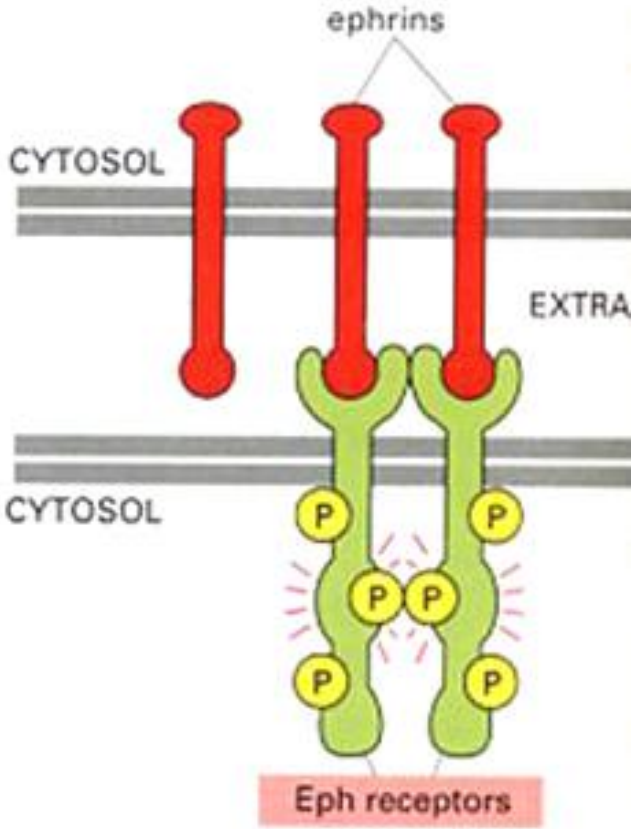
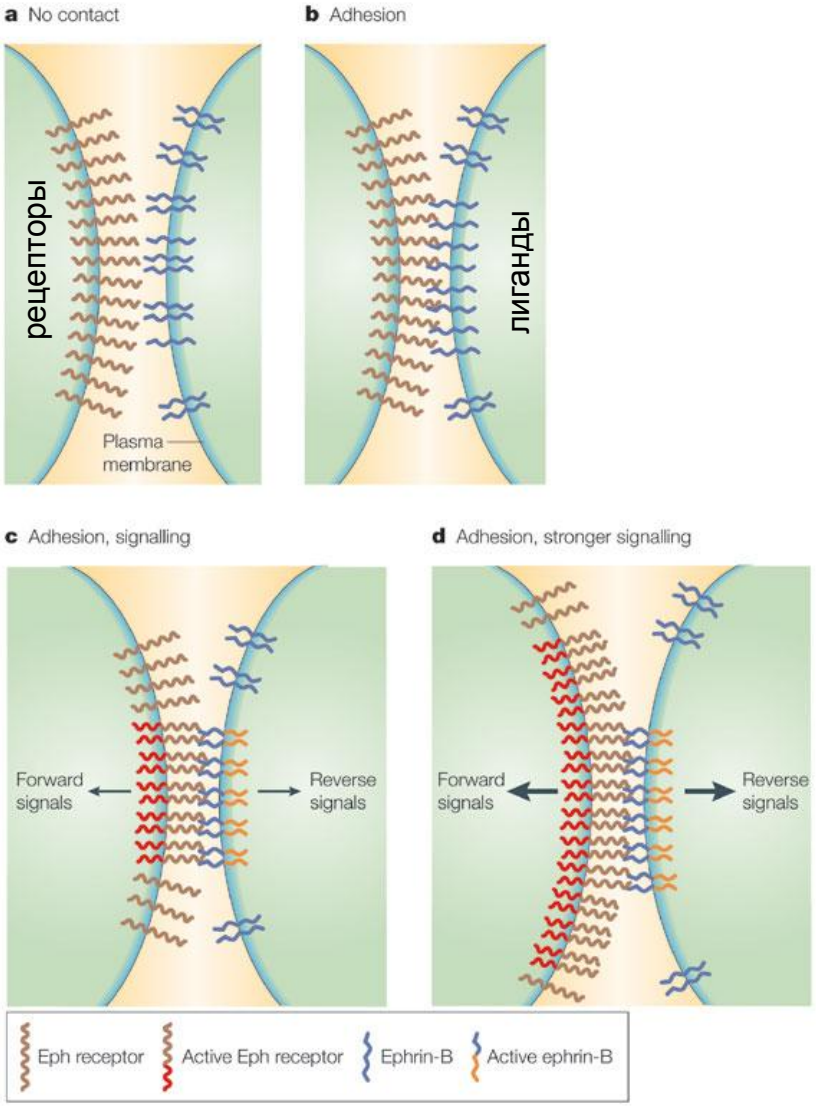
АКТИВАЦИЯ ЭФРИНОВ ПУТЕМ ИХ КЛАСТЕРИЗАЦИИ





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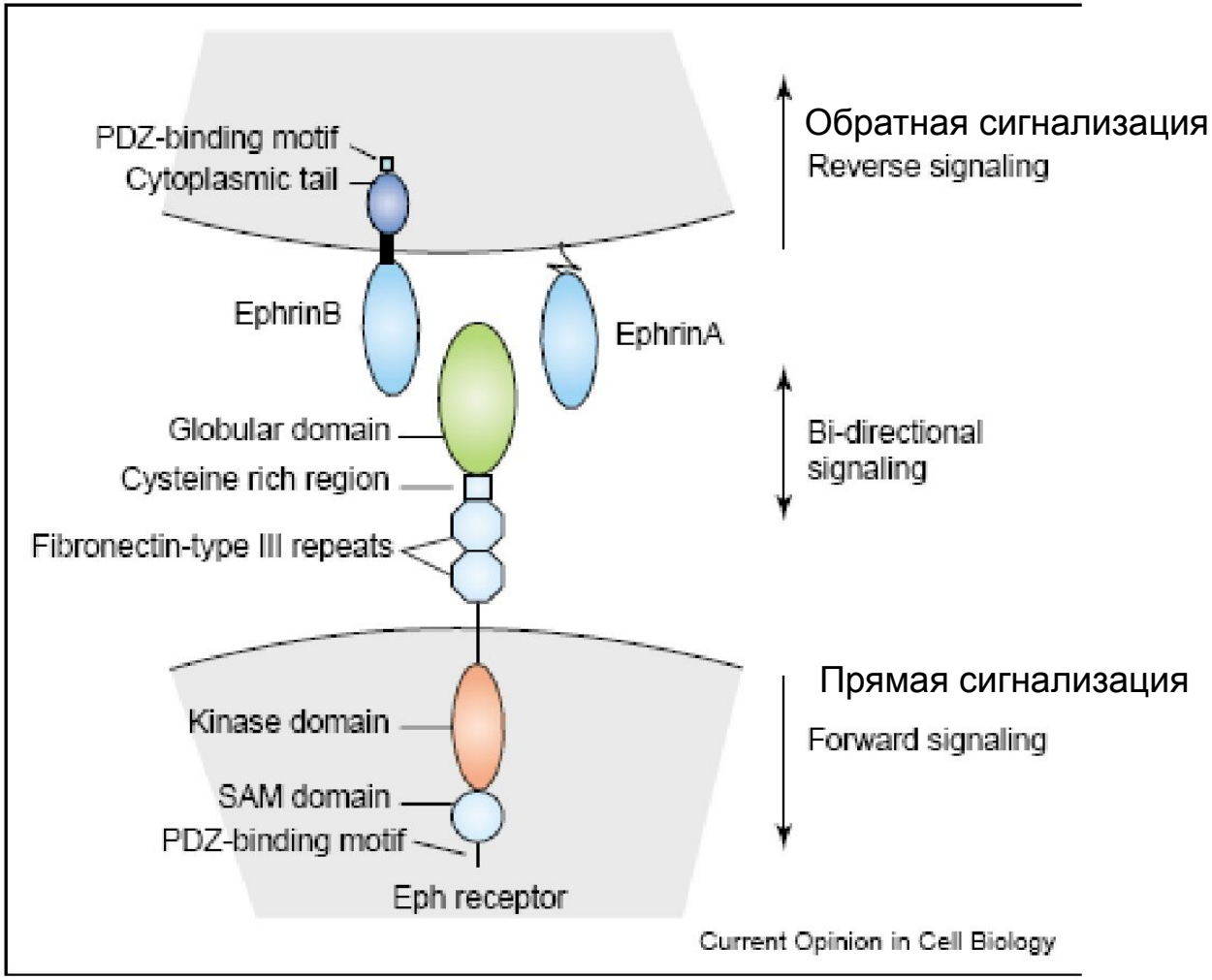
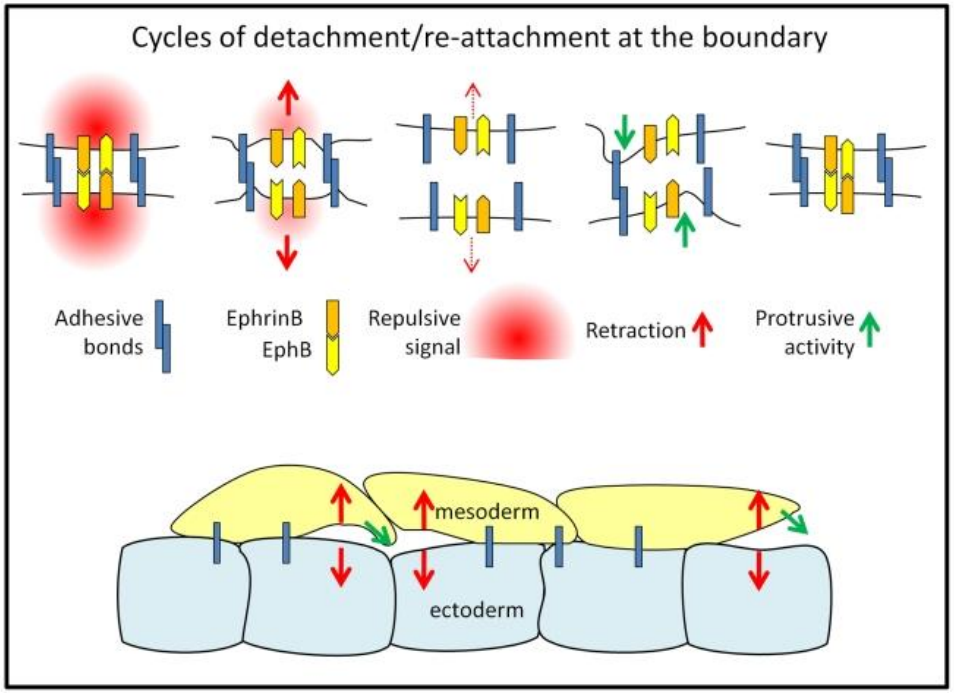
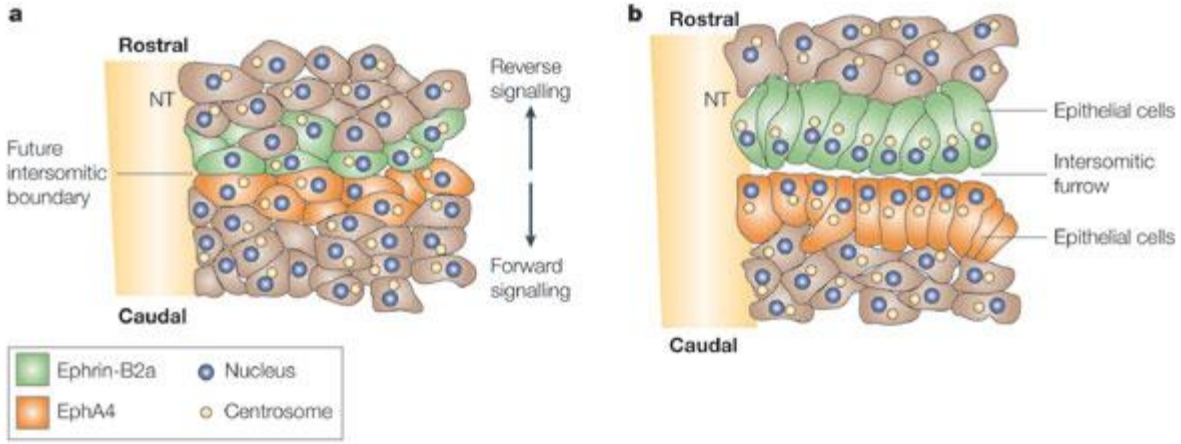
ДВУНАПРАВЛЕННАЯ СИГНАЛИЗАЦИЯ ЧЕРЕЗ ЭФРИНЫ



Циклы отталкивания – прикрепления на экто-мезодермальной границе



Установление межсомитных границ



лиганд

рецептор

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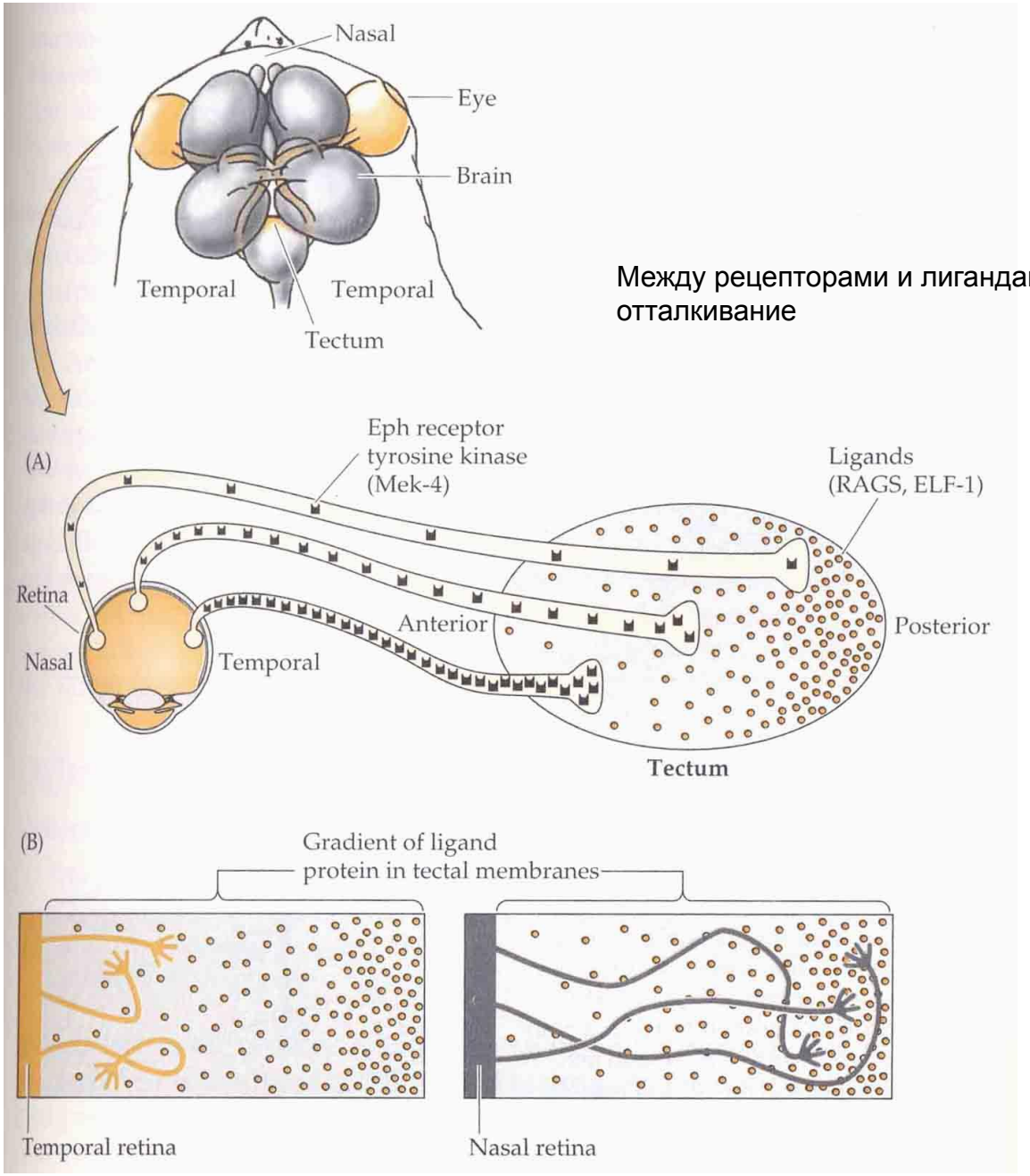
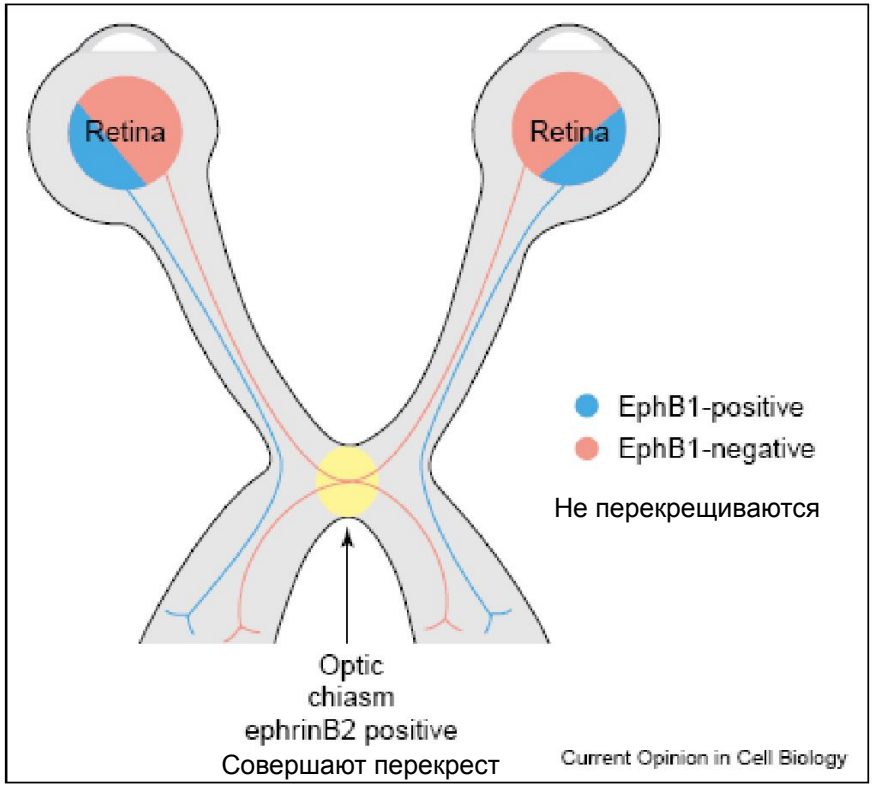
РЕТИНО-ТЕКТАЛЬНАЯ ПРОЕКЦИЯ

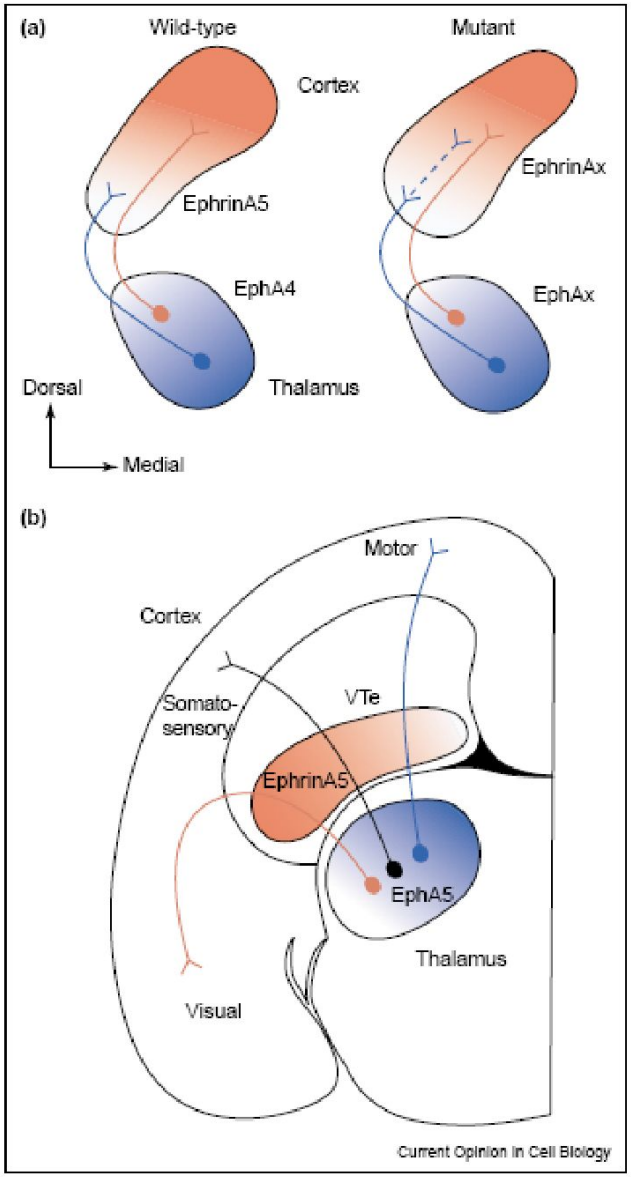


Между рецепторами и лигандами – отталкивание

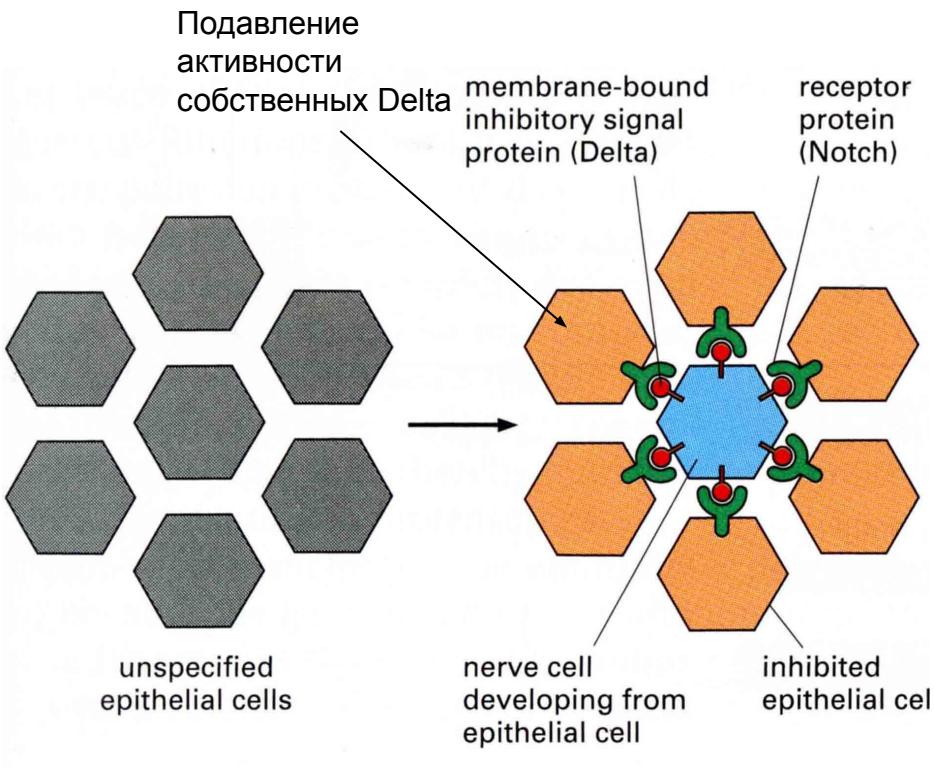
Роль эфриновой сигнализации в перекресте волокон зрительного нерва

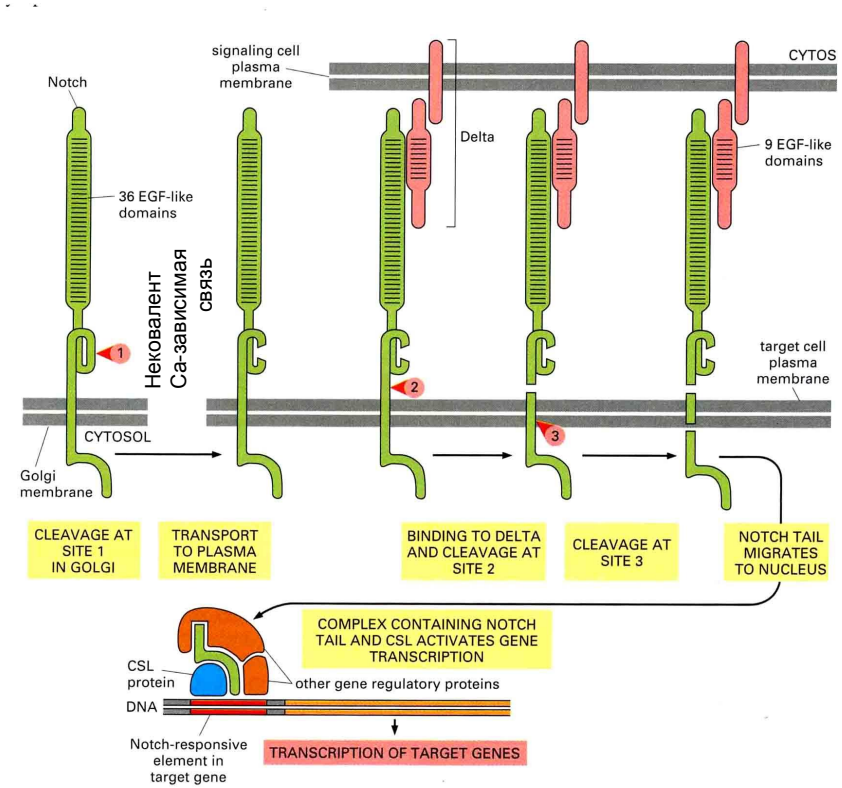


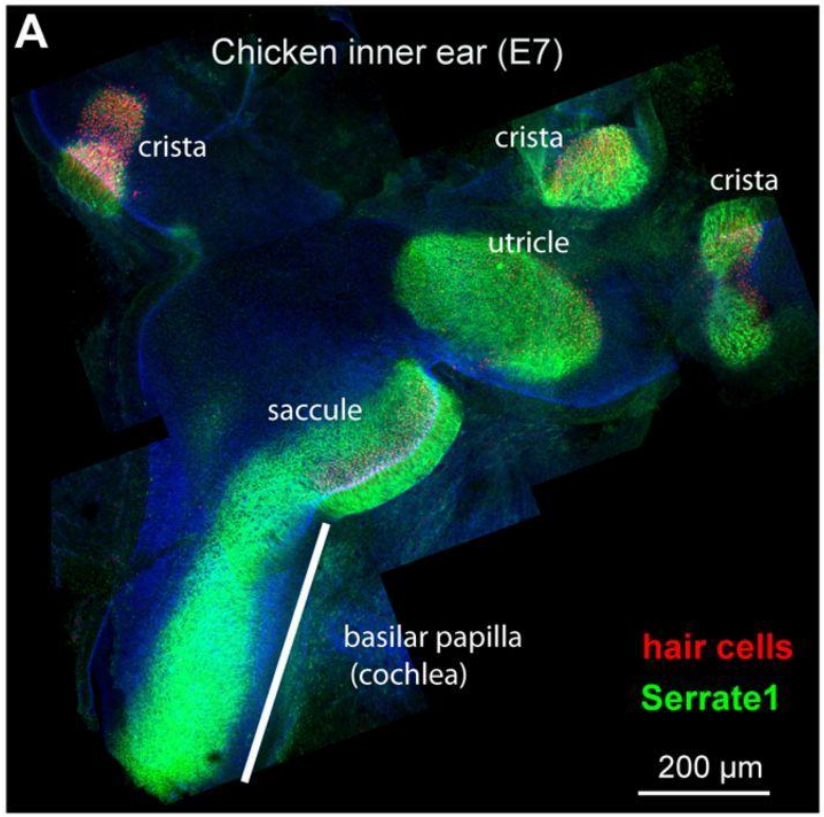
Путь от зрительных бугров к коре

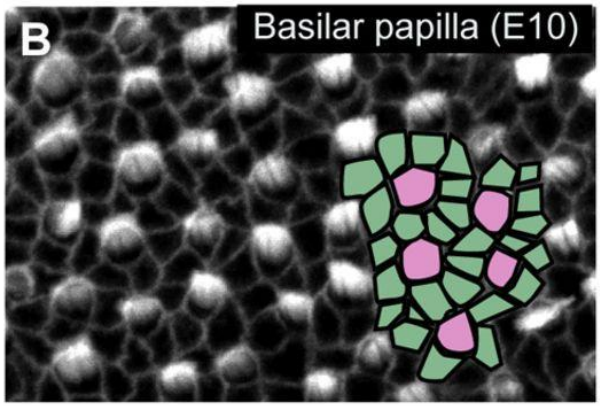


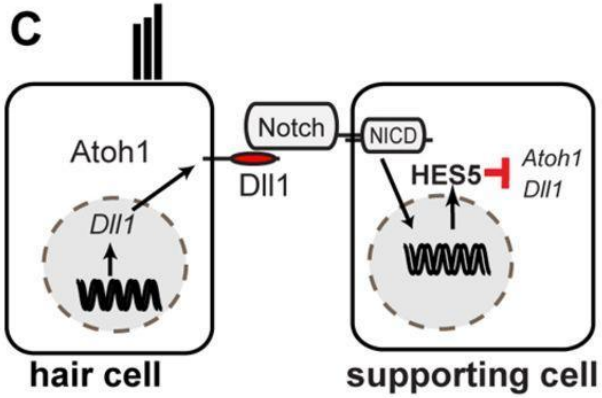
СИГНАЛИЗАЦИЯ DELTA – NOTCH: ВЗАИМОДЕЙСТВИЕ МЕМБРАННО-СВЯЗАННОГО ЛИГАНДА DELTA (КРАСНЫЙ) НА ПОВЕРХНОСТИ БУДУЩИХ НЕРВНЫХ КЛЕТОК С РЕЦЕПТОРОМ NOTCH, ПРИВОДЯЩЕЕ К РАСЩЕПЛЕНИЮ ПОСЛЕДНЕГО И ПОДАВЛЕНИЮ НЕЙРАЛЬНОЙ ДИФФЕРЕНЦИРОВКИ В СЛЕДУЮЩЕМ РЯДУ КЛЕТОК

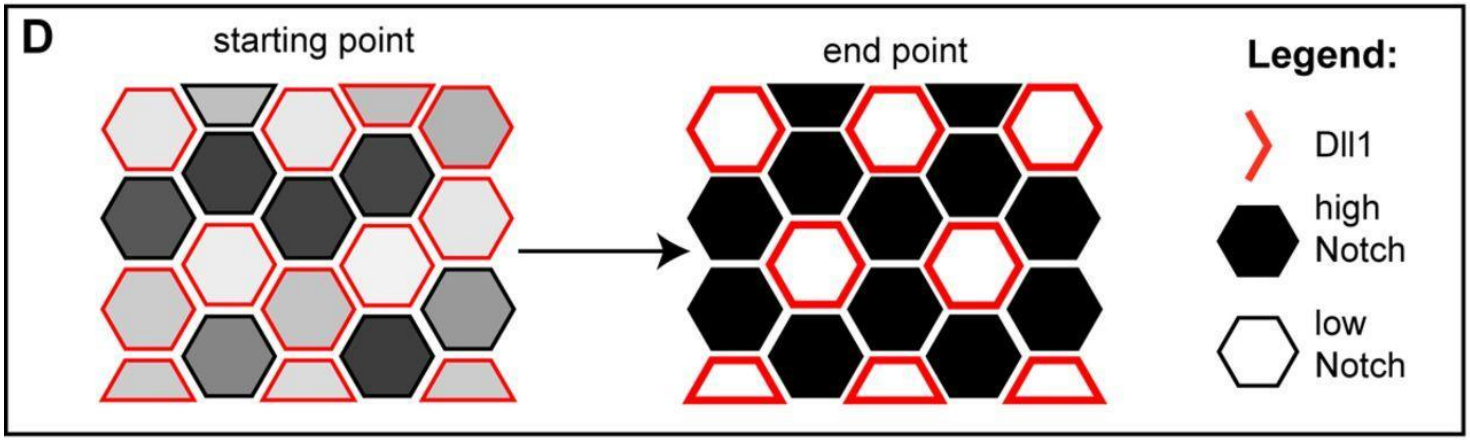





A
Chicken inner ear (E7)
crista
crista
crista
utricle
saccule
basilar papilla
(cochlea)
hair cells
Serrate1
200 µm


B
Basilar papilla (E10)


C
Atoh1
Dll1
Notch
Dll1
NICD
HES5
Atoh1
Dll1
hair cell
supporting cell


D
starting point
end point
Legend:
Dll1
high Notch
low Notch

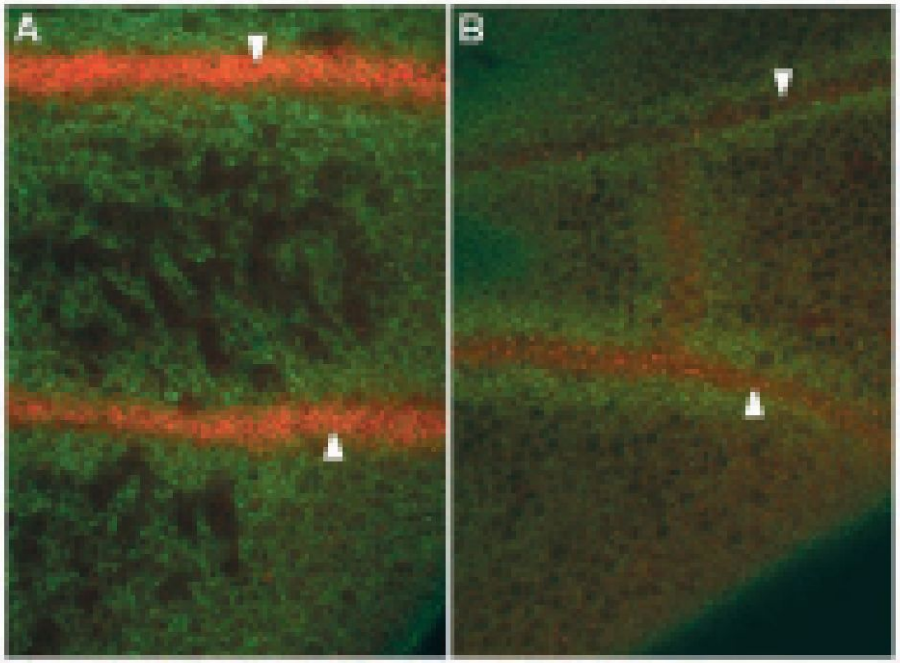
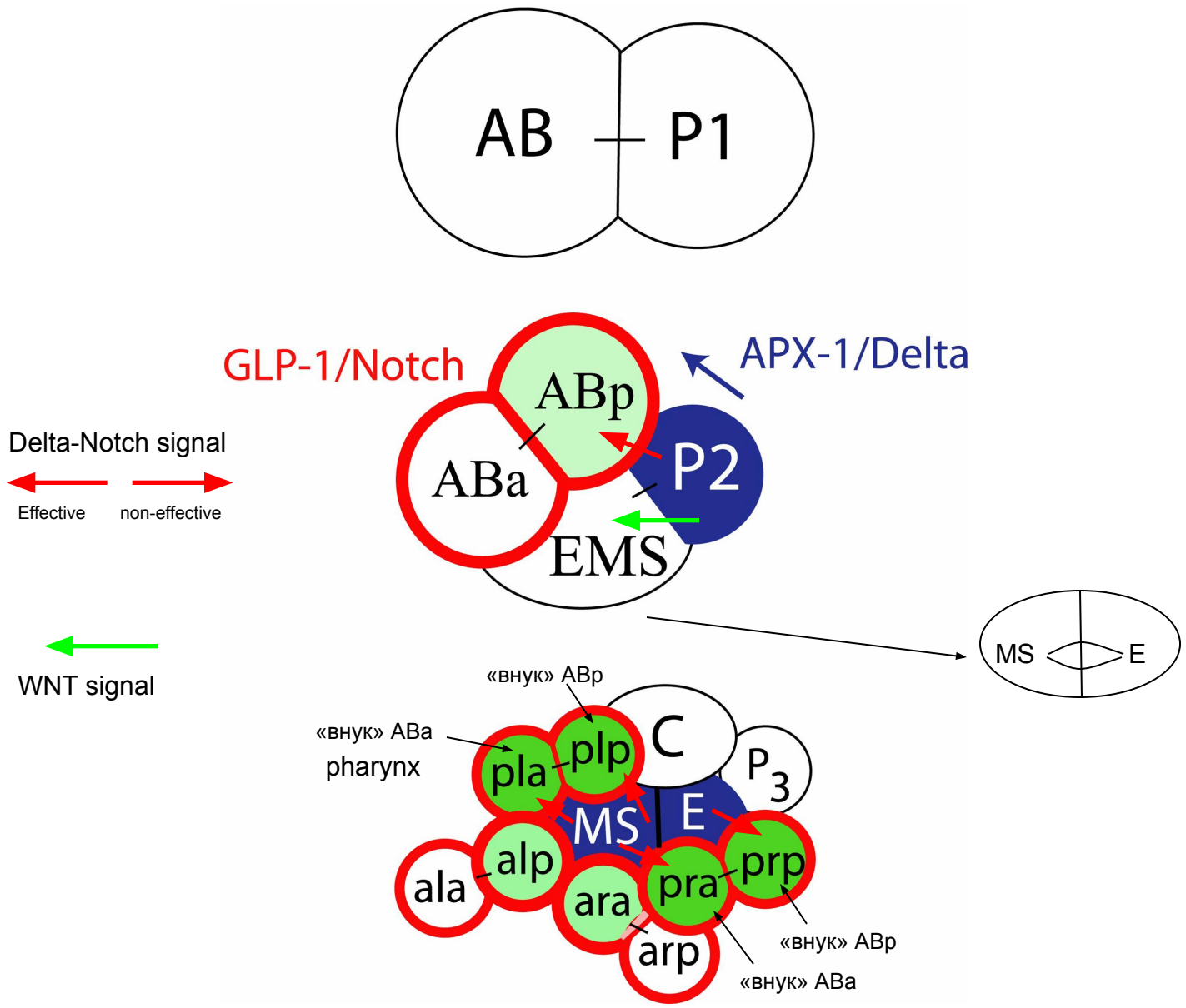


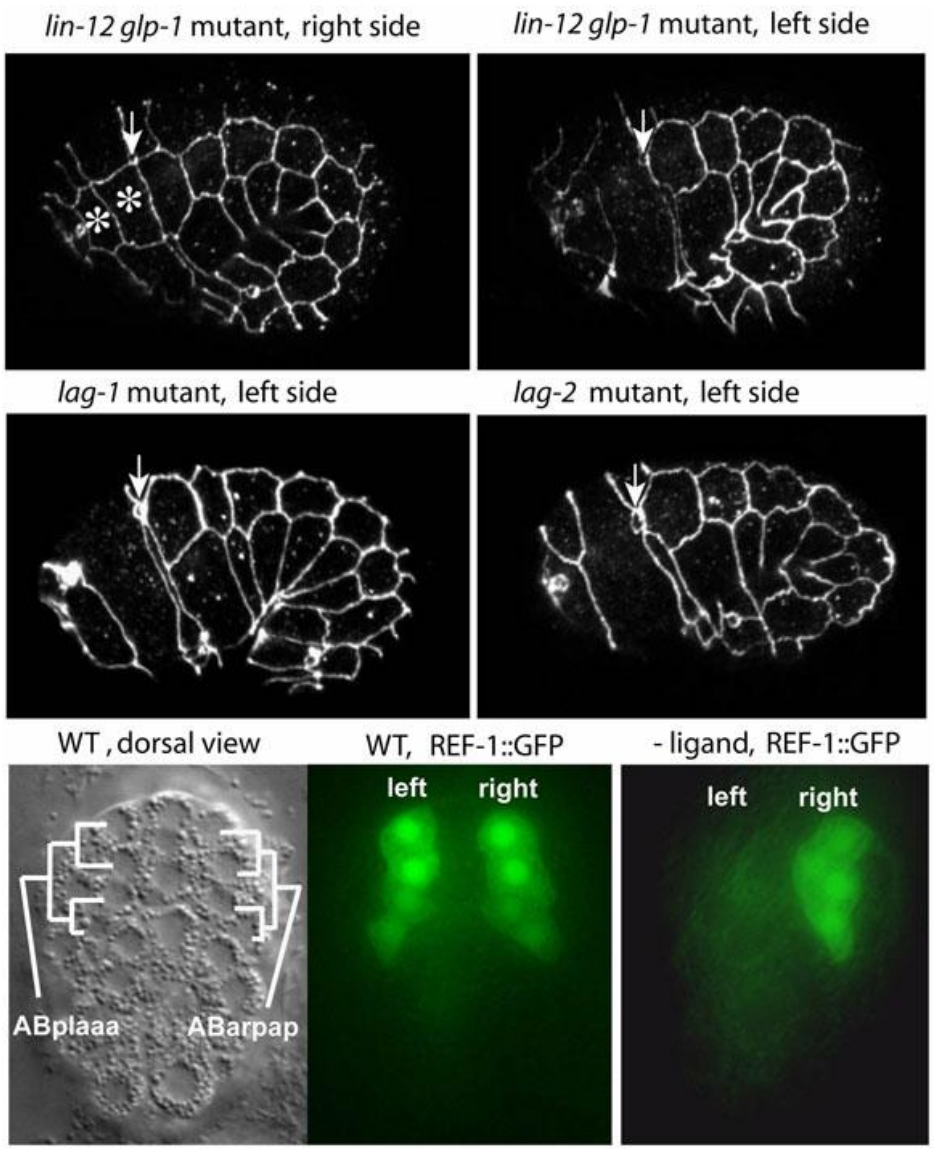
Fig. 3. Delta and Notch protein expression in pupal wing discs. Discs stained for Delta and Notch, as described in Materials and Methods. Delta signal, red; Notch signal, green. (A) 24 hour APF disc with presumptive L3 and L4 vein cells marked (Δ). (B) 30 hour APF disc with presumptive L4 and L5 vein cells marked (Δ).

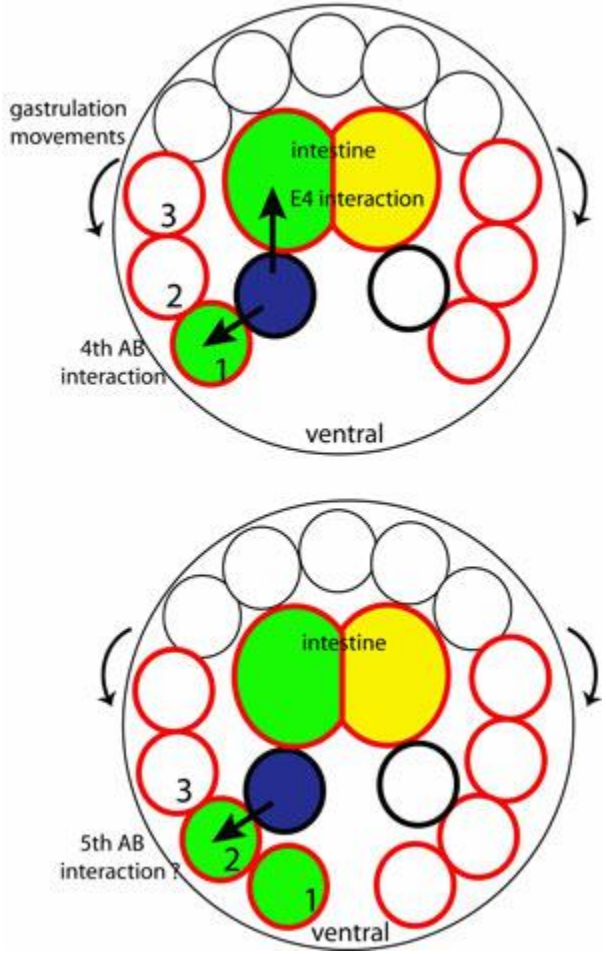
DELTA-NOTCH и Wnt сигнализация в раннем развитии C. elegans



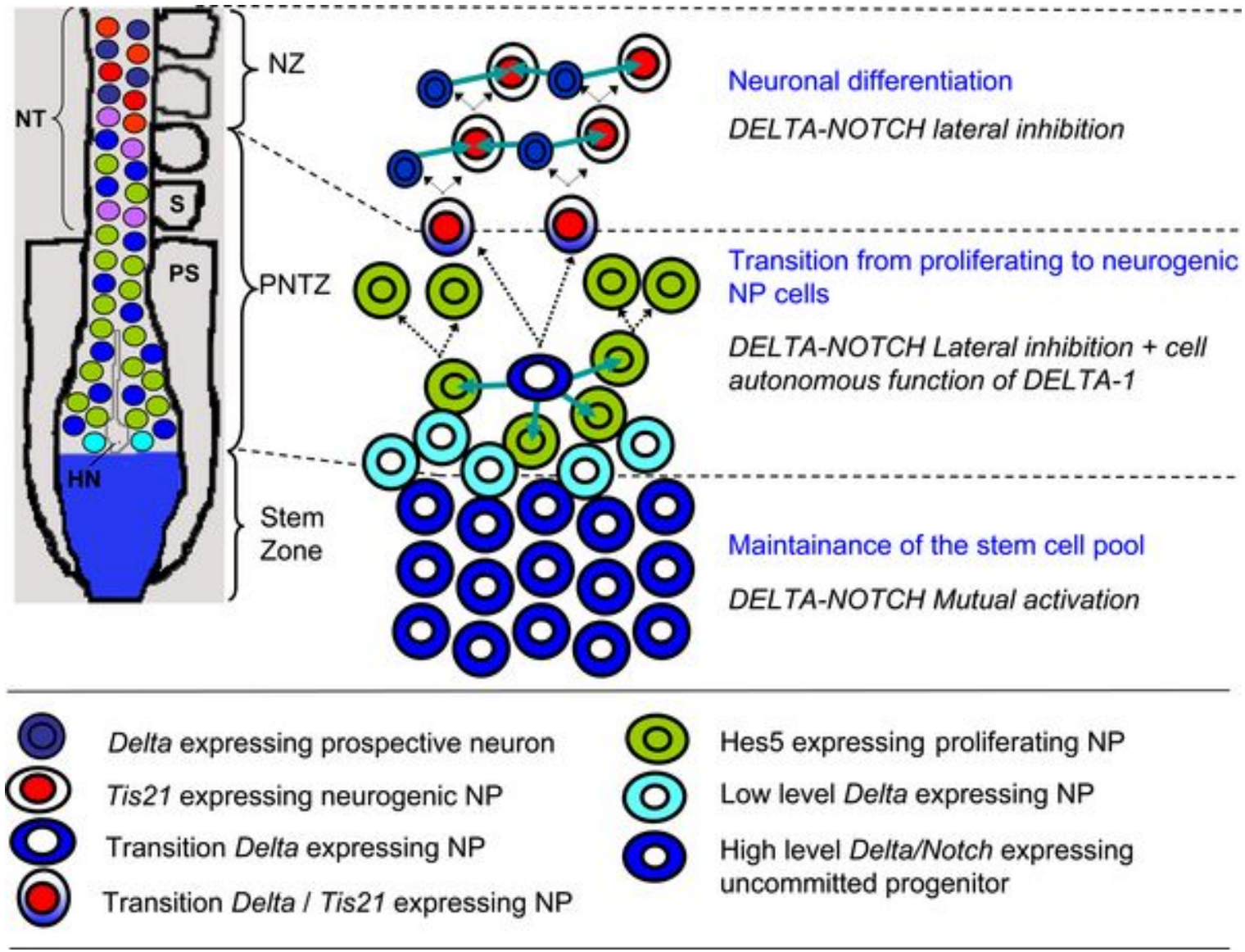
DELTA-NOTCH ИНДУКЦИИ В ПОЗДНЕМ РАЗВИТИИ C.ELEGANS

Для клеток левой стороны головы необходима индукция



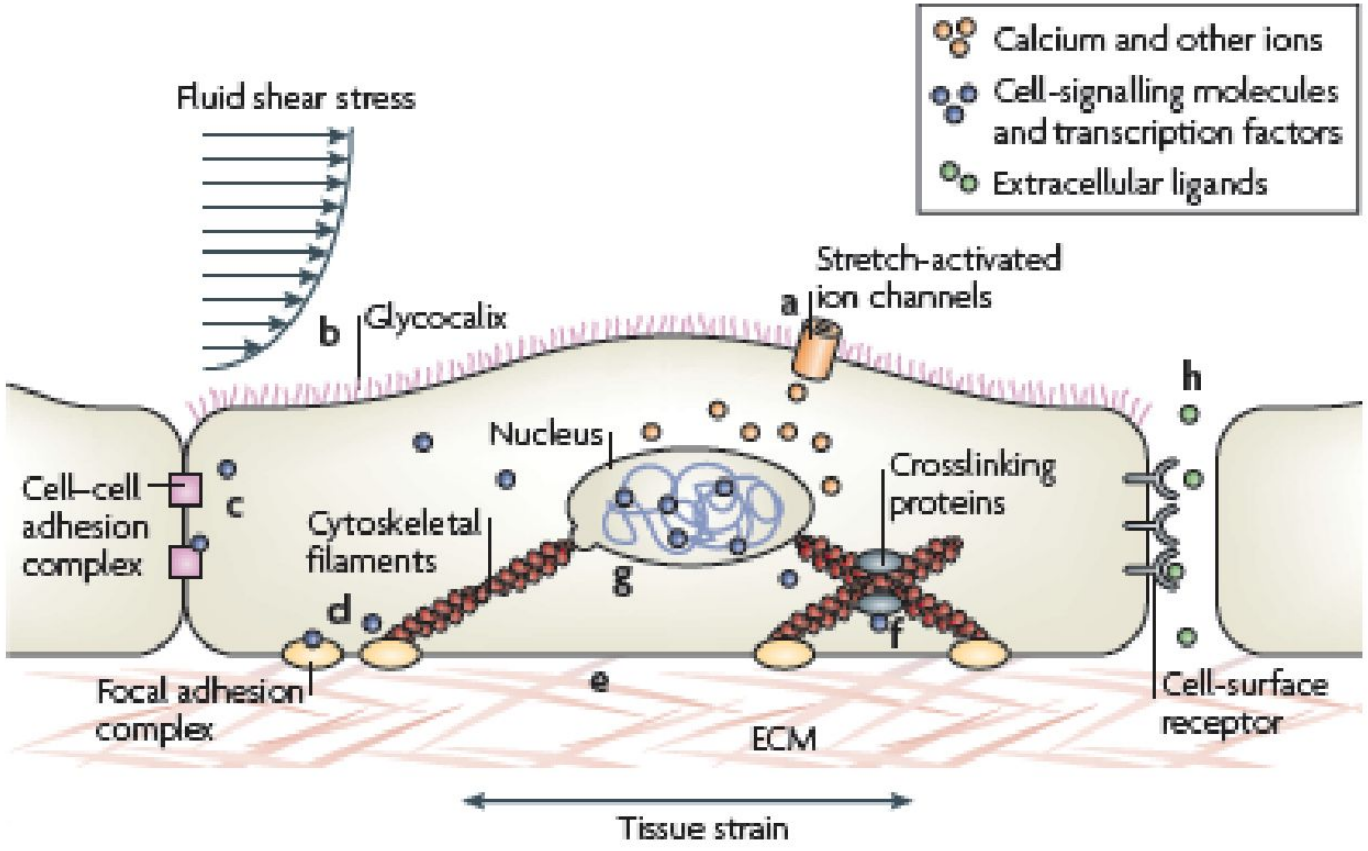


- **Figure 9. A working model for the involvement of DELTA-NOTCH signalling in the trans from proliferation to neurogenesis in the developing chick spinal cord.**



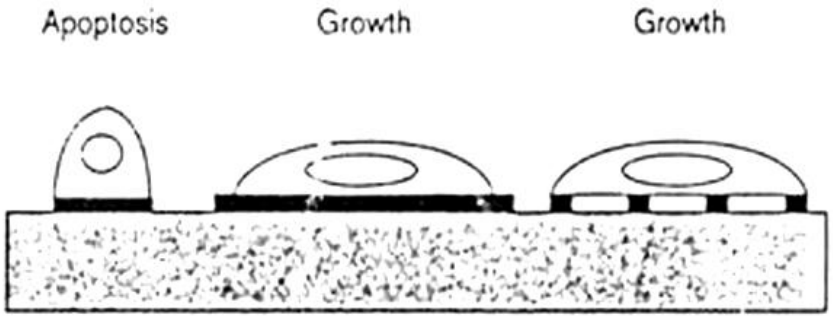
Hämmerle B, Tejedor FJ (2007) A Novel Function of DELTA-NOTCH Signalling Mediates the Transition from Proliferation to Neurogenesis in Neural Progenitor Cells. PLoS ONE 2(11): e1169. doi:10.1371/journal.pone.0001169

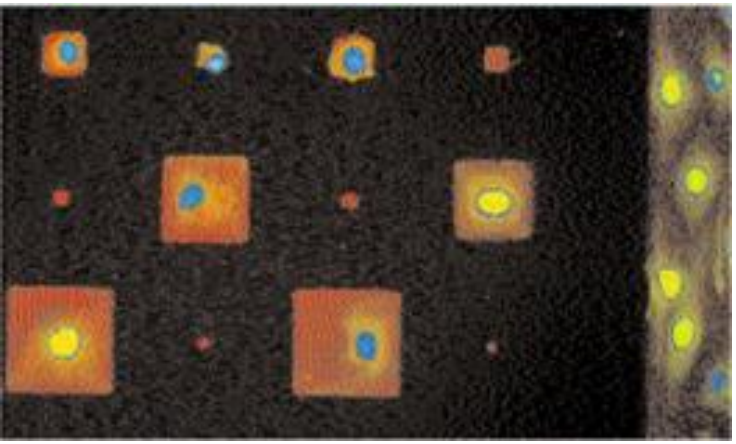
МЕХАНИЧЕСКИЕ СИЛЫ, ДЕЙСТВУЮЩИЕ НА КЛЕТКИ

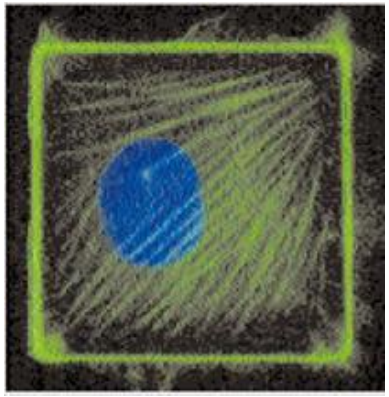


МЕХАНИЧЕСКИЕ НАПРЯЖЕНИЯ КАК ФАКТОР ВЫЖИВАНИЯ И ДИФФЕРЕНЦИРОВКИ: КЛЕТКИ НА «ОСТРОВКАХ»

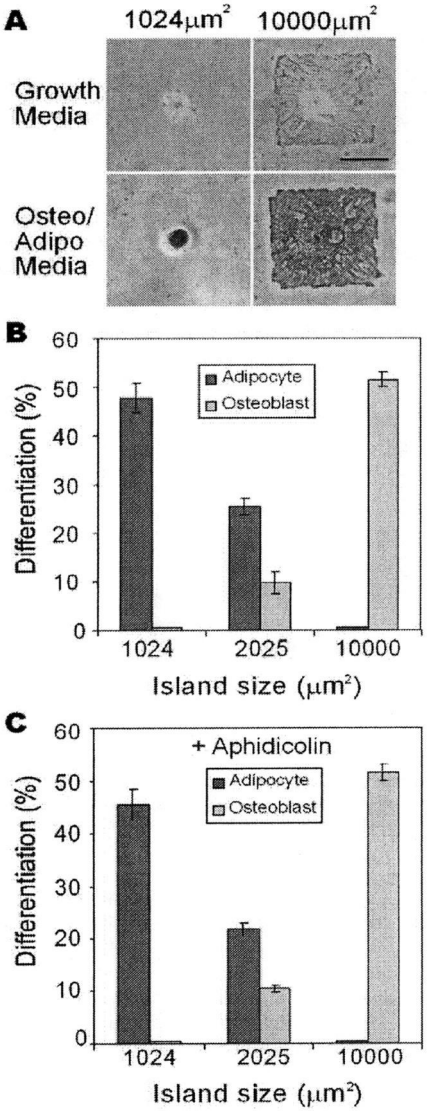
Chen et al. Geometric control of Cell life and death.
Science (1997) 276. no. 5317:1425 - 1428





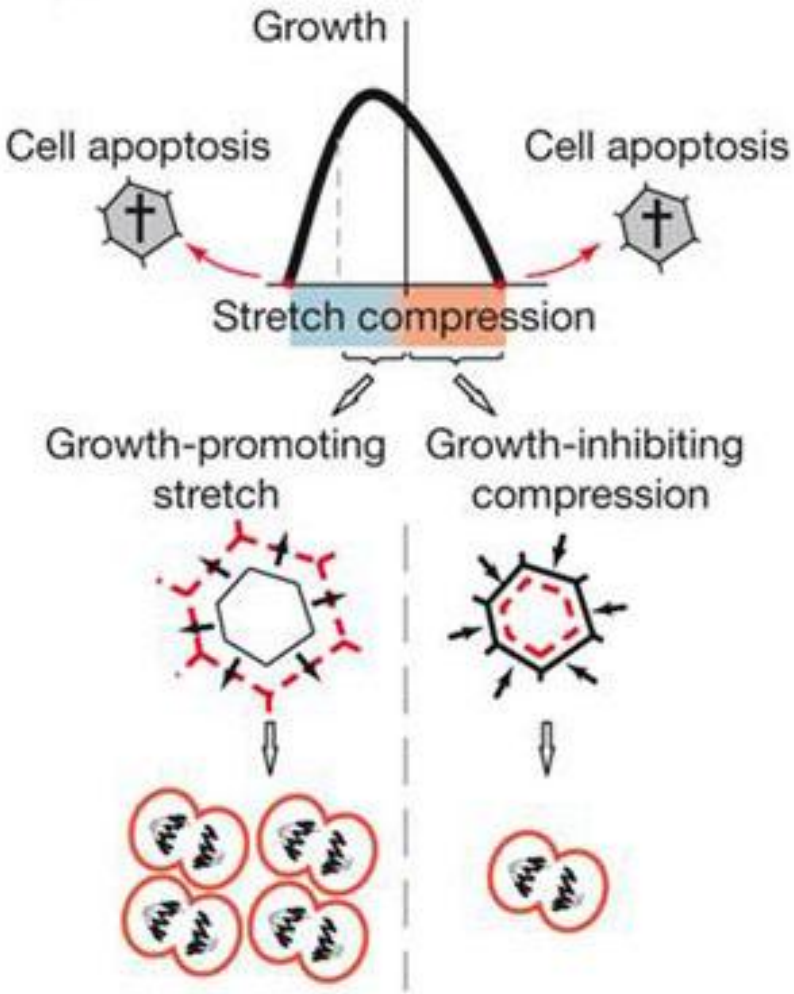


Натяжение предотвращает апоптоз



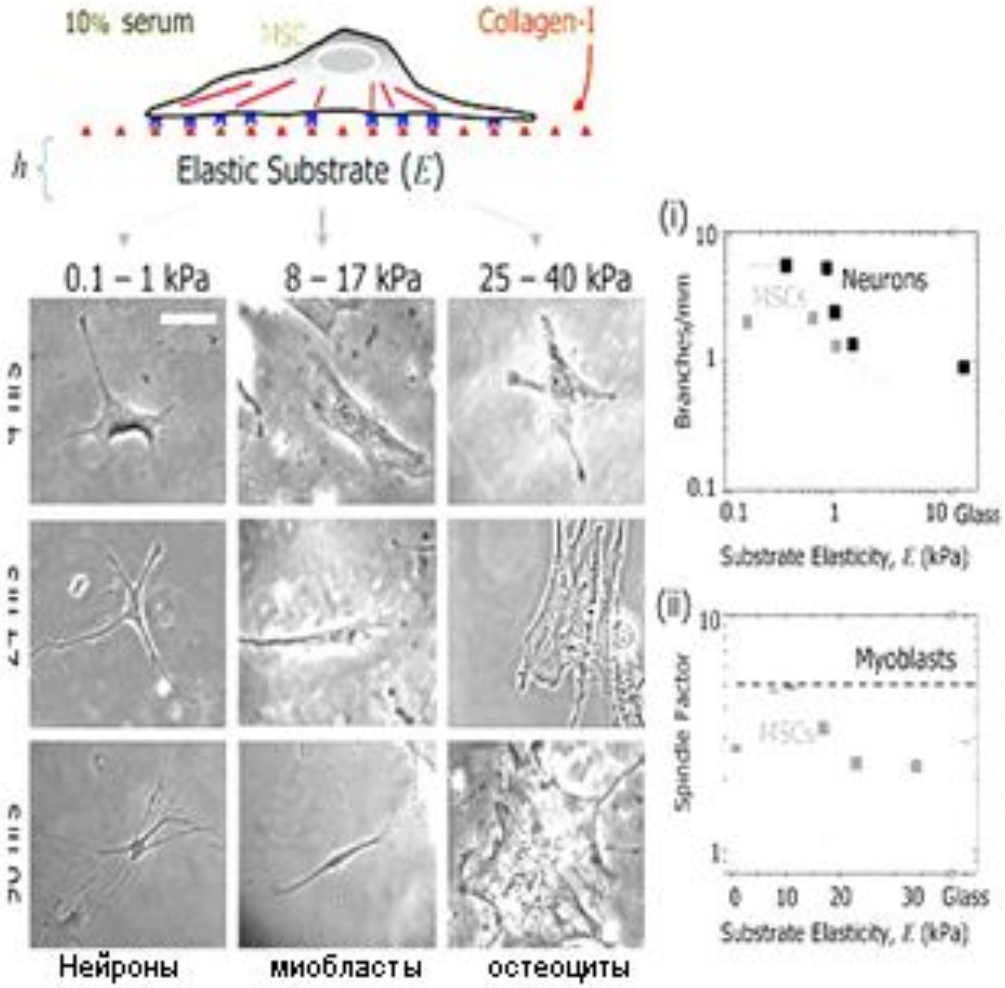
ВЫБОР ПУТИ ДИФФЕРЕНЦИРОВКИ ЗАВИСИТ ОТ СТЕПЕНИ РАСПЛАСТАННОСТИ КЛЕТКИ (R. McBeath et al. (2004) Developmental Cell 6: 483-495.

РАСТЯЖЕНИЕ СПОСОБСТВУЕТ РОСТУ, СЖАТИЕ ПОДАВЛЯЕТ РОСТ
ЧРЕЗМЕРНЫЕ НАПРЯЖЕНИЯ ВЕДУТ К АПОПТОЗУ

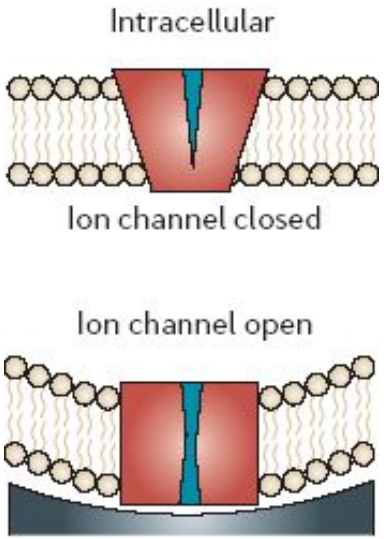


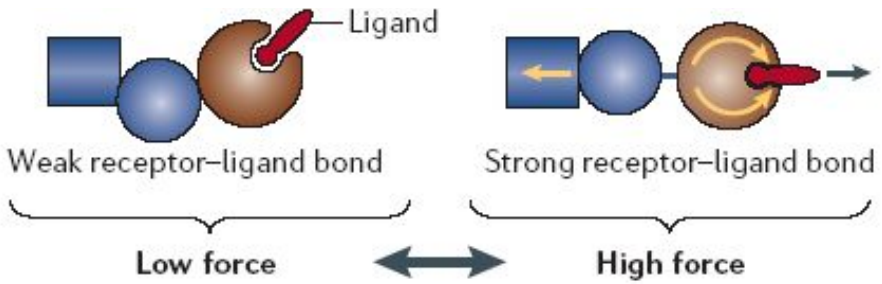
МЕХАНИЧЕСКИЕ СВОЙСТВА СУБСТРАТА МОГУТ ДЕТЕРМИНИРОВАТЬ ПУТИ ДИФФЕРЕНЦИРОВКИ СТВОЛОВЫХ КЛЕТОК

(Engler et al., Cell *126*, 677-689 (2006)

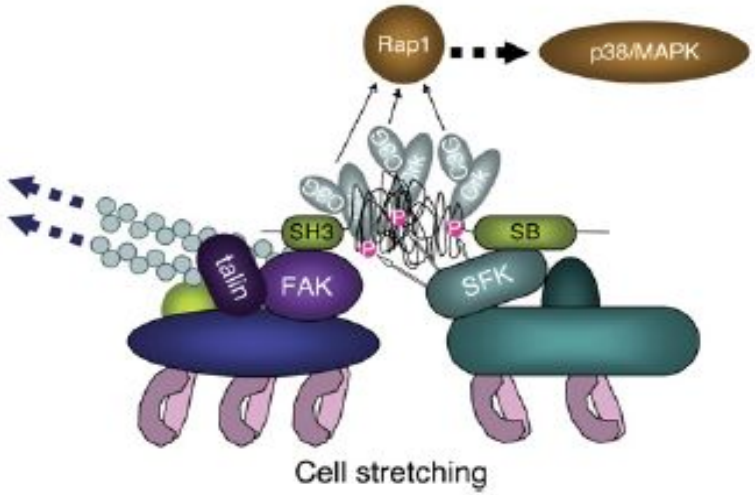


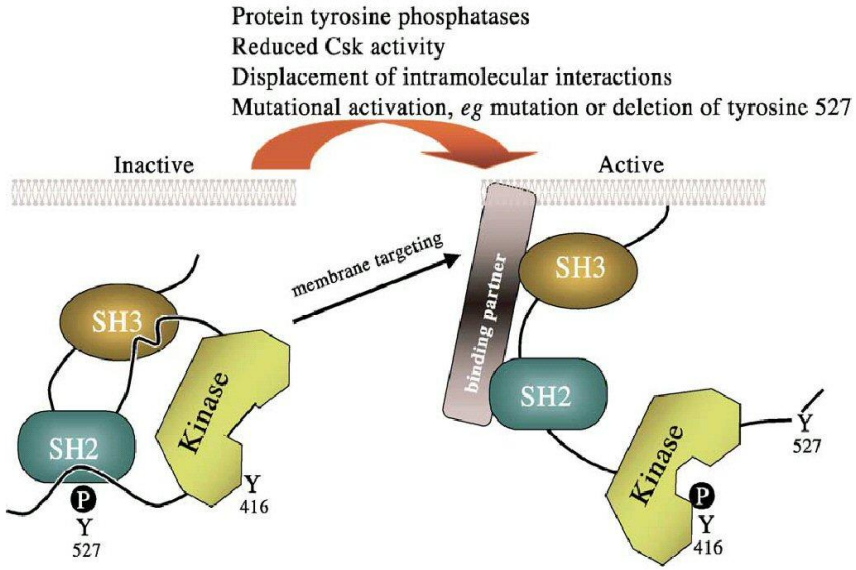
РЕЦЕПТОРЫ МЕХАНИЧЕСКИХ НАПРЯЖЕНИЙ



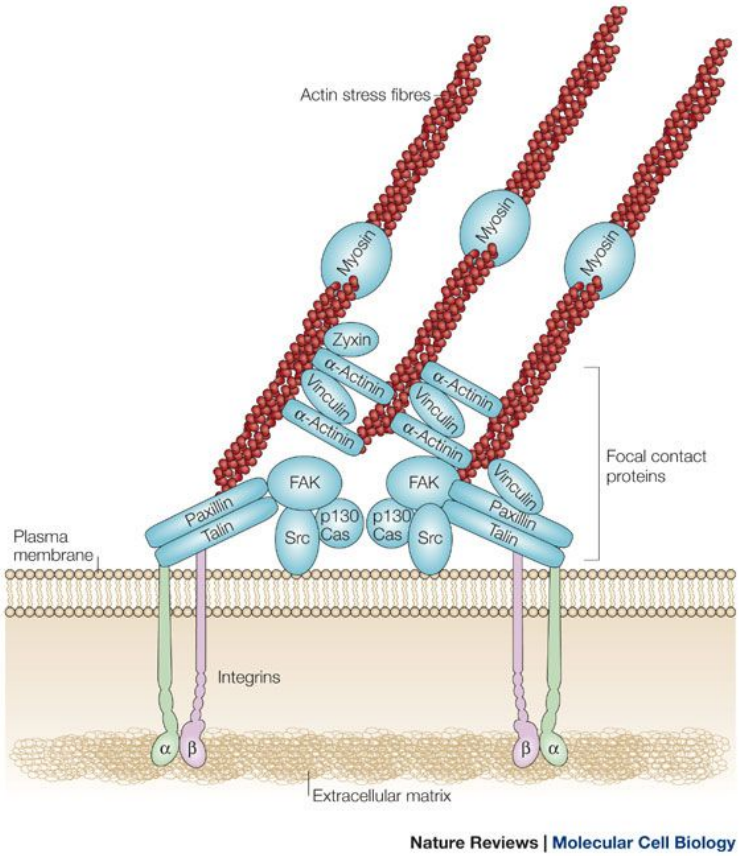


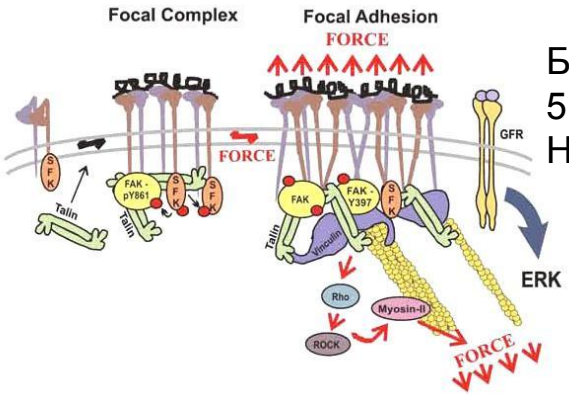
РАСТЯЖЕНИЕ CAS СПОСОБСТВУЕТ ЕГО ФОСФОРИЛИРОВАНИЮ





ФОКАЛЬНЫЕ КОНТАКТЫ: МЕХАНОЗАВИСИМАЯ СБОРКА, ОБРАТНЫЕ СВЯЗИ С ВНУТРИКЛЕТОЧНЫМИ СОКРАТИТЕЛЬНЫМИ МЕХАНИЗМАМИ





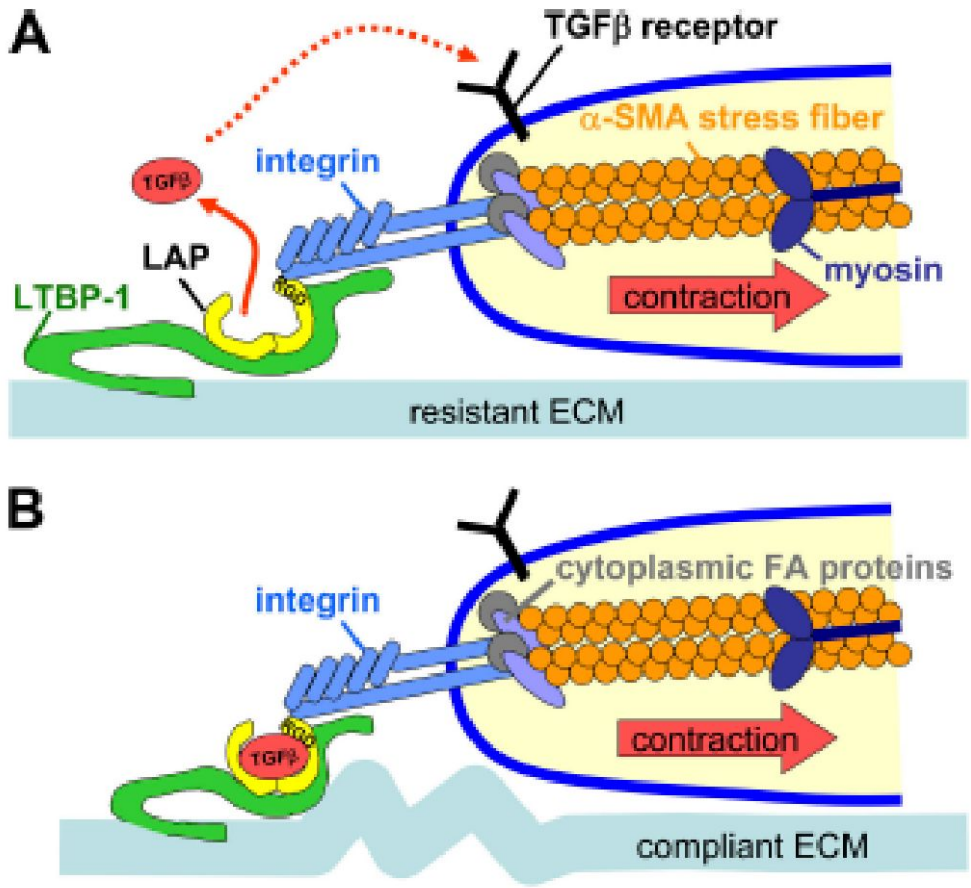
Базовые напряжения в FA – 5,5 nN/ μm^2 = $5{,}5 \times 10^3$ Pa.
На одну молекулу интегрина ~ $3 – 5 \times 10^{-12}$ N
(достаточно для растяжения)

Фокальные контакты → RhoGTP* ↔ RhoGDP → Rho-зависимая киназа → Киназа легких цепей миозина → натяжение → Рост ФК → Фокальные контакты

COOPERATION OF MECHANICAL FACTORS WITH MATRIX-BOUND CHEMICAL MORPHOGENES

Wipff et al.

The Journal of Cell Biology, Vol. 179, No. 6, December 17, 2007 1311–1323
http://www.jcb.org/cgi/doi/10.1083/jcb.200704042



ECM tension →
Myoblast differentiation

No differentiation

ДИНАМИЧЕСКИЙ БАЛАНС МЕХАНИЧЕСКИХ СИЛ В МЕЖКЛЕТОЧНЫХ КОНТАКТАХ ТИПА ADHERENT JUNCTIONS

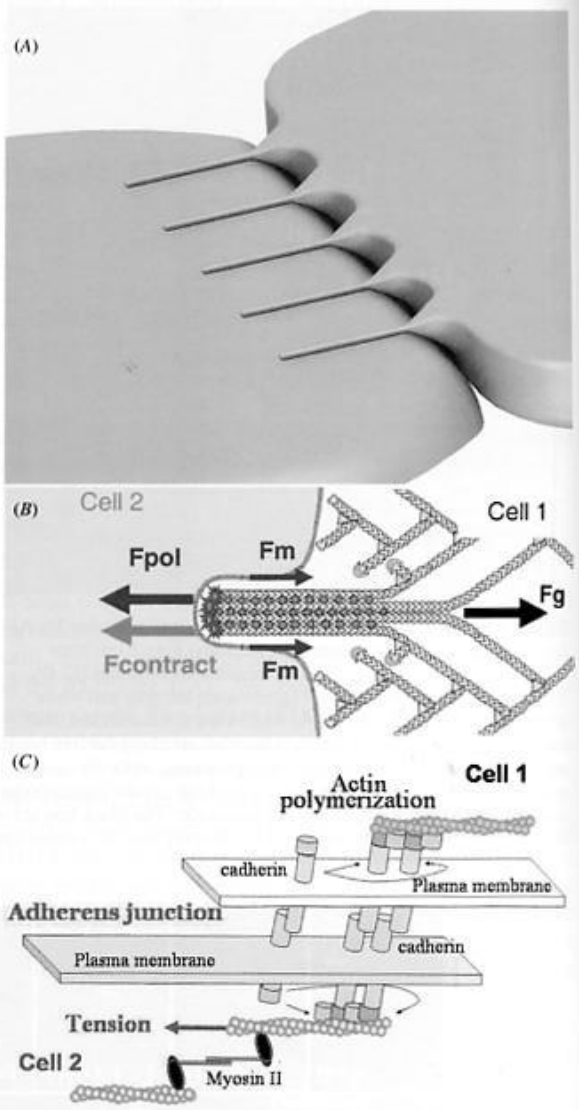
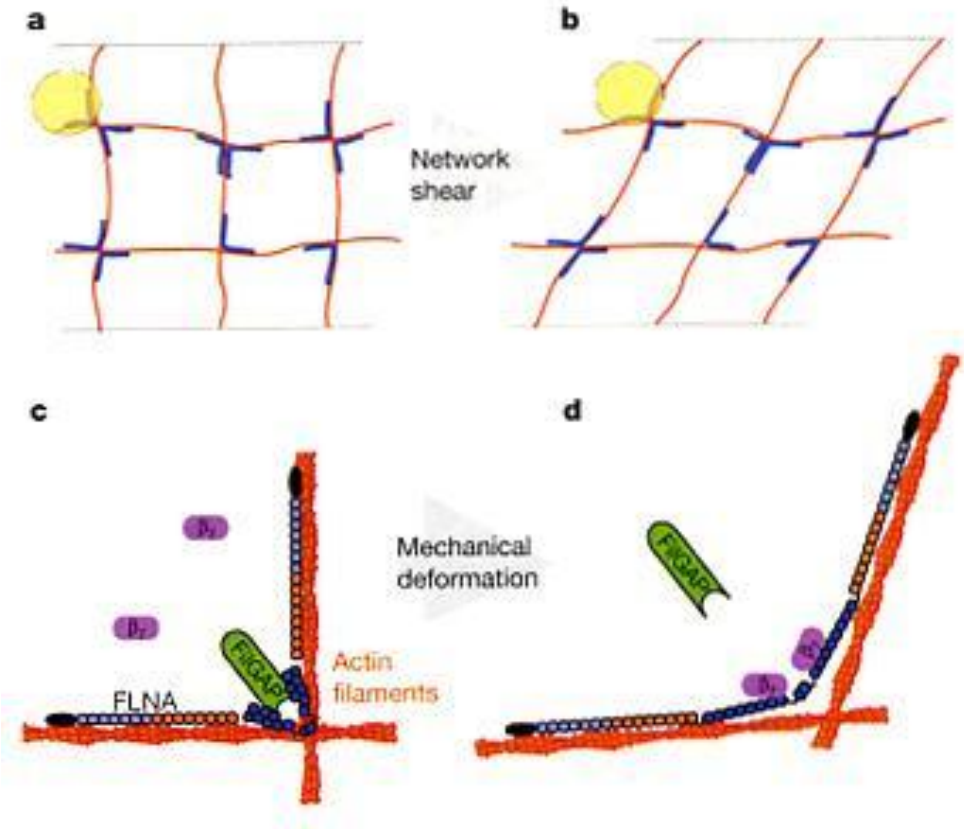


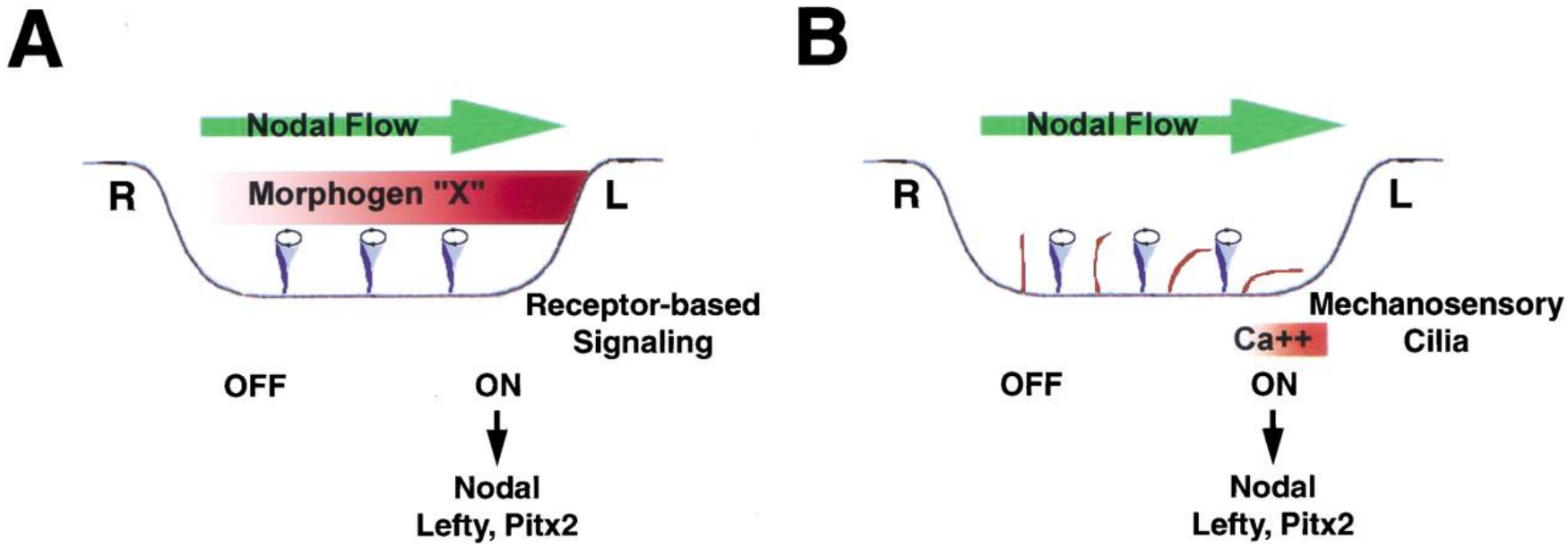
Figure 5. Representation of the AJ finger assembly. (A) 3D view of the donor/acceptor cell scheme. (B) Detailed top view of a single finger projected by Cell 1 onto Cell 2; the actin cytoskeleton is depicted in Cell 1, and the relevant forces are depicted with the subscripts contract, g, m and pol referring to contractility, gel, membrane and polymerization respectively. (C) A molecular model of the adherens junction, showing the different connecting units as grey and pink cylinders in contact with the cytoskeletal structures of both the donor and acceptor cell.

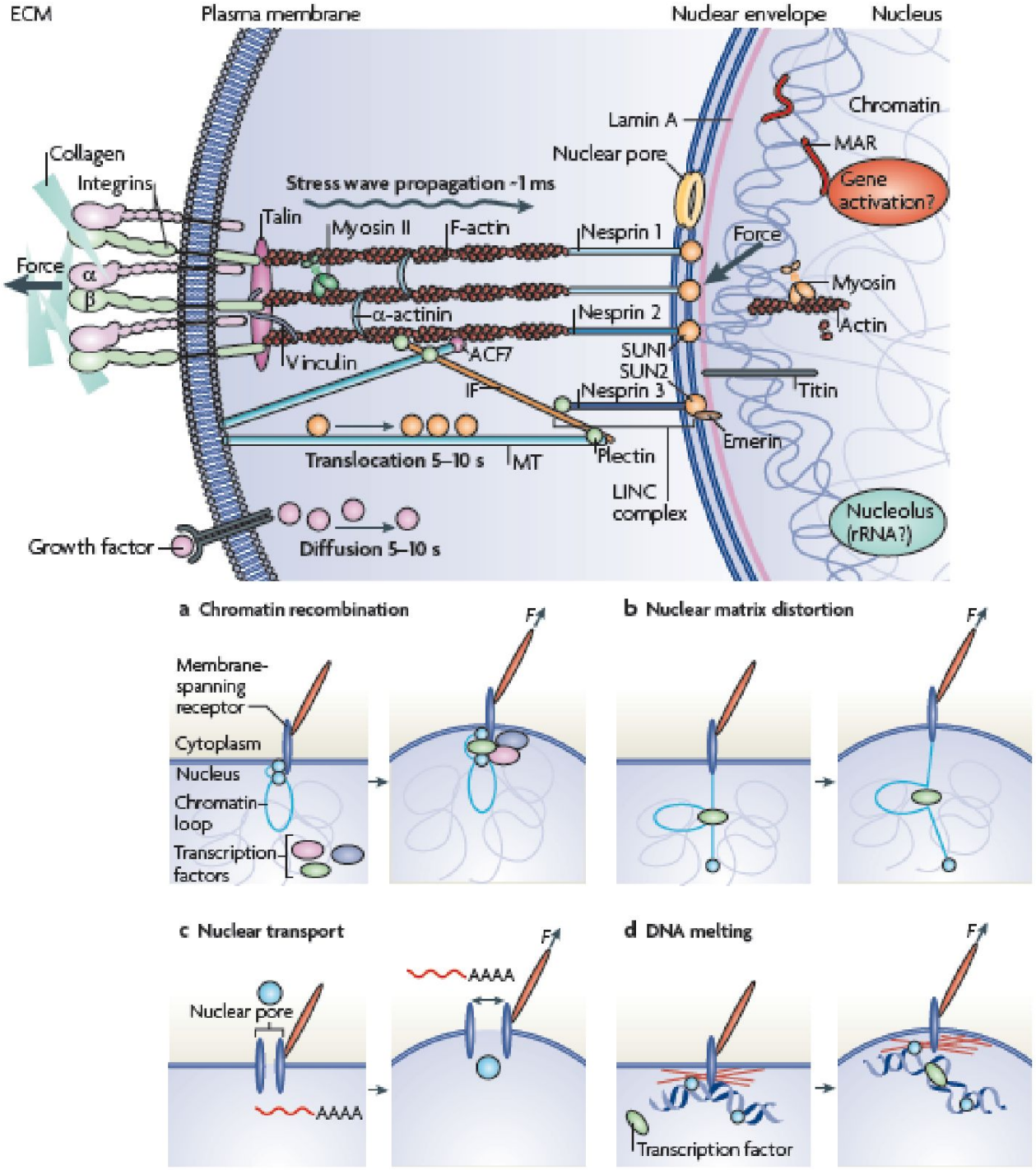
Филамин как центральный механотрансдуктор цитоскелета

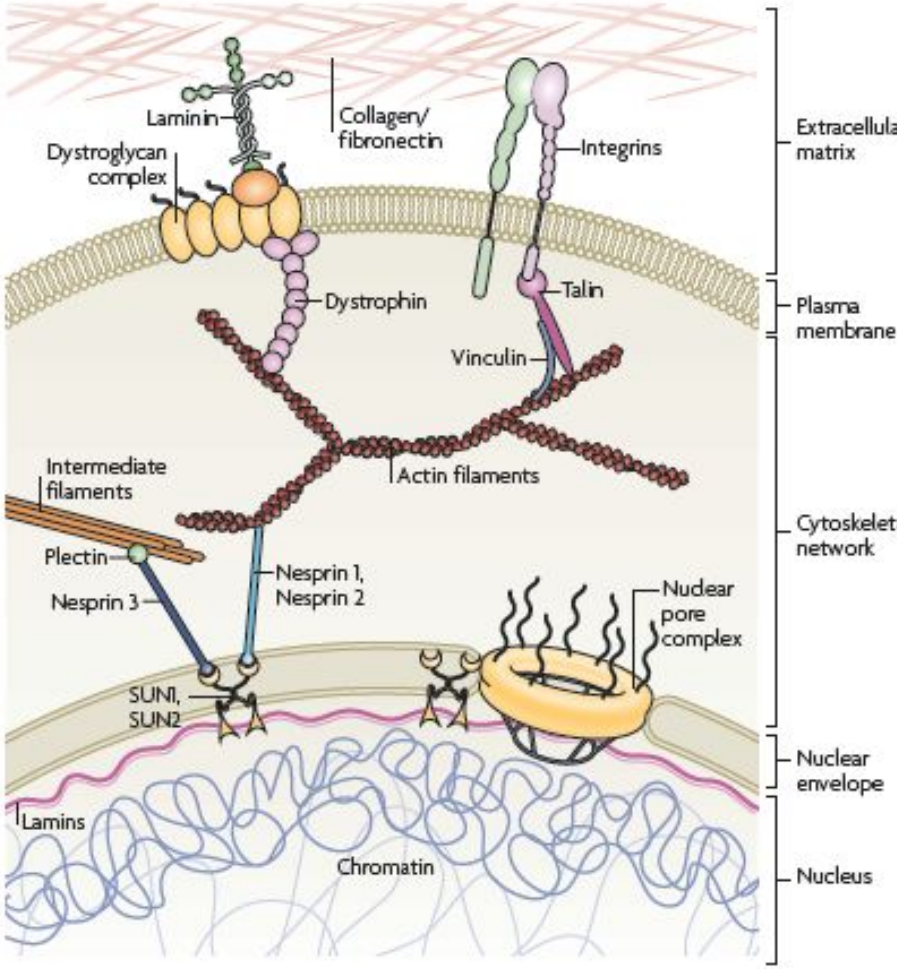


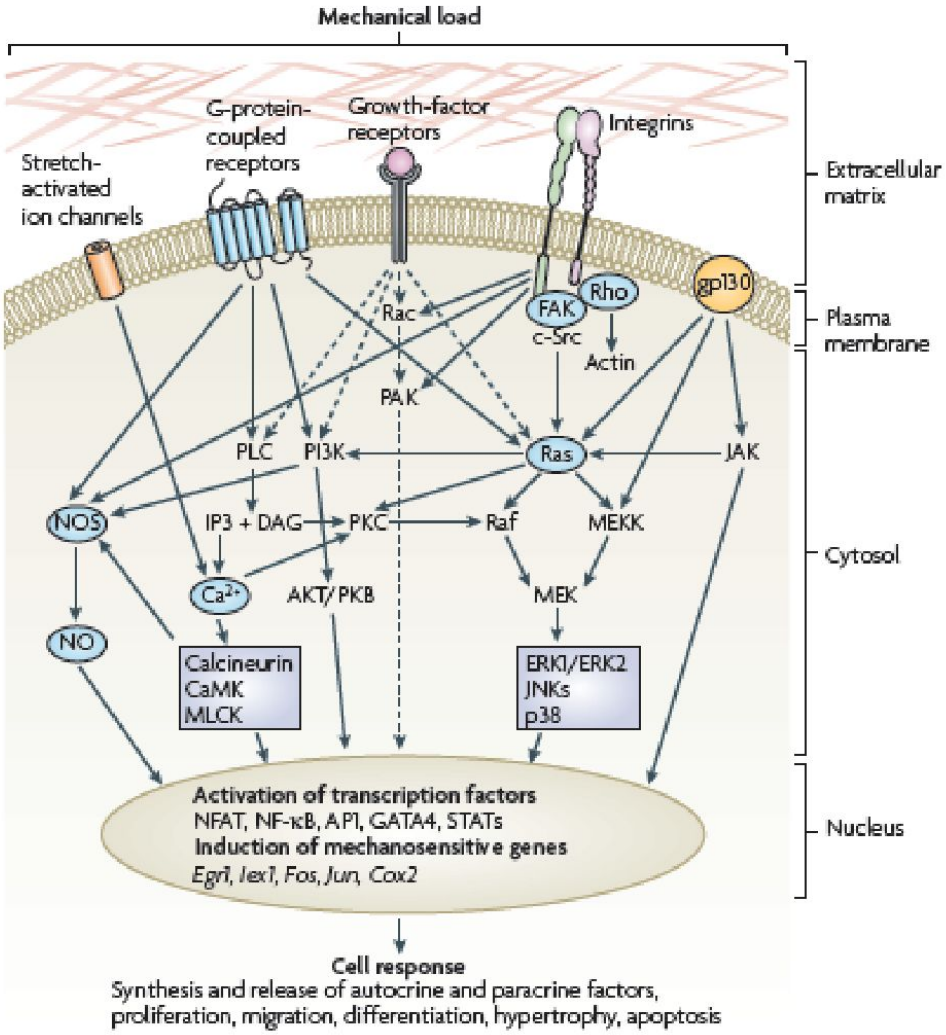
При деформации актинового геля как внешней силой, так и миозином II, филамин утрачивает сродство к FilGAP (GTP-ase associating protein specific for RAC – регулирует распластывание клеток и блеббинг) и повышает сродство к β-интегринам (Nature 2011)

Механозависимые реснички



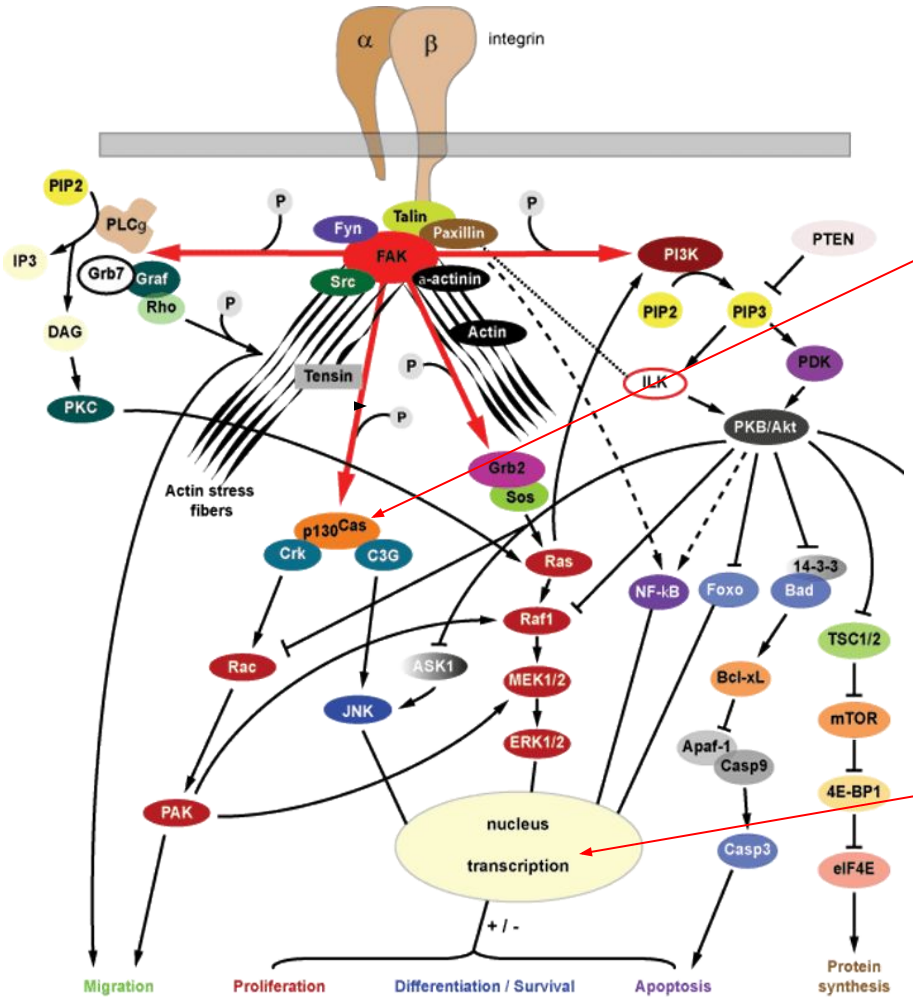

ECM
Plasma membrane
Nuclear envelope
Nucleus
Collagen
Integrins
Force
α
β
Talin
Stress wave propagation ~1 ms
Myosin II
F-actin
Nesprin 1
Nesprin 2
Nesprin 3
α-actinin
Vinculin
ACF7
IF
SUN1
SUN2
Lamin A
Nuclear pore
Chromatin
MAR
Gene activation?
Force
Myosin
Actin
Titin
Emerin
Plectin
LINC complex
Translocation 5–10 s
MT
Growth factor
Diffusion 5–10 s
Nucleolus (rRNA?)
a Chromatin recombination
Membrane-spanning receptor
Cytoplasm
Nucleus
Chromatin loop
Transcription factors
F
b Nuclear matrix distortion
F
c Nuclear transport
Nuclear pore
AAAA
AAAA
F
d DNA melting
Transcription factor
F

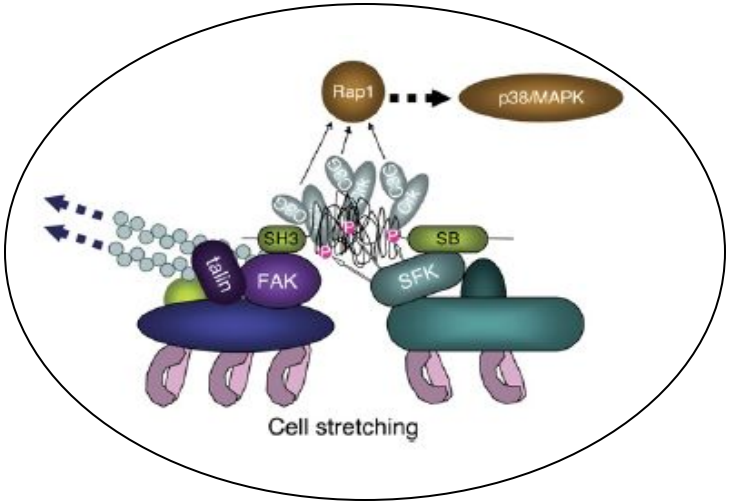

Laminin
Collagen/
fibronectin
Dystroglycan
complex
Integrins
Extracellula
matrix
Dystrophin
Talin
Plasma
membrane
Vinculin
Intermediate
filaments
Actin filaments
Cytoskelet
network
Plectin
Nesprin 1,
Nesprin 2
Nesprin 3
Nuclear
pore
complex
SUN1,
SUN2
Nuclear
envelope
Lamins
Chromatin
Nucleus


Mechanical load
G-protein-
coupled
receptors
Growth-factor
receptors
Integrins
Stretch-
activated
ion channels
Extracellular
matrix
Rac
FAK
Rho
gp130
c-Src
Actin
Plasma
membrane
PAK
PLC
PI3K
Ras
JAK
NOS
IP3 + DAG
PKC
Raf
MEKK
Cytosol
Ca2+
AKT/PKB
MEK
NO
Calcineurin
CaMK
MLCK
ERK1/ERK2
JNKs
p38
Activation of transcription factors
NFAT, NF-κB, AP1, GATA4, STATs
Induction of mechanosensitive genes
Egr1, Jex1, Fos, Jun, Cox2
Nucleus
Cell response
Synthesis and release of autocrine and paracrine factors,
proliferation, migration, differentiation, hypertrophy, apoptosis

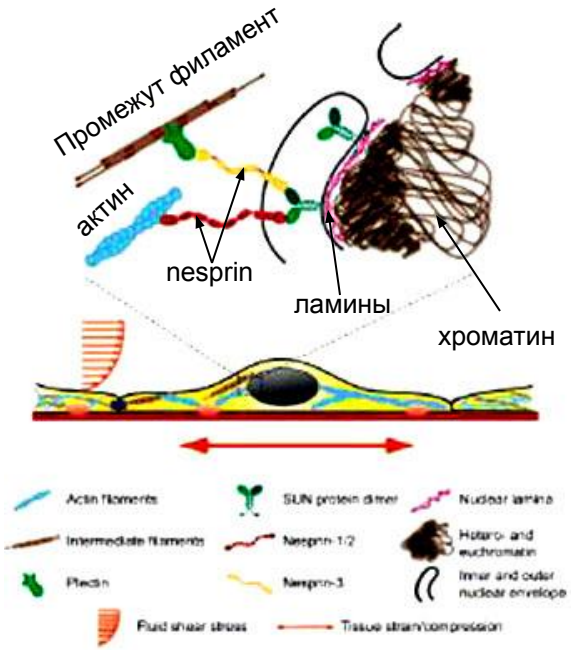
СИГНАЛЬНЫЕ ПУТИ, ИДУЩИЕ ОТ ФОКАЛЬНЫХ КОНТАКТОВ

МЕХАНИЧЕСКОЕ РАСТЯЖЕНИЕ УСИЛИВАЕТ ТИРОЗИН-ФОСФОРИЛИРОВАНИЕ p130 CAS

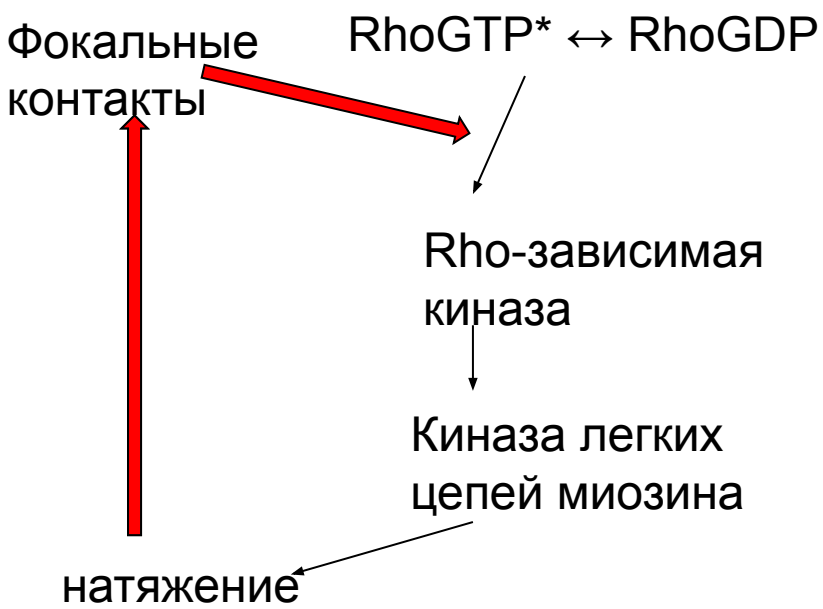




МЕХАНИЧЕСКИЕ СИГНАЛЫ В ЯДРО



ОБРАТНЫЕ СВЯЗИ С УЧАСТИЕМ Rho-БЕЛКОВ И МЕХАНИЧЕСКИХ НАПРЯЖЕНИЙ



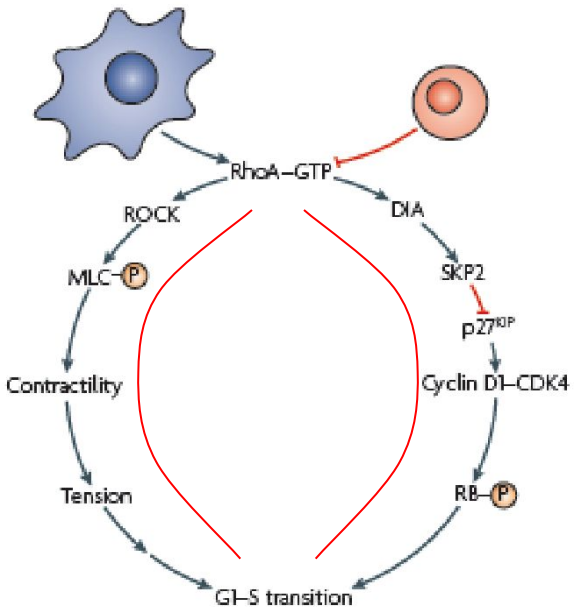


Figure 2 | **Cell shape regulates proliferation through the small GTPase RhoA.** Restricting cell spreading decreases proliferation through the regulation of RhoA activity. RhoA promotes G1–S-phase transition and cell proliferation through two pathways. First, the RhoA effector, Rho kinase (ROCK), increases myosin light chain (MLC; also known as MYL) phosphorylation to generate cellular contractility. This generates the tension in the cell that is required for proliferation[57,58]. Second, the RhoA effector, diaphanous (DIA), activates the ubiquitin ligase SKP2 to inhibit the cyclin-dependent kinase (CDK) $p27^{KIP}$ (also known as CDKN1B). $p27^{KIP}$ can no longer degrade the cyclin D1–CDK4 complex, so this complex phosphorylates retinoblastoma protein (RB), thereby leading to the G1–S-phase transition[55,56]. Restricting cell shape decreases RhoA activity in some cell types, so these two pathways are not activated. Without contractility and tension generation as well as SKP2 activity, G1–S-phase transition is blocked and proliferation is reduced.