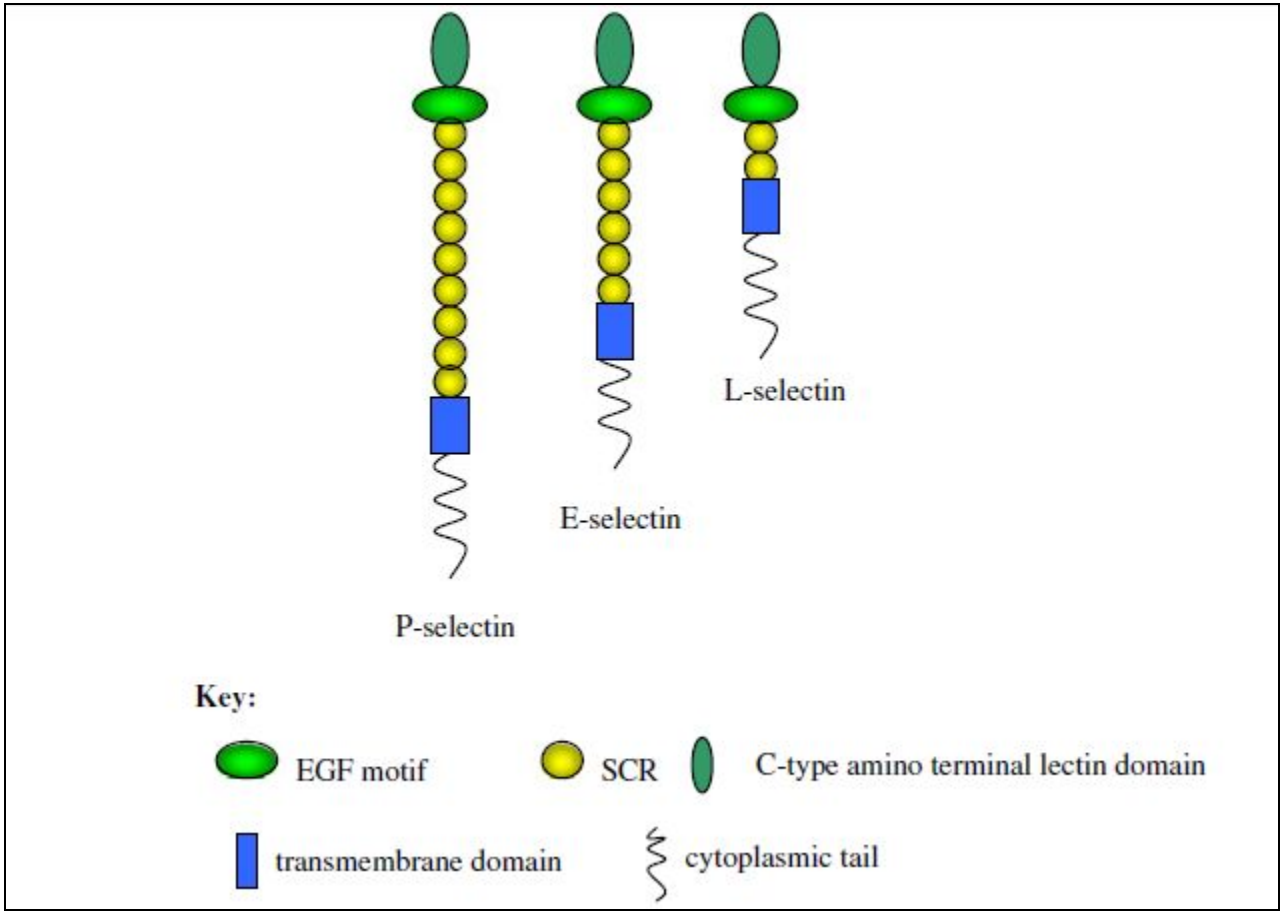
Функции селектинов

- Медленная миграция интраваскулярных лейкоцитов
- E-селектин: Адгезия к эндотелиальным клеткам
- Адгезия подвижная, не прочная
- Непрочная адгезия через LFA/ICAM-1 & VLA-4/VCAM-1

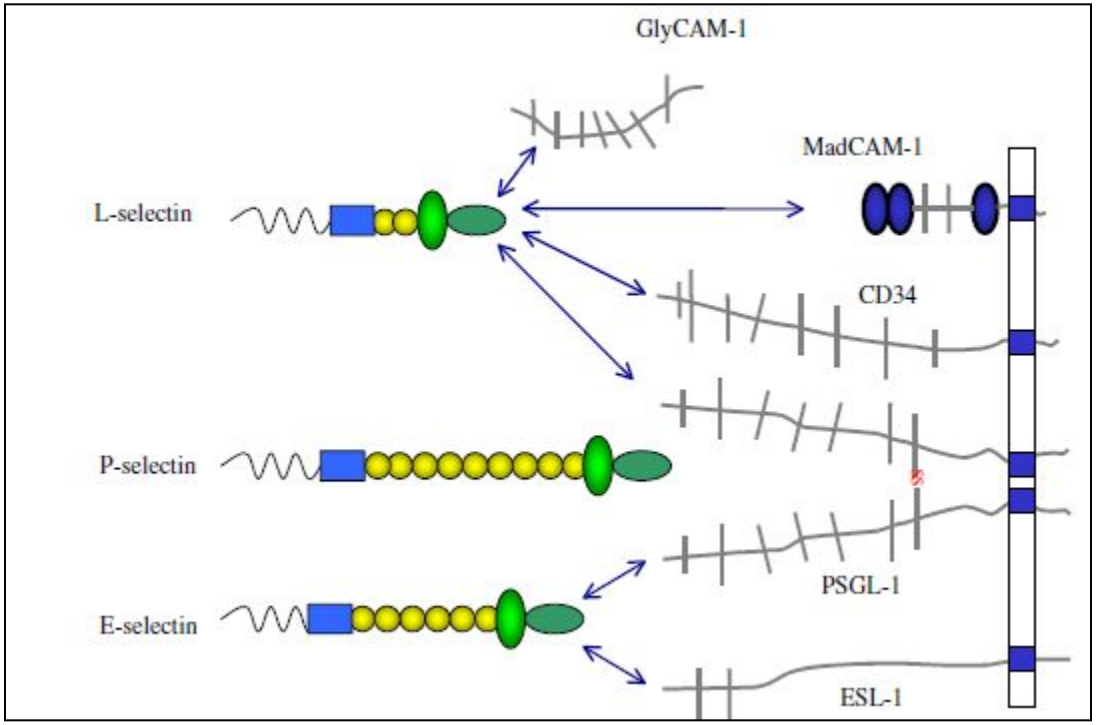
Номенклатура селектинов

Designation (alternative nomenclature)	Regulation of expression	Cellular distribution
L-(leukocyte) selectin (CD62L, LECAM-1, LAM-1, $gp90^{mel}$)	Constitutively expressed on leukocytes, monocytes and neutrophils. Expression is controlled by proteolytic shedding from the cell surface after cell–cell adhesion.	All circulating leukocytes, including subpopulations of lymphocytes.
P-(platelet) selectin (CD62P, GMP-140, PADGEM)	Rapidly elicited to the surface of platelets and endothelial cells by thrombin or histamine; also transcriptionally induced by cytokines. Transiently expressed for approximately 1 h before internalisation and degradation.	Stored in the membranes of Weibel-Palade bodies of endothelial cells and the α-granules of platelets, megakaryocytes and activated endothelial cells.
E-(endothelial) selectin (CD62E, ELAM-1)	Transcriptionally induced and rapidly elicited to the surface of endothelial cells in response to cytokine activation. Expression is transient, peaking within 4–6 h and declining to baseline levels within 24 h	Activated endothelial cells.

Структура селектинов



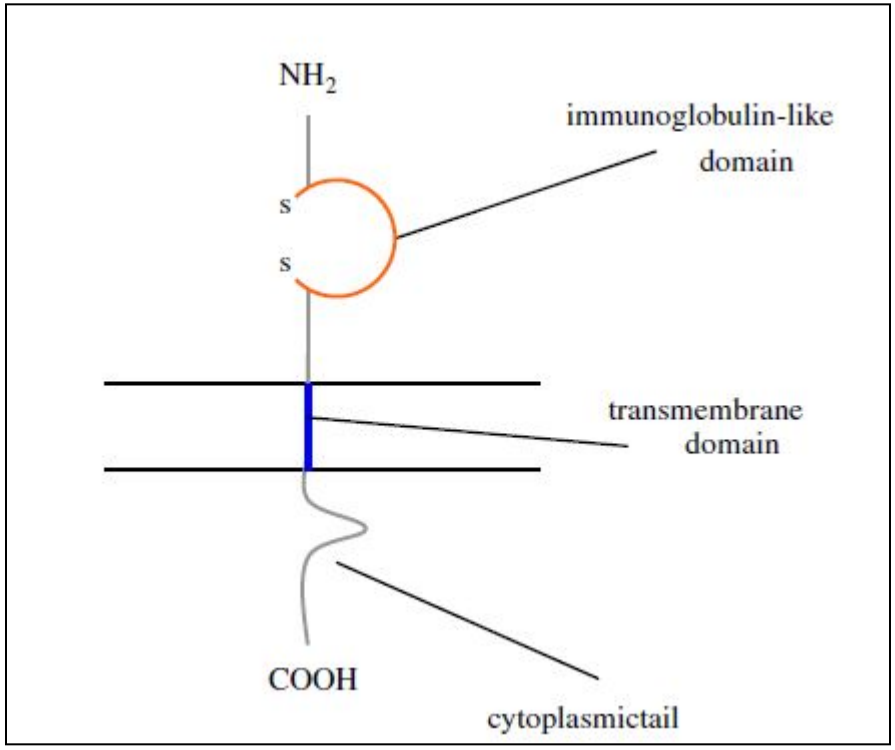
Партнеры для селектинов



Некоторые (IgSF CAMs)

Молекулы	Лиганды	Распределение
Adhesion molecule on glia (AMOG)		Glial Neural migration
L1CAM	Axonin	Neural
Myelin-associated glycoprotein (MAG)	MAG	Myelin
Myelin-oligodendrocyte glycoprotein (MOG)		Myelin; Oligodendrocytes
NCAM-1 (CD56)	NCAM-1 via polysialic acid Modulated by Sialyltransferase X Polysialyltransferase	Neural cells

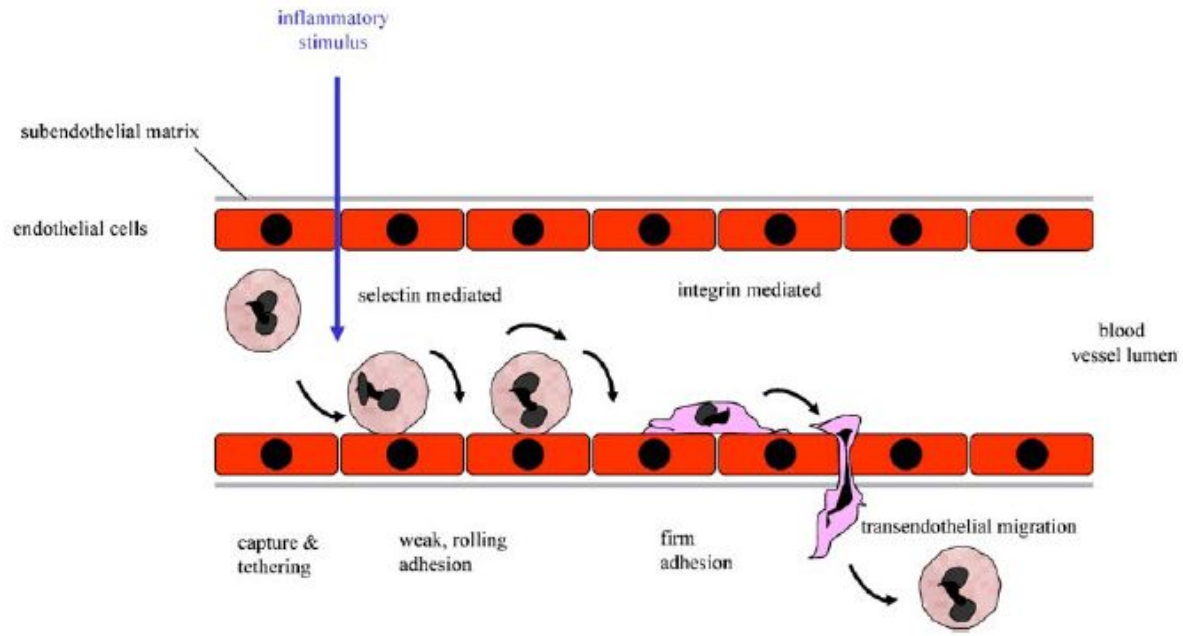
Общая структура IgSF



Примеры клеточной миграции и адгезии

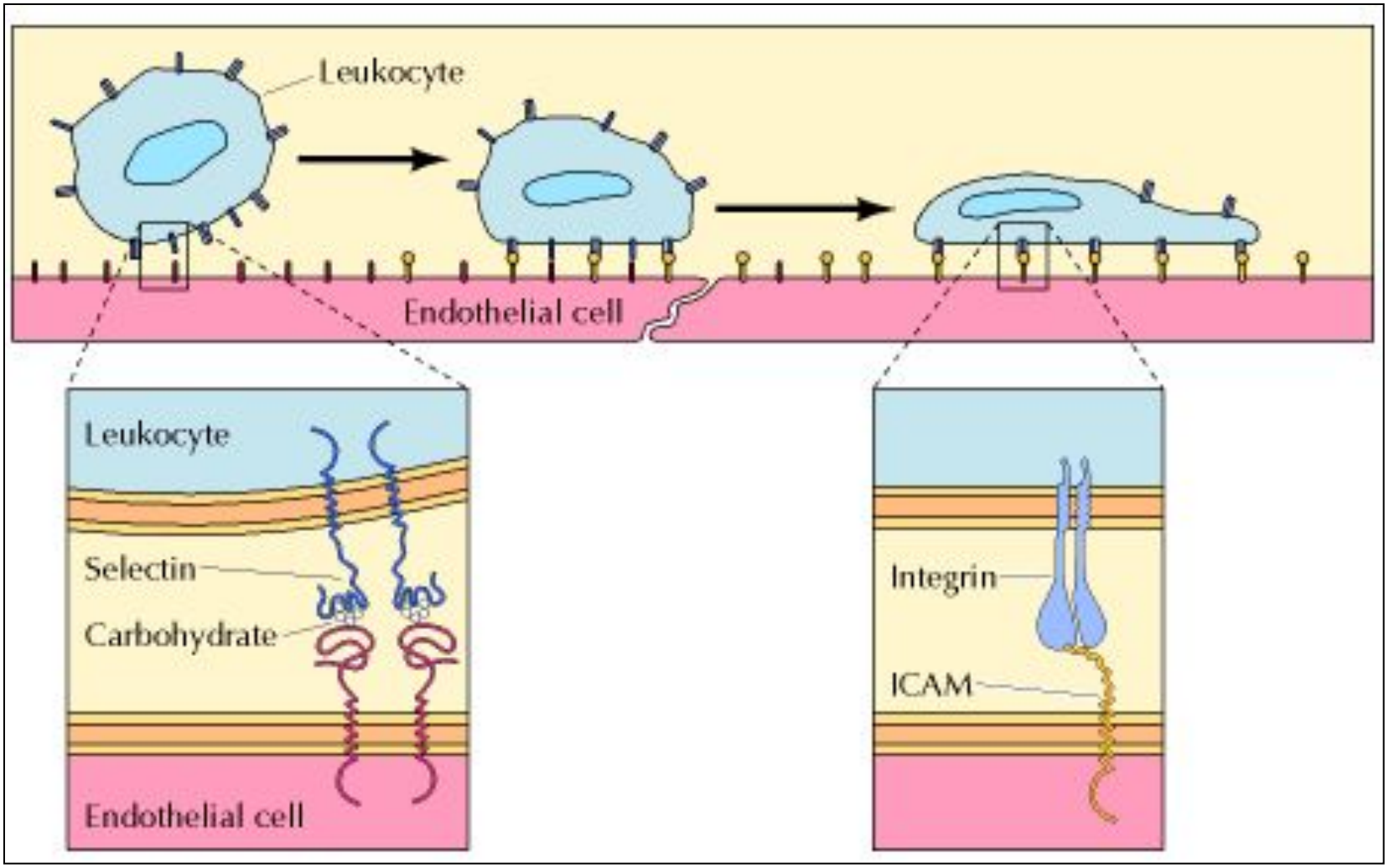
Механизм клеточной миграции

Взаимодействие лимфоцитов с васкулярным эндотелием



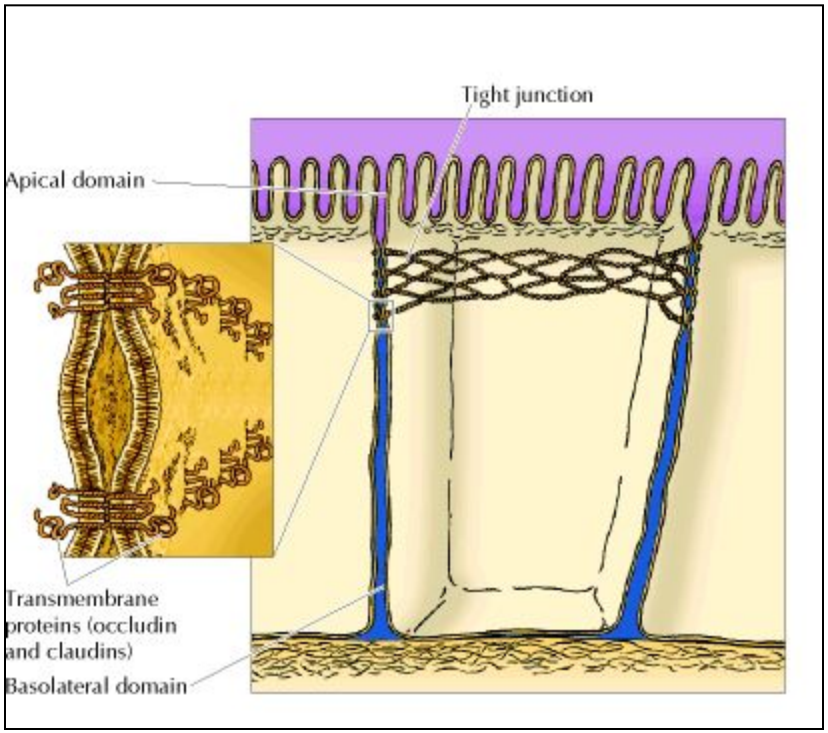
After cytokine stimulation, initial tethering and rolling of the lymphocytes to the endothelium mainly involves the selectins on endothelial cells recognising their carbohydrate binding partners on lymphocytes. The later firm adhesion and subsequent transmigration involves mainly the integrins expressed by lmphocytes recognising their ligands, including ICAM and PECAM-1, on the activated endothelium.

Адгезия между лейкоцитами и эндотелиальными клетками

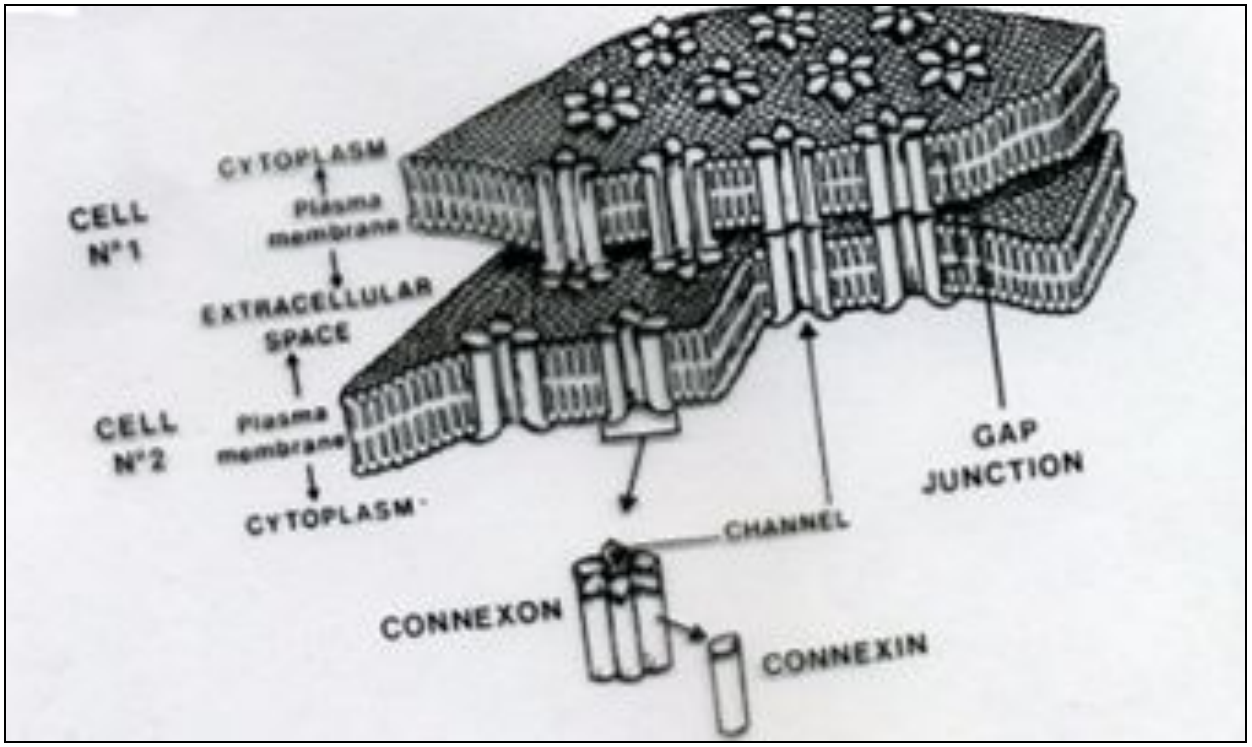


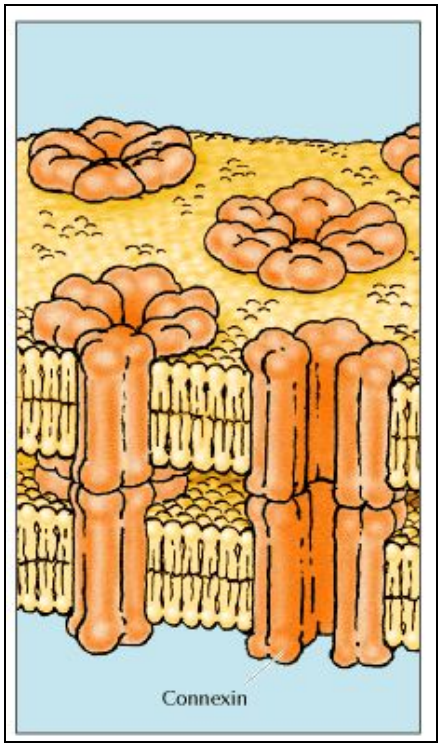
Межклеточные контакты

Плотные контакты

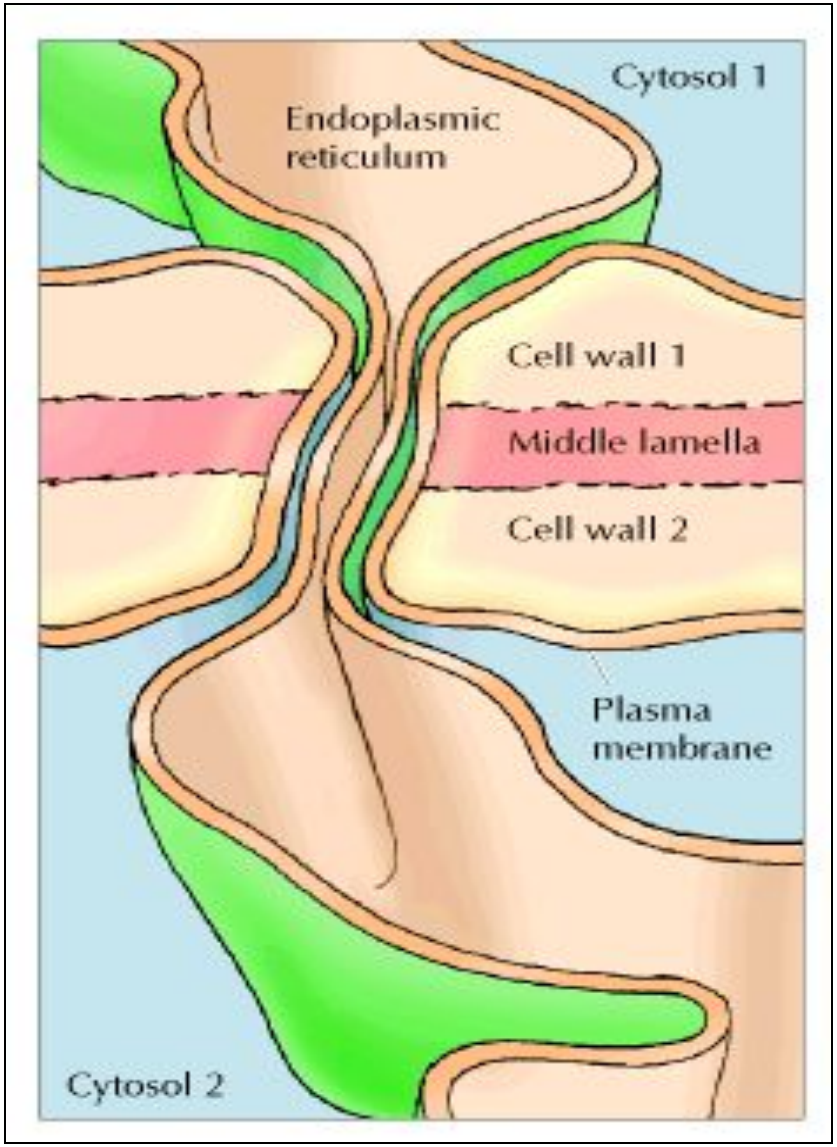


Щелевые контакты





Взаимодействие плазмодесмата



Металлопротеиназы

- Zn^{2+} и Ca^{2+} – зависимые
- **Matrix metalloproteinases** (MMPs) – (суперсемейство метзинцин) - Zn-зависимые эндопептидазы

Zn-св. мотив: HExxHxxGxxH

- Представители: Адамализины, серрализины и астрацины

Классификация ММР

- ММР-19; ММРs 11, 14, 15, 16 и 17; ММР-2,3 и ММР-9;

Это:

- Коллагеназы, желатиназы, стромелизины и мембранные ММРs (МТ-ММРs)

Коллагеназы

- Эти MMPs расщепляют 3-х спиральные фибриллярные коллагены хрящей и костей на различные ¾ и ¼ фрагменты.

- коллагены MMP-1 (междуузловая коллагеназа)
- MMP-8 (нейтрофильная коллагеназа_
- MMP-13 (коллагеназа 3)
- MMP-18
- MMP-14 (MT1-MMP)

Стромелизины

- **Расщепляют экстраклеточные матричные белки, но не коллаген**

Члены семейства:

- MMP-3 (стромелизин 1, прожелатиназа)
- MMP-10 (стромелизин 2)
- MMP-11 (стромелизин 3)
- MMP-11 схож с MT-MMPs, активируется конвертазой

Желатиназы

Основные субстраты:

Коллаген IY типа и желатин

Имеют дополнительной домен – желатин-св. домен к активном центре, который располагается непосредственно перед Zn-связывающей последовательностью. Это формирует отдельную фолдинговую субъединицу , которая не разрушает структуру каталитического домена.

- MMP-2 (экспрессируется во многих тканях)
- MMP-9 (преимущественно в нейтрофилах).

Функции MMPs:

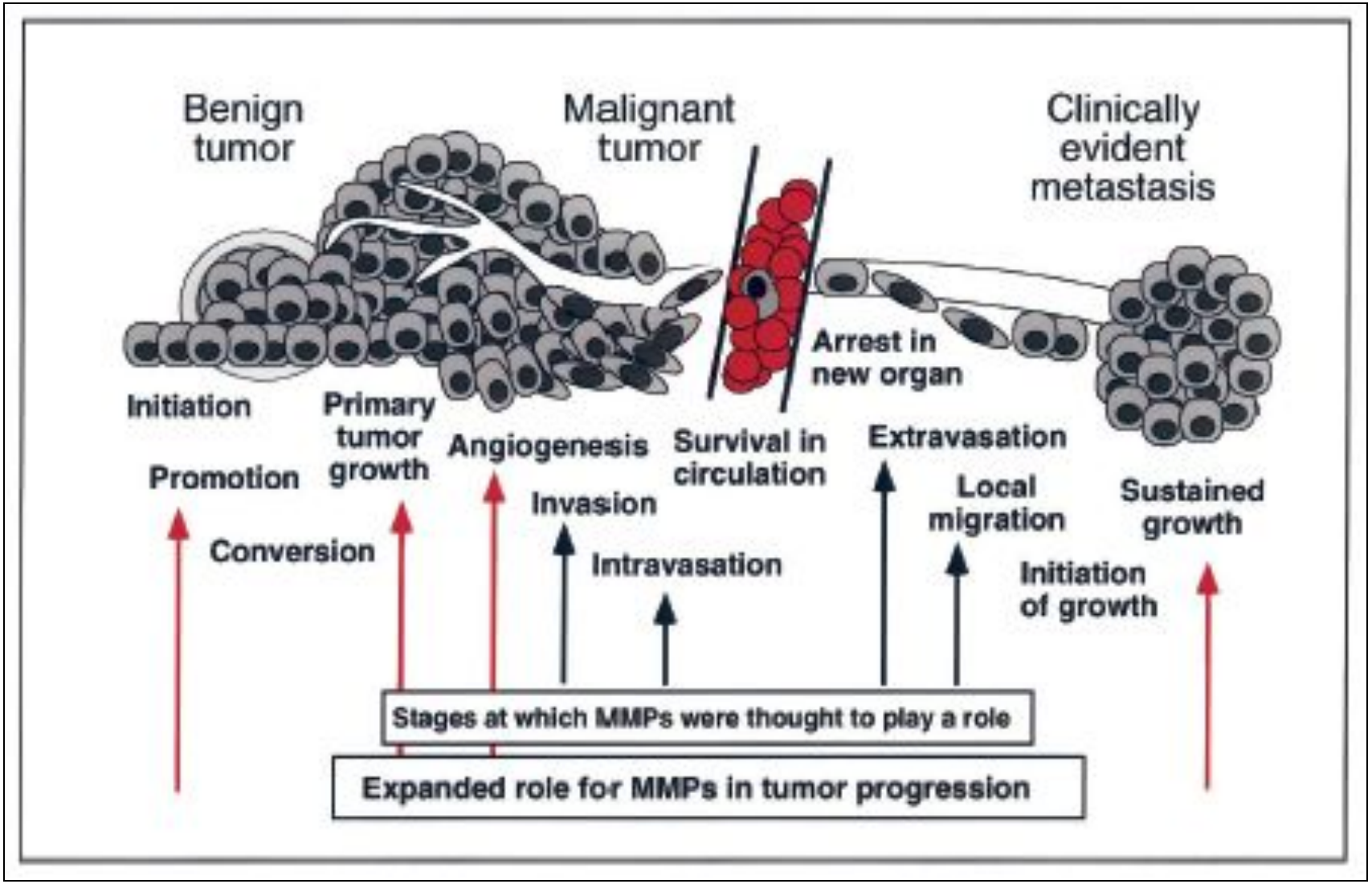
Ремодулирование тканей, связанное с такими процессами, как:

Морфогенез, ангиогенез, репарация тканей, цирроз, артрит, метастазы.

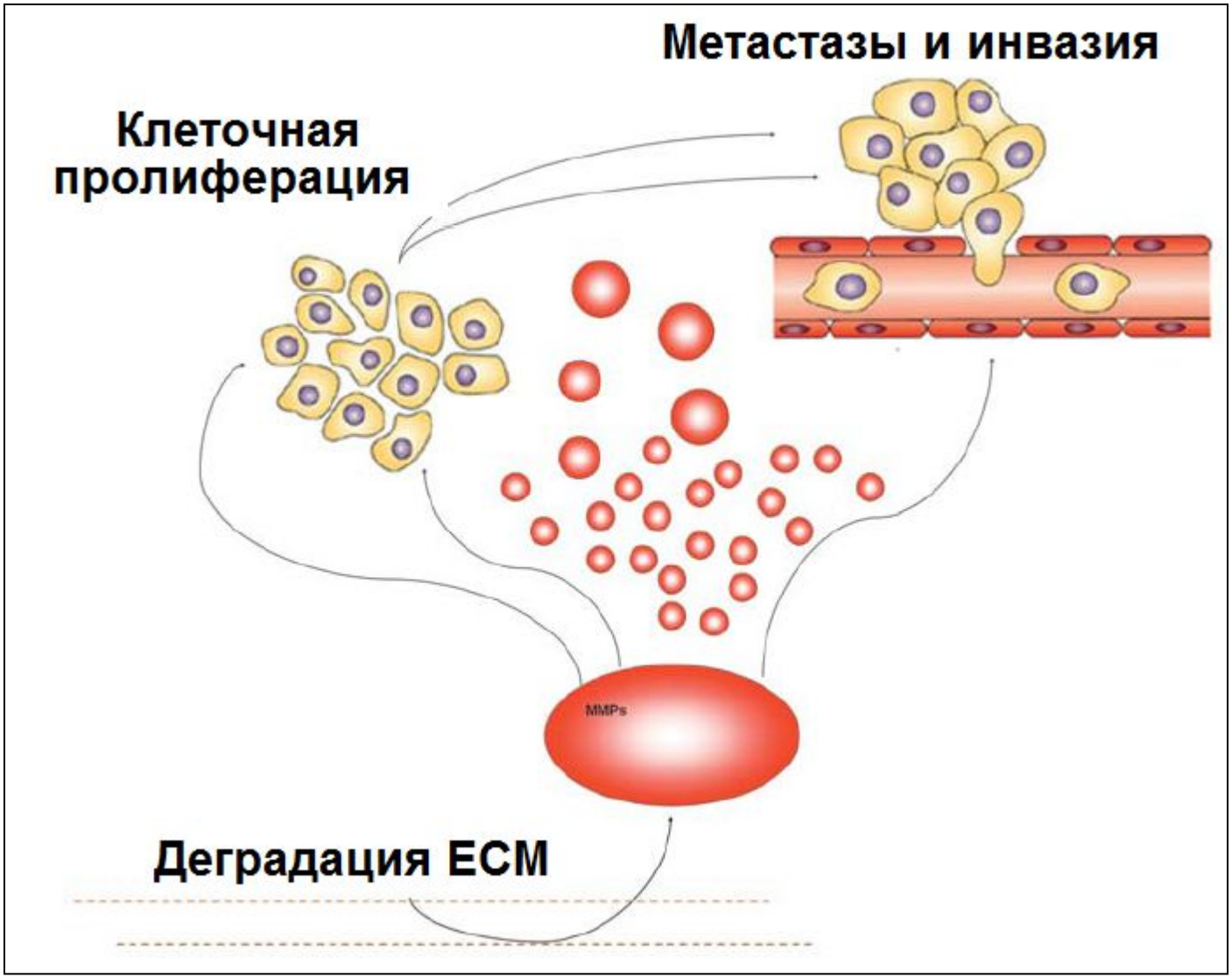
MMP-2 и MMP-9 – метастазы

MMP-1 – Ревматоидный и остео-артрит.

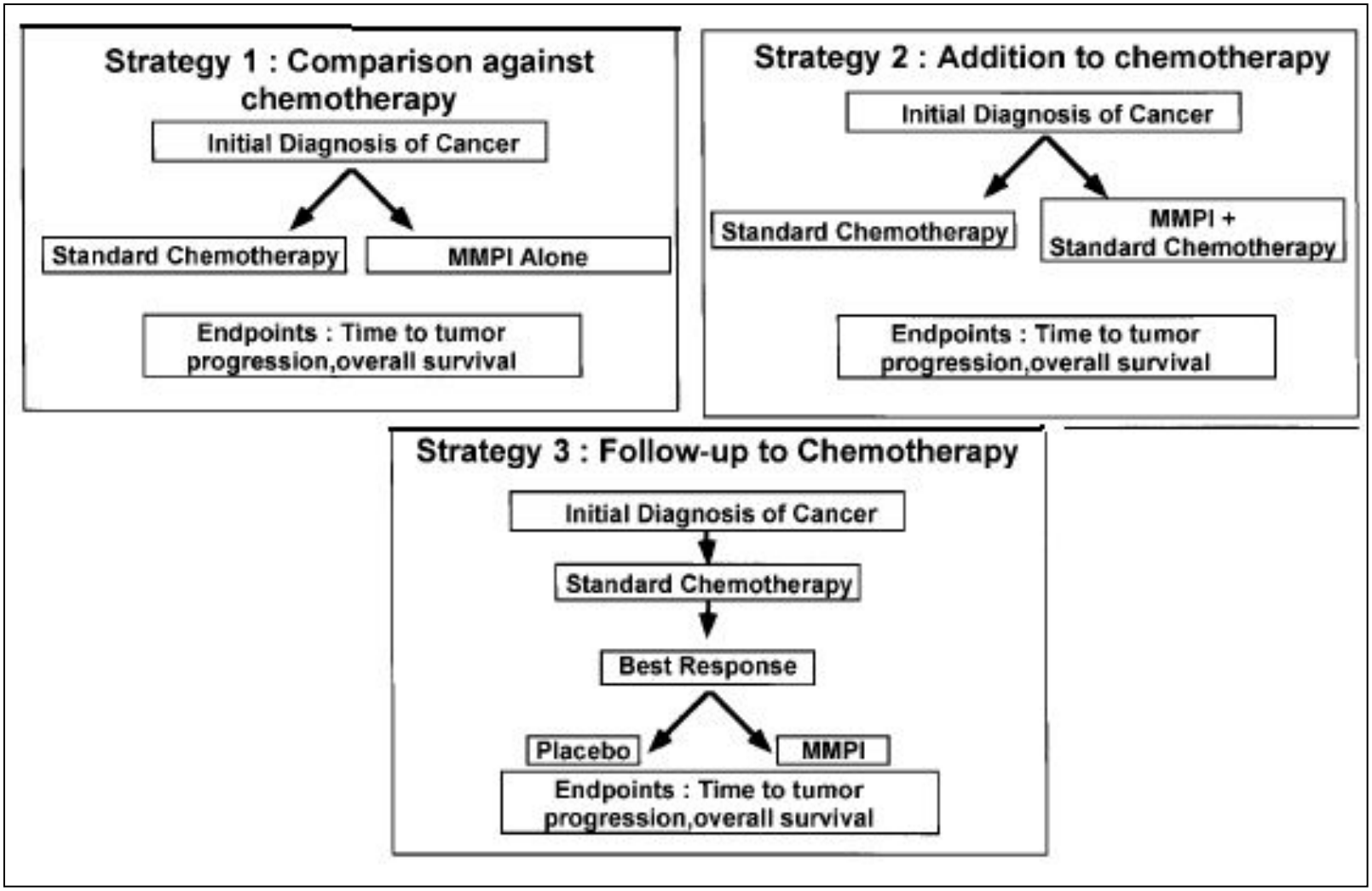
MMPs в прогрессии рака (1)



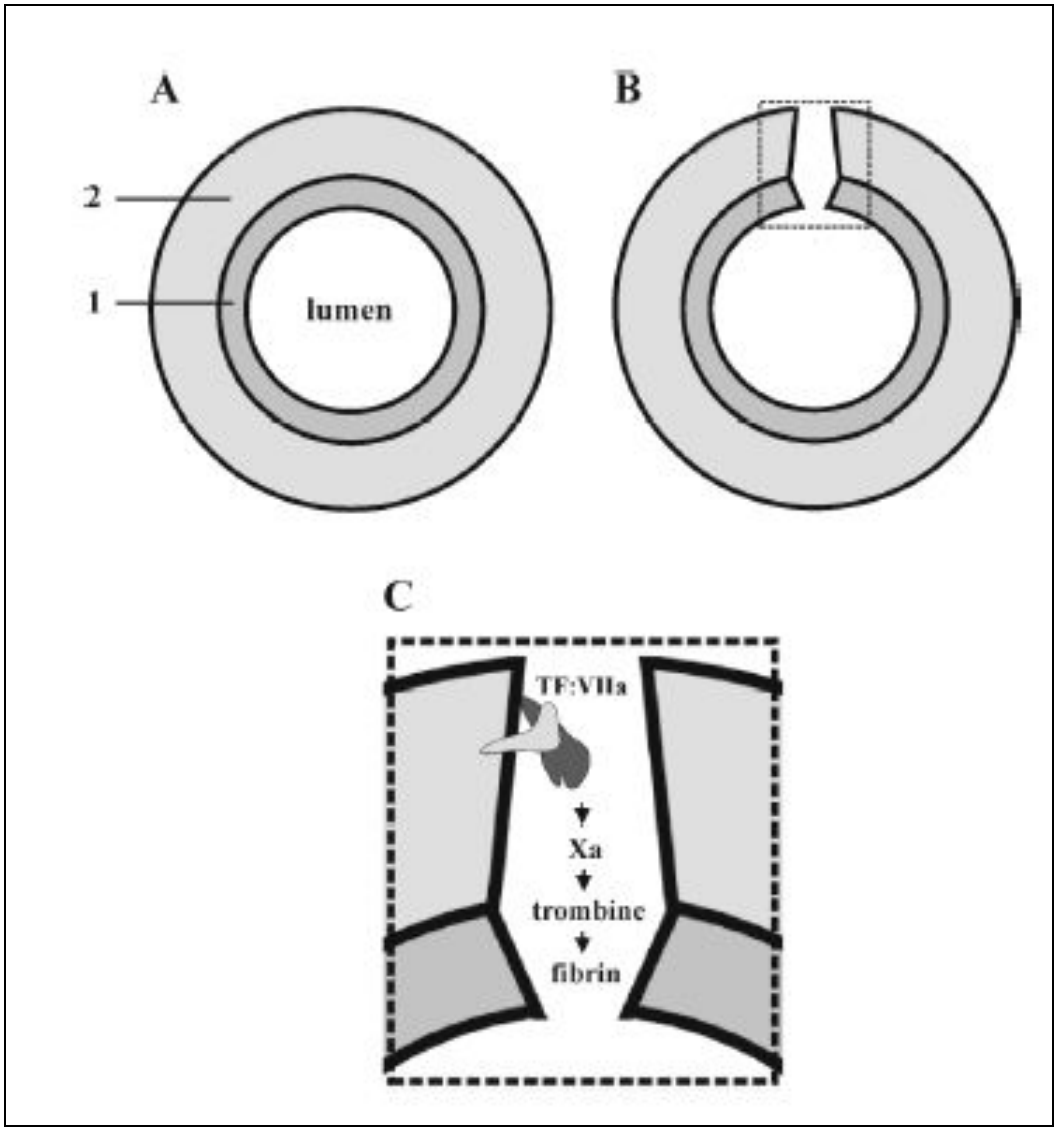
MMPs в прогрессии рака (2)



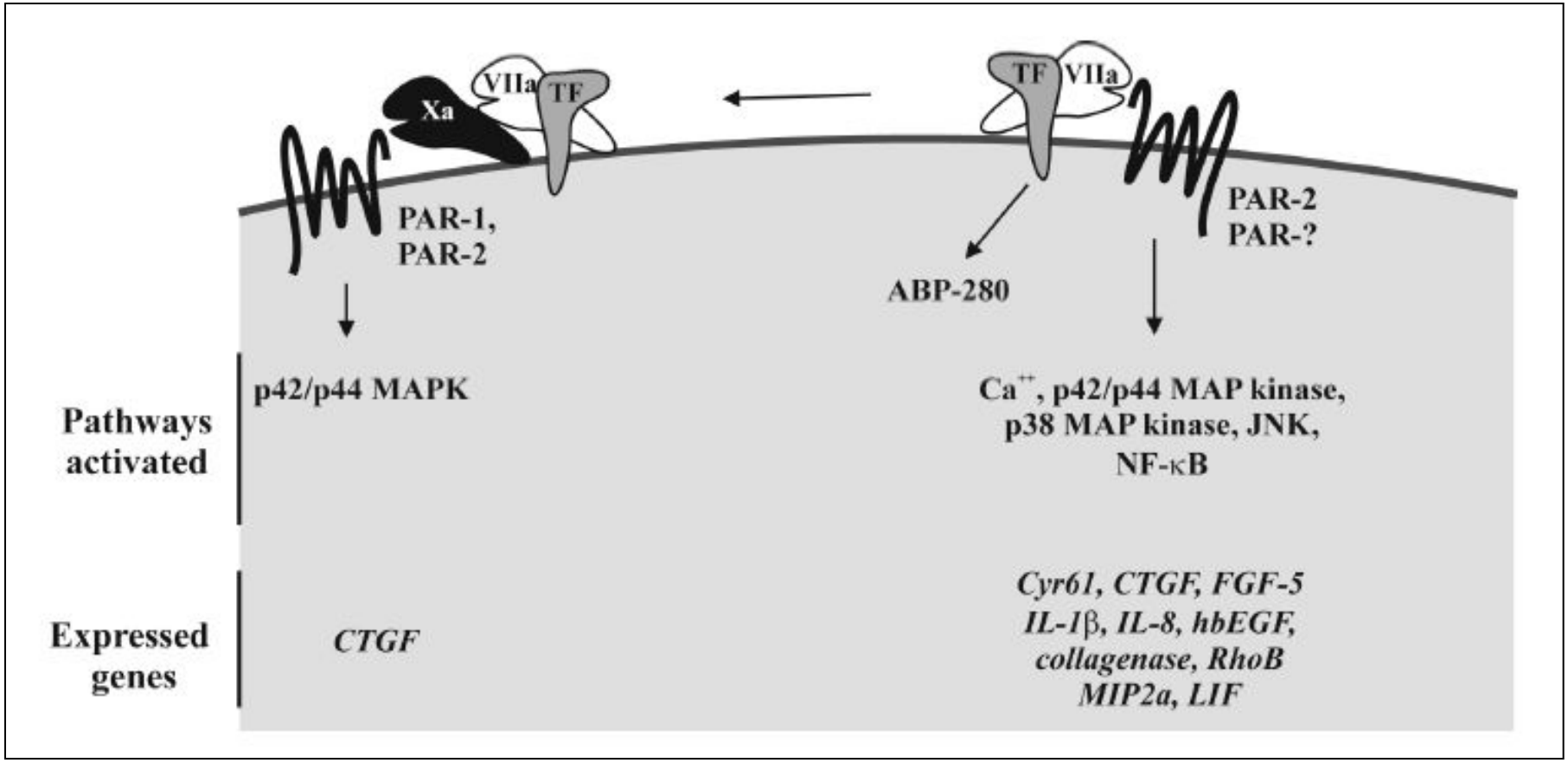
Стратегия применения ингибиторов MMPs



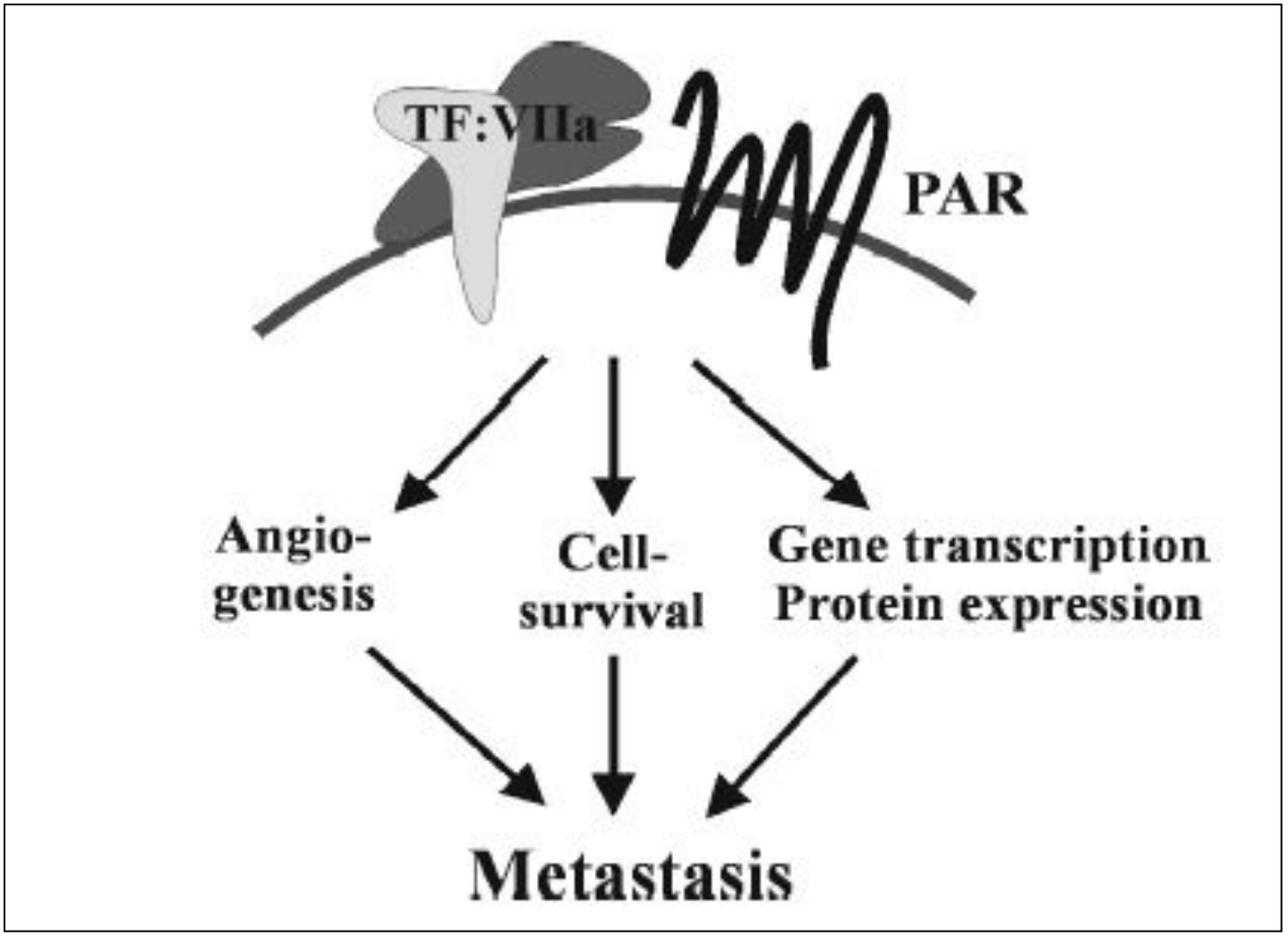
Образование активного комплекса TF



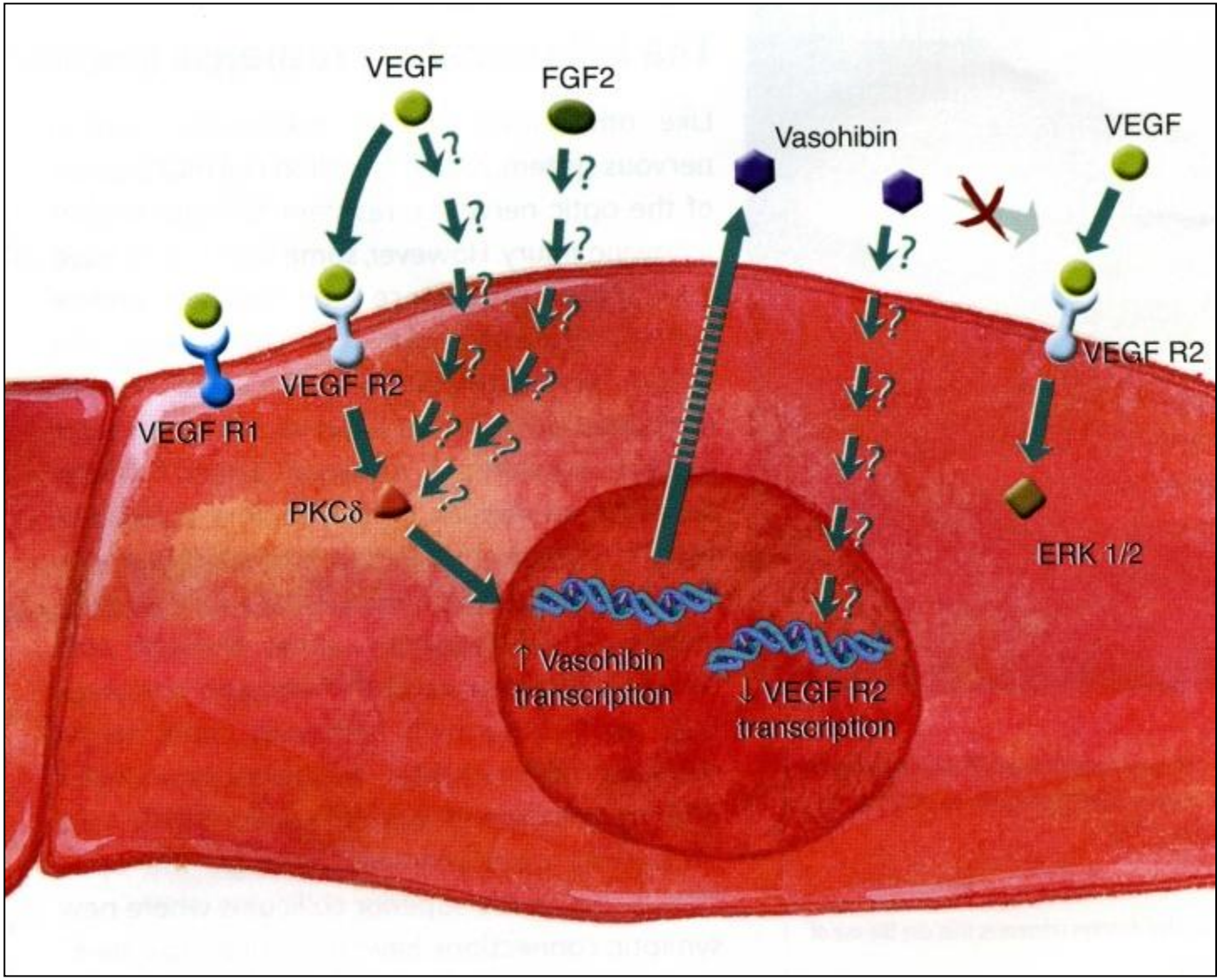
TF в передаче клеточного сигнала



Связь между образованием TF комплекса и метастазами

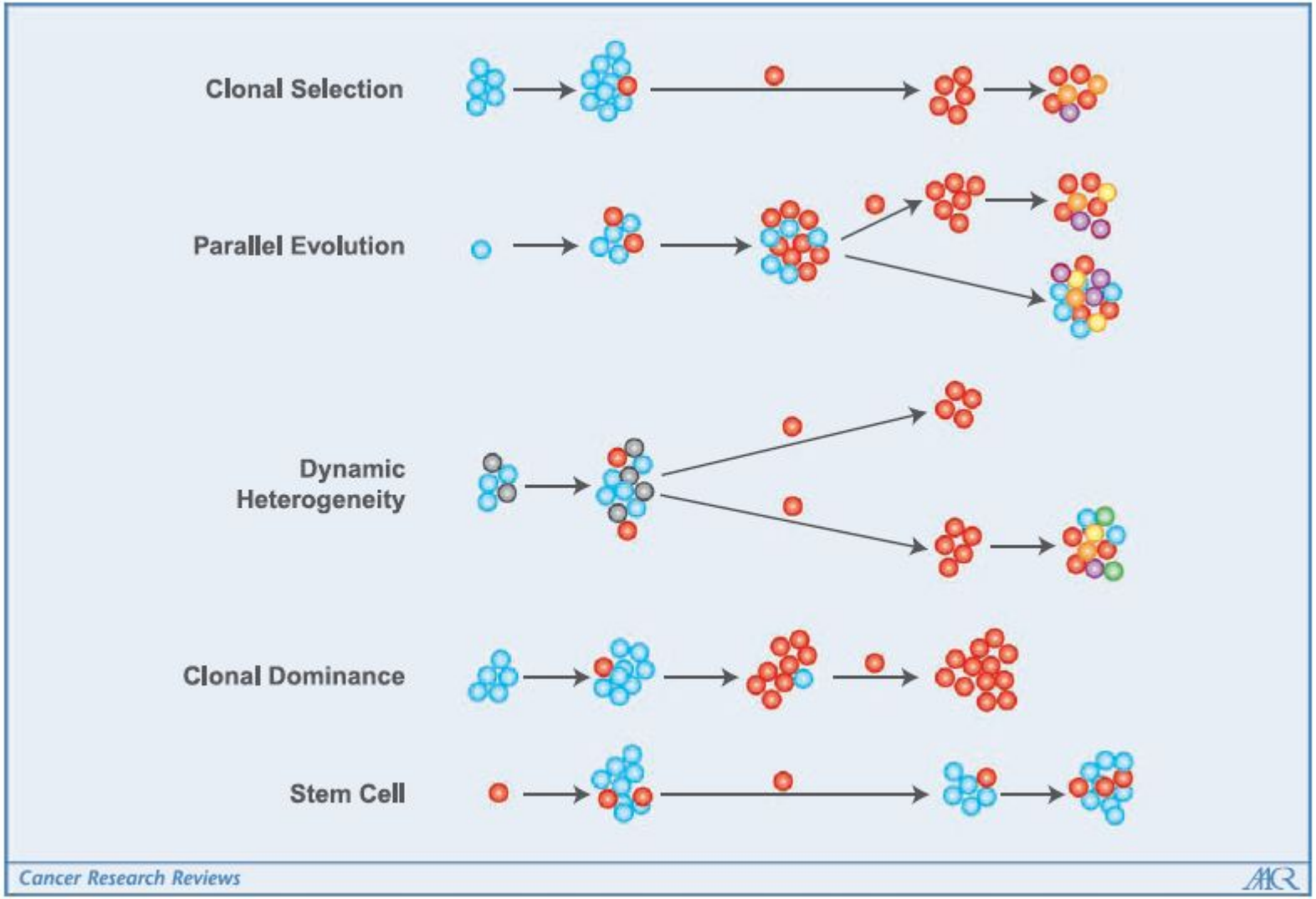


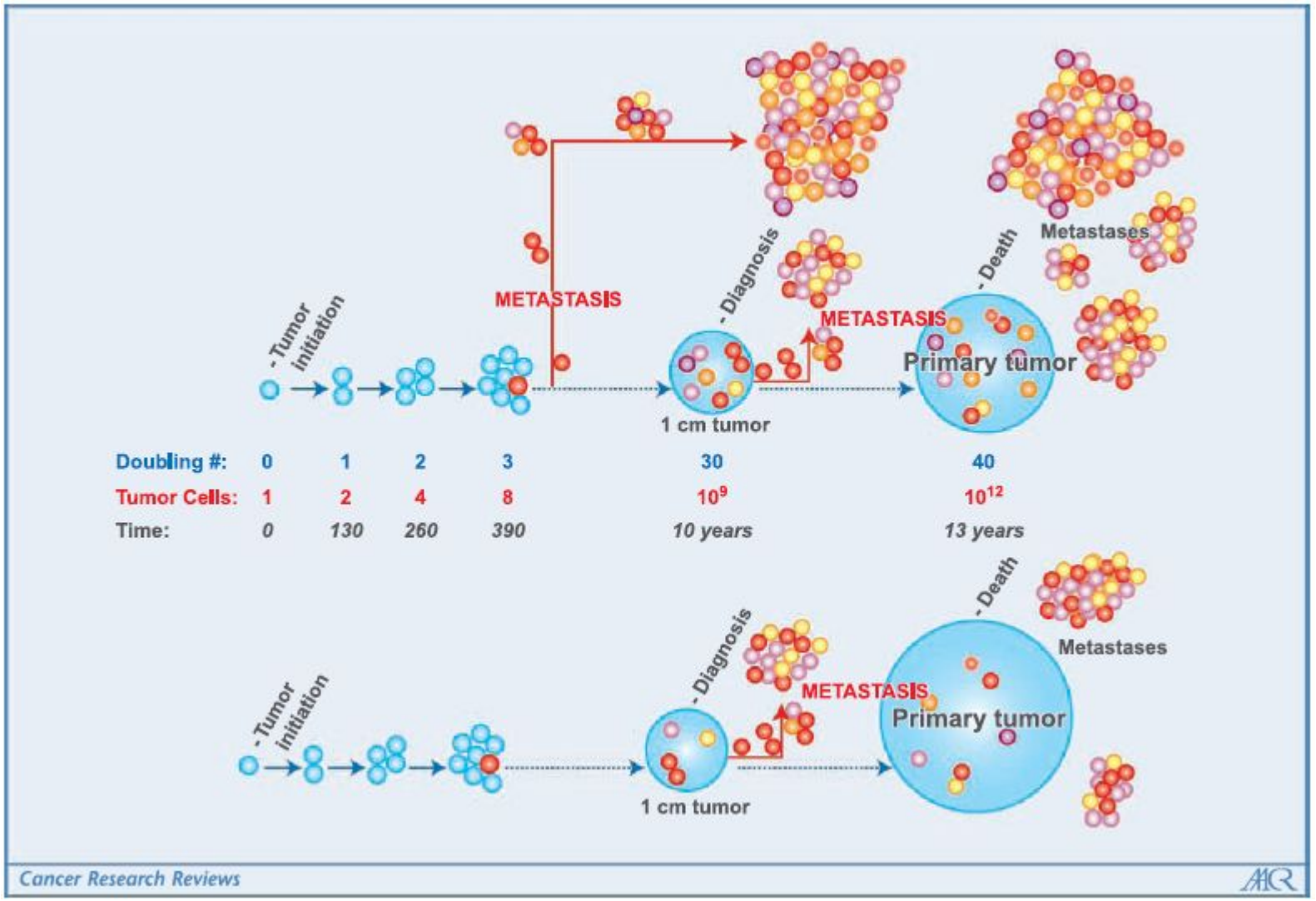
Ангиогенез


VEGF
FGF2
Vasohibin
VEGF
VEGF R2
VEGF R1
VEGF R2
PKCδ
ERK 1/2
↑ Vasohibin transcription
↓ VEGF R2 transcription

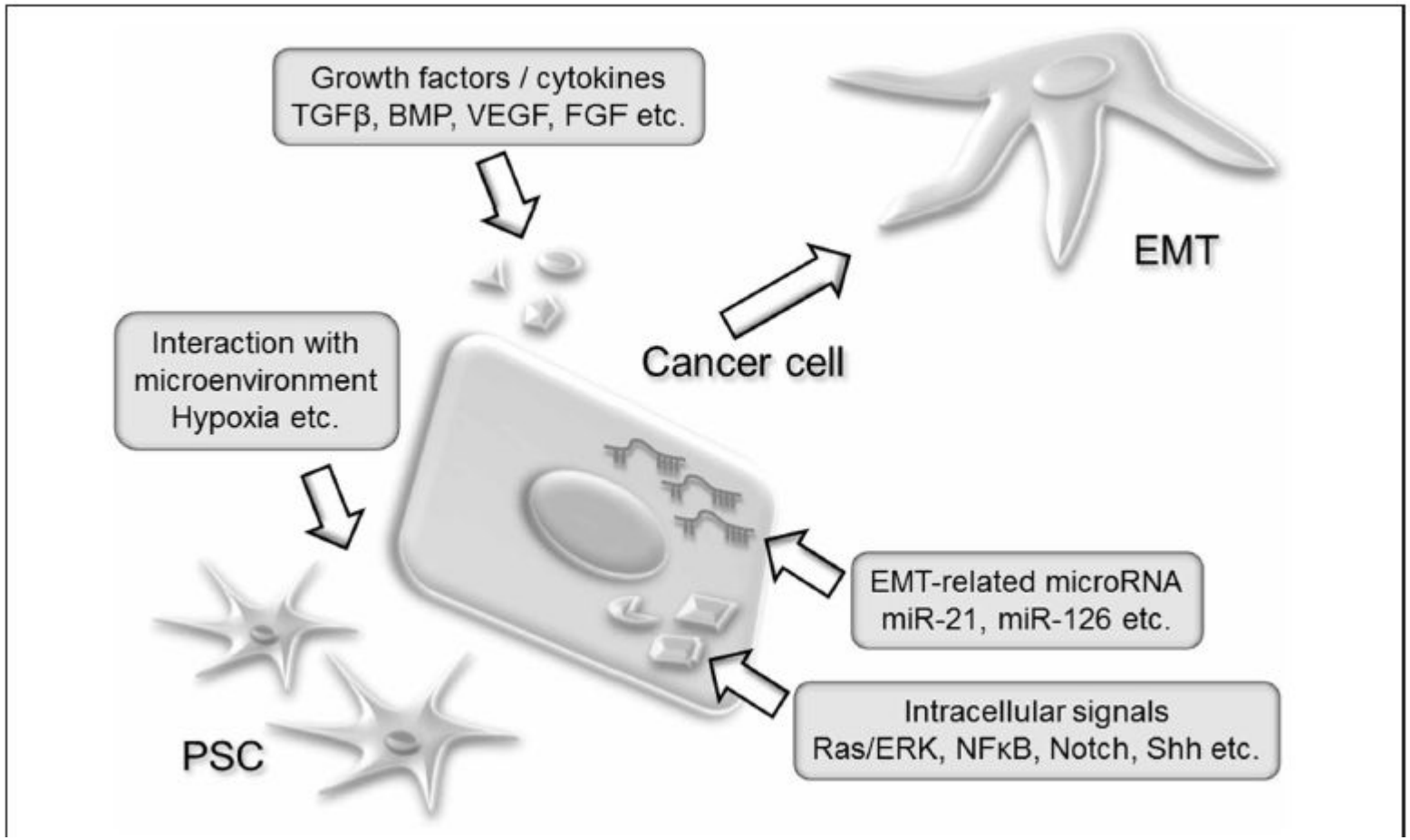
- Механизмы метастазирования

Метастазы


Clonal Selection
Parallel Evolution
Dynamic Heterogeneity
Clonal Dominance
Stem Cell
Cancer Research Reviews
AACR

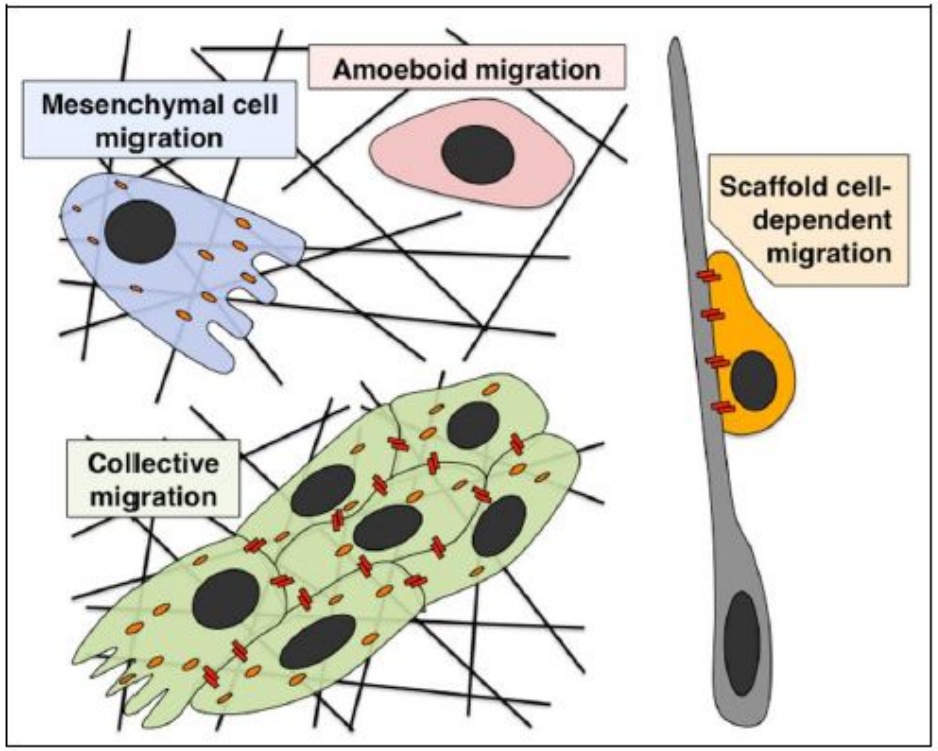

- Tumor initiation
METASTASIS
- Diagnosis
1 cm tumor
METASTASIS
- Death
Primary tumor
Metastases
Doubling #: 0 1 2 3 30 40
Tumor Cells: 1 2 4 8 10^9 10^{12}
Time: 0 130 260 390 10 years 13 years
- Tumor initiation
- Diagnosis
1 cm tumor
METASTASIS
- Death
Primary tumor
Metastases
Cancer Research Reviews
AACR

EMT-эпителиально-мезенхимальная трансзиция

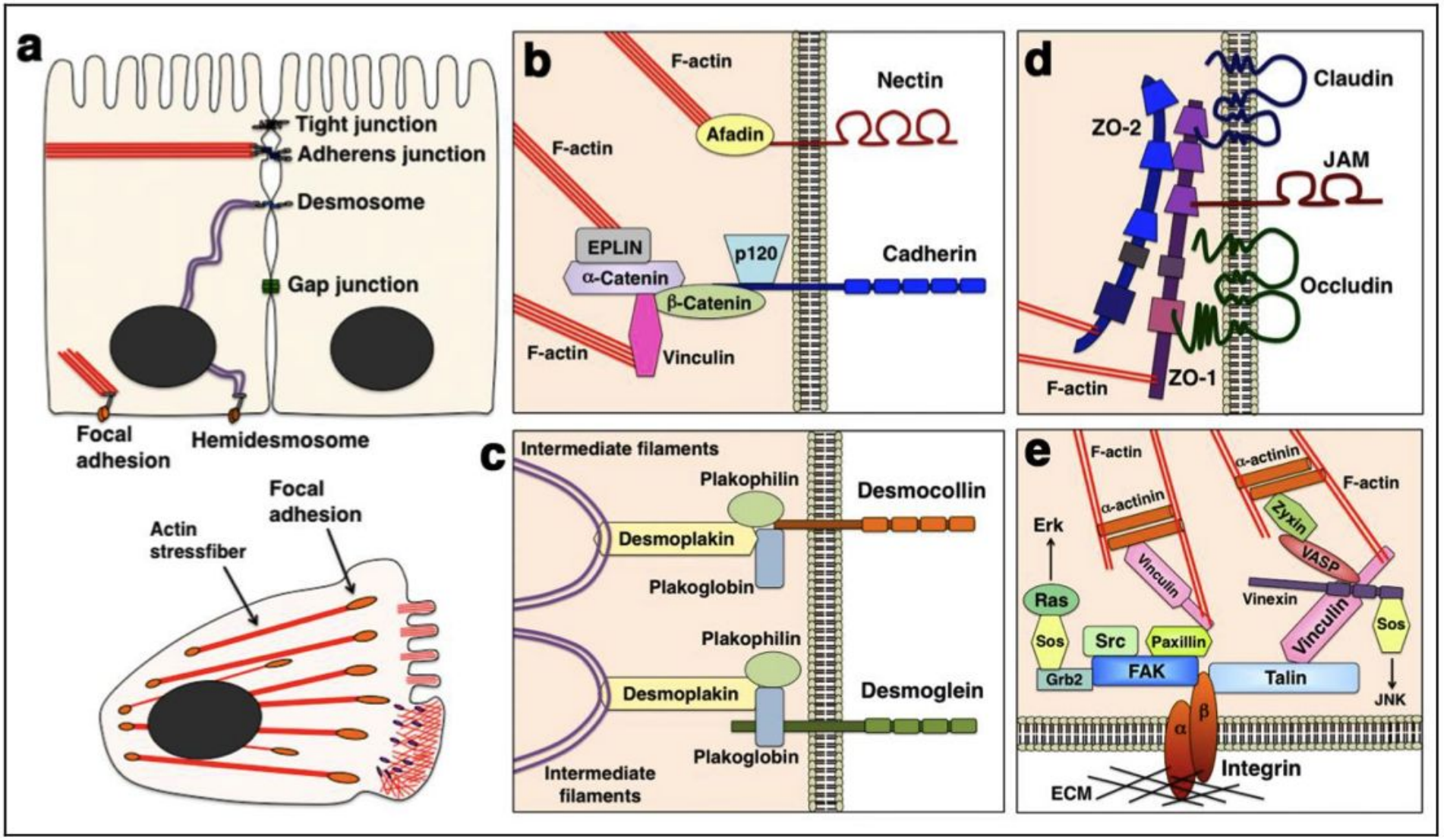


Классификация типов миграции

Classification of cell migration types. Orange dots: cell-ECM adhesions, Red rectangles: cell-cell adhesions, Black bars: ECMs. See Introduction.

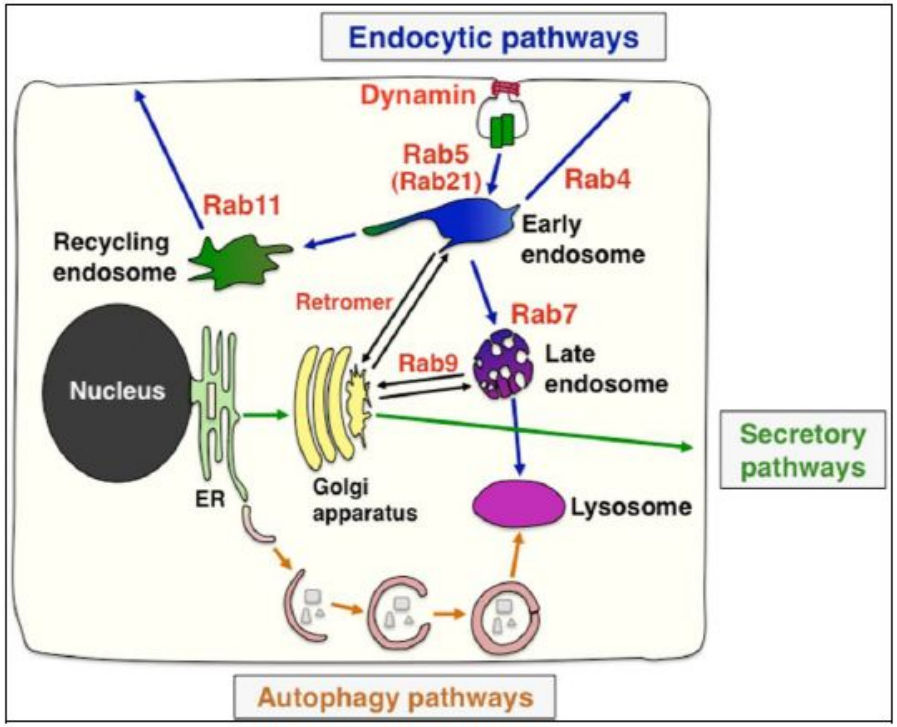


	Cell-Cell adhesion	Cell-ECM adhesion
Mesenchymal single cell migration	Not required	Essential
Amoeboid single cell migration	Not required	Not required
Collective cell migration	Essential	Essential
Scaffold cell-dependent cell migration	Essential	Not or less required


a
Tight junction
Adherens junction
Desmosome
Gap junction
Focal adhesion
Hemidesmosome
Focal adhesion
Actin stressfiber
b
F-actin
Nectin
Afadin
F-actin
EPLIN
α-Catenin
p120
Cadherin
β-Catenin
F-actin
Vinculin
c
Intermediate filaments
Plakophilin
Desmocollin
Desmoplakin
Plakoglobin
Plakophilin
Desmoplakin
Desmoglein
Plakoglobin
Intermediate filaments
d
Claudin
ZO-2
JAM
Occludin
F-actin
ZO-1
e
F-actin
α-actinin
α-actinin
F-actin
Zyxin
Erk
VASP
Vinculin
Vinexin
Ras
Vinculin
Sos
Src
Paxillin
Sos
Grb2
FAK
Talin
JNK
β
α
Integrin
ECM

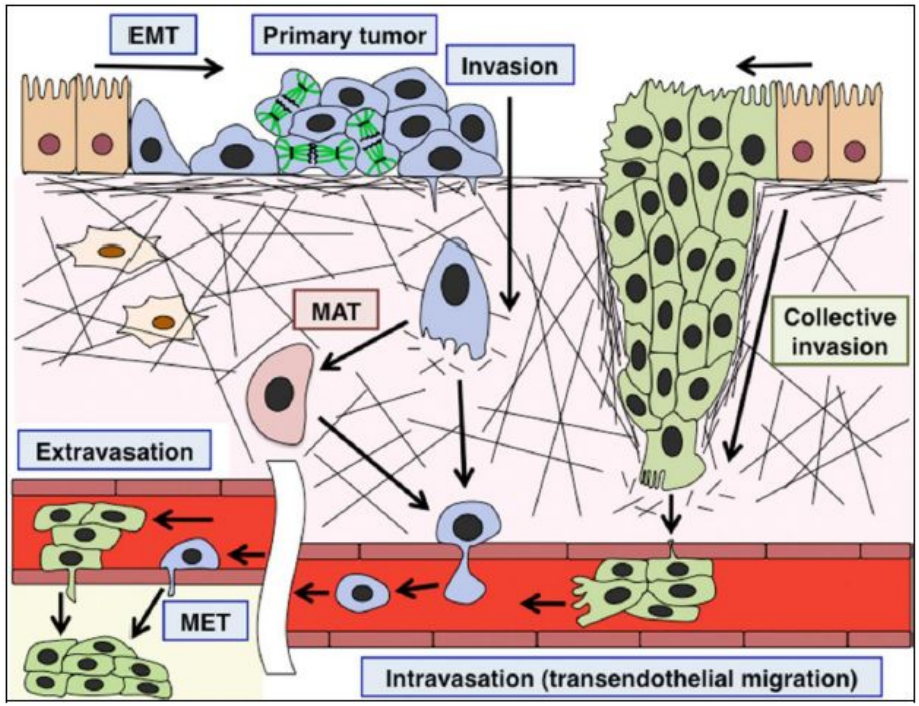
Внутриклеточный трафик

Intracellular trafficking pathways. Three major trafficking pathways are endocytic pathways (blue arrows), secretory pathways (green arrows) and autophagy pathways (orange arrows). Some cargo molecules are transported from endosomes to trans-Golgi network via retrograde pathways.



Этапы метастазирования

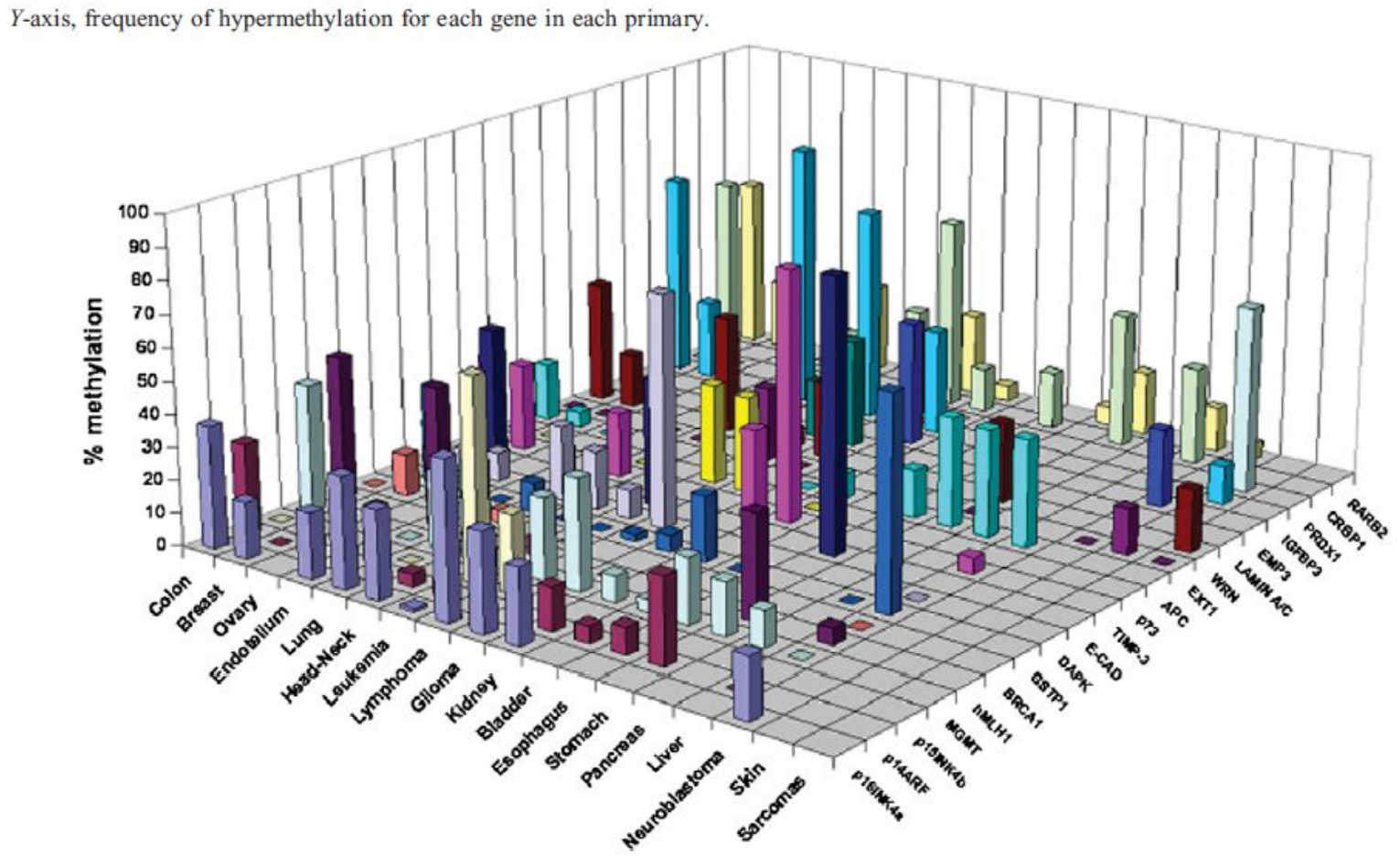
EMT-mediated invasion and collective invasion in cancer metastasis. Normal epithelial cells (orange cells) undergo EMT and form a primary tumor (blue cells). Some primary tumor cells invade and migrate into blood circulation as a multicellular strand (green cells). EMT: epithelial-mesenchymal transition, MAT: mesenchymal-amoeboid transition, MET: mesenchymal-epithelial transition.



Эпигенетические темы в канцерогенезе

- Метилирование генома
- Селекторные гены (ген “eyeless”, Neuro D-bhLh, c/EPPα-LZ, MyoD и Myf5
- Наследование образцов экспрессии (инактивация X хр., эффект положения гена white
- Ауторегуляторная петля и бистабильный статус
- Белки PcG и trx

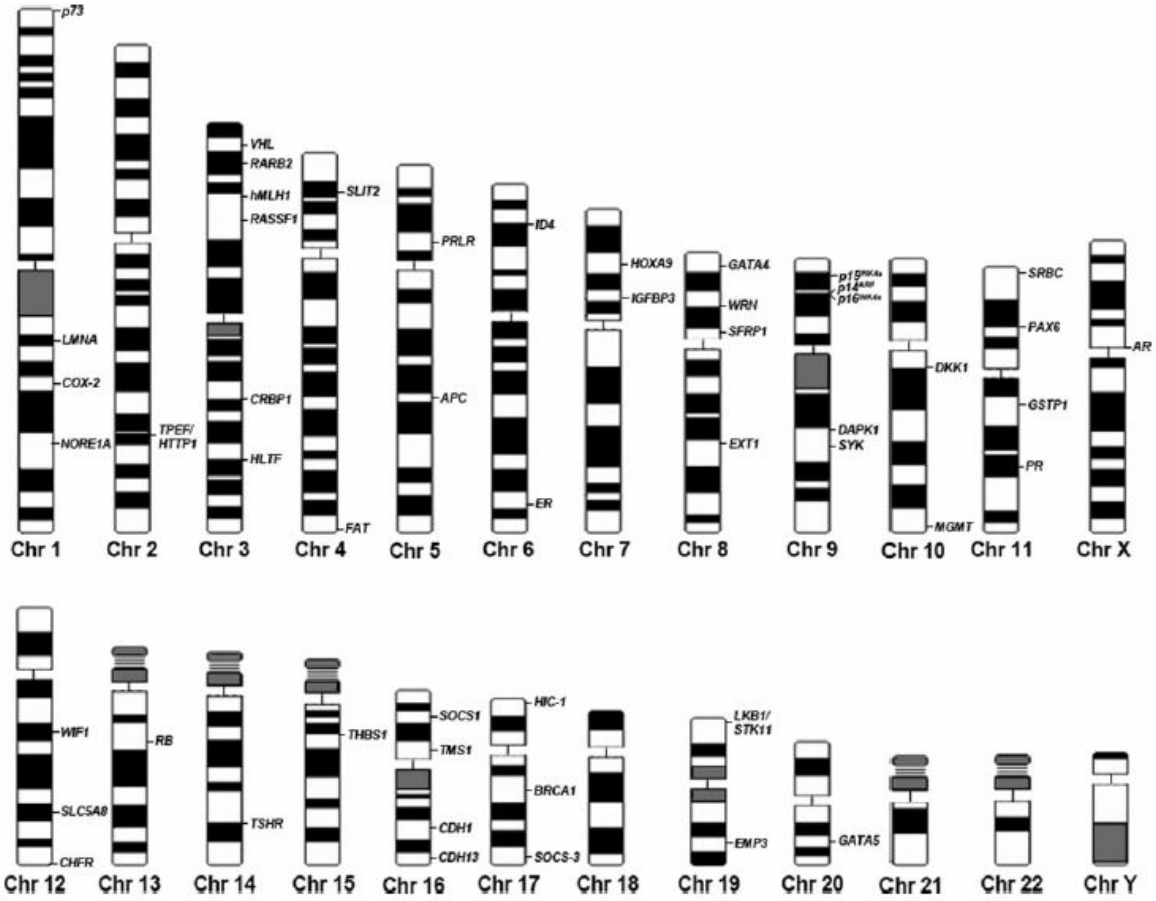
Профиль гиперметилирования CpG островков при раке



Гиперметирование РСГ

Pathways	Representative hypermethylated genes
DNA repair	hMLH1, MGMT, WRN, BRCA1
Hormone response	Estrogen, progesterone, androgen, prolactin and thyroid-stimulating hormone receptors
Vitamin response	RARB2, CRBP1,
Ras signaling	RASSFIA, NOREIA
Cell cycle	p16INK4a, p15INK4b, Rb
P53 network	p14ARF, p73, HIC-1
Cell adherence and invasion	E-cadherin, H-cadherin, FAT cadherin, EXT-1, SLIT2, EMP3
Apoptosis	TMS1, DAPK1, WIF-1, SFRP1
Wnt signaling	APC, DKK-1, IGFBP-3
Tyrosine kinase cascades	SOCS-1, SOCS-3, SYK
Transcription factors	GATA-4, GATA-5, ID4
Homeobox genes	PAX6, HOXA9
Other pathways	GSTP1, LKB1/STK11, THBS-14, COX-2, SRBC, RIZ1, TPEF/HPP1, SLC5A8, Lamin A/C
microRNAs	miR-127 (targeting BCL6), miR-124a (targeting CDK6)

Хромосомная карта гиперметилирования РСГ



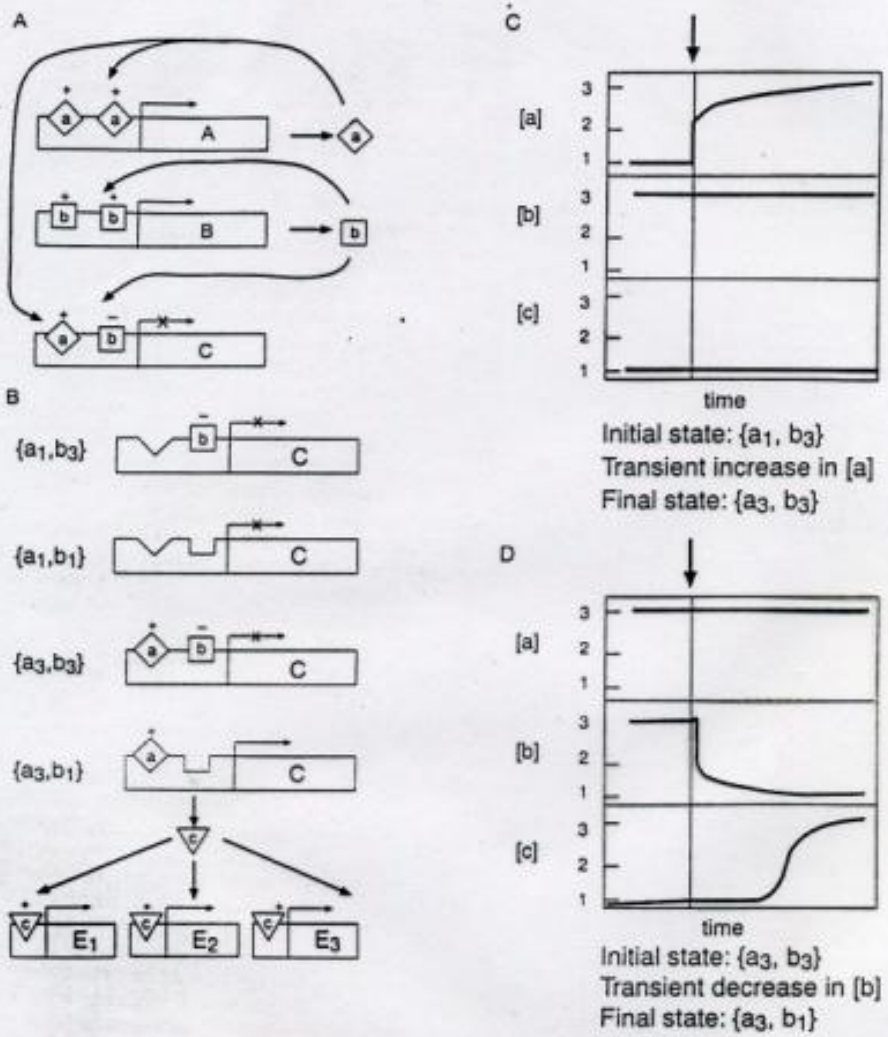
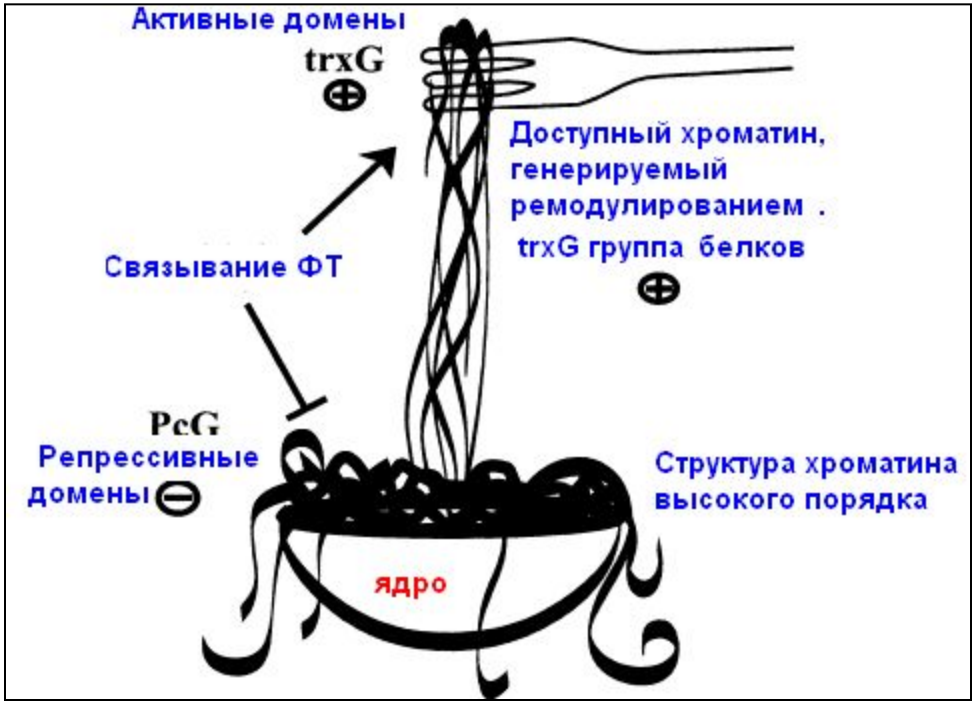
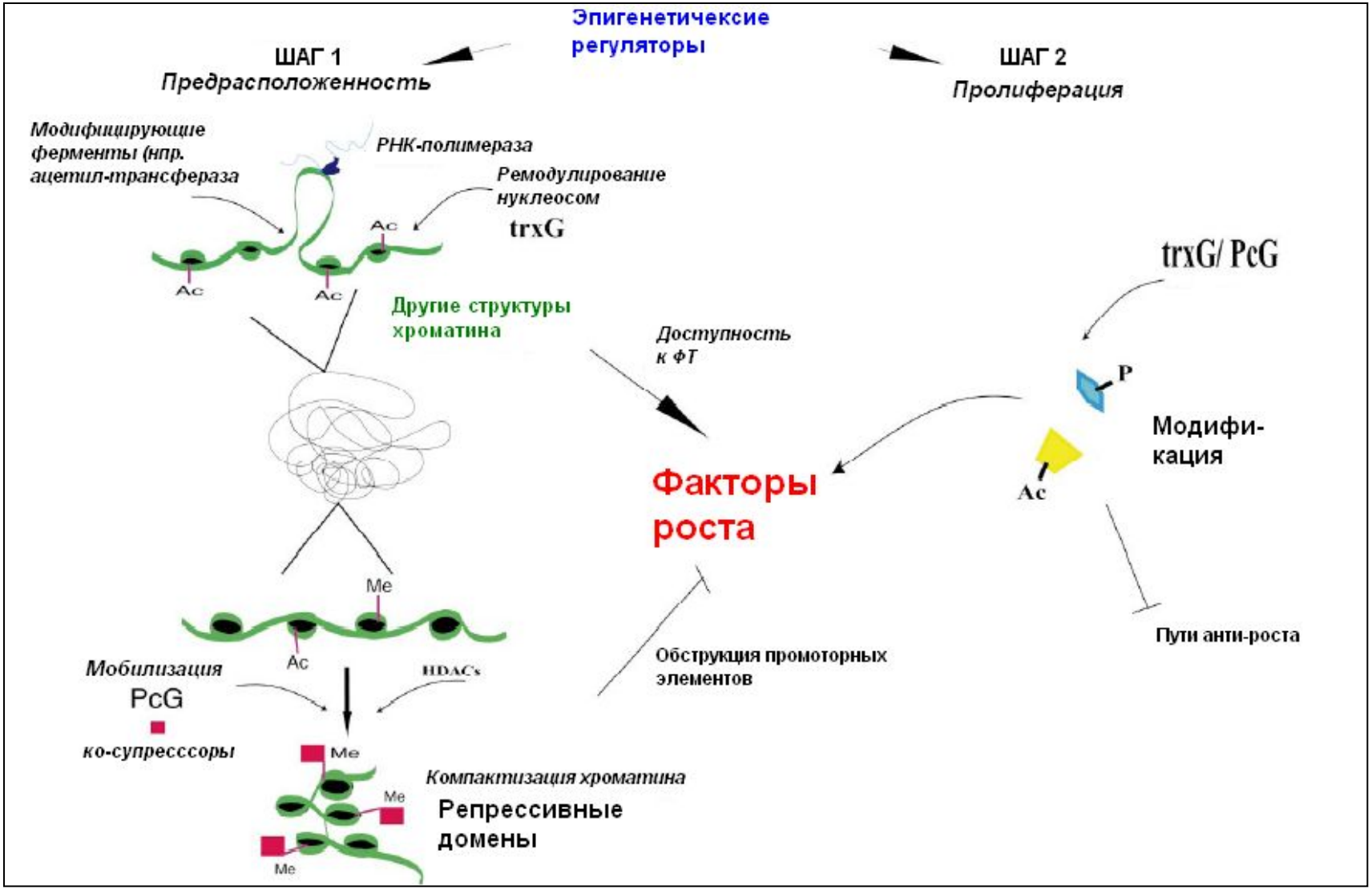


Figure 2. A model for epigenetic alterations in carcinogenesis. (A) The genes A and B are positively autoregulated by their gene products, a (diamond) and b (square) as described in Figure 1. The gene C is positively regulated by a, negatively regulated by b, and produces a gene product, c (triangle), that activates transcription of a battery of genes, E_1, E_2, E_3. . .E_N, that are necessary for cell division. (B) The four possible steady-states of [a] and [b] are denoted as $\{a_3,b_3\}$, $\{a_1,b_1\}$, $\{a_3,b_3\}$, and $\{a_3,b_1\}$. The state of the binding sites for a and b in the C gene promoter is diagrammed. The transcriptional state of gene C is indicated by a rightward-facing arrow if transcription is on, and by an "X" on the arrow if transcription is off. The product of gene C in turn activates transcription of the downstream battery of effector genes, E_1 through E_N. (C) With the system initially in the normal steady-state $\{a_1,b_3\}$, an externally applied insult (bold arrow) introduces a transient increase in [a]. The system switches to steady-state $\{a_3,b_3\}$, but gene C remains transcriptionally inactive. (D) With the system initially in the steady-state $\{a_3,b_3\}$, an externally applied insult (bold arrow) introduces a transient decrease in [b]. The system switches to steady-state $\{a_3,b_1\}$, which activates transcription of gene C. A particular solution to the equations describing the system gave the following steady-state concentrations of a, b, and c (in arbitrary units) consistent with the behavior described in Figure 2; for $\{a_1,b_3\}$, [a] = 0.01, [b] = 7.9, and [c] = 0.04; for $\{a_1,b_1\}$, [a] = 0.01, [b] = 0.01, and [c] = 0.13; for $\{a_3,b_3\}$, [a] = 4.4, [b] = 7.9, and [c] = 0.36; and for $\{a_3,b_1\}$, [a] = 4.4, [b] = 0.01, [c] = 13.

«Spaghetti dish», объясняющая функции PcG и trxG



Эпигенетические механизмы



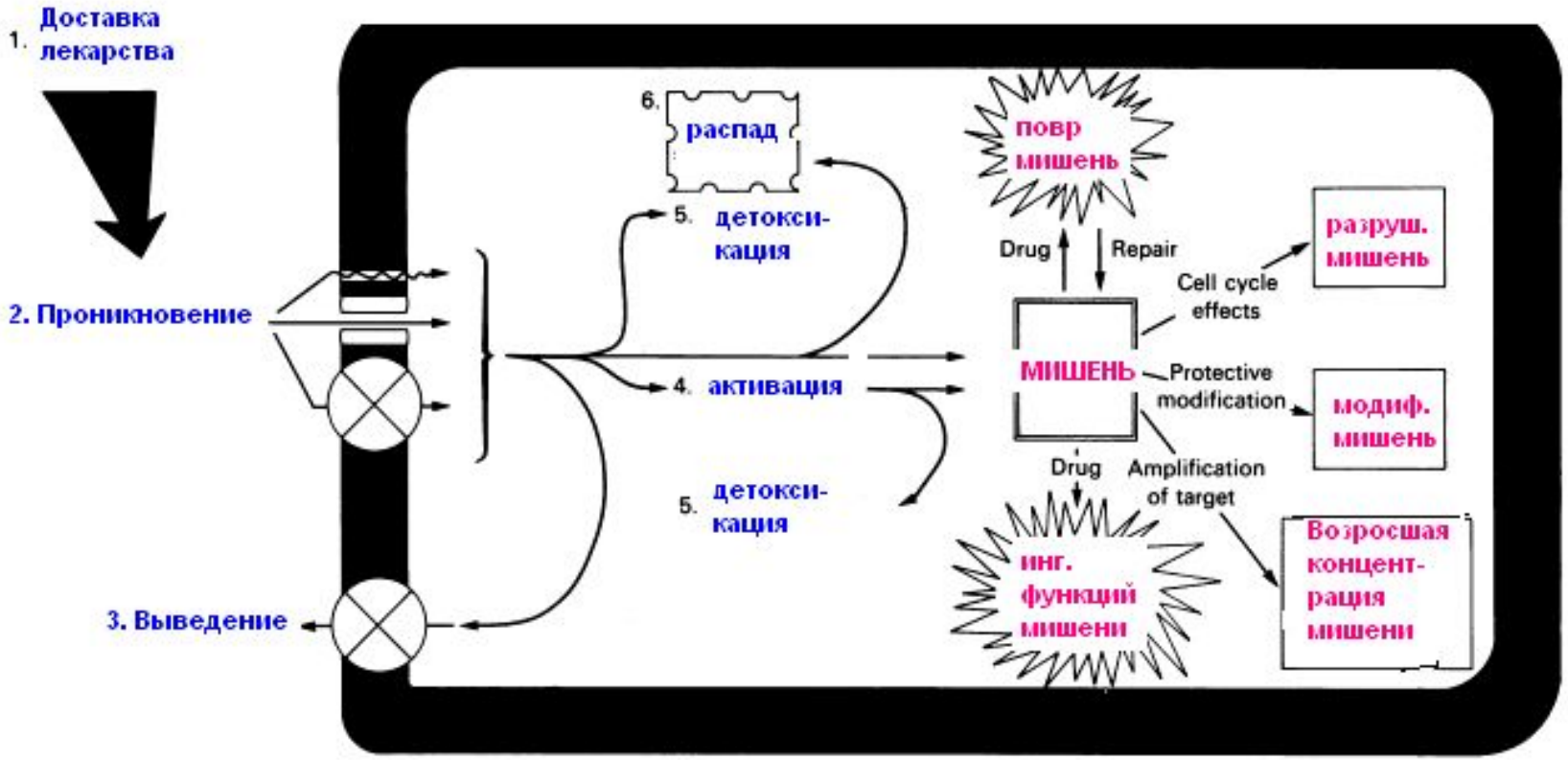
Канцерогены как эффекторы эпигенетических изменений

- Изменения в структуре хроматина
- Нарушение ДНК-св. способности ФТ
- Прямая инактивация репрессорного белка
- Нарушение метилирования
- Усиление репликации ДНК

а). Митогены (ФБ) б) РР

- Цитотоксичные эффекты (метапирилен, D-лимонен, 2,4,4-3-метил-2-пентанол, сахарин)
- усиление митотической рекомбинации (Афлатоксин В1
- Имитация гормонов (РАН, TCCD)

Молекулярный механизм лекарственной резистентности



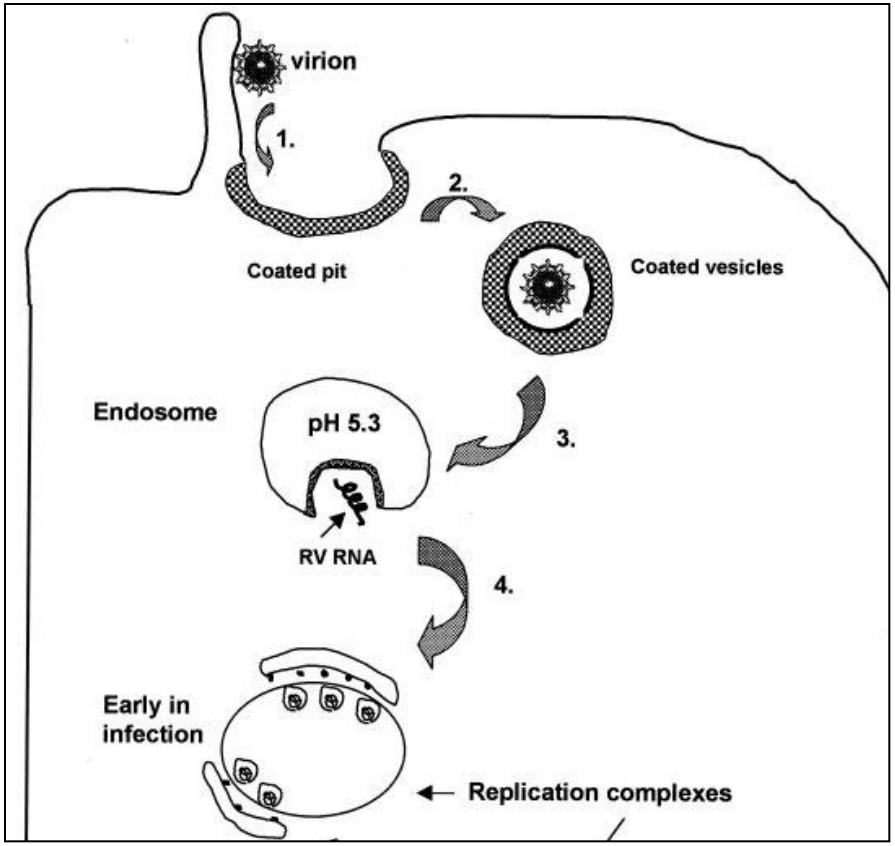
Тератогенез

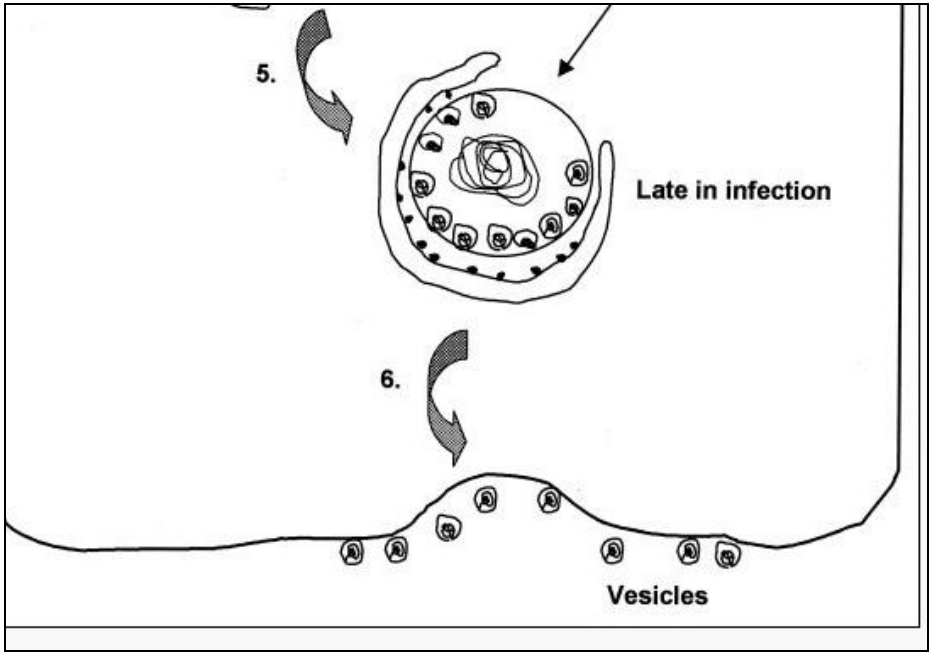
- Факторы внешней среды (тератогены)
- Вирусы
- Воспаление
- Эндокринные нарушения
- Генетические нарушения

Ксенобиотики-тератогены

- TCCD
- PCBs, PAHs

Жизненный цикл RV





Лекарства с тератогенным эффектом

Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
ACE inhibitors: benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	Hypertension	Second or third trimester (13th wk–term)	Oligohydramnios, intrauterine growth retardation, neonatal renal failure, hypotension, pulmonary hypoplasia, hypocalvaria, joint contractures, death
Amiodarone	Thyroid disorder	10 wk–term	Neonatal thyroid dysfunction or goitre
Aminopterin (≥ 1–3 mg/d)	Cancer	Organogenesis (18–60 d)	CNS, limb and skeletal defects
Antiepileptic drugs: carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, trimethadione, valproic acid	Epilepsy	Organogenesis (18–60 d)	CNS, cardiac, eye, gastrointestinal and genitourinary defects, facial dysmorphism and digital hypoplasia, growth retardation
Coumarin derivatives: dicumarol, warfarin	Thromboembolic disorders	For CNS defects: unknown; for other defects: second part of first trimester (6–9 wk)	Nasal hypoplasia, stippled epiphyses, vertebral abnormalities, CNS and ocular defects, cutaneous hematomas, intracranial hemorrhage, growth retardation, stillbirth
Cyclophosphamide	Cancer, transplant rejection	Organogenesis (18–60 d)	Skeletal and ocular defects, cleft palate
Danazol (≥ 200 mg/d)	Endometriosis, fibrocystic breast disease, hereditary angioedema	Unknown	Virilization of external genitalia in female fetuses
Diethylstilbestrol (1.5–150 mg/d)	Ovarian insufficiency, postcoital	First and second trimesters (1–24 wk)	Vaginal/cervical carcinoma in females and genital tract abnormalities in males and females

Продолжение

Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
Methotrexate (≥ 12.5 mg/wk)	Cancer, rheumatic disease	Organogenesis (18–60 d)	Large fontanelles, abnormal head shape, craniosynostosis, ocular and skeletal defects
Methylene blue (Intra-amniotic injection)	Twin pregnancy (as an aid to amniocentesis)	Second trimester when amniocentesis is generally performed	Jejunal atresia
Penicillamine	Cystinuria, rheumatoid arthritis	Unknown	Connective tissue abnormalities resembling cutis laxa with loose skin, hernias, loose joints, flat face, small jaw
Quinine (≥ 2 g/d)	Leg cramps, malaria	First–third trimesters (1 wk–term)	Deafness, abortion
Radioiodine (296–8325 MBq)	Thyroid carcinoma, thyroid disorder	End of first–third trimester (10 wk–term)	Fetal hypothyroidism and goitre
Retinoids (oral): acitretin, eretinate, isotretinoin	Dermatologic disease	Organogenesis (18–60 d)	CNS and ear defects, microagnathia, cleft lip/palate, cardiac and great vessel defects, thymic abnormalities, eye anomalies, limb defects
Tetracycline derivatives: chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline	Infection	Second or third trimester (13th wk–term)	Staining of primary dentition
Thalidomide	Insomnia, oropharyngeal and esophageal ulcers associated with AIDS, immuno-pathologic disease, graft-versus-host disease	Organogenesis (27–40 d)	Limb reduction, cardiac, urogenital, renal, orofacial, ocular and gastrointestinal defects, cranial nerve anomalies, microtia

Недавно выявленные тератогены

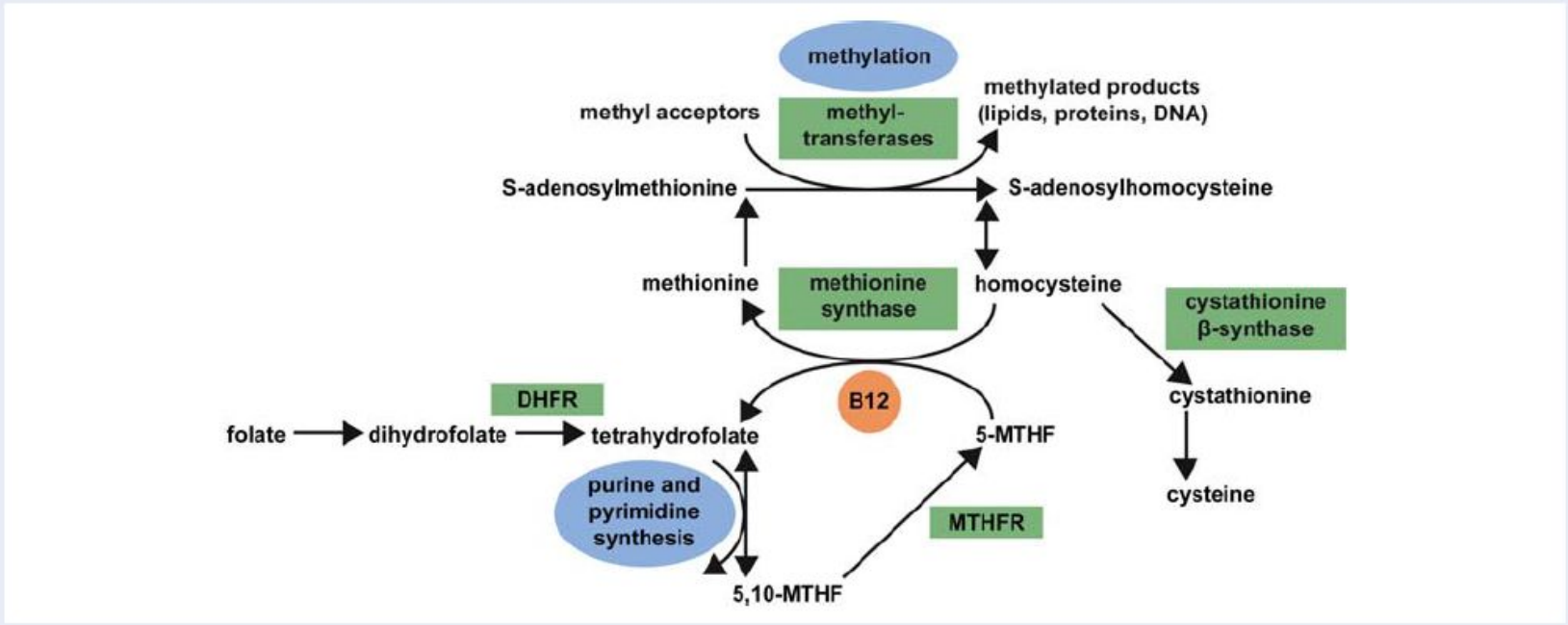
Exposure	Indication for treatment	Most susceptible period, post conception	Risk in embryo or fetus	Comments
Fluconazole (chronic, parenteral doses, 400–800 mg/d)	Mycotic infection	First trimester (1–12 wk)	Four children have been described with a similar and rare pattern of congenital anomalies. The features seen in these children are brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease	1) Risk appears to be more likely with high-dose, chronic, parenteral use 2) A single, oral dose of fluconazole (150–200 mg) is unlikely to pose a substantial teratogenic risk
Methimazole (usual therapeutic doses)	Hyperthyroidism	First trimester (1–12 wk)	Aplasia cutis congenita, skull hypoplasia, dystrophic nails and supernumerary nipples. Three children exhibited a characteristic pattern of malformations including facial dysmorphism, scalp defects, severely hypoplastic nipples, choanal atresia, esophageal atresia, psychomotor delay and growth retardation	1) Risk of fetal goitre or congenital anomalies is minimal to small 2) Untreated or inadequately treated maternal hyperthyroidism during pregnancy may lead to life-threatening complications of thyrotoxicosis and an increased risk of fetal death
		Second–third trimesters (10 wk–term)	Infants of women who are treated for Graves' disease during pregnancy with methimazole are at increased risk of hyperthyroidism due to placental transfer of thyroid-stimulating immunoglobulins as well as of hypothyroidism and goitre due to the medication	3) Fetal hypothyroidism and goitre are unlikely to be caused by methimazole treatment before about 10 wk after conception when the fetal thyroid begins to function
Misoprostol (usual therapeutic oral doses)	Peptic ulcer disease, cervical ripening, pregnancy termination	First–second trimesters (1–24 wk)	Moebius anomaly, terminal transverse limb reduction defects, arthrogryposis multiplex congenita and talipes equinovarus	1) The risk of congenital anomalies resulting from vascular disruptions has been associated with unsuccessful attempts to induce abortion early in pregnancy 2) No consistent adverse effect has been observed in newborns of women who were given misoprostol for cervical ripening and induction of labour near term
Trimethoprim (usual therapeutic doses)	Bacterial infection, *pneumocystis carinii* pneumonia	First trimester (1–12 wk)	Neural tube defects, oral clefts, hypospadias and cardiovascular defects	The absolute risk of neural tube defects in infants of women treated with trimethoprim during the first 2 months of pregnancy is about 1%

Механизмы тератогенного действия лекарств

Фолатный антагонизм

- water-soluble B vitamin, occurs in high
- concentrations in certain natural foods (fruits, leafy green vegetables,
- beans and liver) as polyglutamate. The synthetic form, folic acid (a
- monoglutamic acid), is used in food fortification and vitamin preparations.
- Folic acid has a higher bioavailability than food folate

Folate–homocysteine–methionine метаболизм



B12, vitamin B_{12}; DHFR, dihydrofolate reductase; MTHF, methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reductase.

Лекарства, связанные с фолатным антагонизмом

Medical drugs associated with folate antagonism

Medication	Main indication	Interference with folate metabolism
Carbamazepine	Epilepsy, bipolar disorder	Impairment folate absorption
Cholestyramine	Hypercholesterolemia	Impairment folate and vitamin B_{12} absorption
Cyclosporine	Transplants, psoriasis, atopic dermatitis	Possible interference folate dependent remethylation
Lamotrigine	Epilepsy, bipolar disorder	Inhibition DHFR
Metformin	Diabetes	Interference vitamin B_{12}
Methotrexate	Cancer, some auto-immune diseases (rheumatoid arthritis, psoriasis)	Inhibition DHFR
Nicotinic acid	Hypercholesterolemia	Decrease acitivity CBS
Phenobarbital	Epilepsy	Impairment folate absorption
Phenytoin	Epilepsy	Impairment folate absorption, decrease activity methionine synthase, possible decrease activity MTHFR
Primidone	Epilepsy	Impairment folate absorption
Pyrimethamine	Malaria	Inhibition DHFR
Sulfasalazine	Inflammatory bowel disease, rheumatoid arthritis	Inhibition DHFR
Triamterene	Hypertension, edema	Inhibition DHFR
Trimethoprim	Urinary tract infection	Inhibition DHFR
Valproic acid	Epilepsy, migraine headache	Antimetabolite of folate

CBS, cystathione β-synthase; DHFR, dihydrofolate reductase; MTHFR, methyltetrahydrofolate reductase.

Neural Crest Cell Disruption

- - нарушения в аорте
- - нарушения в развитии нервной системы
- и др. нарушения

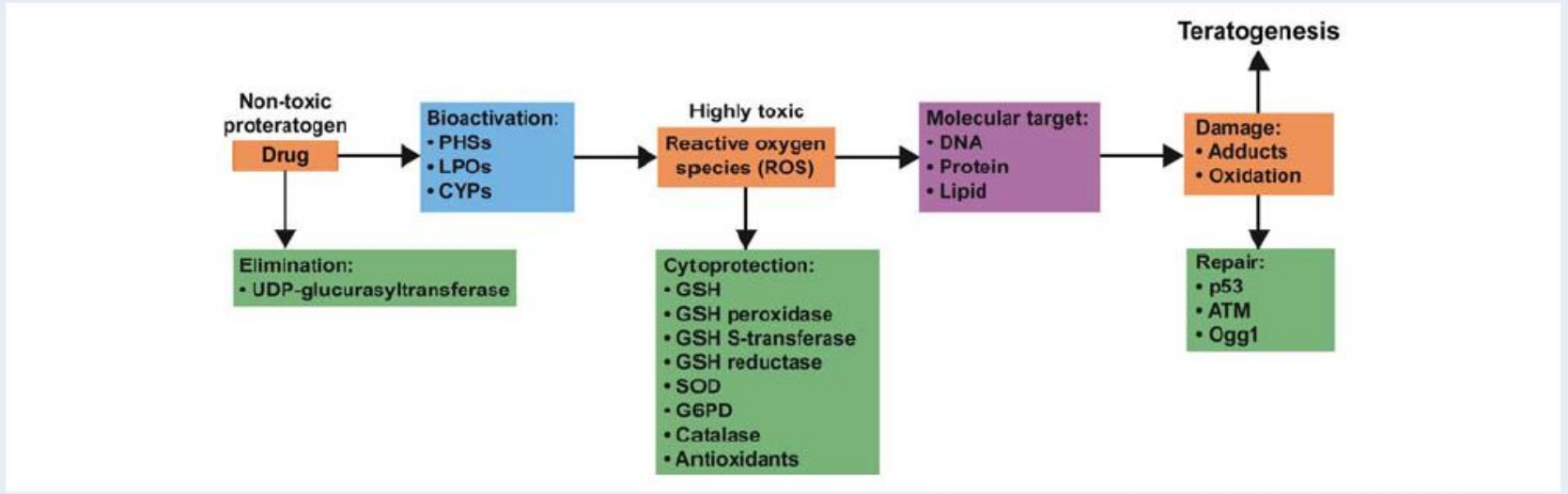
Endocrine Disruption: Sex Hormones

- diethylstilbestrol (DES) – нарушения в гормональном балансе
- - множественные нарушения

Окислительный стресс

- *In vivo*, некоторые лекарства, известные как агенты восстановительного цикла, используются, в том числе, для лечения эпилепсии, аритмии и рака, проходит реакцию одно-электронного восстановления с выходом свободных радикалов.

Молекулярные и биохимические основы тератогенеза, индуцированного ОС

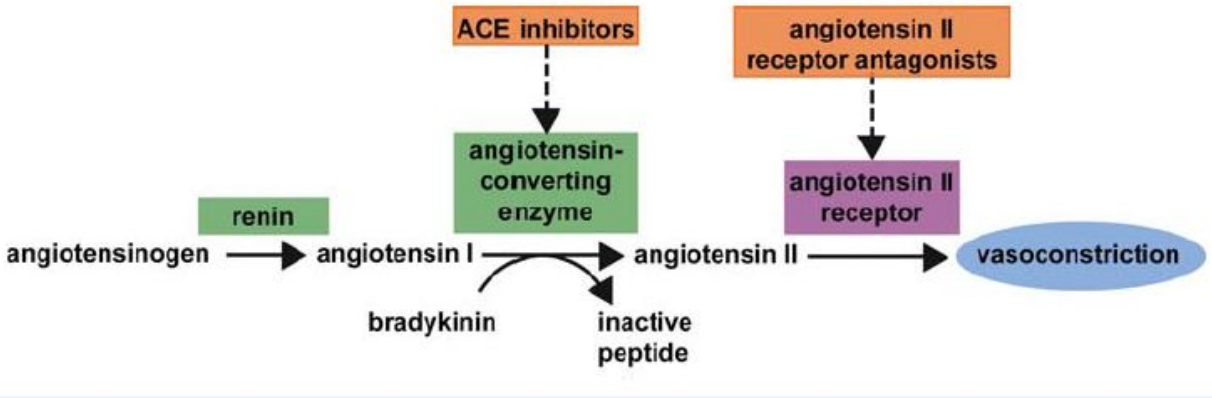


ATM, ataxia telangiectasia mutated; CYP, cytochrome P450; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; LPO, lipoxygenase; Ogg1, oxoguanine glycosylase 1; PHS, prostaglandin H synthase; SOD, superoxide dismutase; UDP, uridine diphosphate. Modified from Winn and Wells (1995) with kind permission from Wiley-Blackwell.

Васкулярные нарушения

- В первые 3 месяца развития
- Нарушение циркуляции крови в uterine-placental unit, the placental-fetal unit

Специфические рецепторы или тератогенез, опосредованный ферментами



The renin–angiotensin system. ACE, angiotensin-converting enzyme.

Другие механизмы

- Hydroxymethylglutaryl-coenzyme A Reductase
- Ацетилаза гистоновCyclooxygenase-1 (Non-steroidal anti-inflammatory drugs)
- N-methyl-D-aspartate receptors (миграция нейронов)
- 5-Hydroxytryptamine receptors
- and transporters (Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter)

Другие механизмы

- 1. Carbonic anhydrase. Carbonic anhydrases are metalloenzymes that catalyze the reversible hydration of CO2 into the bicarbonate ion and protons. This reaction
- is involved in many biological processes, including pH homeostasis,
- respiration, biosynthetic reactions and bone resorption.
- 2. g-Aminobutyric acid receptors
- In vertebrates, g-aminobutyric acid (GABA) is the major inhibitory
- neurotransmitter, which binds to specific transmembrane GABA
- receptors. Extraneuronal GABA-ergic systems are thought to be
- present in other tissues as well, including the testis

Результат применения лекарств

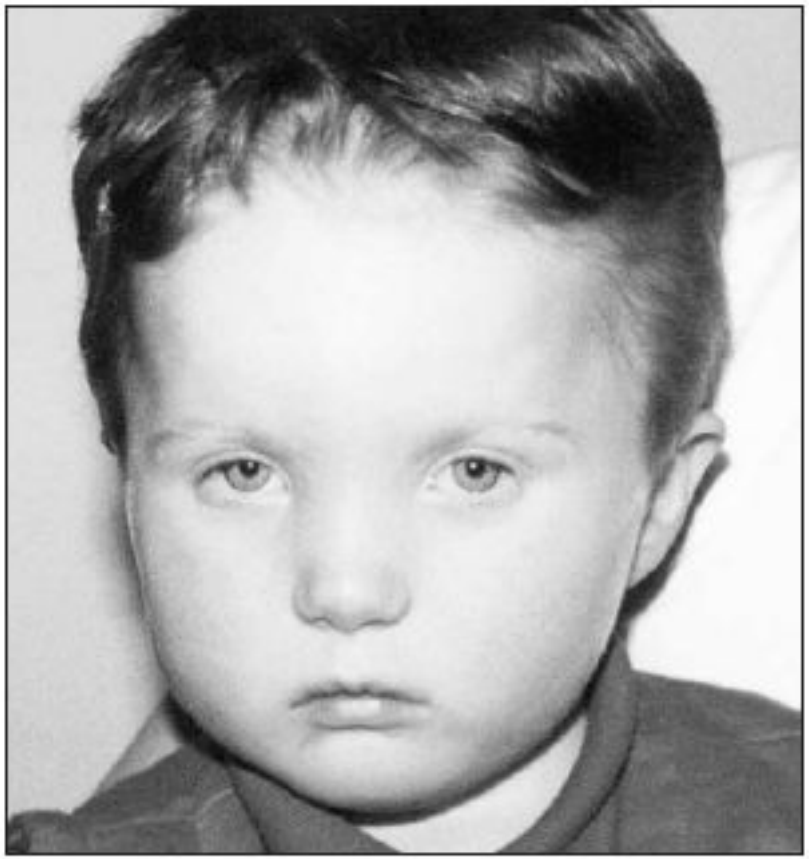
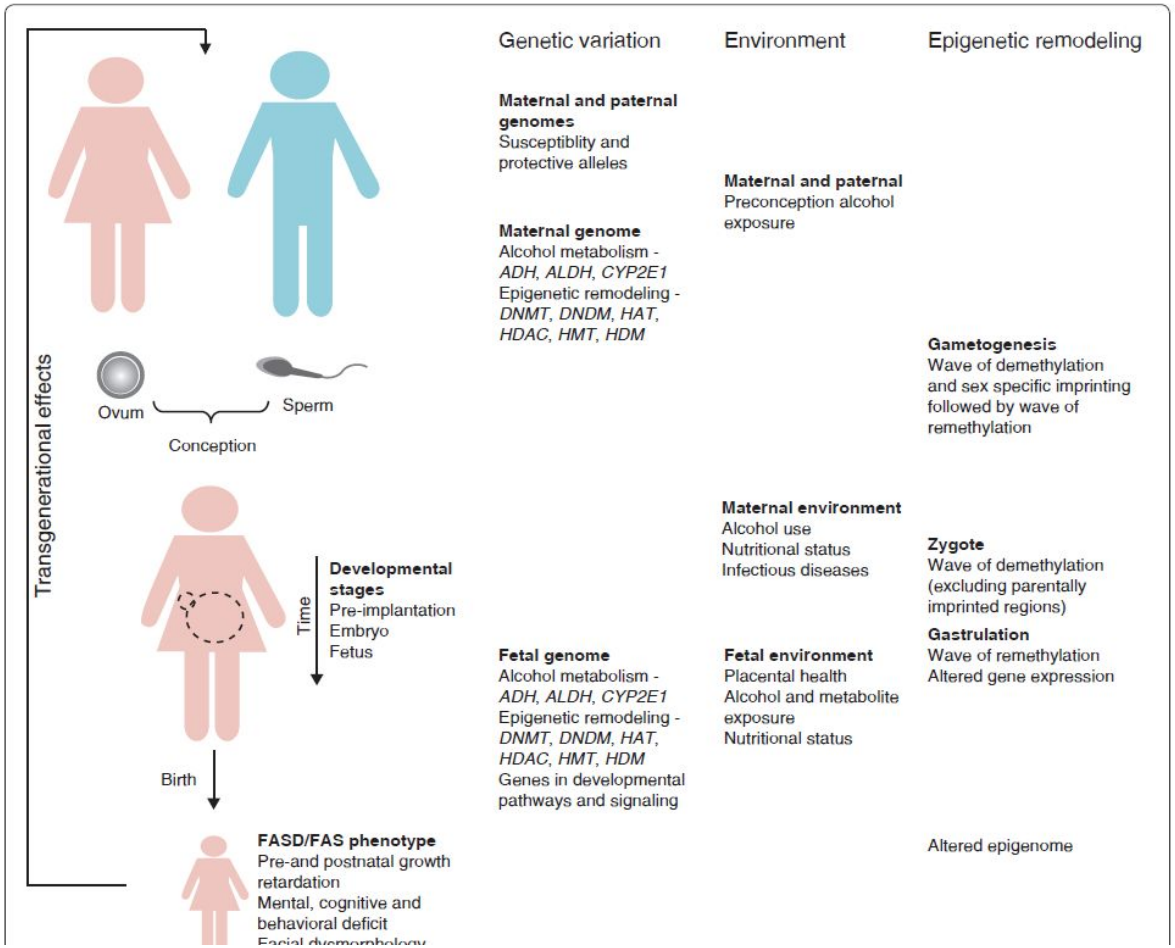


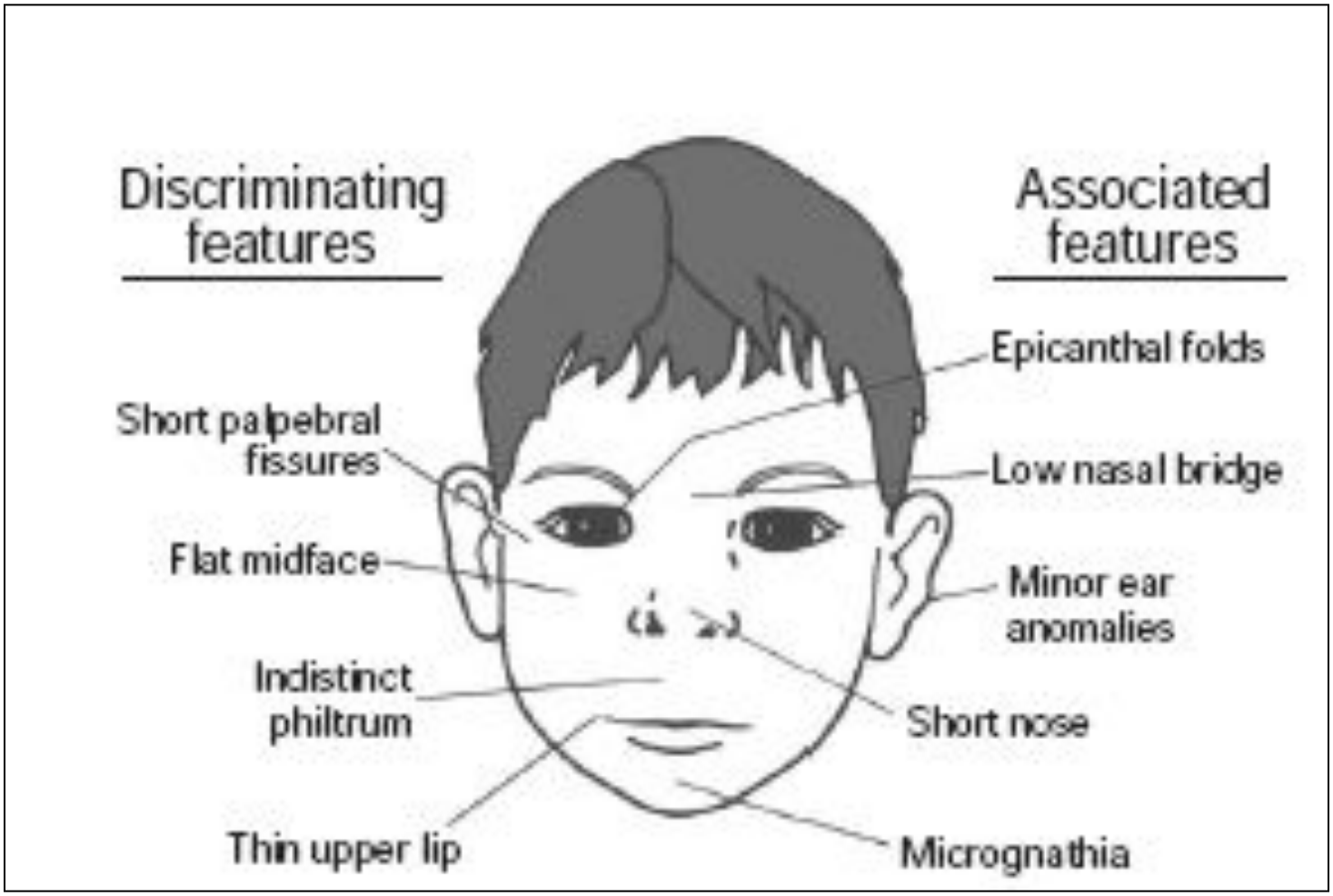
Fig. 1: Minor facial anomalies in a 3-year-old boy whose mother was treated with carbimazole (a prodrug that is completely metabolized to methimazole) for the treatment of Graves' disease during pregnancy (picture provided by Drs. L.C. Wilson, B.A. Kerr, R. Wilkinson, C. Fossard and D. Donnai). Reprinted with permission from Wiley-Liss, Inc. (*Am J Med Genet* 1998;75:220-2).

Фетальный алкогольный синдром

Развитие ФАС



Признаки фетального алкогольного синдрома (FAS)



Развитие исследований

- Reprod Toxicol. 2013 Jan;35:117-24. doi: 10.1016/j.reprotox.2012.10.007. Epub 2012 Oct 23.
- **Teratogenic effects of diabetic conditions in chick heart in ovo and in micromass culture may be prevented by addition of vitamin C and folic acid.**
- Memon SMemon S, Pratten MK.
- **Source**
- Centre for Integrated Systems Biology and Medicine, School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK.
- **Abstract**
- Maternal diseases like diabetes mellitus may cause developmental defects. Supplementation with folic acid and vitamin C during the periconceptional period has been shown to prevent some neural tube and congenital heart defects. Hearts were dissected from 5 days-old White Leghorn chick embryos, the cells isolated and cultured in micromass under diabetic conditions, with and without folic acid and vitamin C. Contractile activity, cell viability (resazurin reduction) and protein assays were performed. Results indicated diabetic conditions reduced contractile activity and cell viability, whilst vitamin C (100 μM) and folic acid (1 mM) administered concurrently significantly improved them to values comparable with the control. Day 3 chick embryos in ovo were injected with glucose+hydroxybutyrate or a combination of these and vitamins. Diabetic conditions caused gross and histological malformations, but these effects were abrogated by vitamin supplement. Teratogenic effects on heart development could possibly be prevented by vitamin supplementation during pregnancy.

Hum Reprod. 2013 Oct 9. [Epub ahead of print]

Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks.

van Gelder MM, de Jong-van den Berg LT, Roeleveld N.

Abstract

STUDY QUESTION:

What is the current state of knowledge on the human risks of drugs suspected to be associated with teratogenic mechanisms?

SUMMARY ANSWER:

Evidence for the presence or absence of human risks of birth defects is scarce or non-existent for the majority of drugs associated with teratogenic mechanisms.

WHAT IS KNOWN ALREADY:

Medical drugs suspected to be associated with teratogenic mechanisms are dispensed to a significant proportion of women in the first trimester of pregnancy. However, an overview of the current state of knowledge on the human teratogenic effects of these drugs is lacking.

STUDY DESIGN, SIZE, DURATION:

We performed an extensive literature review of studies in the English language which examined the associations between selected drugs and specific birth defects. The literature was identified from MEDLINE and EMBASE from database inception (January 1946 and January 1974, respectively) through December 2012 using 287 terms for the drugs of interest. We only included studies if they specified birth defect subtypes and, specifically for cohort studies, involved live born infants.

PARTICIPANTS/MATERIALS, SETTING, METHODS:

Of 14 406 potentially relevant articles, 556 full-text articles were assessed for eligibility and 250 met the inclusion criteria. The studies included were divided into four categories according to their design to increase the validity of our study.

MAIN RESULTS AND THE ROLE OF CHANCE:

Epidemiologic studies assessing teratogenic risks were identified for less than half of the drugs included in the review. A substantial variation in study design and data collection methods was observed. When the data collection method is of questionable validity, study quality may be affected considerably. For only 15 drugs of interest, birth defects were assessed in at least 1000 infants in cohort studies, and 13 of these were associated with one or more specific birth defects. The majority of associations observed in case-control studies are as yet unconfirmed. For most drugs and drug groups, however, the numbers of exposed infants studied were too small to draw any conclusions regarding their human teratogenic risks.

LIMITATIONS, REASONS FOR CAUTION:

The validity of our review is limited by the validity and reporting of the studies from which the data were extracted. Some relevant studies might have been missed owing to the exclusion of articles not in the English language and publication bias.

WIDER IMPLICATIONS OF THE FINDINGS:

It is a cause of concern that the drugs most often dispensed in the first trimester of pregnancy are not necessarily the drugs for which teratogenic risks have been studied. Future studies should focus on those drugs that are most commonly used during pregnancy and for which the teratogenic risks are unknown, such as iron preparations, serotonin receptor agonists or antagonists, drugs used in fertility treatment, dihydrofolate reductase inhibitors.

STUDY FUNDING/COMPETING INTEREST(S):

Marleen van Gelder was supported by the Netherlands Organisation for Scientific Research/NWO (grant no. 021.001.008). No competing interests are declared. TRIAL REGISTRATION NUMBER: N/A.