

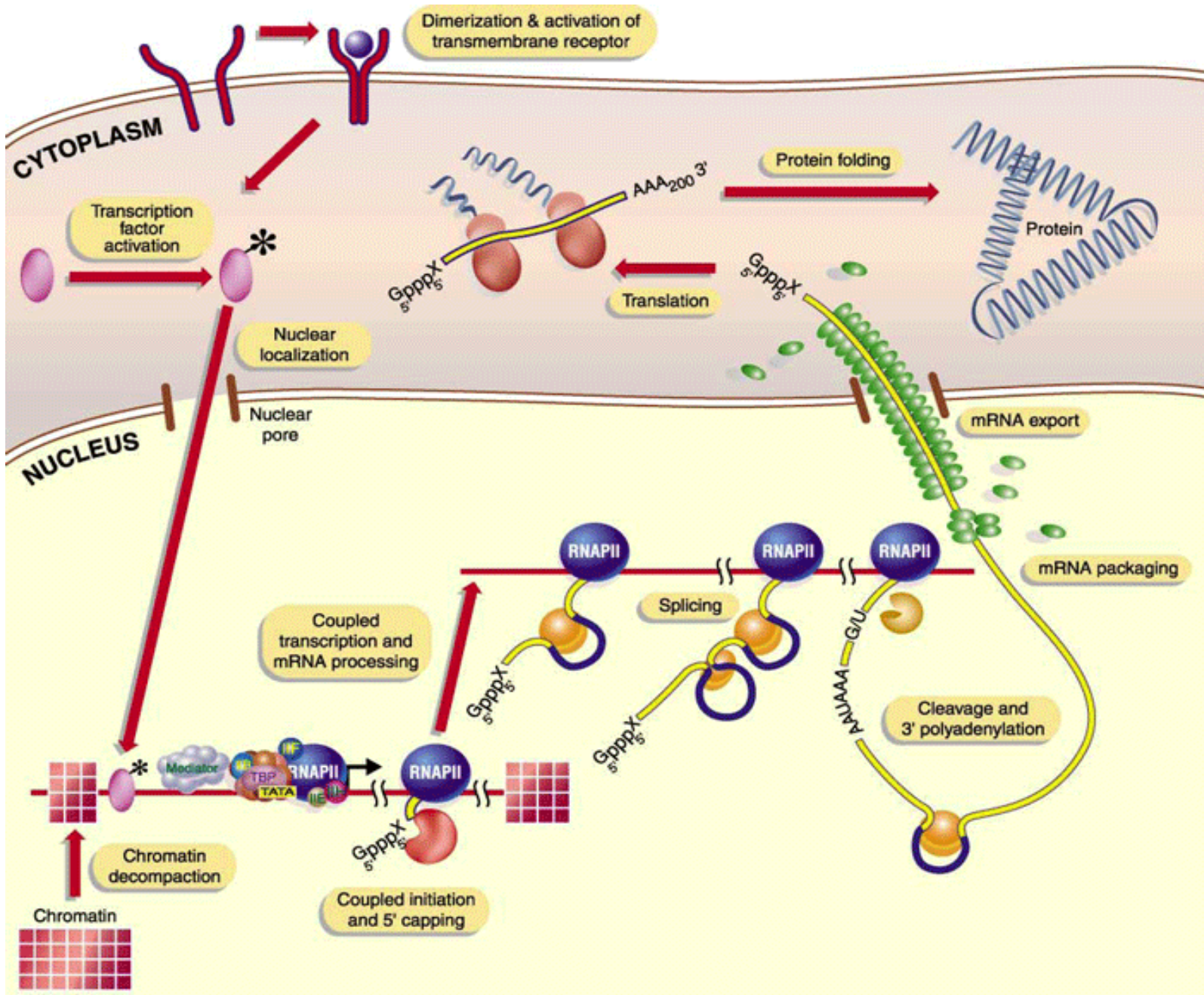
***Buněčná migrace a buněčná polarita v  
embryonálním vývoji***

Vítězslav Bryja

## Osnova

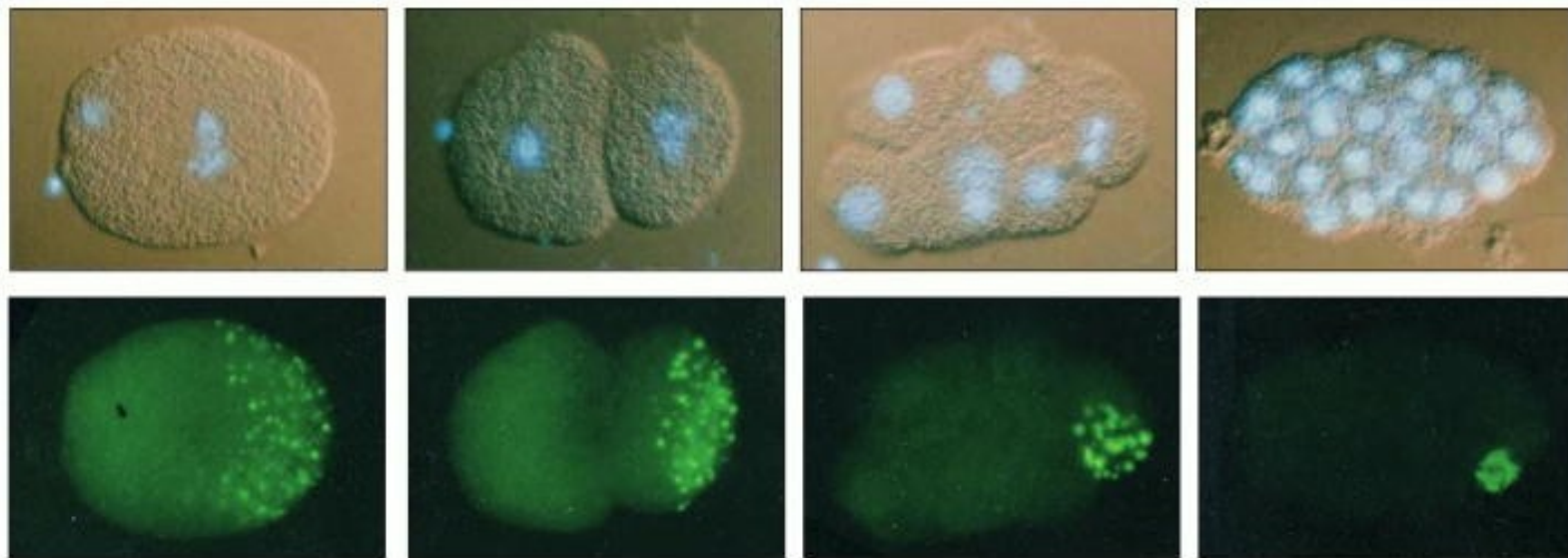
- Asymetrická segregace determinant ve vajíčku/zygotě
- Planární buněčná polarita
- Buněčné procesy a principy při kolektivní migraci
- „Migrace“ částí buněk
- Společný sub-buněčný základ určení polarity a migrace

## **Segregace cytoplazmatických determinant ve vajíčku**



# Vznik asymetrie – *C. elegans*

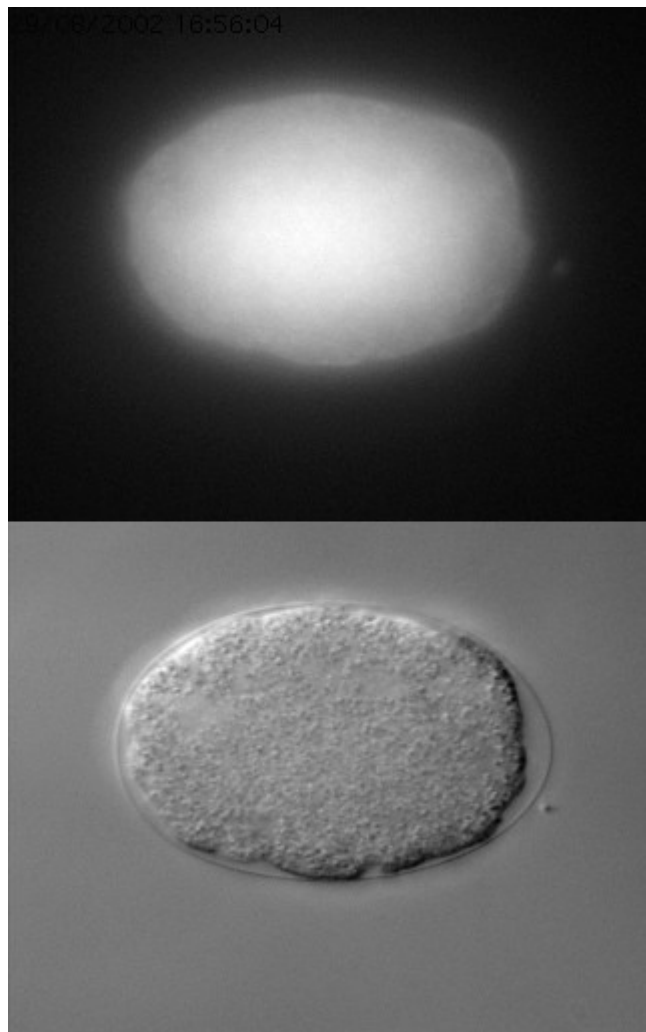
Model: První buněčná dělení na modelu háďátka (*Caenorhabditis elegans*)



**Asymmetric divisions segregating P granules into the founder cell of the *C. elegans* germ line.**

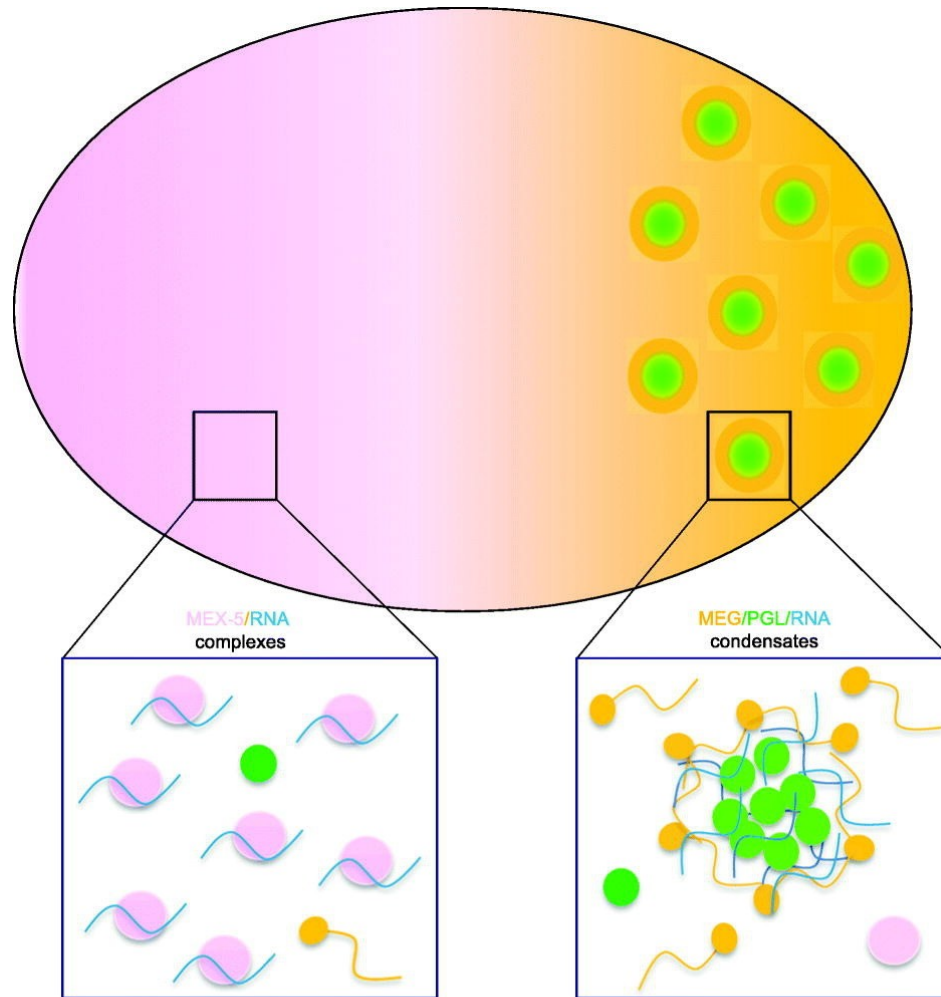
The micrographs in the upper row show the pattern of cell divisions, with cell nuclei stained blue with a DNA-specific fluorescent dye; below are the same cells stained with an antibody against P granules. These small granules (0.5–1  $\mu\text{m}$  in diameter) are distributed randomly throughout the cytoplasm in the unfertilized egg (not shown). After fertilization, at each cell division up to the 16-cell stage, both they and the intracellular machinery that localizes them asymmetrically are segregated into a single daughter cell. (Courtesy of Susan Strome.)

# Segregace P granul a vznik asymetrie



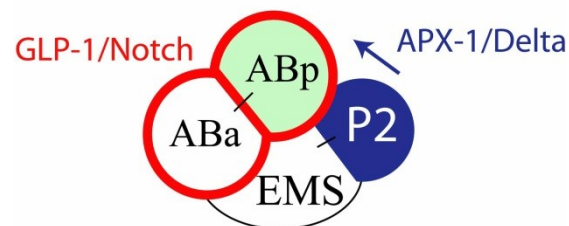
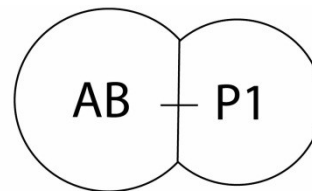
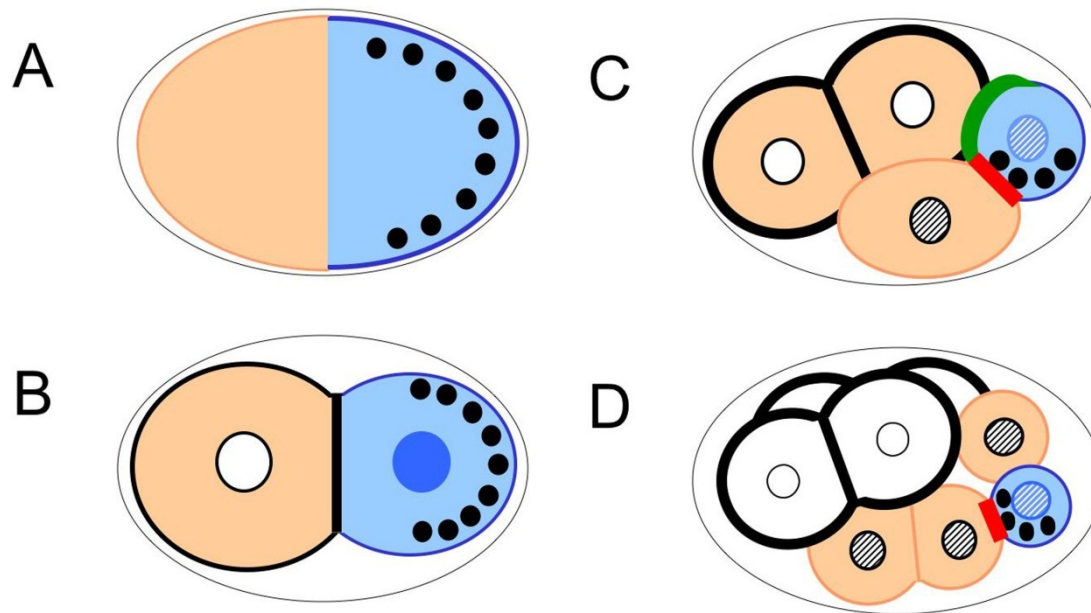


# Princip fázové separace



**RNA competition model for P granule asymmetry in the 1-cell embryo:**  
RNA-induced phase separation of P granule proteins is suppressed in the anterior cytoplasm by MEX-5, an RNA-binding protein that prevents P granule proteins from accessing RNA

# I symetrické dělení vede ke vzniku asymetrických dceřiných buněk (role Notch)





# Notch a vznik asymetrie

- legenda k obrázku:

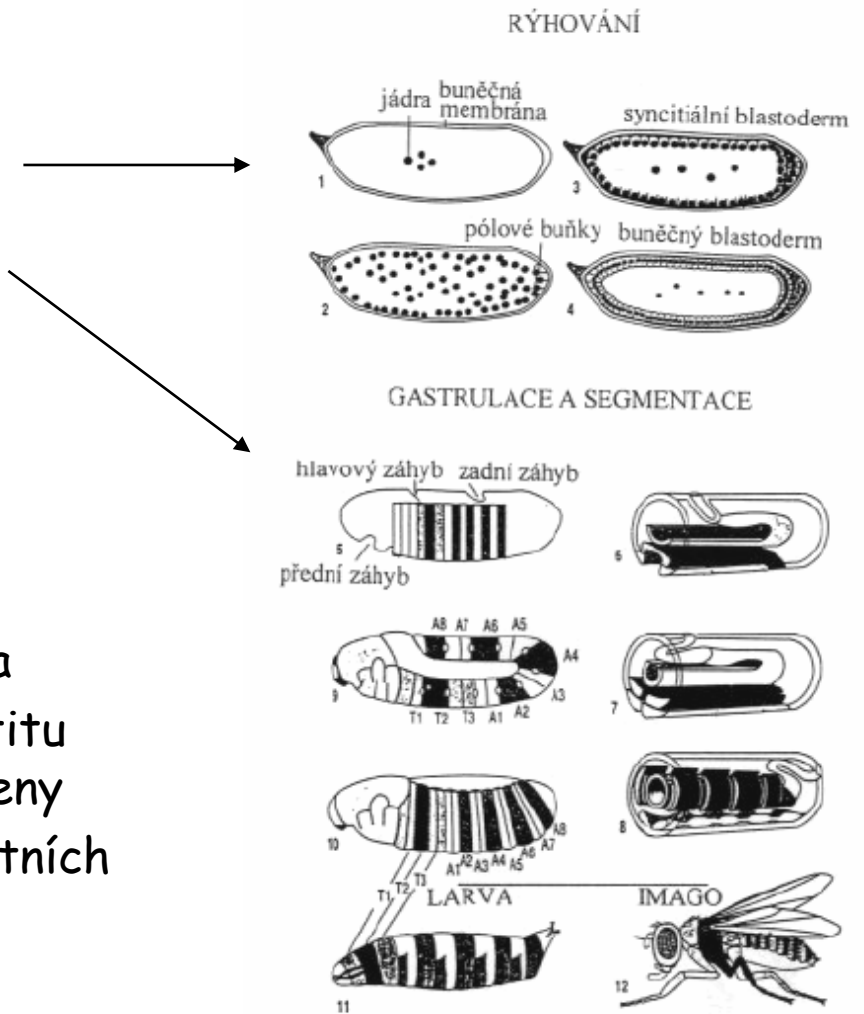
**Asymmetric localization of polarity mediators and cell fate determinants in the early embryo.** P granules: black discs; cytoplasmic POS-1, MEX-1, and cytoplasmic and nuclear PIE-1: blue; nuclear PAL-1: hatched; MEX-5 and MEX-3: peach; plasma membrane localized GLP-1: black; membrane localized APX-1: green; membrane localized MES-1: red. Although shown discreetly localized for simplicity, the cytoplasmic proteins are present at low levels in the opposite domain before division, and in the sister cell after division. In addition, MEX-5, MEX-3, MEX-1, POS-1 and PIE-1 are also present on P granules. (A) MEX-5, MEX-3, MEX-1, PIE-1, POS-1 and P granules are uniformly present in the cytoplasm just after fertilization, but become asymmetrically localized during the one-cell stage. (B) The anterior and posterior determinants are differentially segregated to AB and P1 as a result of the first asymmetric division. GLP-1 protein first appears in AB at the two-cell stage, and PIE-1 protein enters the nucleus in addition to being cytoplasmic. As the cell cycle proceeds (not shown), posterior determinants become restricted to the posterior half of P1, while MEX-5 appears in the anterior half of P1. (C) In the four-cell embryo, GLP-1 is expressed on membranes of both AB cells, but only ABp is in contact with the P2 cell expressing APX-1. MES-1 is enriched at the cell contact between P2 and EMS; MES-1/SRC-1 signaling in conjunction with Wnt signaling polarizes the EMS cell, such that it will divide asymmetrically. As the cell cycle proceeds, posterior determinants within P2 become asymmetrically localized as in previous P cells. MEX-5 disappears from the AB cells, but is still present in the anterior daughters of each P division.

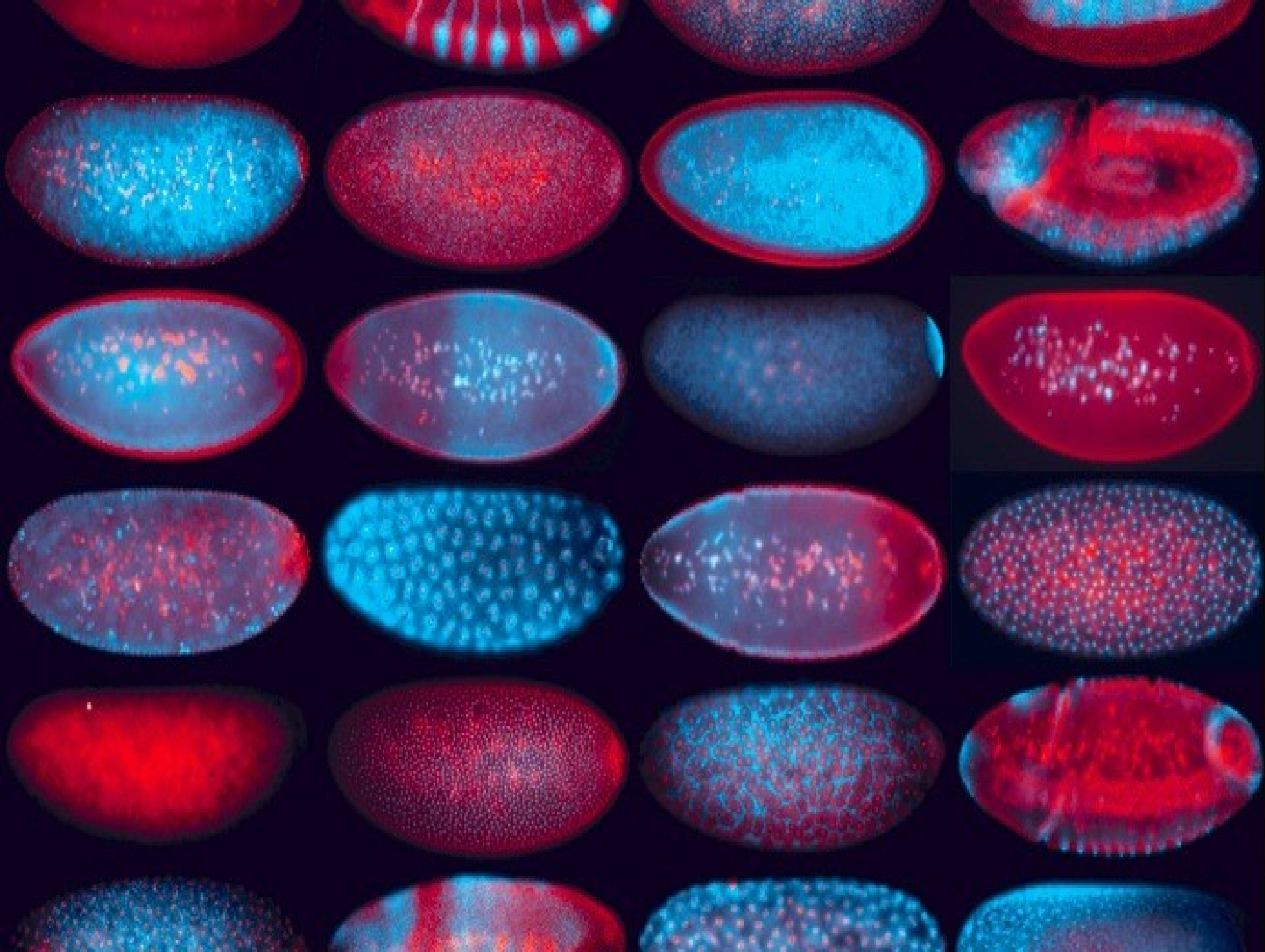
# Embryonální vývoj *Drosophila melanogaster*

- vaječná buňka
- syncytiální blastoderm
- buněčný blastoderm
- gastrulace a segmentace

## Zúčastněné geny

- g. maternálního účinku
- g. řídící článkování těla
- g. zodpovědné za identitu článků - homeotické geny
- g. řídící tvorbu kompletních orgánů



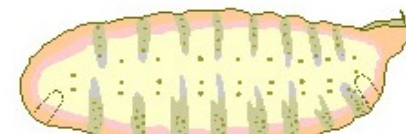
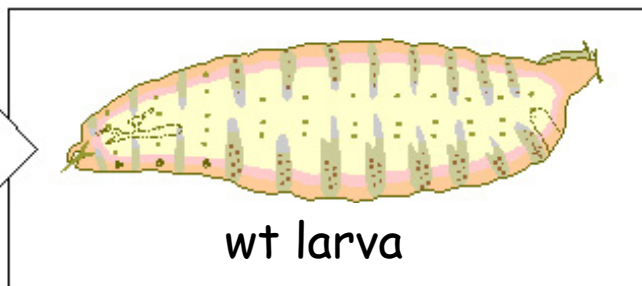
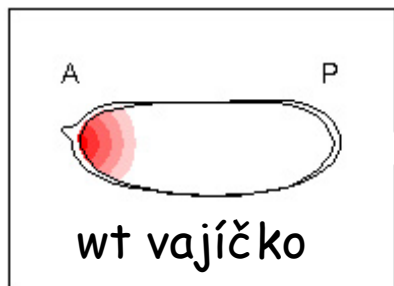


# Maternální geny

- ➔ Transkripce ve vaječnÍku, translace až po fertilizaci
  - a) Určující anterior-posterior polaritu: např. nanos, bicoid, oskar, gurken
  - b) Určující dorso-ventrální polaritu: dorsal, toll

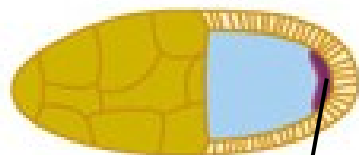
# Maternální geny

## bicoid

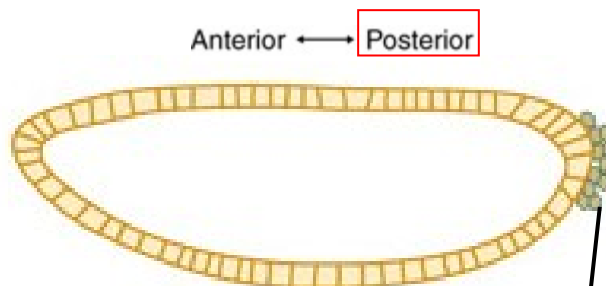


[http://www.mun.ca/biology/desmid/brian/BIOL3530/DB\\_Ch05/fig5\\_4.jpg](http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch05/fig5_4.jpg)

## oskar



oskar mRNA



zárůdečné buňky

<http://www.nature.com/ncb/journal/v4/n5/images/ncb0502-e117-f1.jpg>

# Důvody lokalizace mRNA

1. lokalizace mRNA zabraňuje nežádoucí expresi jinde než v místě potřeby
  - ▶ př. cytoplazmatické determinanty v embryu D. melanogaster - *oskar*, *nanos*; změna lokalizace vede k vývojovým abnormalitám
2. rychlejší reakce na lokální požadavek proteinu
  - ▶ důležité především u velkých, polarizovaných buněk (např. neurony)

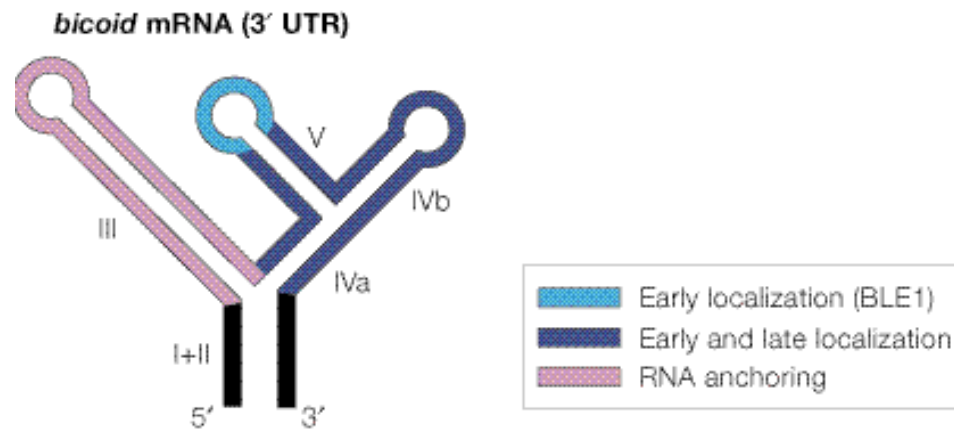


# Mechanismy lokalizace mRNA

- 1) místně specifická syntéza (vzácná)
  - *gurken* mRNA u *Drosophily melanogaster*
- 2) lokální ochrana před degradací
  - degradace nesprávně lokalizovaných transkriptů
  - vyžaduje dva odlišné cis-elementy v 3' UTR oblasti (degradační a protekční)
  - evolučně konzervované
- 3) difúze a ukotvení
  - pasivní difúze cytoplazmou až do zachycení vazeb. proteinem
  - *nanos*, *cyklin B*, *gcl* - posterior oocyty *Drosophila*
- 4) aktivní transport
  - řízený cytoplazmatický transport za účasti cytoskeletu (myosiny, dyneiny, kinesiny + organely a další struktury)

# Sekvenční elementy zajišťující lokalizaci mRNA

Př. *bicoid* mRNA  
 - >600 nukleotidů



# Tvorba mRNA tělísek (fázová separace)

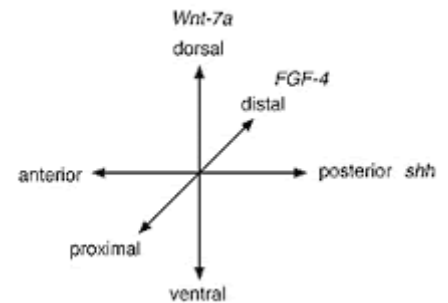
- 30 mRNA molekul
- shluknutí do transportních částic
- *oskar* mRNA - putuje na jiných *oskar* mRNA molekulách
- *bicoid* mRNA - tvorba dimerů

# Regulace translace

- ▶ mRNA není translatována dokud se nedostane do svého cílového místa
- ▶ Proteiny interagující s 5 -UTR:
  - ▶ stabilizátory mRNA a inhibitory translace
  - ▶ zesilovače translace (enhancery)
- ▶ Proteiny interagující s 3 -UTR:
  - ▶ stabilita a lokalizace mRNA
  - ▶ význam polyadenylace mRNA -> vyšší stabilita mRNA

# Nekanonická Wnt dráha (dráha planární buněčné polarity – PCP)

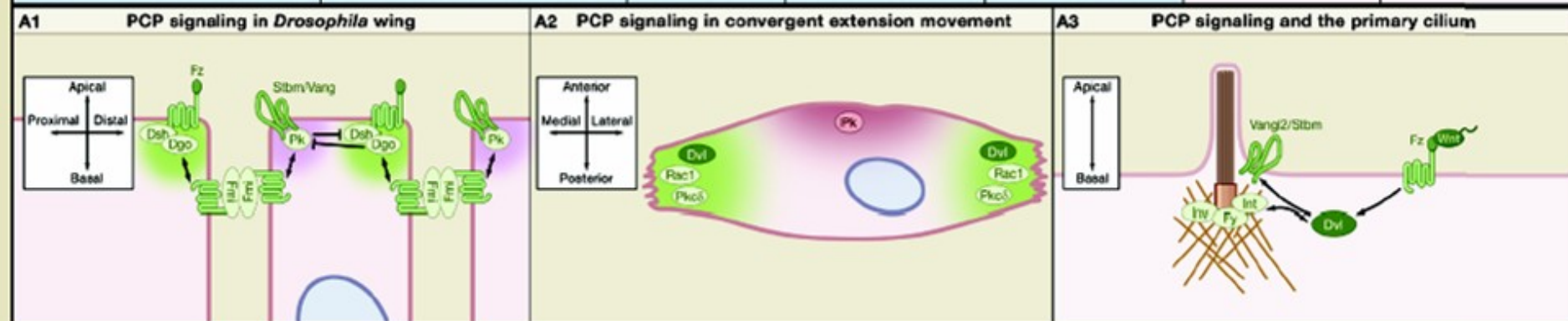
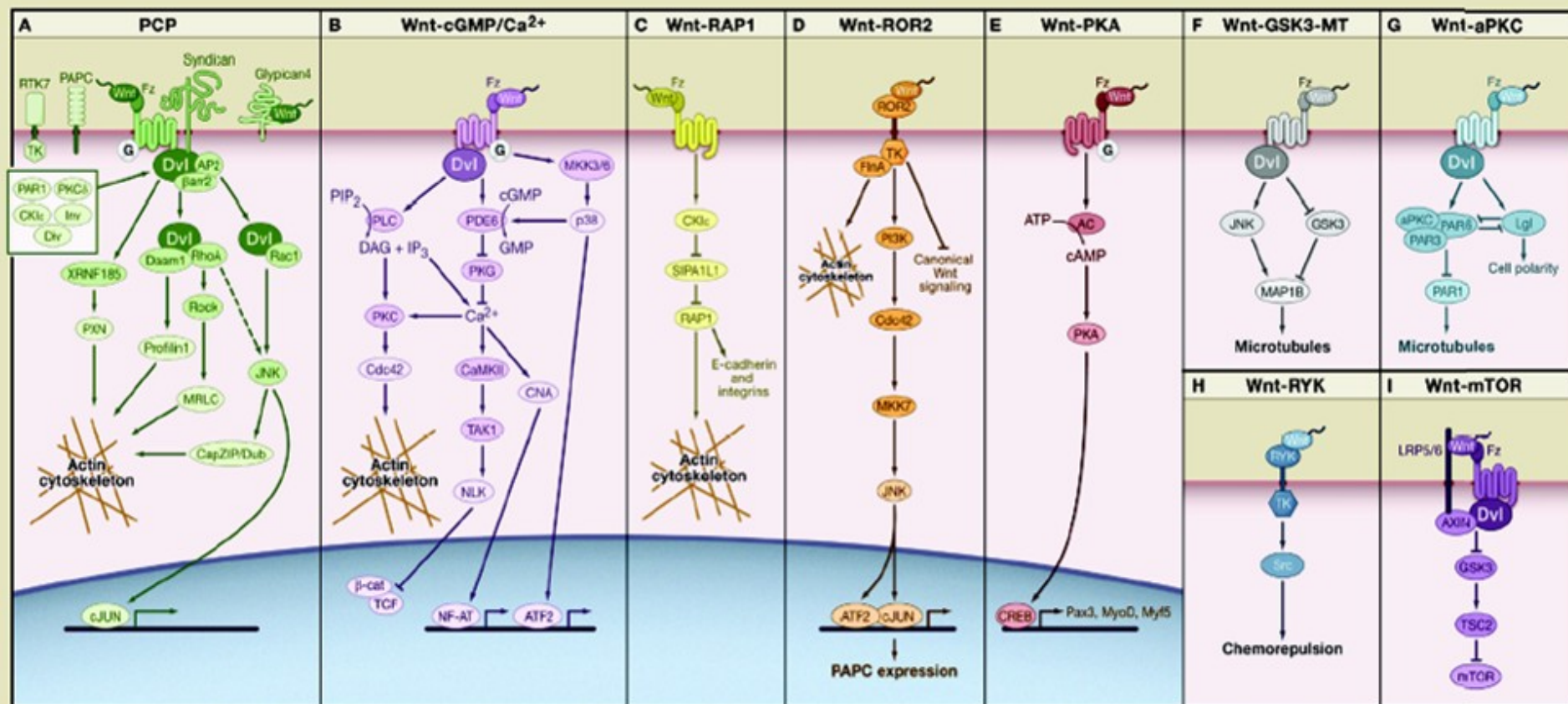
- ustavení proximo-distální polarity v epitelu
- konvergentní extenze
- regulace morfogeneze



# SnapShot: Noncanonical Wnt Signaling Pathways

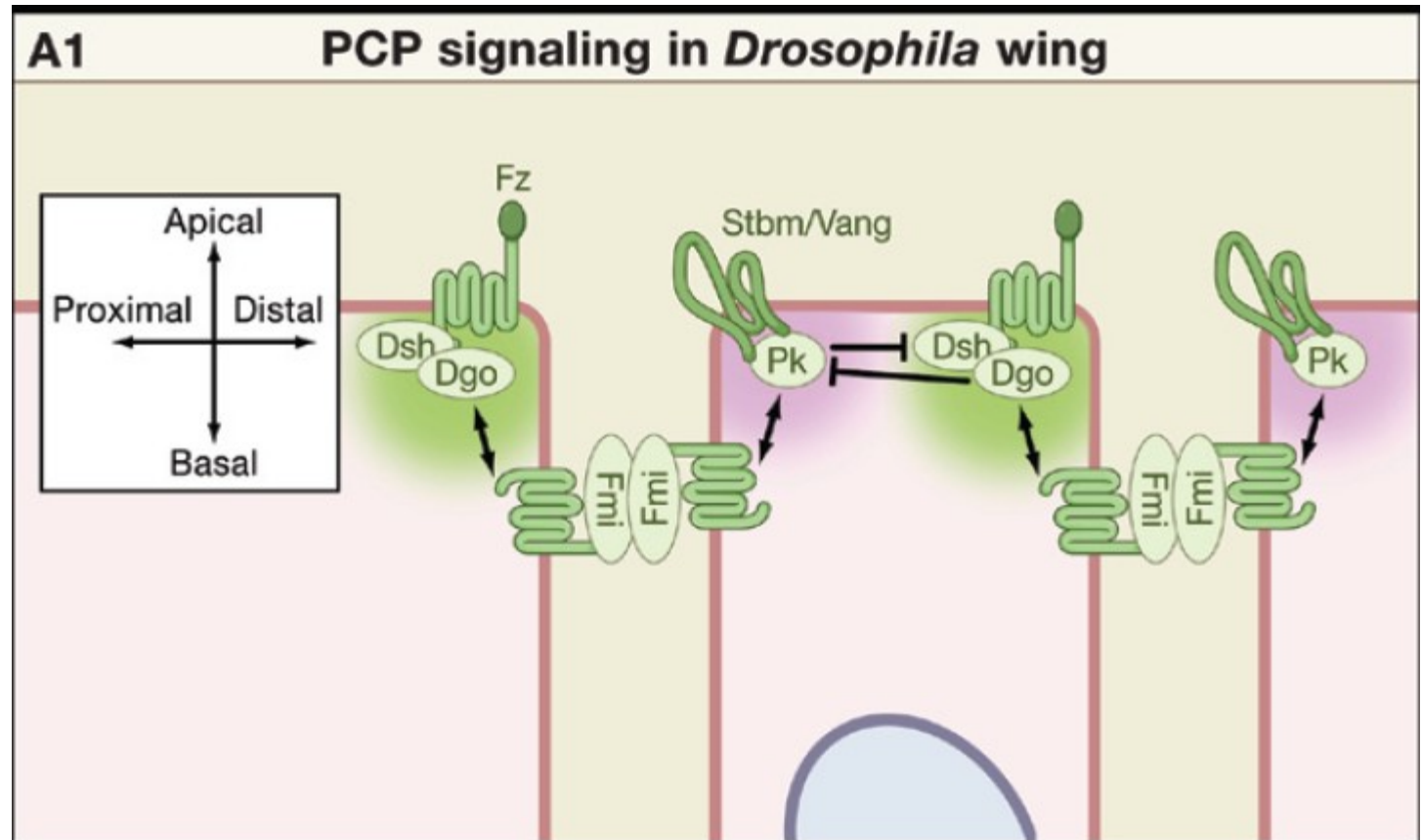
Mikhail V. Semenov,<sup>1</sup> Raymond Habas,<sup>2</sup> Bryan T. MacDonald,<sup>1</sup> and Xi He<sup>1</sup>

<sup>1</sup>Children's Hospital Boston, Harvard Medical School, Boston, MA 02115, USA; <sup>2</sup>University of Medicine and Dentistry of New Jersey, Piscataway, NJ 08854, USA





# Planární buněčná polarita v křídle octomilky

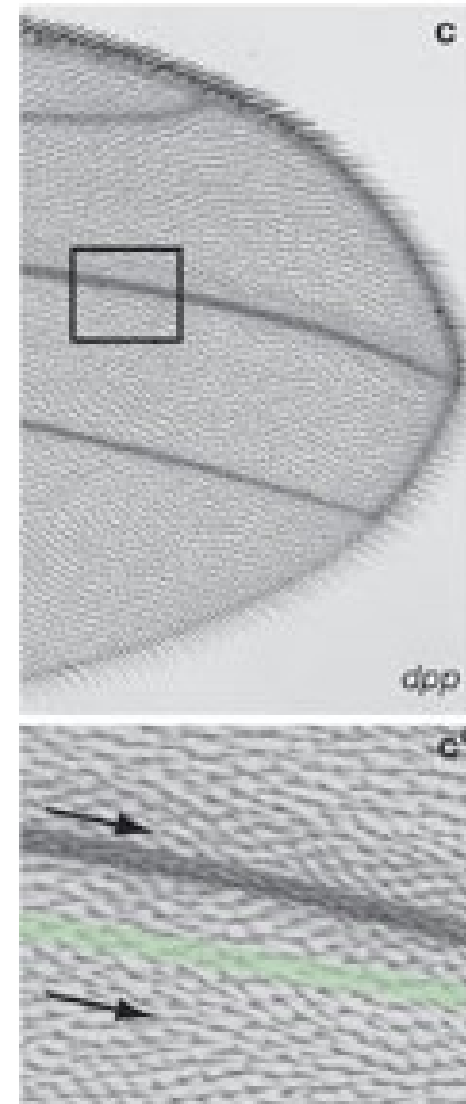
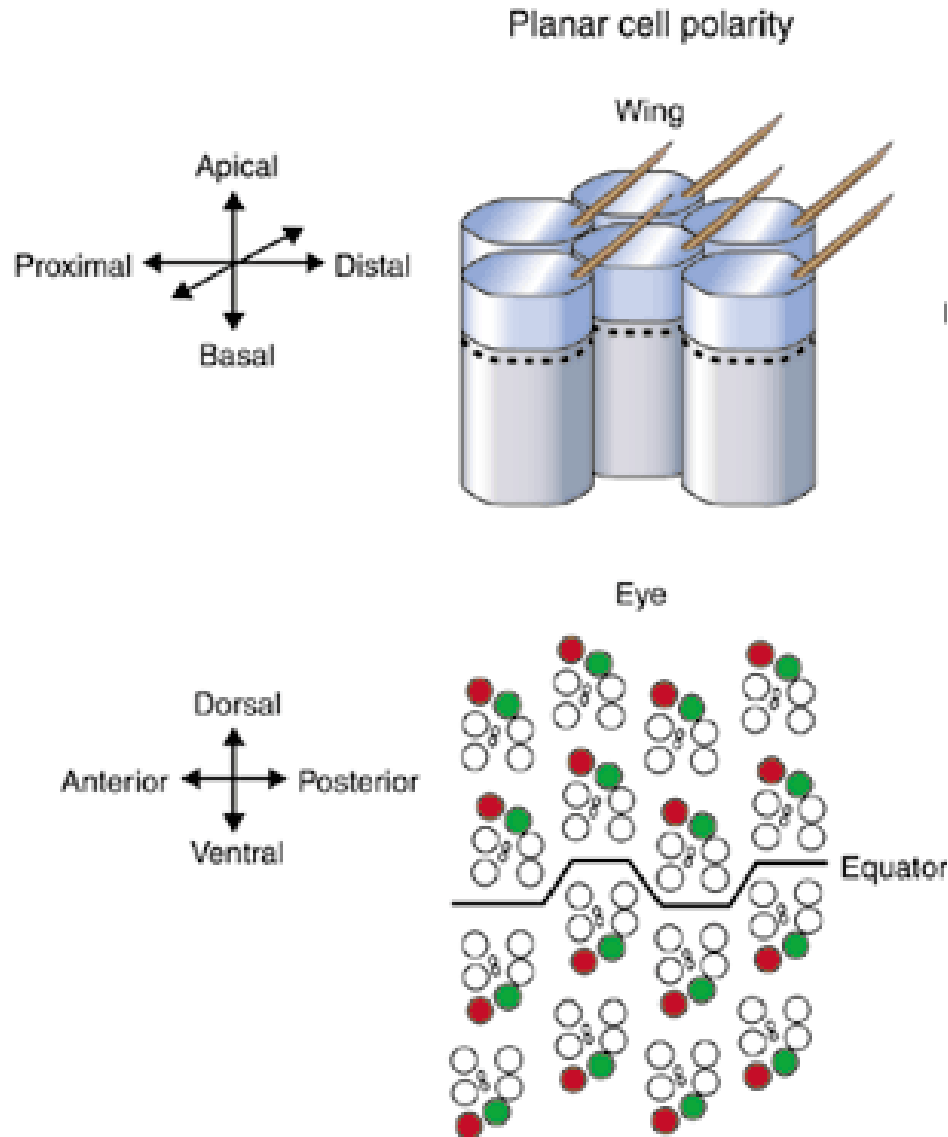


Distální: Dsh – Dishevelled (DVL)    Fz – Frizzled (FZD)

Proximální: Stbm (Strabismus) – VANGL    Pk – Prickle

Stabilizující: Fmi (Flamingo) - CELSR

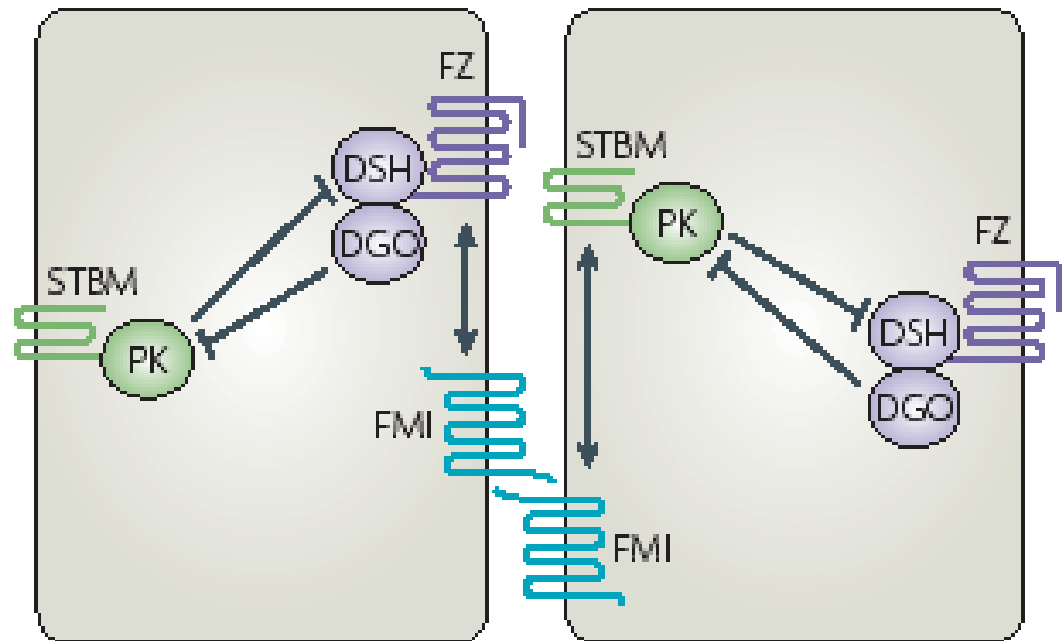
# *Drosophila* – planární buněčná polarita (planar cell polarity, PCP)



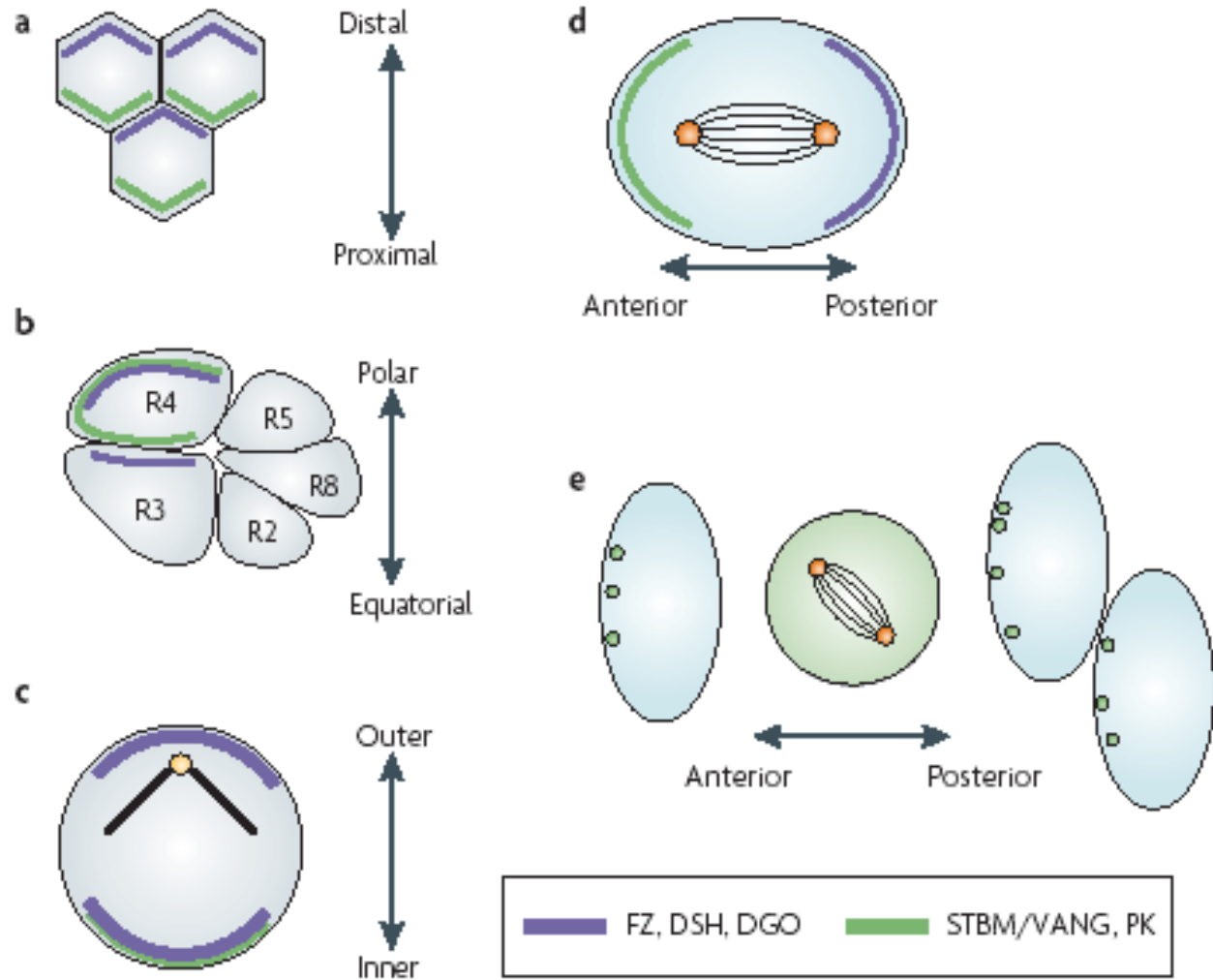
# Molekulární mechanismus ustavení PCP

## Box 1 | Molecular interactions between the Fz/PCP core factors

The molecular logic of the formation and separation of the Frizzled–Dishevelled–Diego (FZ–DSH–DGO) and Prickle–Strabismus (PK–STBM) complexes has started to be unravelled. In FIG. 2 are reported examples of the localization of each complex in various tissues. The figure is an apical view of two cells that have attained asymmetric localization of the two complexes.



# Molekulární mechanismus ustavení PCP

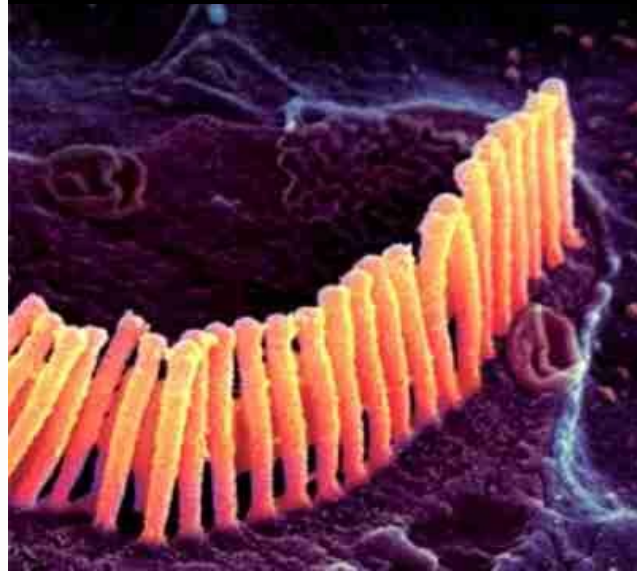
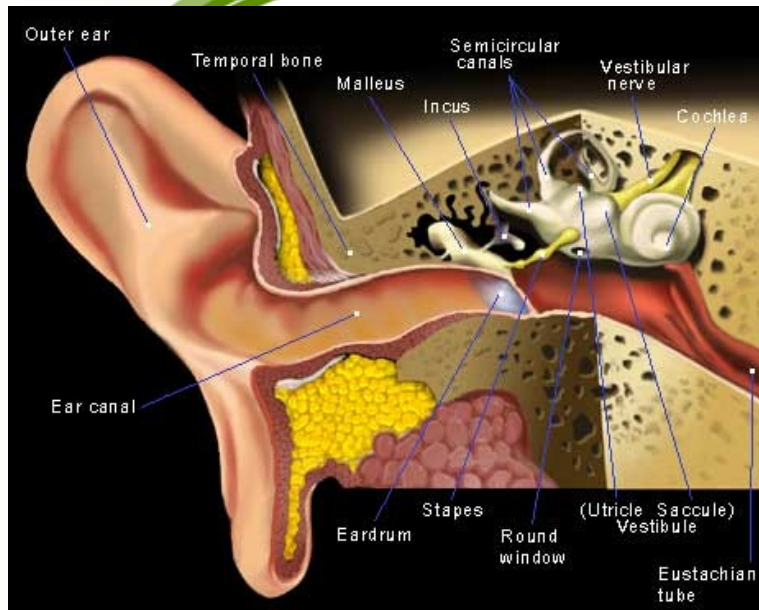


# Molekulární mechanismus ustavení PCP

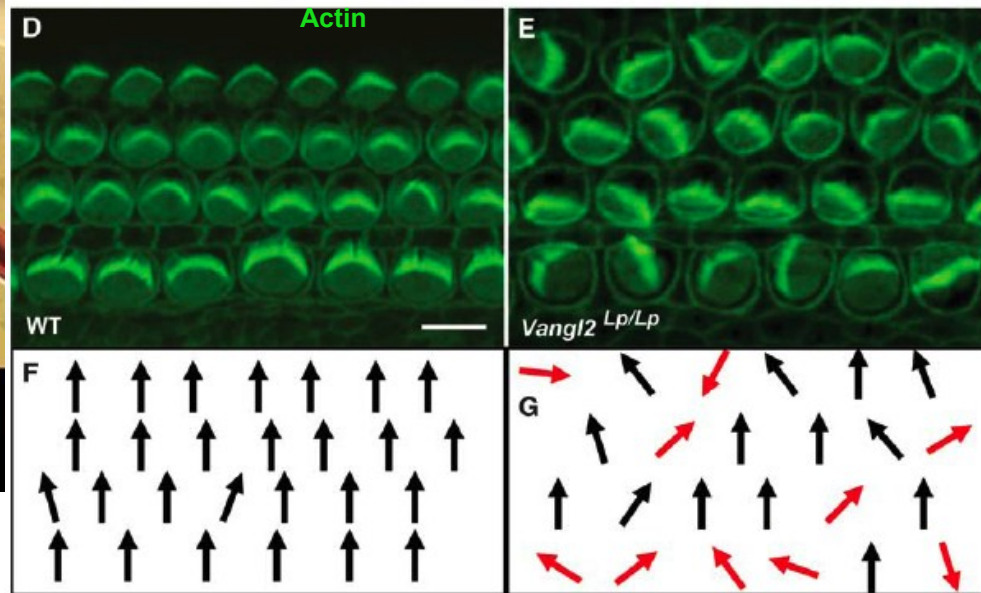
- legenda k obrázku:

Figure 2 | Subcellular distribution of core Fz/PCP factors in *Drosophila melanogaster* and vertebrates. a–c | Examples of cells with epithelial character (marked by grey shading). *Drosophila melanogaster* wing cells and eye R3 and R4 cells and mouse sensory hair cells in the cochlea (inner ear) are shown in a, b and c, respectively. d,e | Examples of dividing cells. The spindle orientation in the *D. melanogaster* sensory organ precursor (SOP) cells depends on the asymmetric distribution of the Frizzled (Fz)/planar cell polarity (PCP) factors (as shown in d), as does the orientation of neuroectodermal cells in zebrafish (as shown in e; note that during mitosis the asymmetric distribution of PK is lost and then re-established). Depending on the tissue, only a subset of the respective proteins has been analysed (the *D. melanogaster* wing is the only tissue in which all proteins were analysed; all but DSH have been analysed in the eye). These illustrations represent the localizations patterns of PCP proteins at the proposed time of signalling. In the wing, asymmetry of Flamingo (FMI) has been reported earlier, but the relevance of this is unknown<sup>82</sup>. Note that in the mouse inner ear (as shown in c) vang-like 2 (VANGL2) and FZ3/FZ6 localize to the same side of the cells; it is not known whether other Fz family members localize with the DSH homologues DVL1 and DVL2 to the opposite side. During zebrafish gastrulation (as shown in e) Prickle (Pk), which is represented by green circles, is cytoplasmic during cell division but regains polarity after separation of the daughter cell. Only PK has been analysed in this context, but its localization depends on the presence of Strabismus (STBM).

# PCP v epitelu u savců: vnitřní ucho



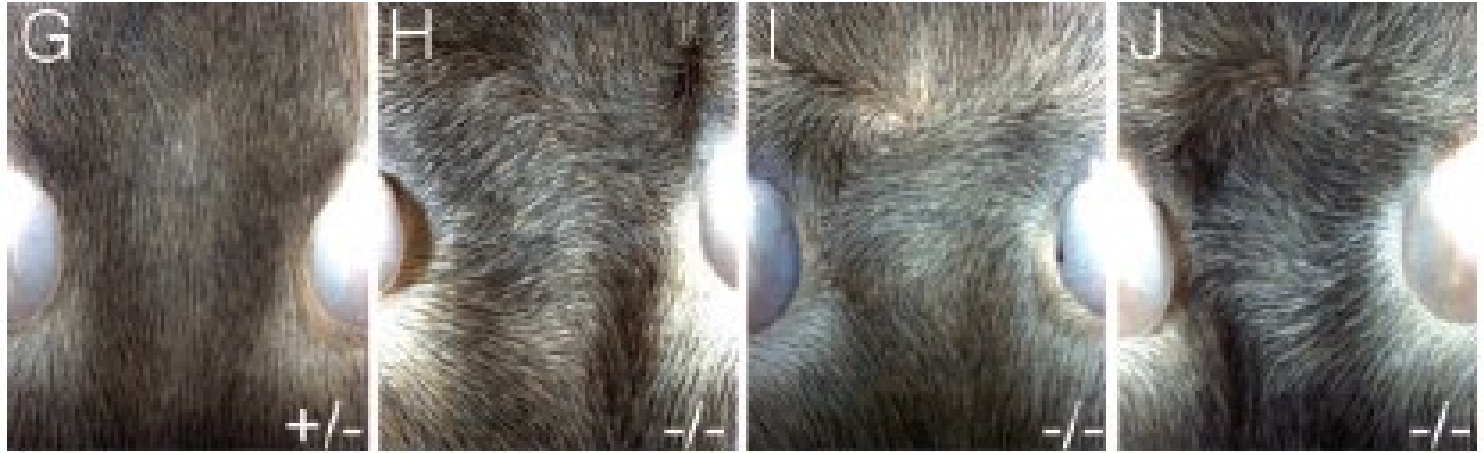
## Orientace stereocilií vláskových buněk ve vnitřním uchu



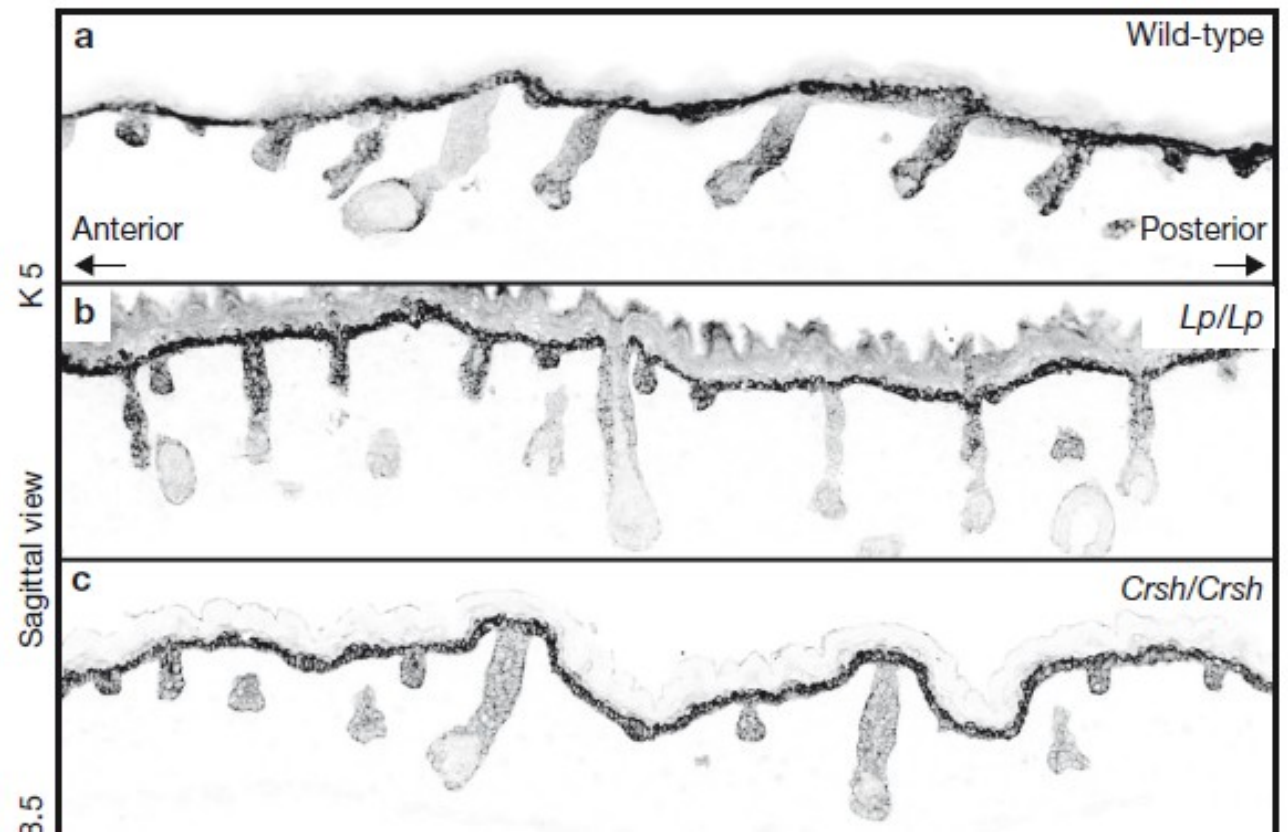
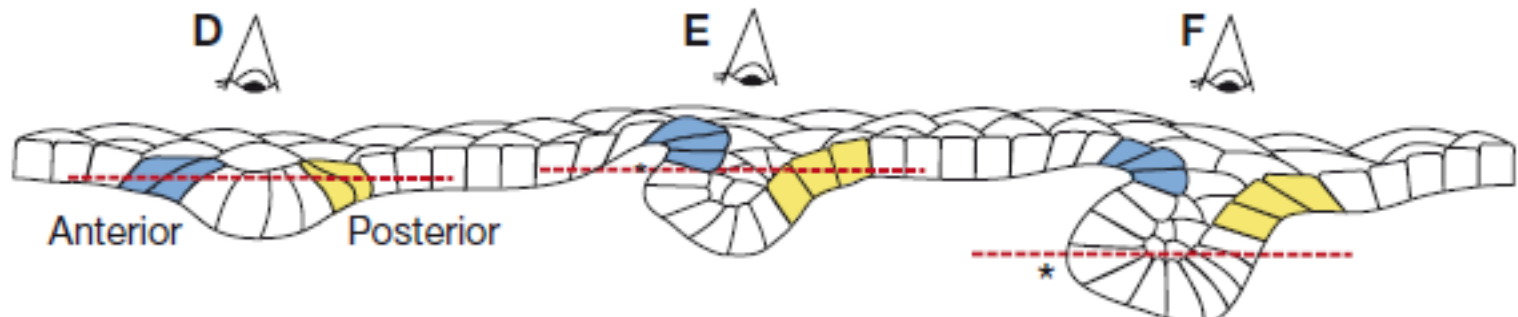
Qian et al., 2007, Dev. Biol.



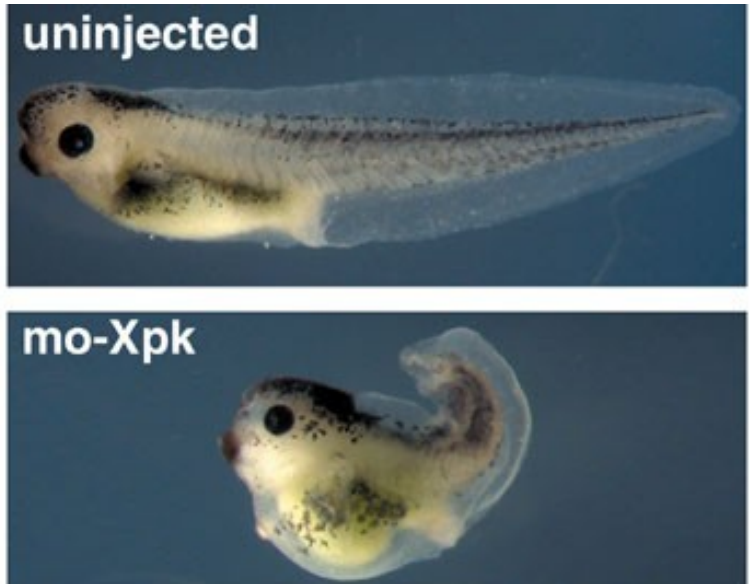
# Poruchy v nekanonické signální dráze Wnt u savců



# Poruchy v nekanonické signální dráze Wnt u savců



# Wnt/PCP dráha a konvergentní extenze



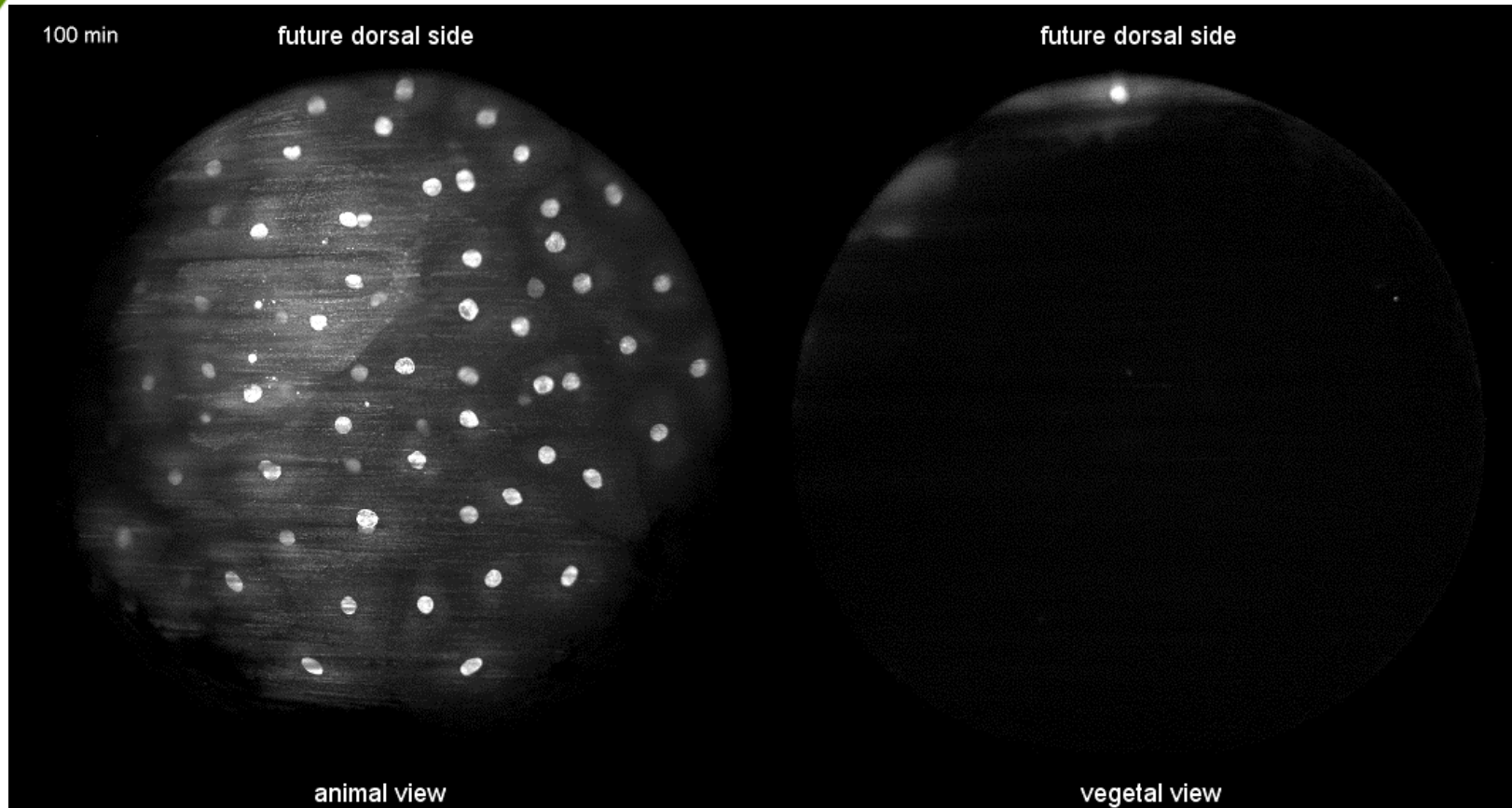
Ortology „klíčových“ genů zapojených do PCP signalizace vykazují u obratlovců typické fenotypy související s prodlužováním tělní osy

## Konvergentní extenze (CE) - video

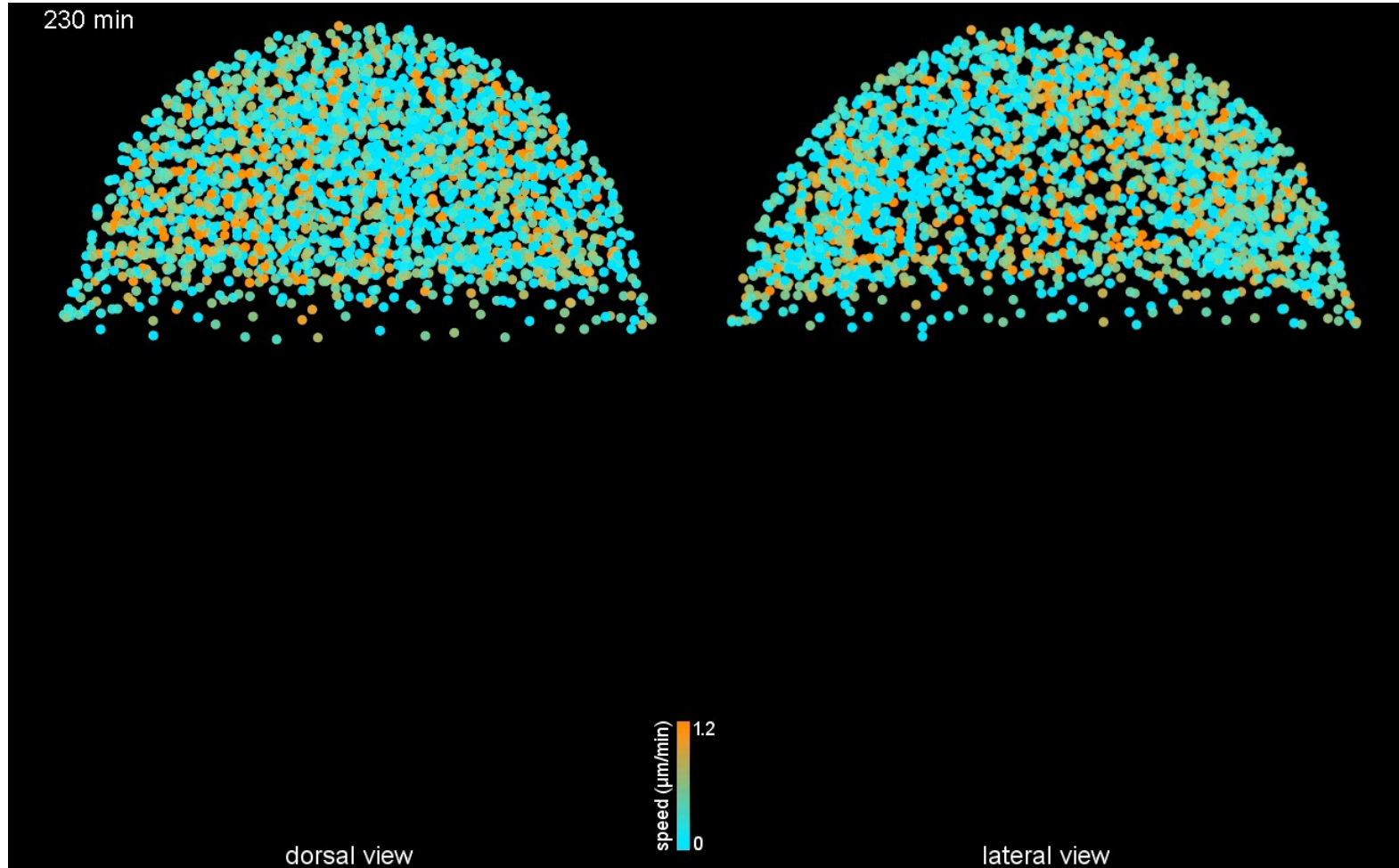




# Konvergentní extenze (CE) - video

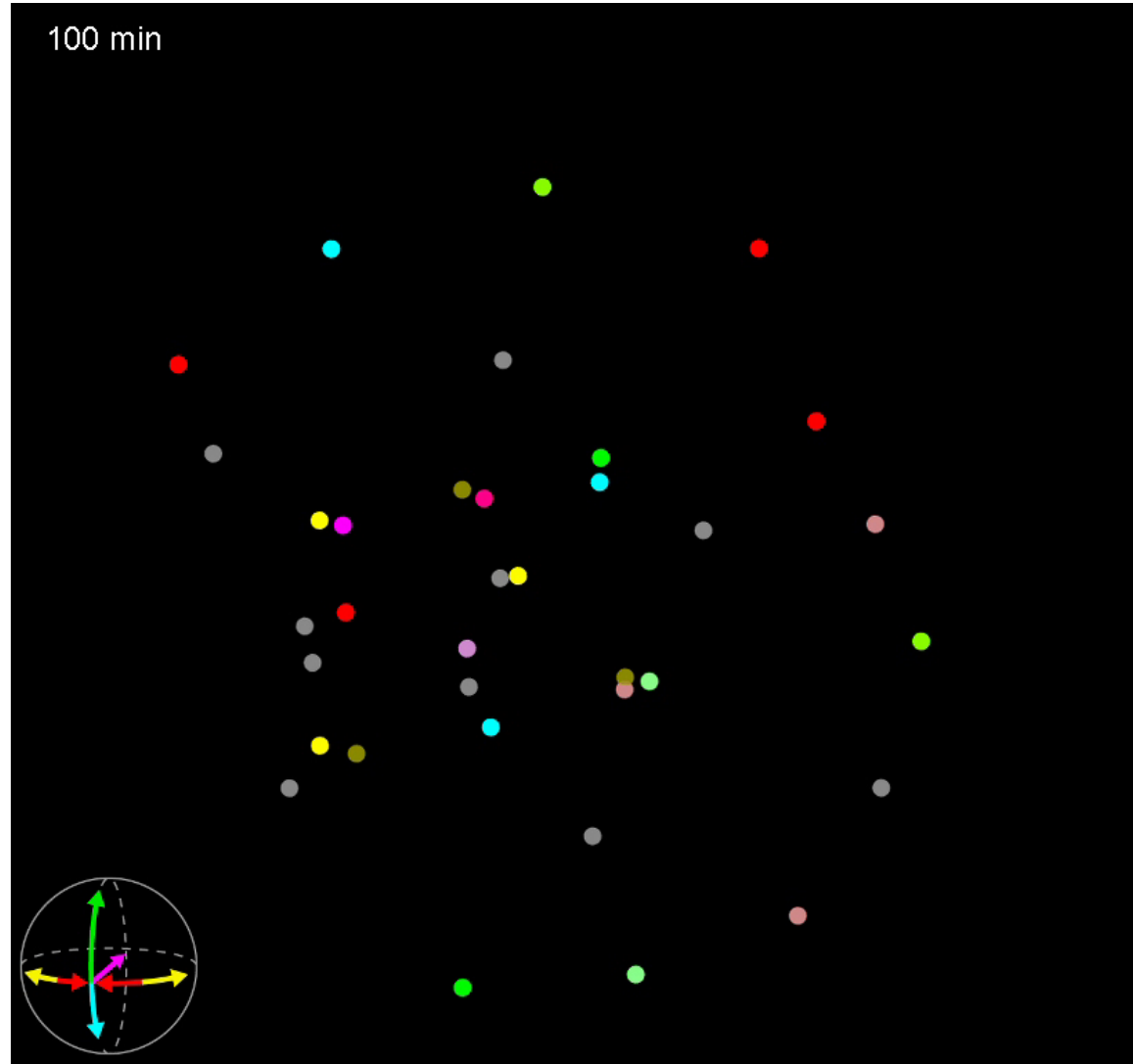


# Konvergentní extenze (CE) - video

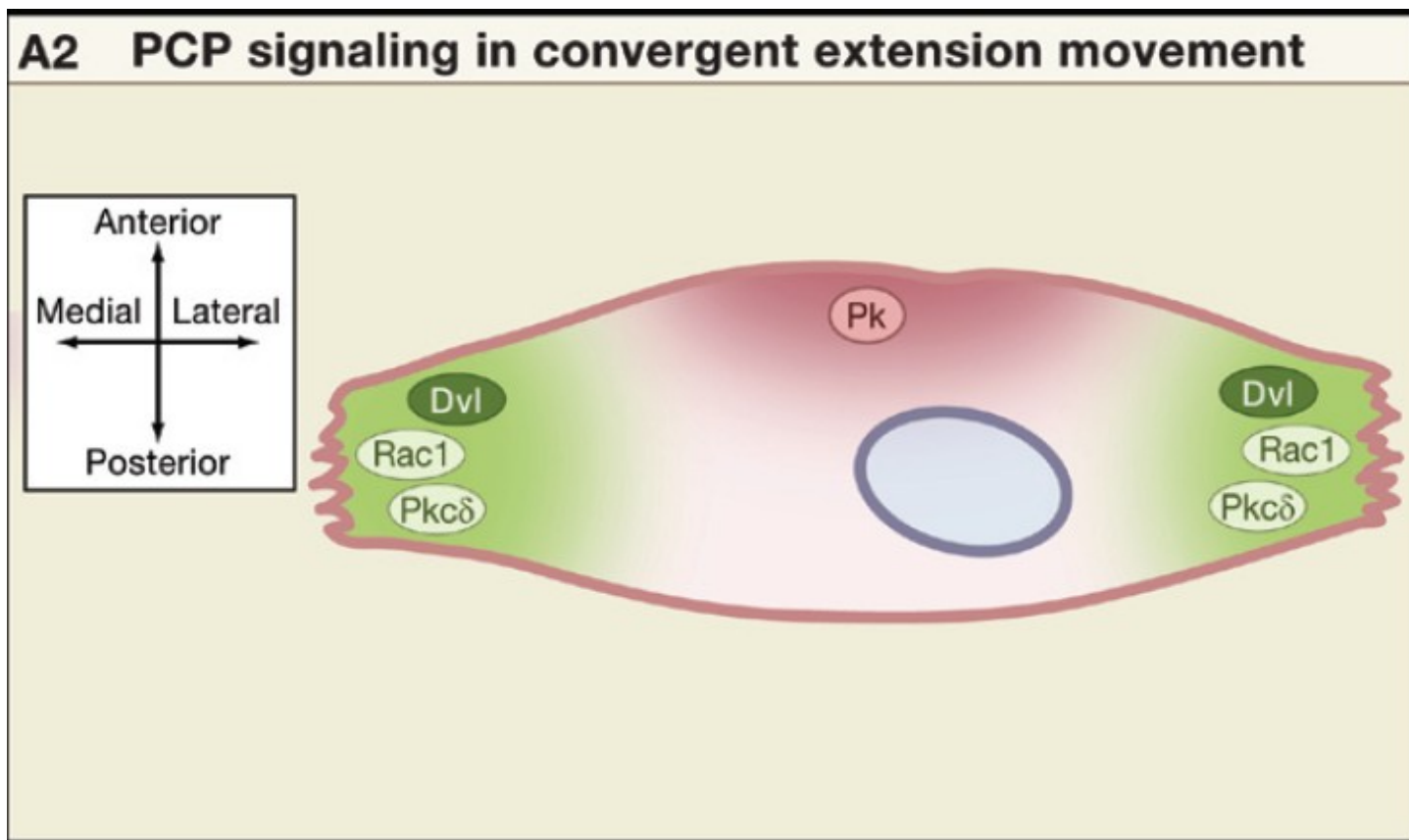




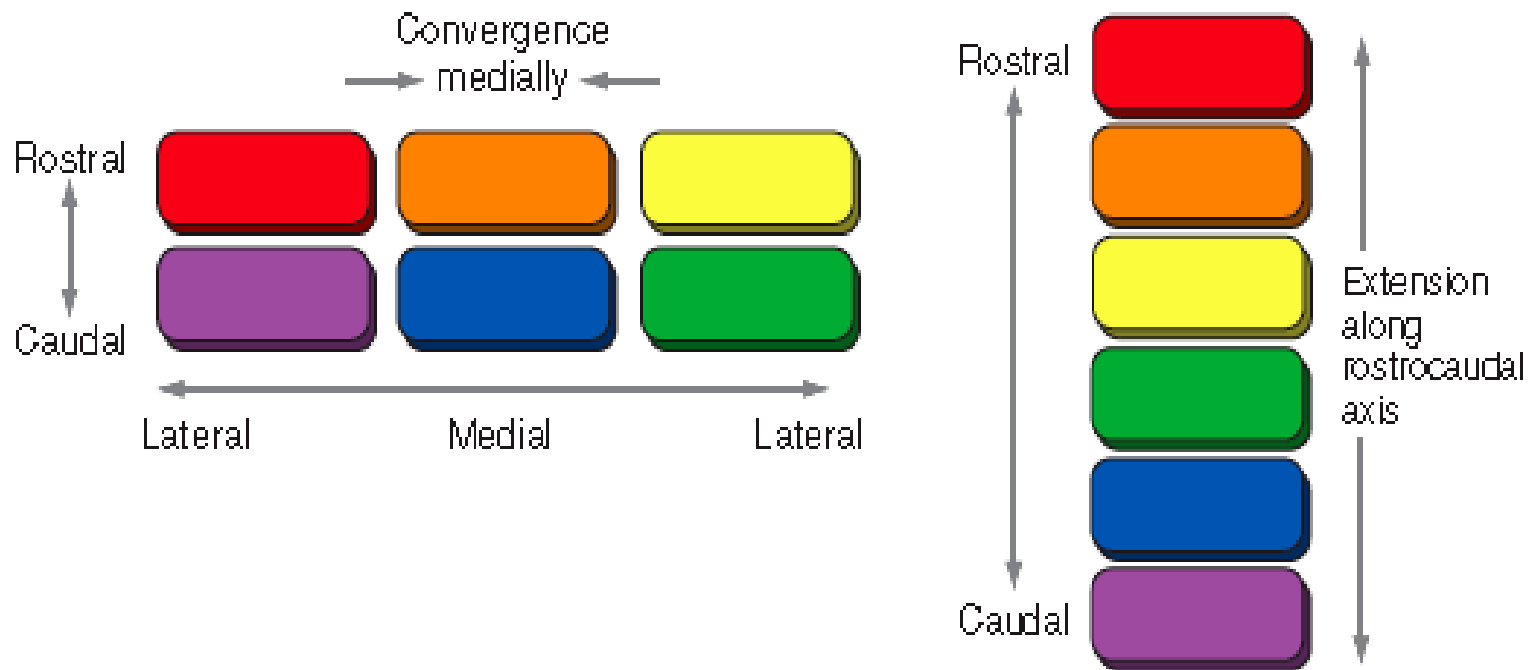
# Konvergentní extenze - video



# PCP dráha při konvergentní extenzi

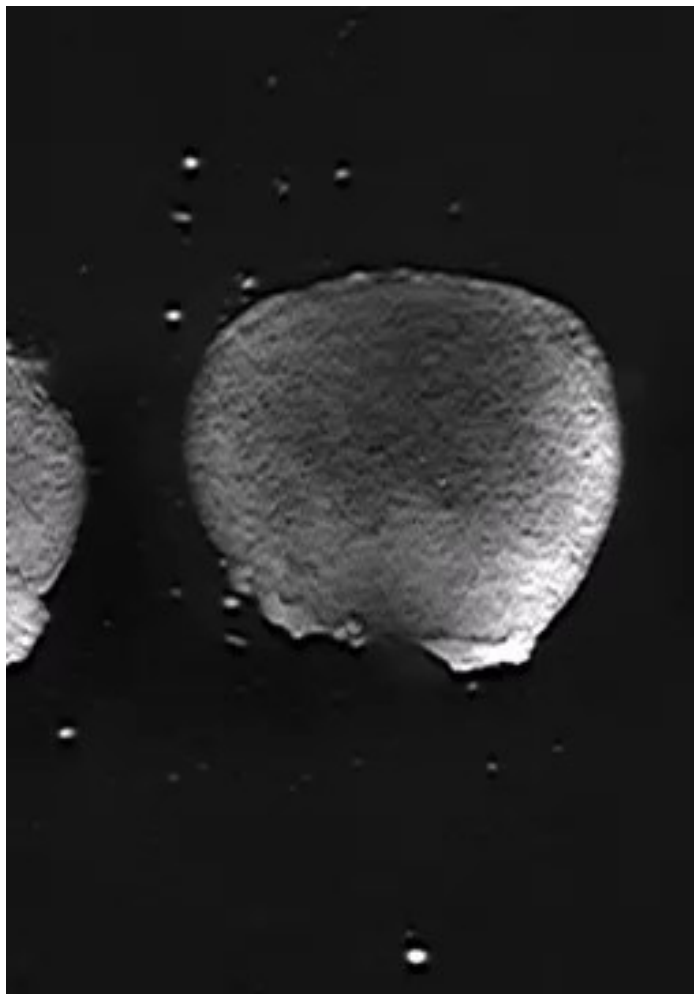


# Buněčný princip konvergentní extenze

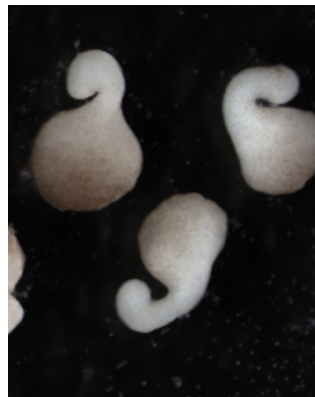
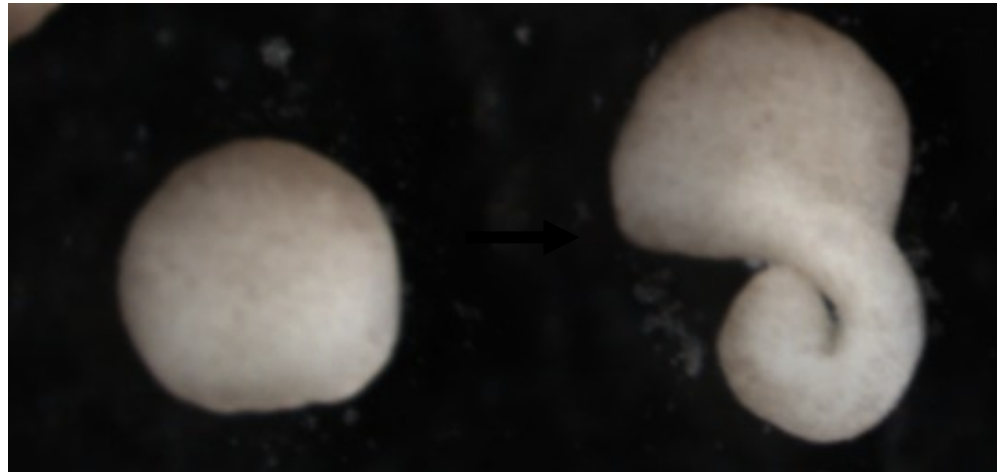


Konvergentní extenze – migrace buněk směrem ke středu těla – vede k prodlužování tělní osy

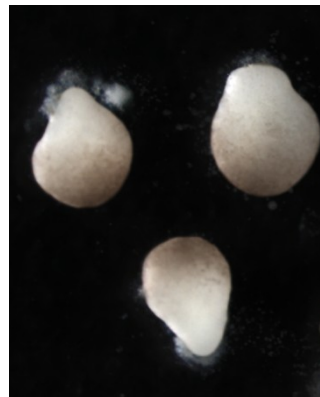
## Možnosti studia CE - Kellerovy explantáty (Xenopus)



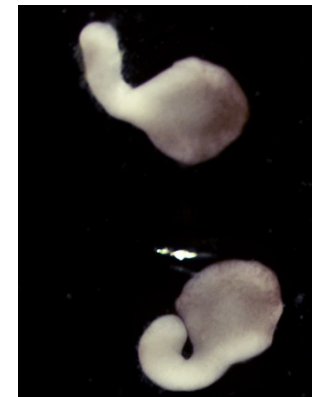
## Možnosti studia CE - Kellerovy explantáty (Xenopus)



control

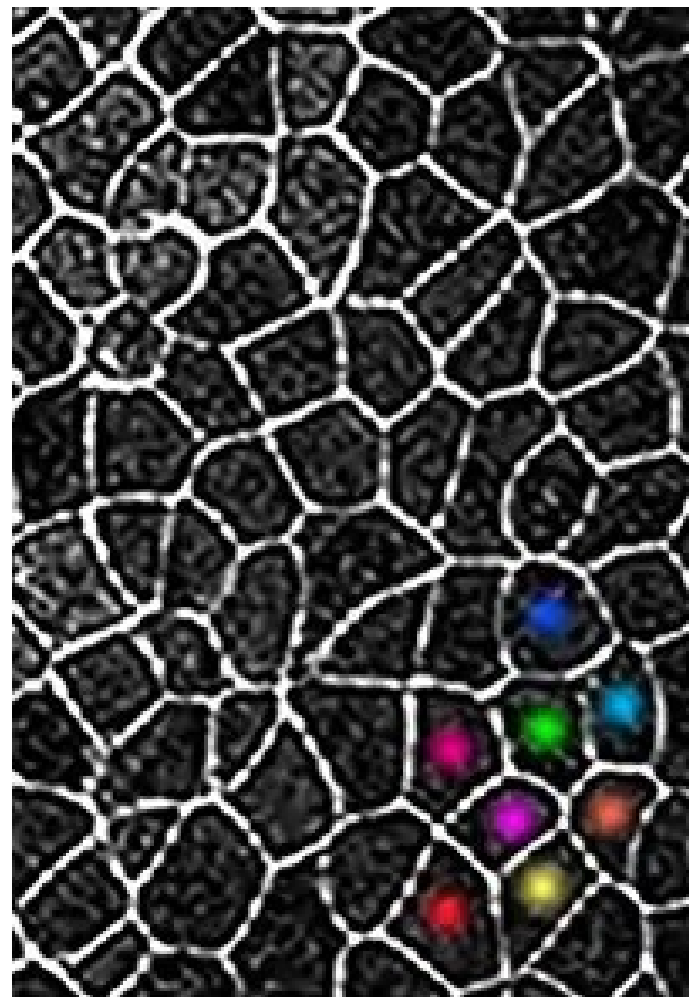
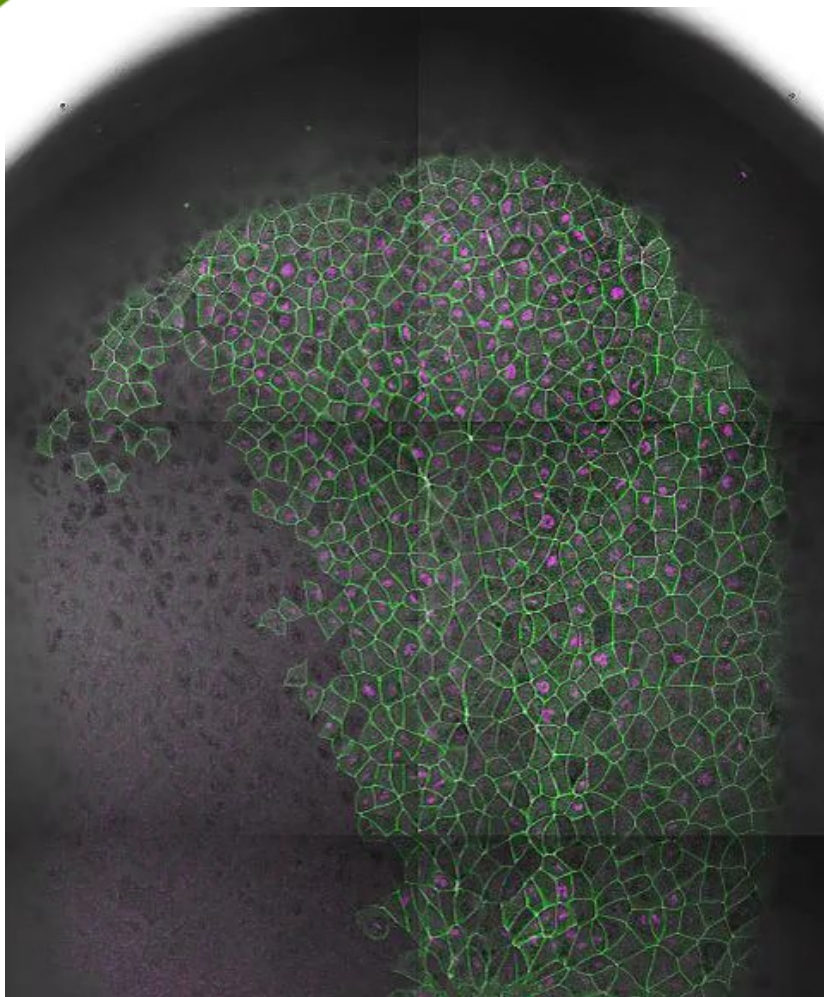


XLRP5 MO



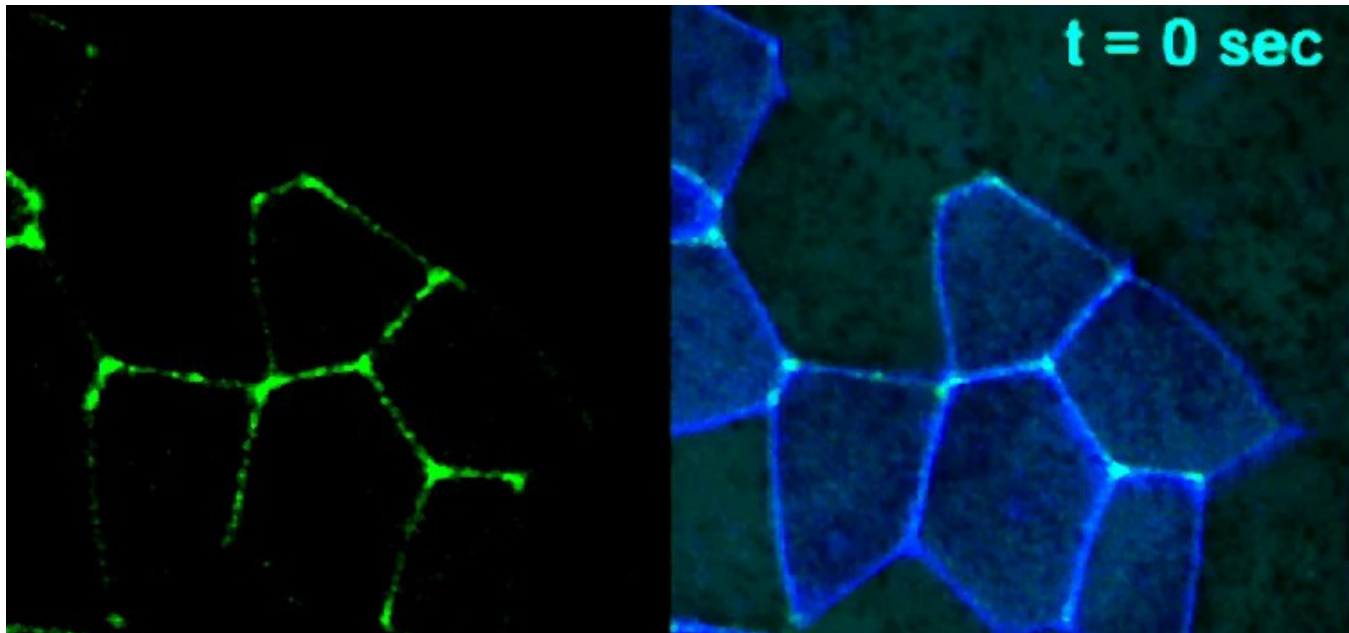
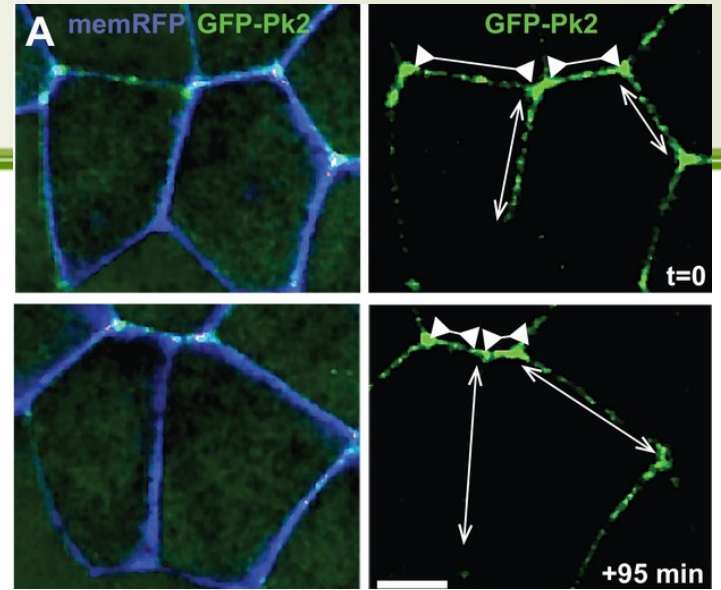
XLRP5 MO  
+ mLrp5

## Změny tvaru buněk při CE

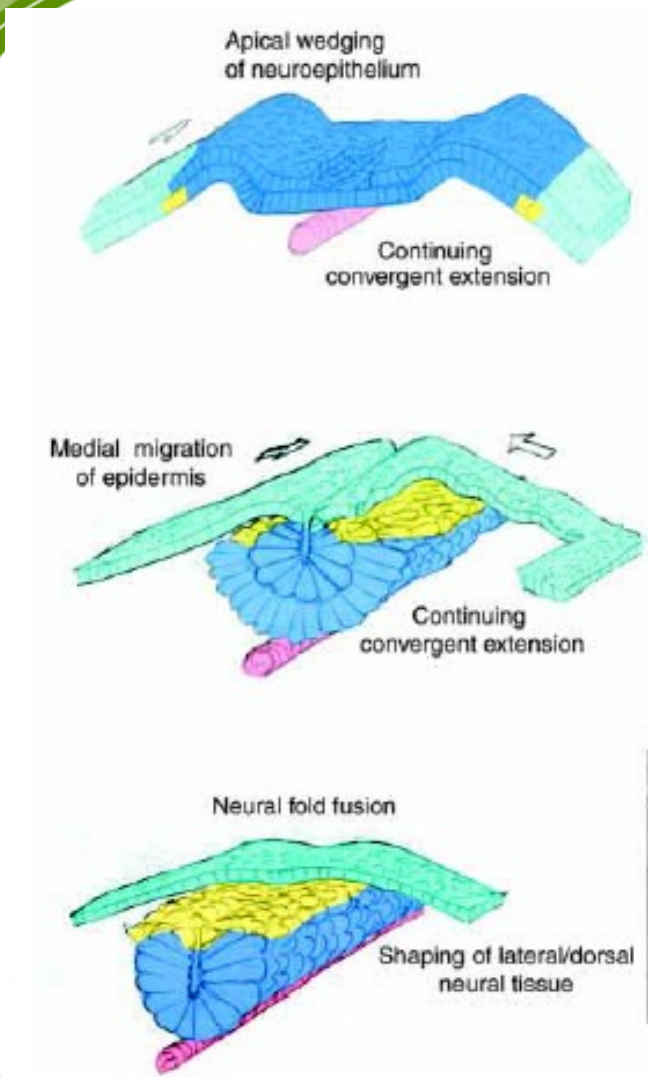




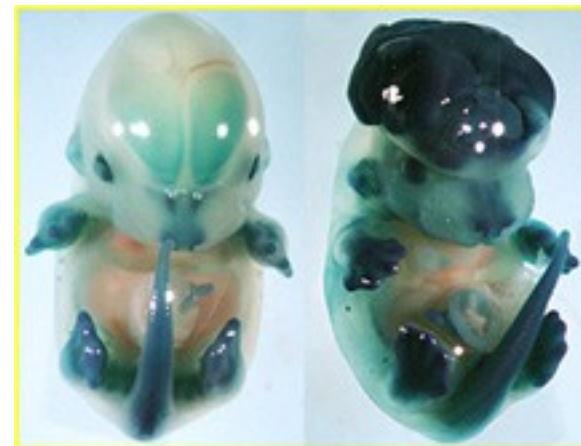
# PCP proteiny aktivují během CE aktino-myosinový cytoskelet



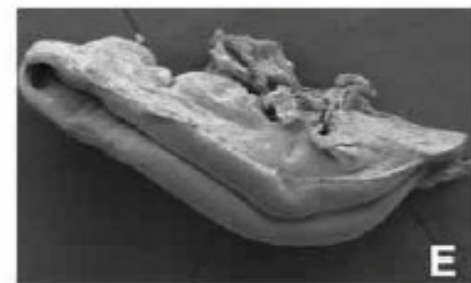
# Důsledky narušené konvergentní extenze (CE)



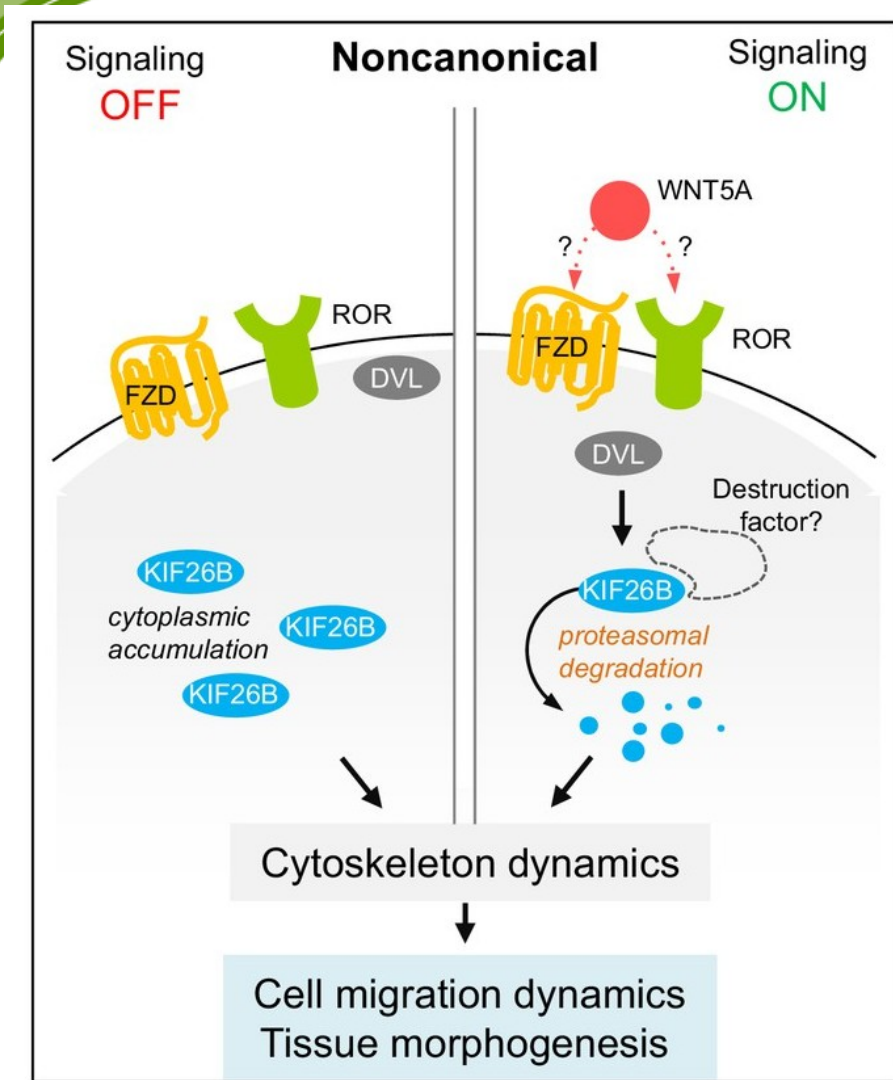
## Exencefalie



## Syndromy rozštěpu páteře

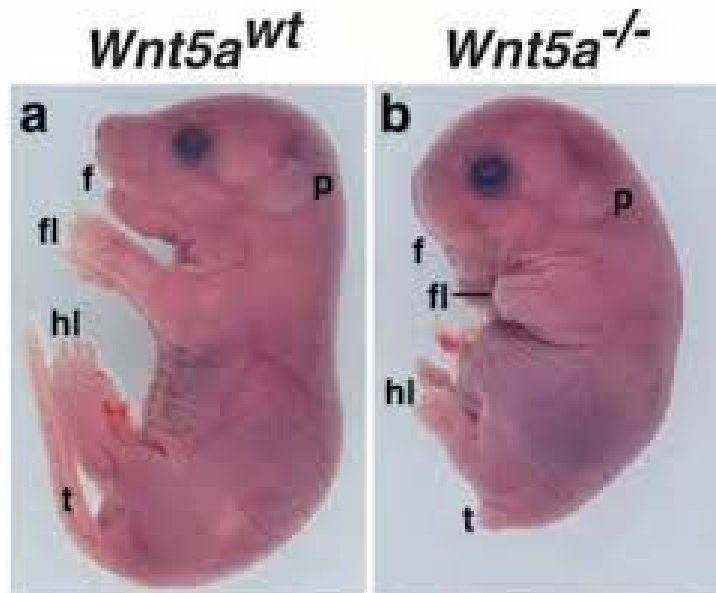


# Wnt/PCP dráha při morfogenezi

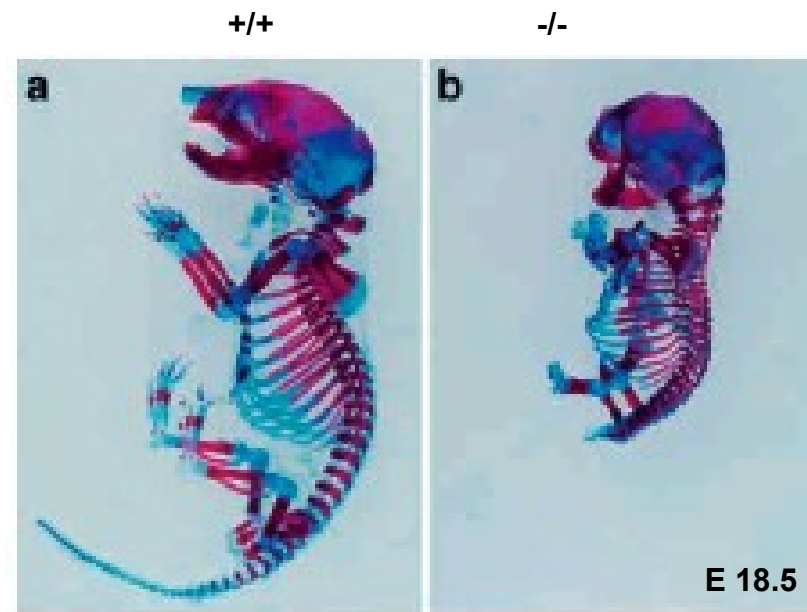


Klíčové molekuly:  
 Wnt5a (ligand)  
 ROR1 a ROR2 (receptory)  
 DVL (dishevelled) –  
 cytoplazmatický protein

# Wnt5a knockout embryo



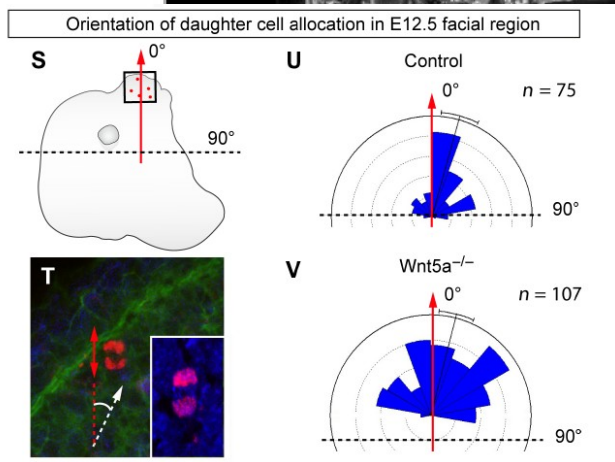
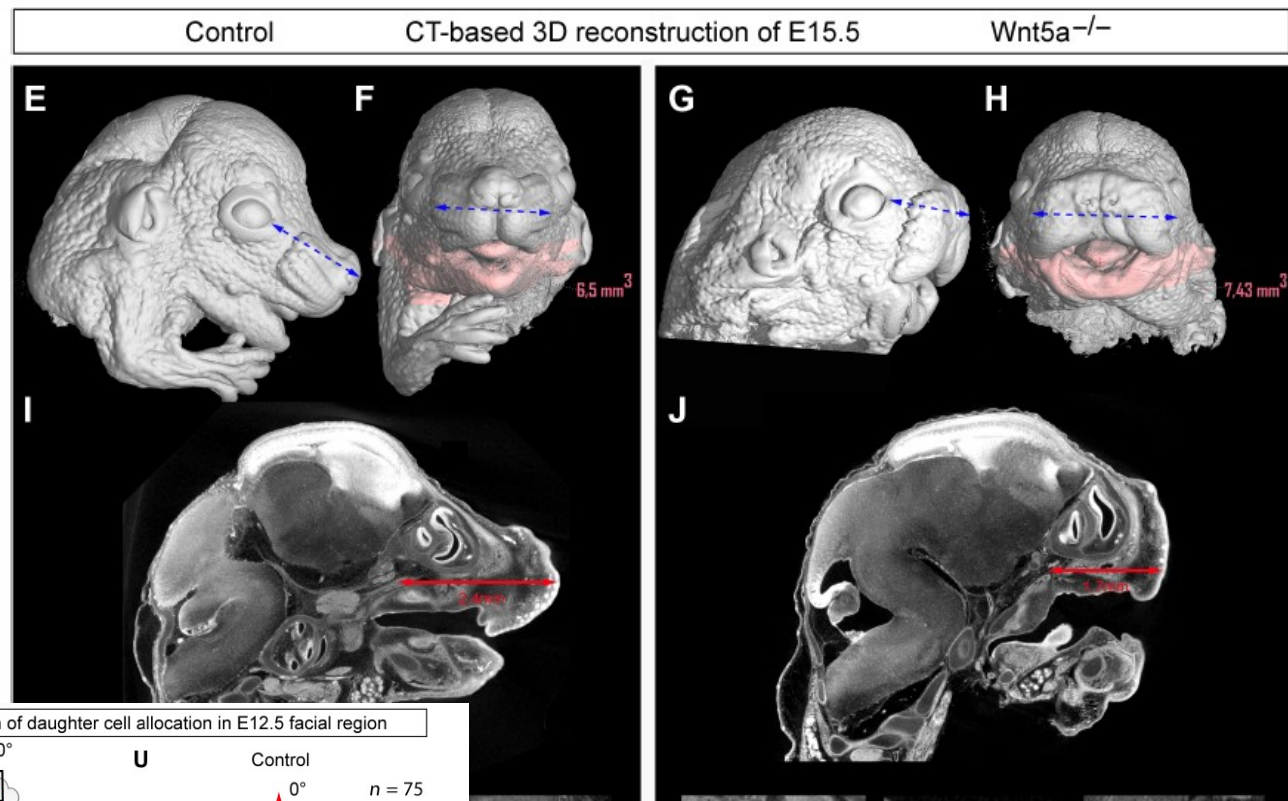
- defekty v morfogenezi struktur vystupujících z těla (outgrowth) jako jsou končetiny, ocas, hlavové struktury nebo genitálie



Yamaguchi et al., 1999



# Wnt/PCP ovlivňuje morfogenezi díky kontrole buněčné orientace a asymetrického dělení



RESEARCH ARTICLE

LIFE SCIENCES

## Analysis of neural crest-derived clones reveals novel aspects of facial development

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# Mutace v ROR2 (a také WNT5A a DVL3) způsobují Robinowův syndrom



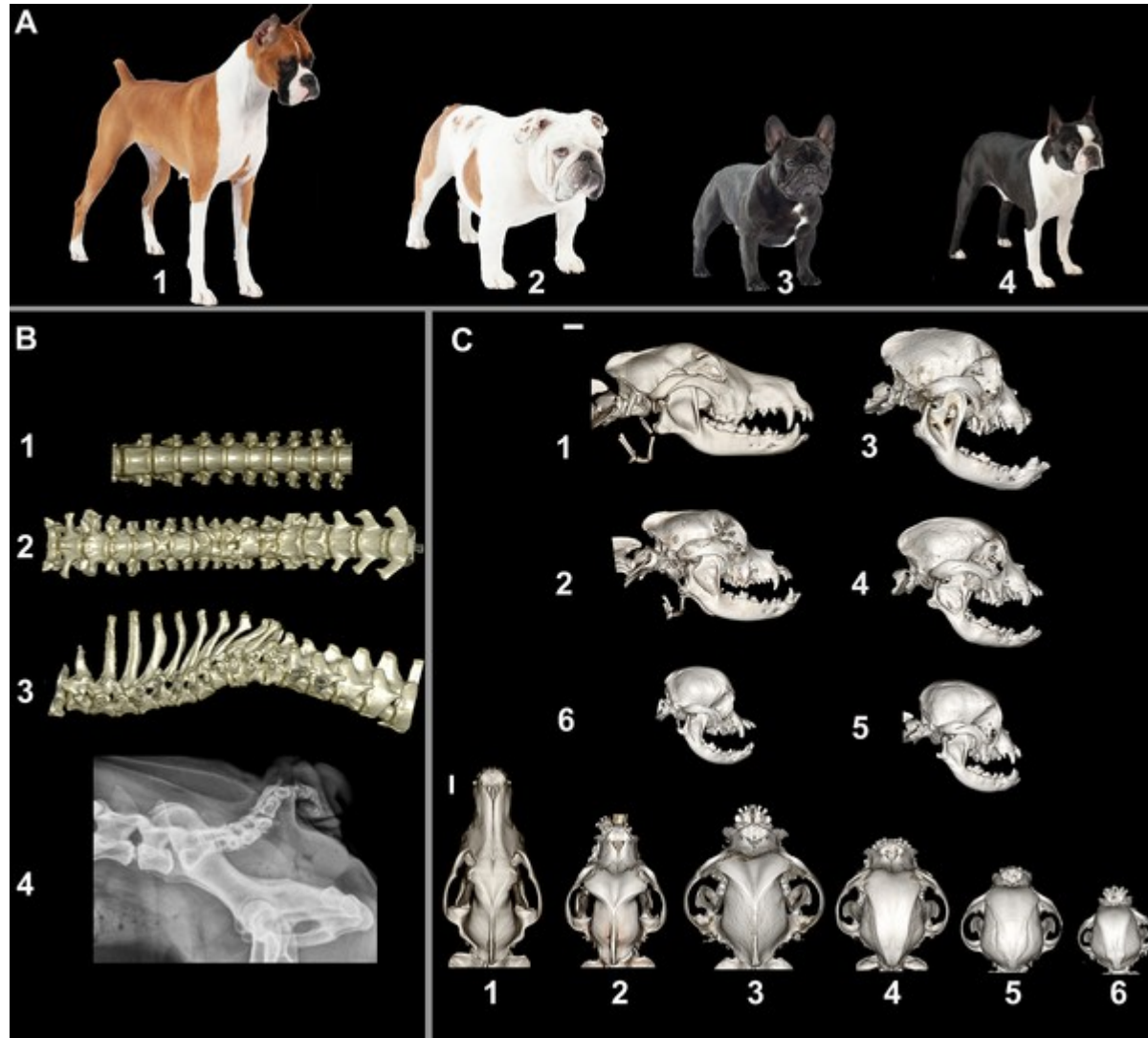
RRS



Robinowův syndrom – soubor příznaků autozomálně dominantně dědičné dyschondroplazie. Trpasličí vzrůst je disproportionální, přítomna je brachymelie, vystouplé čelo s hypertelorismem, hypoplazie dolní čelisti s četnými anomáliemi zubů, hypoplazie skrota a penisu, kryptorchismus. Plodnost a duševní vývoj je v normě



Podobná mutace v DVL2 jako je pozorována u pacientů s RS podmiňuje specifický fenotyp buldoků a buldočků



# Migrace buněk neurální lišty

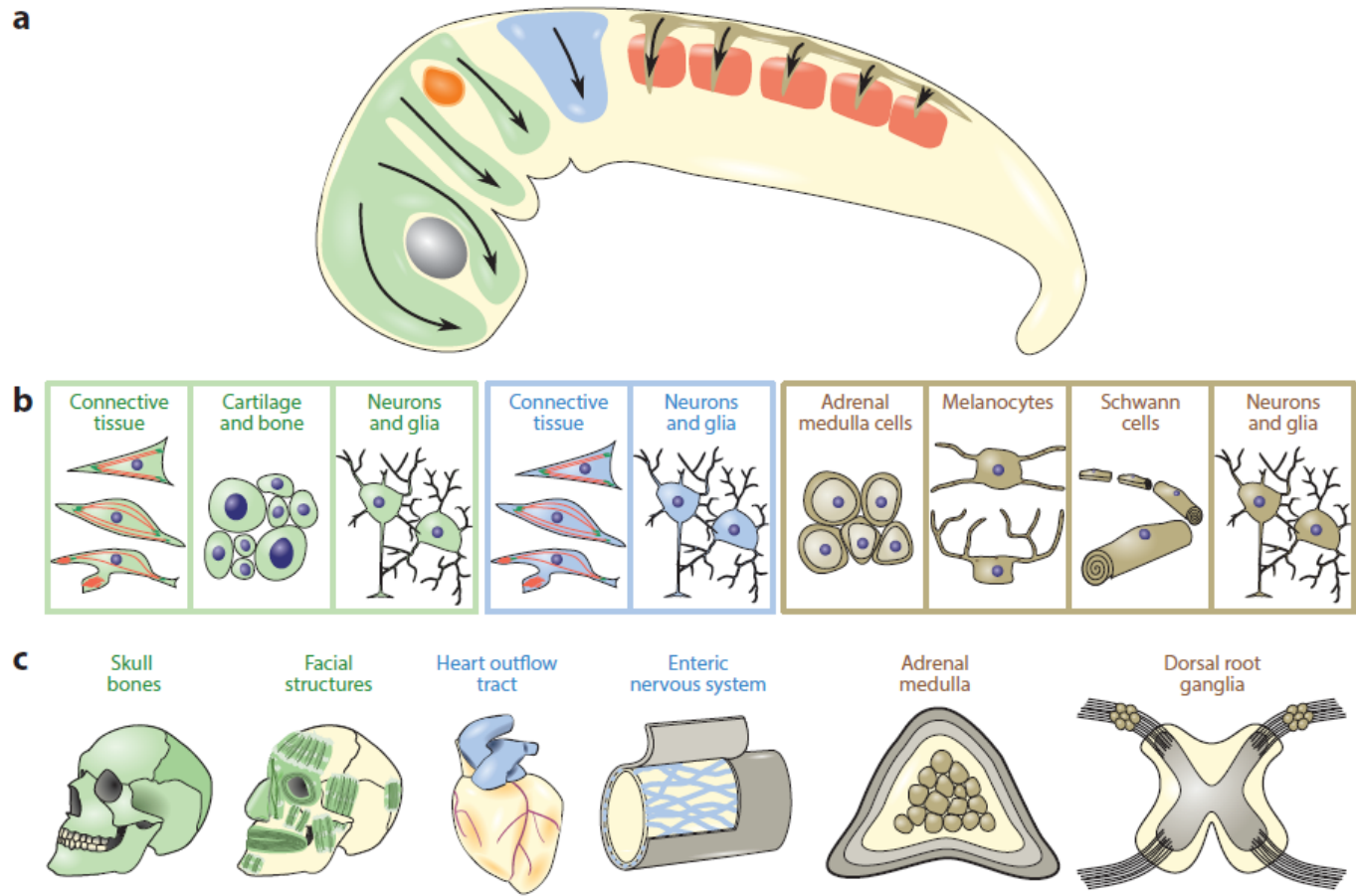
*Annual Review of Genetics*

## Mechanisms of Neural Crest Migration

András Szabó and Roberto Mayor

Department of Cell and Developmental Biology, University College London, London WC1E  
6BT, United Kingdom; email: r.mayor@ucl.ac.uk

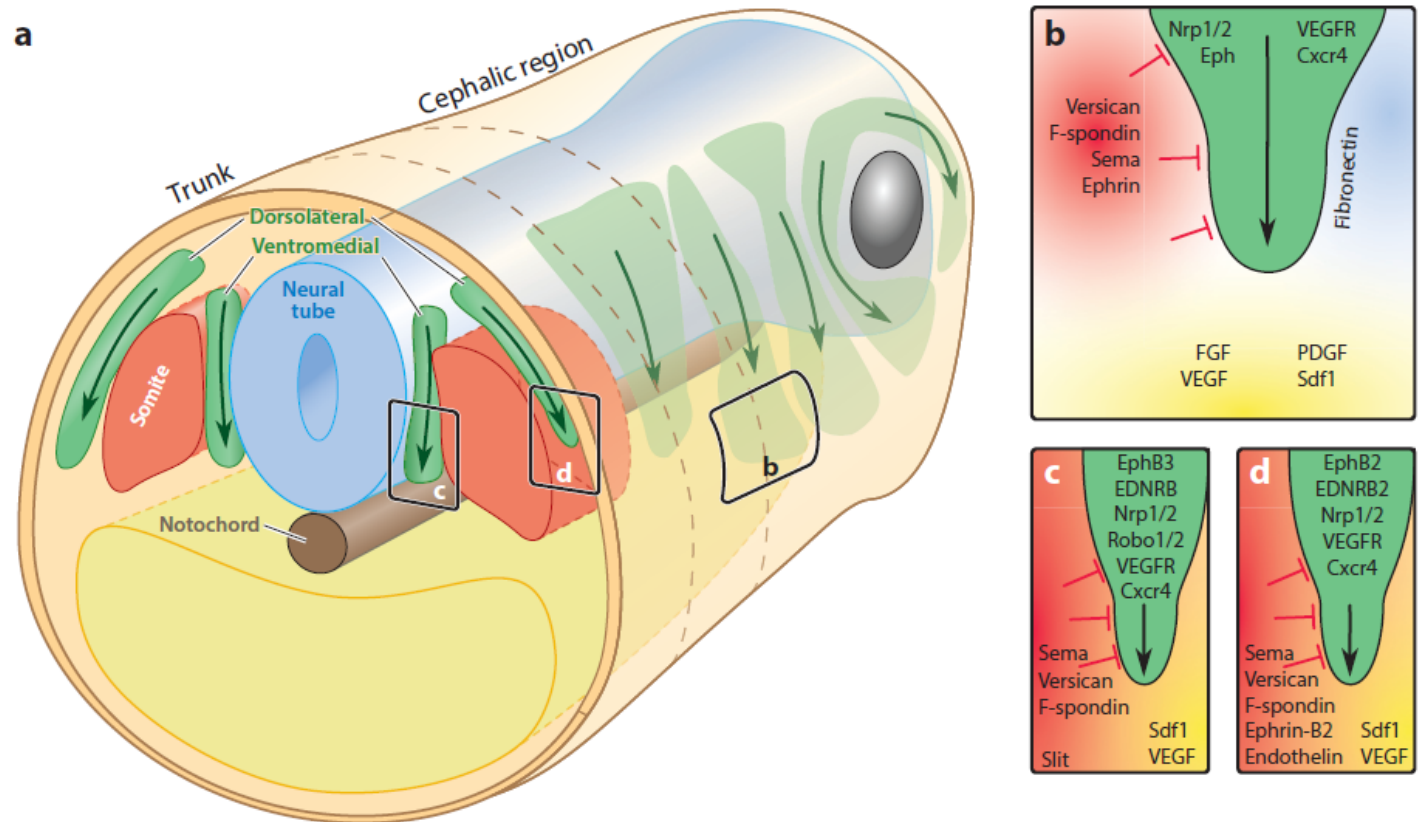
# Přehled hlavních migračních proudů NC – předozadní pohled



**Figure 1**

Neural crest migration and contribution to a variety of tissues and organs. (a) Time of delamination varies according to position, with simultaneous delamination into thick streams in cranial regions and progressive delamination into thin streams in the trunk along the anterior–posterior axis. (b) Examples of neural crest derivatives from the cephalic (green), vagal (blue), and trunk (brown) regions. (c) Examples of neural crest contribution to organs from the three regions.

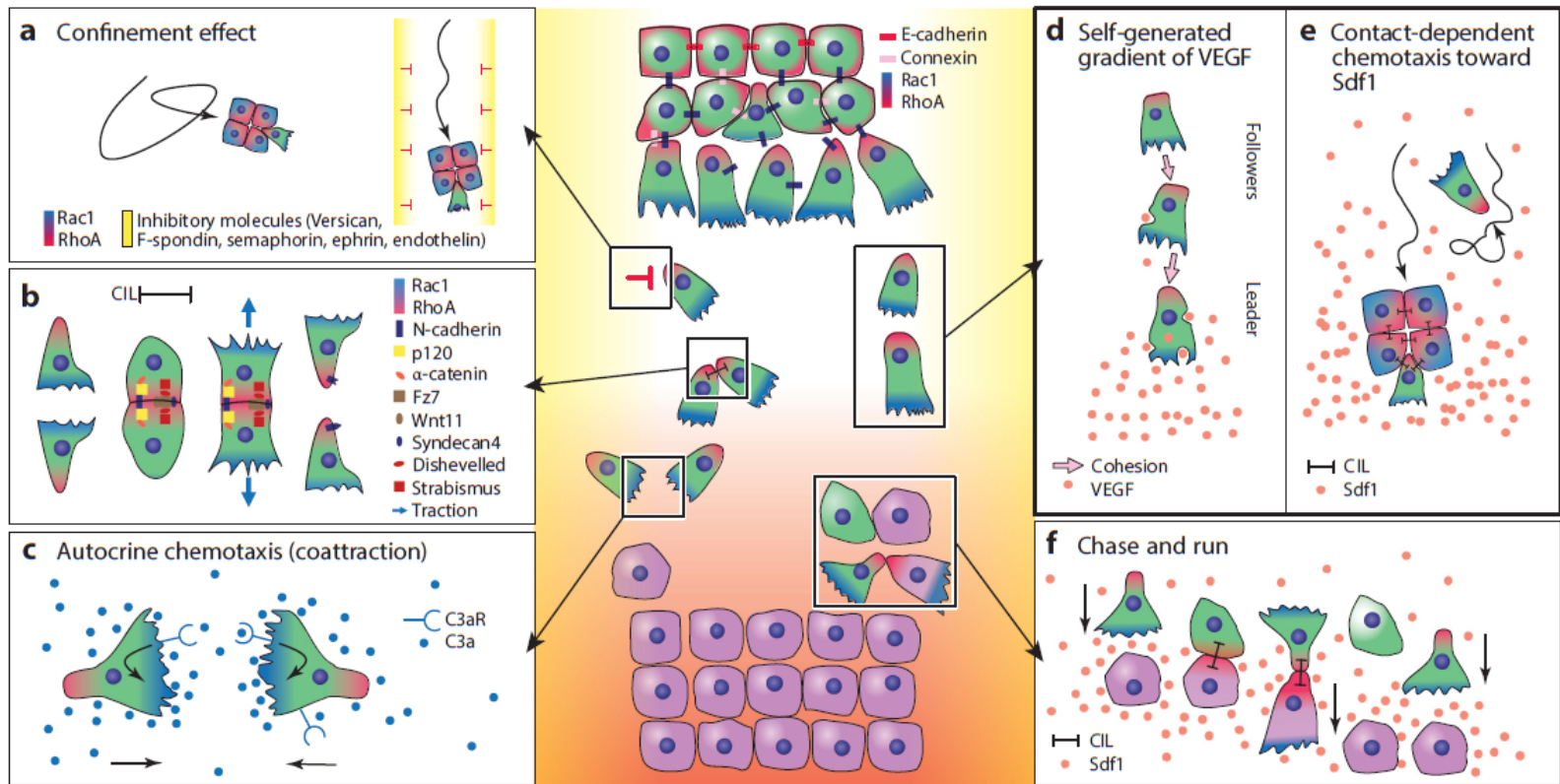
# Dorsolaterální a ventromediální migrace NC a hlavní molekulární regulátory



**Figure 3**

Paths of NC migration are shaped by external positive and negative signals. (a) Characteristic NC paths in the cephalic and trunk regions. Arrows indicate the cephalic, ventromedial trunk, and dorsolateral trunk migratory paths corresponding, respectively, to panels b–d. (b–d) Main external signals inhibiting (red), promoting (yellow), or allowing (blue) NC migration along the (b) cephalic, (c) ventromedial trunk, and (d) dorsolateral trunk streams. Abbreviations: EDNRB, endothelin receptor B; FGF, fibroblast growth factor; NC, neural crest; Nrp1/2, neuropilins 1 and 2; PDGF, platelet-derived growth factor; Sdf1, stromal cell-derived factor 1; Sema, semaphorin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

# Základní principy kontrolující migraci (nejen) buněk neurální lišty

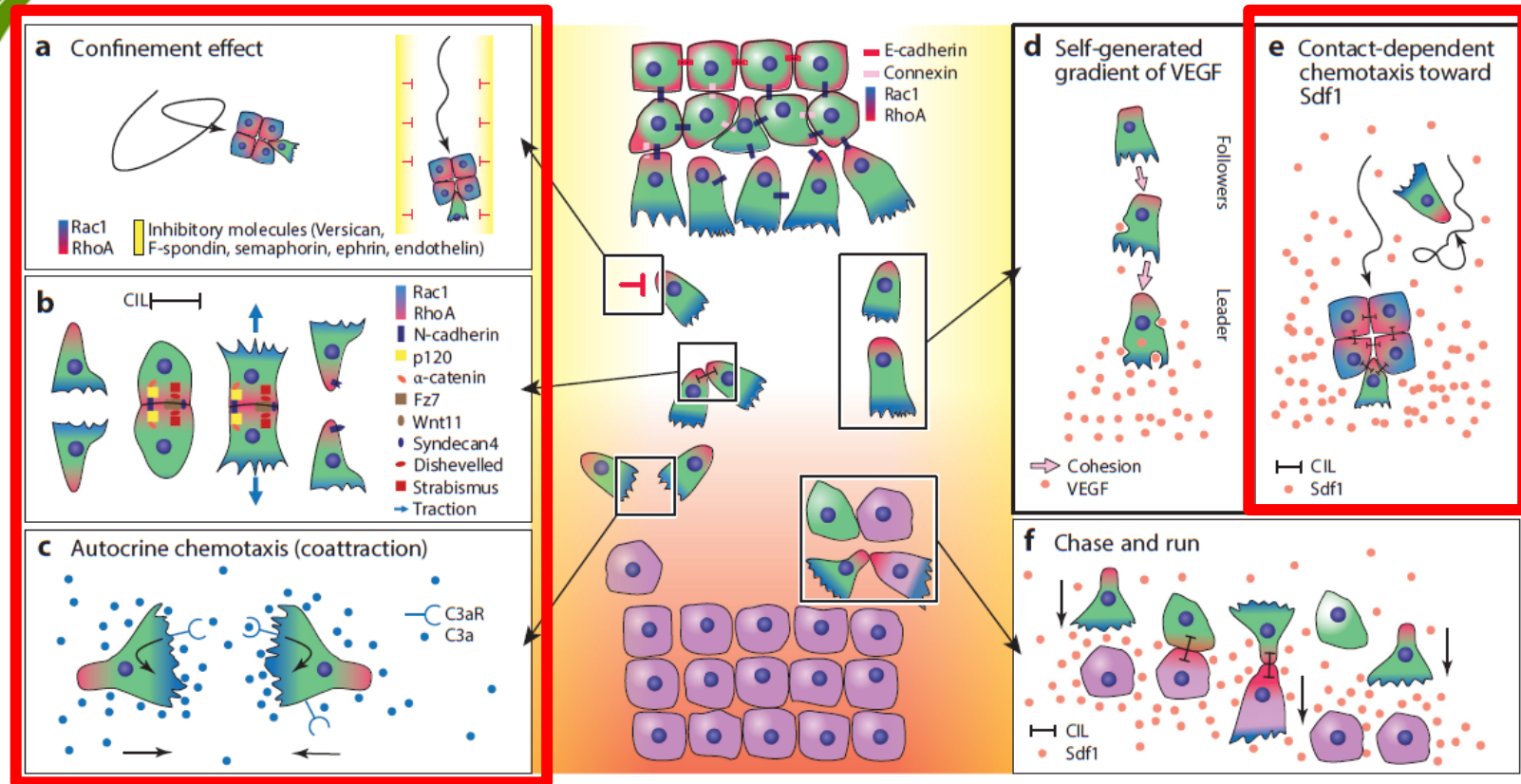


**Figure 4**

Control of collective neural crest (NC) migration. (a) Confinement enhances the persistence of migrating NC. (b) Contact inhibition of locomotion (CIL) polarizes colliding cells. (c) Coattraction, or chemotaxis toward a self-secreted chemokine, helps maintain collectiveness. (d) The self-generated chemoattractant gradient of vascular endothelial growth factor (VEGF) requires a differentiation of leaders and followers. (e) Contact-dependent chemotaxis toward stromal cell-derived factor 1 (Sdf1). (f) The chase-and-run mechanism between NC cells and placodes directs NC migration and coordinates the migration between NC and placodes. Across the panels, colors differentiate the Rac1 (blue) and RhoA (red) activity of NC cells (green) and placodal cells (magenta).



# Základní principy kontrolující migraci (nejen) buněk neurální lišty



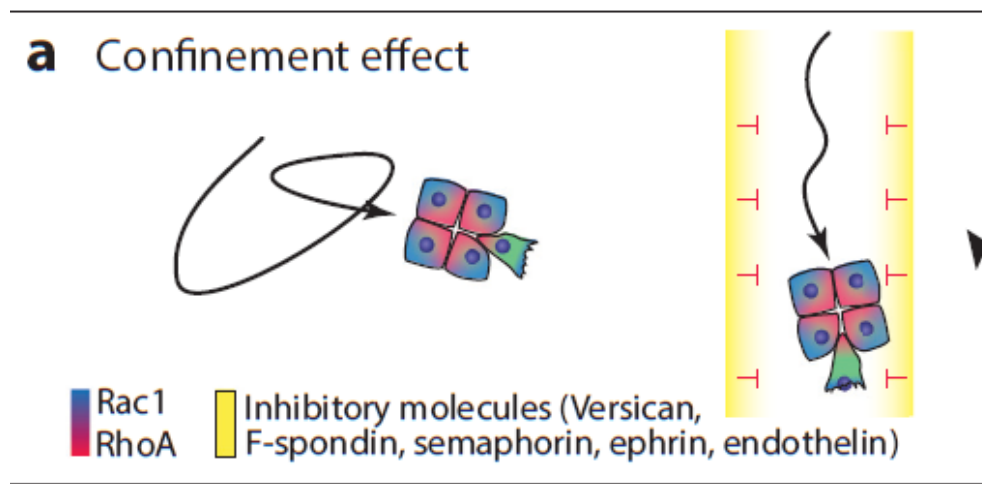
**Figure 4**

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## Omezení trasy (confinement)

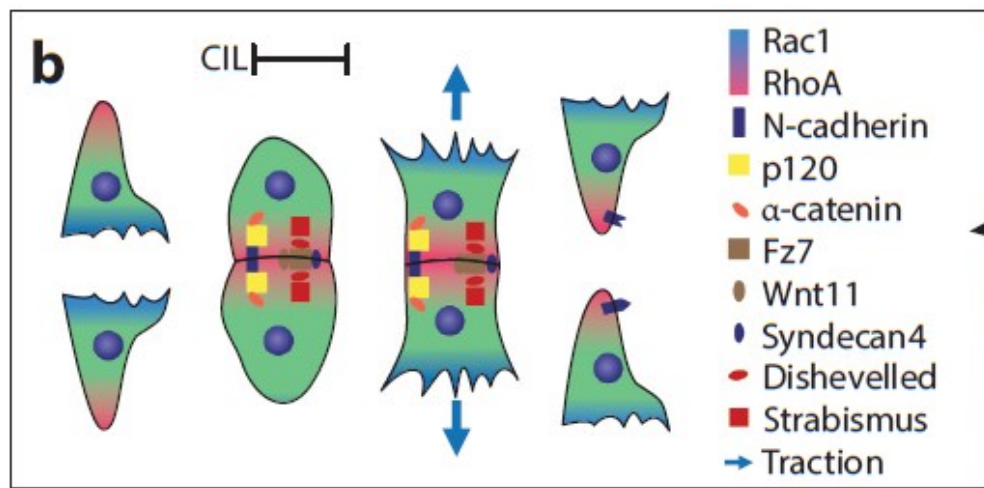
Kolektivní migrace buněk je regulována prostorovým omezením (např. díky molekulám extracelulární matrix jako je proteoglykan versican), které působí jako fyzikálně-chemická bariéra a podporuje vznik organizované migrace v oddělených proudech.



# Kontaktní inhibice lokomoce

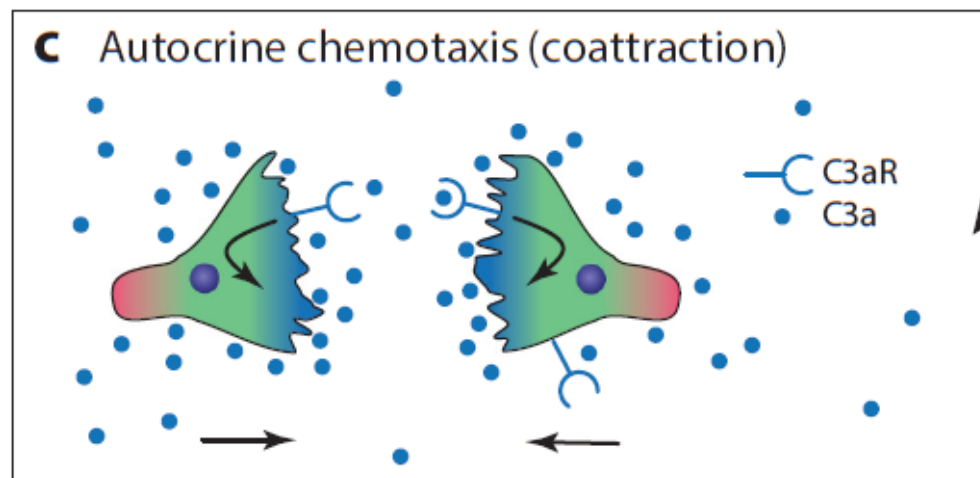
## Contact inhibition of locomotion

Kontaktní inhibice lokomoce (CIL) je proces, při kterém se buňky, které přicházejí do vzájemného fyzického kontaktu, zastaví migraci v původním směru. Po kontaktu reagují repolarizací a migrací v opačném směru.



## Autokrinní chemotaxe (co-attraction)

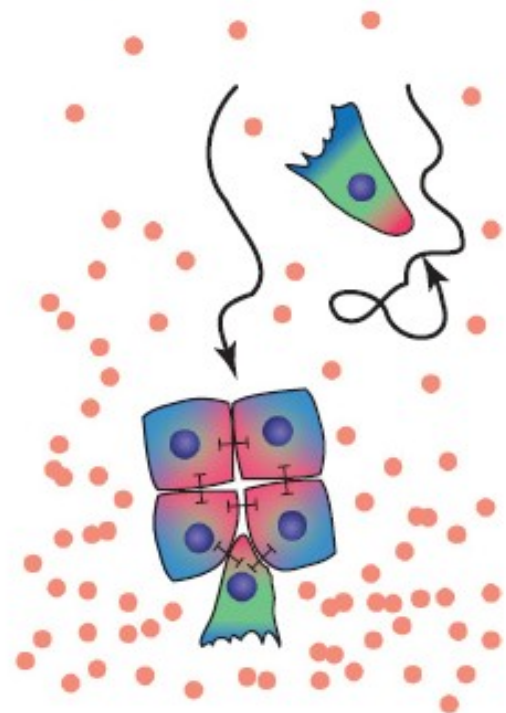
Autokrinní chemotaxe (co-attraction) mezi hromadně migrujícími buňkami je proces, při kterém buňky stejného typu vylučují chemoatraktant (např. součást komplementu C3a v buňkách neurální lišty), který stimuluje další buňky ve skupině, které mají receptory na tento chemoatraktant. Buňky reagují na stimulaci pohybem k sobě navzájem a udržují tak vysokou hustotu buněk.



## Kolektivní chemotaxe

Kolektivní chemotaxe je proces, při kterém jsou buňky schopny účinnější chemotaxe v případě, že jsou ve skupině/společném kontaktu. Typický příklad u buněk NC je chemotaxe směrem k CXCL12 (SDF1)

**e** Contact-dependent chemotaxis toward Sdf1



—|— CIL  
● Sdf1

## Axon guidance

Navádění axonů (axon guidance) – proces(y), kterým je vznikající axon naváděn k cílovým neuronům, se kterými pak navazuje synaptická spojení

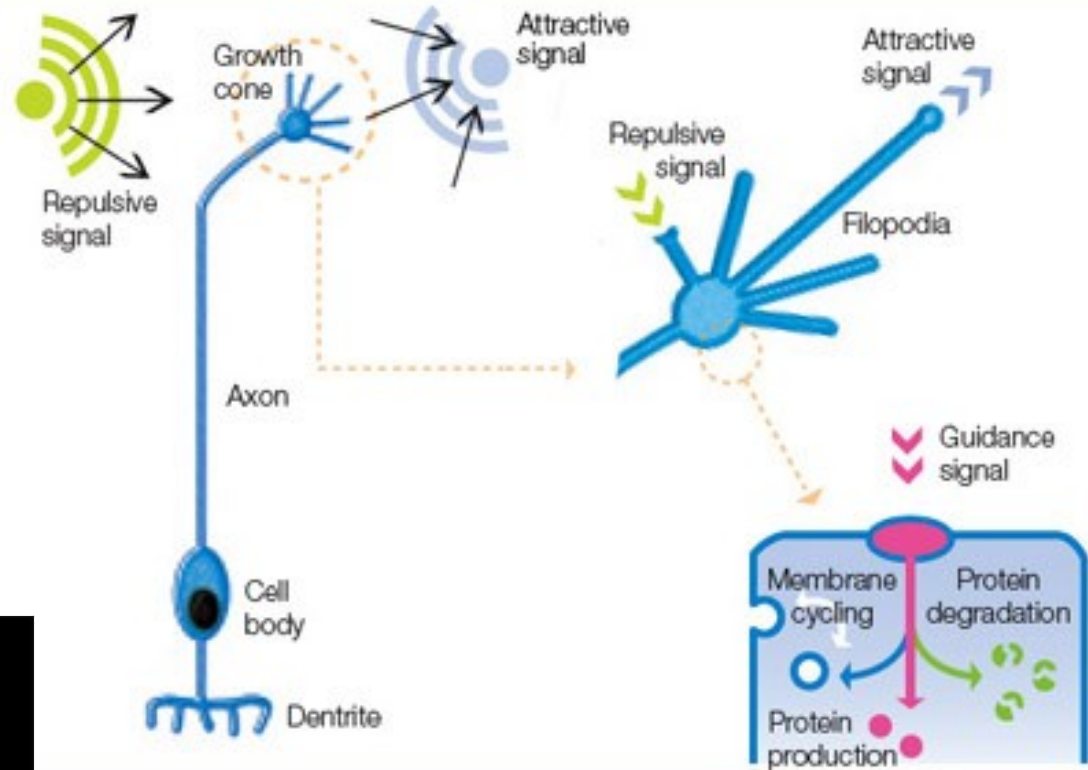
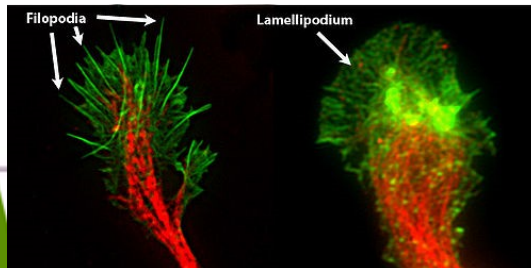
# Navádění axonů – růstový konus

## AXON GUIDANCE

The axon navigates by sensing **attractive and repulsive signals** that influence the leading edge of the axon, called the **growth cone**. The growth cone consists of a series of finger-like projections called **filopodia**. Projections that primarily receive repulsive signals shrink and collapse. Those that receive attractive signals continue to expand, ultimately adopting the role of an axon and forming their own growth cones.

Within a growth cone, the signals trigger responses that can include:

- destruction of existing proteins
- translation of messenger RNAs into new proteins
- membrane cycling, which changes the set of proteins present on the growth cone's surface.



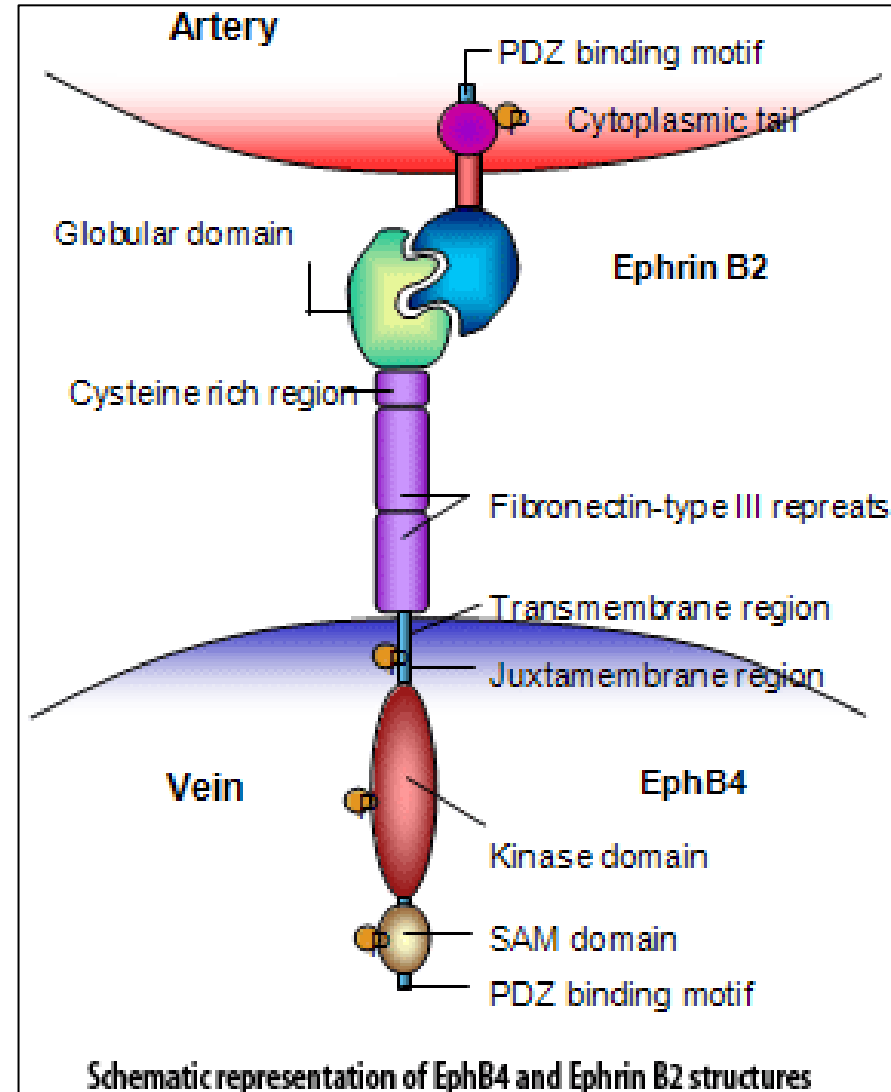


# Molekuly regulující axon guidance

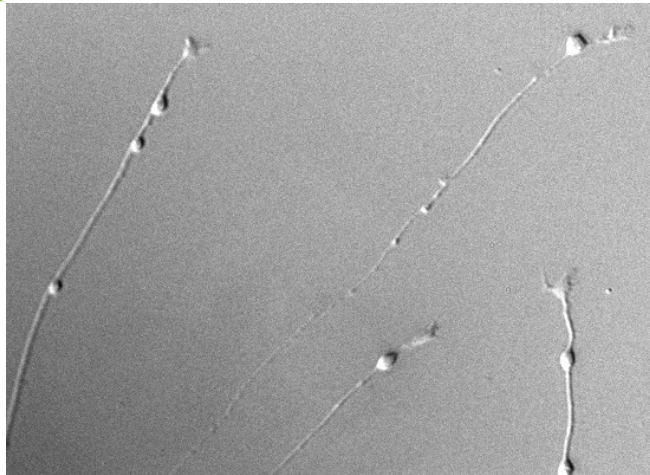
- Slit/Robo
- ephriny
- semaphoriny
- klasické morfogeny (Wnt, BMPs, FGFs...)

# Eph/ephrin komplex

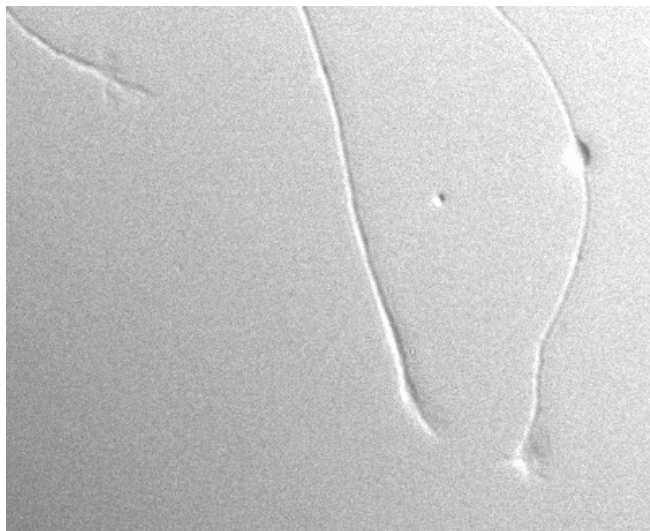
- ephrin – jsou **membránově vázané ligandy** (podobně jako ligandy Notch dráhy)
- ephriny A – na membráně upevněny pomocí tzv. **GPI kotvy**
- ephriny B – transmembránové ligandy, které samy jsou schopny signálovat do buňky
- Eph/ephrin systém je zapojen zejména do „navigace“ buněk (např. buněk cév) či jejich částí (např. navádění axonů v nervové soustavě), a do „contact-mediated cell sorting“ ve vyvíjejícím se embryu. Jde o obecný mechanismus regulující migraci buněk.



# Eph/ephrin komplex



Supporting Information Movie 2. Ephrin-B2 induces extremely rapid growth cone collapse and axon retraction in VT RGCs. Movie depicts VT growth cones treated with ephrin-B2. Frames were captured at 30-second intervals for 45 minutes, replayed at 15 frames per second. 0.5  $\mu\text{g/ml}$  pre-clustered ephrin-B2 was added after 15 minutes (2 second interval in movie).



Supporting Information Movie 4. Inhibiting Rho kinase strongly diminishes axon retraction but does not affect growth cone collapse. Movie depicts VT growth cones pre-treated the Rho kinase inhibitor Y-27632 for 1 hour, followed by treatment with ephrin-B2. Frames were captured at 30-second intervals for 45 minutes, replayed at 15 frames per second. 0.5  $\mu\text{g/ml}$  pre-clustered ephrin-B2 was added after 15 minutes (2 second interval in movie).

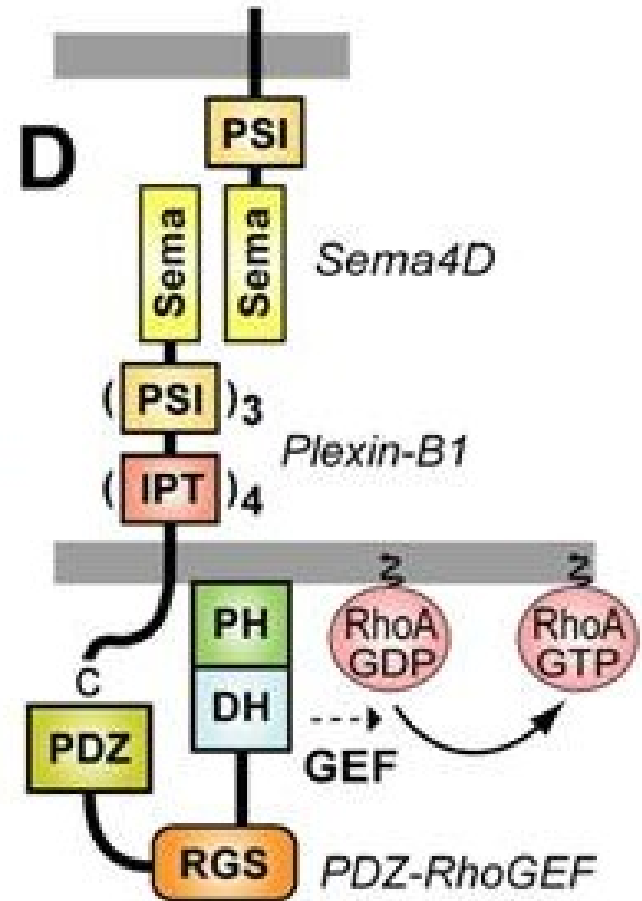
# Molekuly regulující axon guidance

- **Slit/Robo**
- **ephriny**
- **semaphoriny**
- **klasické morfogeny (Wnt, BMPs, FGFs...)**

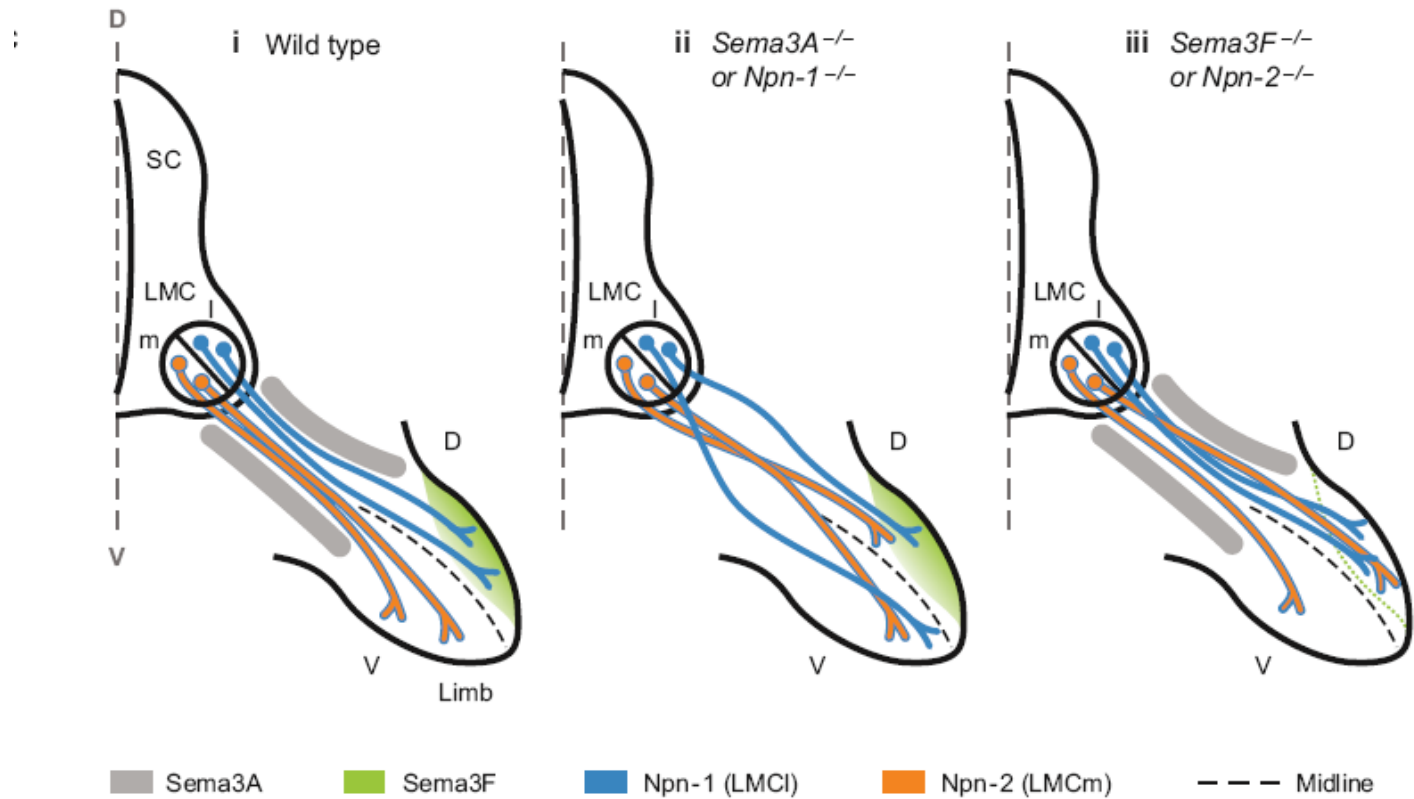
Semaphorin/plexin systém

- semaphorin (Sema4D) je membránově vázaný ligand, který se váže na svůj receptor (plexin nebo neuropilin, Nrp1)

- aktivace vede k aktivaci malých GTPáz (např. RhoA), přestavbě cytoskeletu a změně ve směru navádění



# Neurogeneze



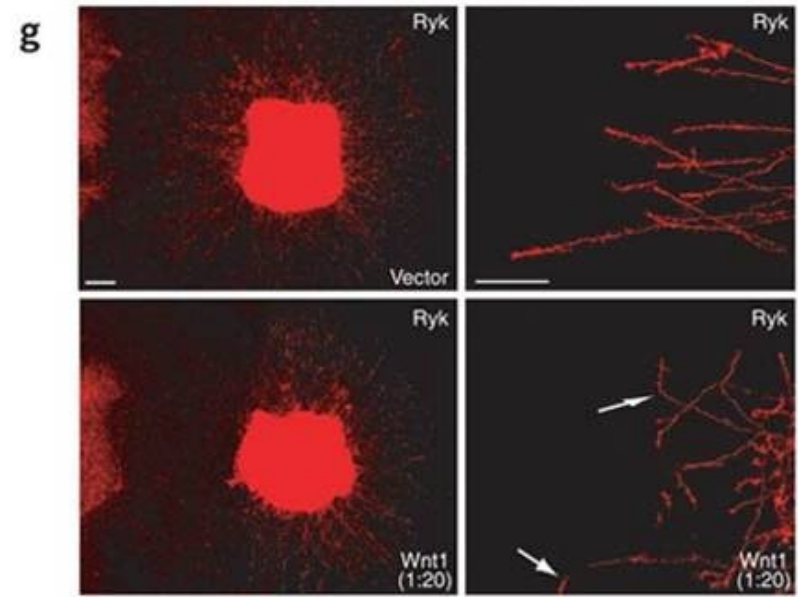
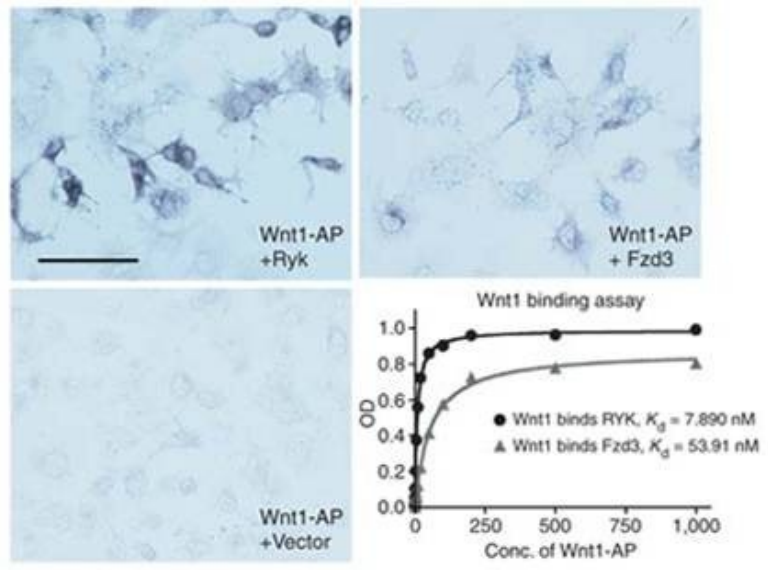
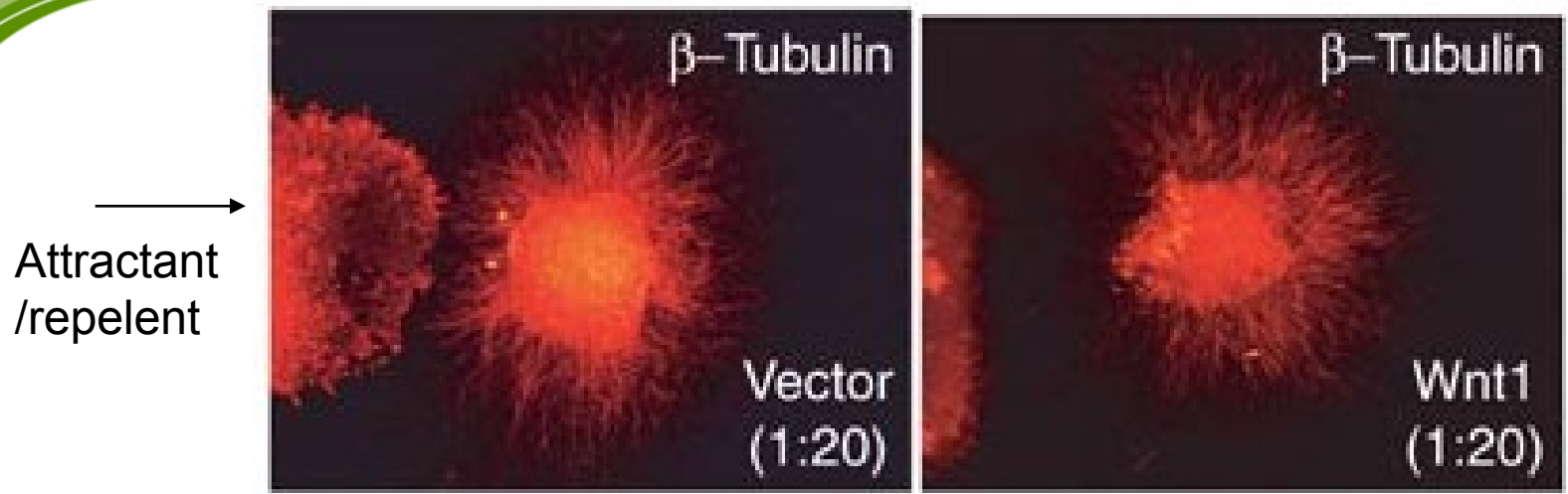
SC-sympathetic ganglion

LMC-Lateral Motor Column

(m-medial;l-lateral)



Možnosti studia migrace – attractant/repellent assays



## **Syntéza a připomenutí**

**Všechny procesy diskutované v dnešní přednášce mají společného jmenovatele na buněčné úrovni: Dynamické procesy na úrovni cytoskeletu – pojďme si to připomenout.**

**Slidy z Biologie živočišné buňky**

# Pohyb buňky po substrátu

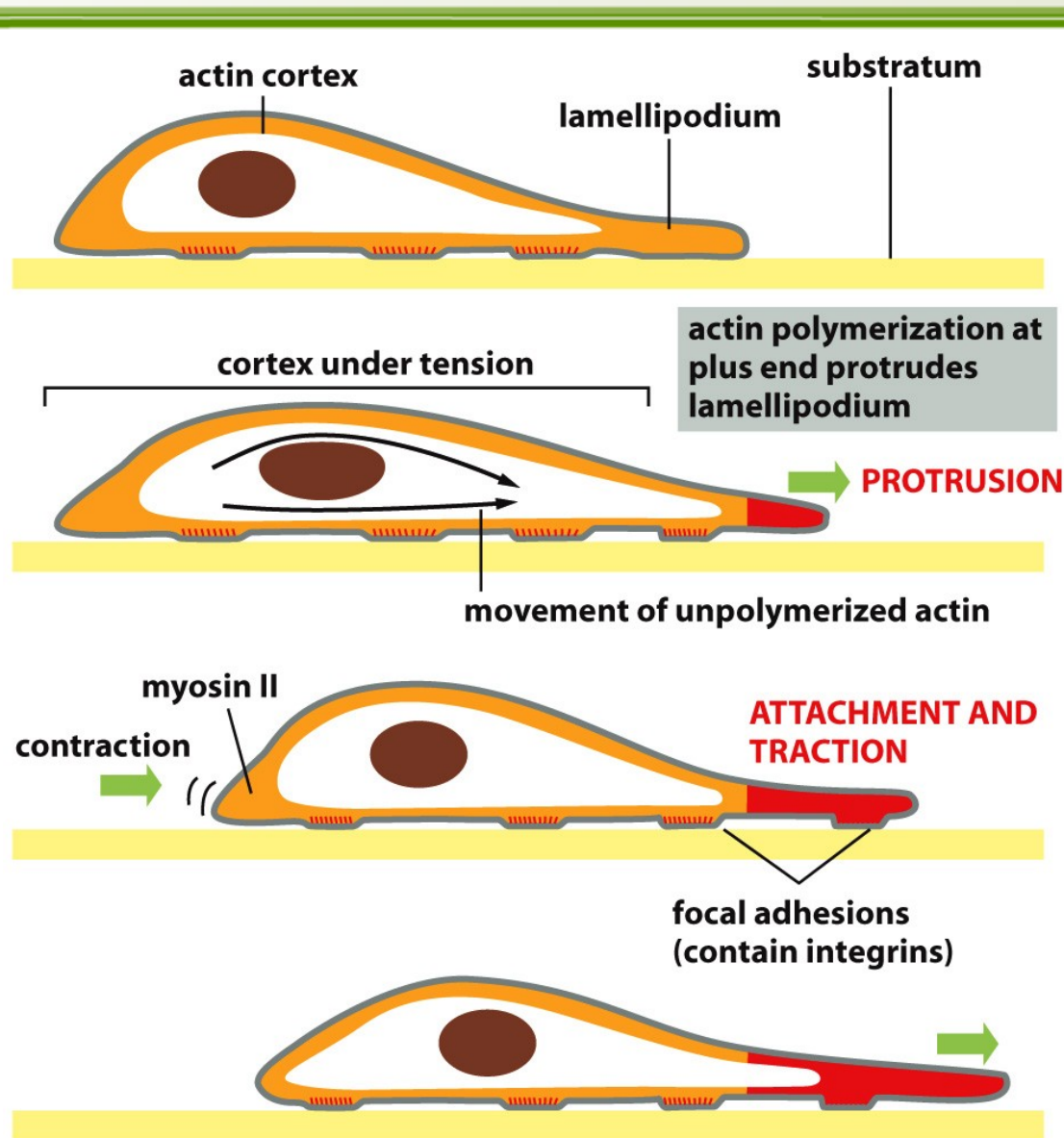
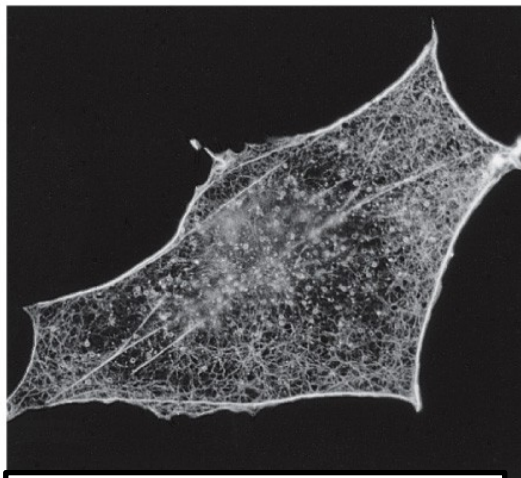


Figure 16-75 Molecular Biology of the Cell 6e (© Garland Science 2015)

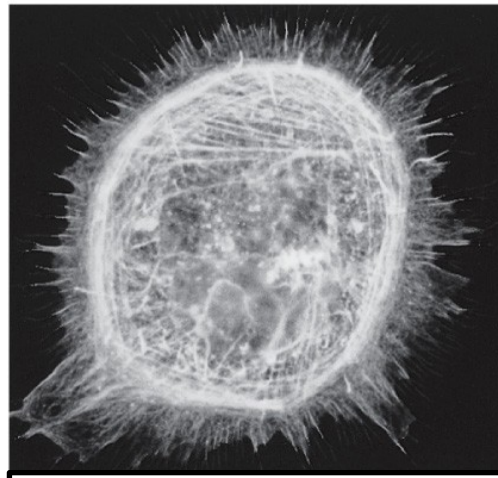
# Pohyb buňky po substrátu

actin staining



Klidová buňka

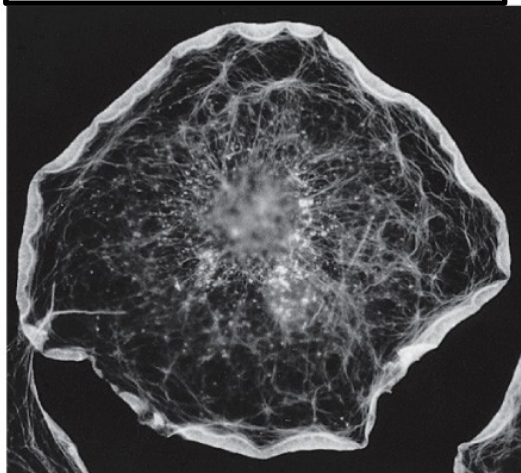
actin staining



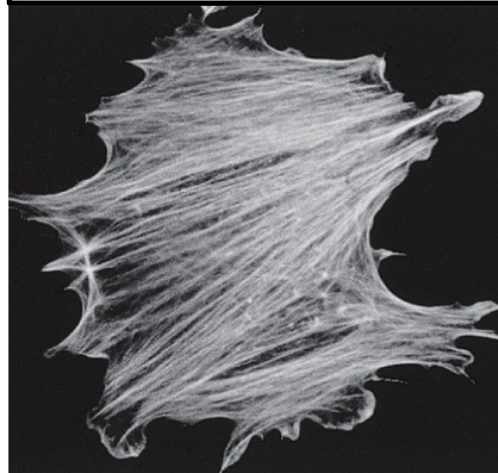
Filopodia

fimbrin

Arp2/3  
filamin



Lamelipodia



Stresová vlákna

non-muscle  
Myosin II  
 $\alpha$ -actinin



# Aktinová síť v lamelipodiu – klíčová role Arp2/3

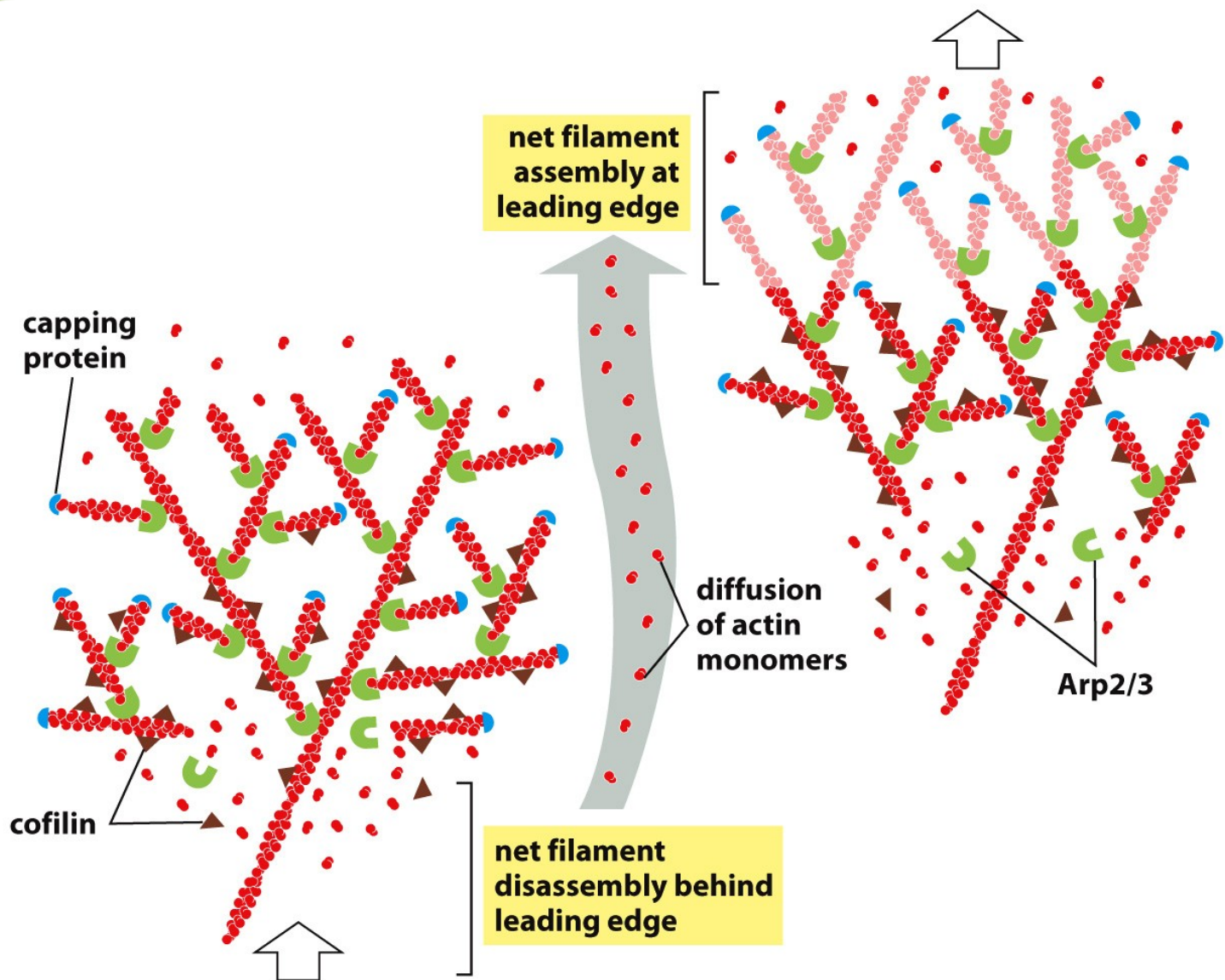


Figure 16-80 Molecular Biology of the Cell 6e (© Garland Science 2015)



# Pohyb buňky po substrátu – klíčová role integrinů

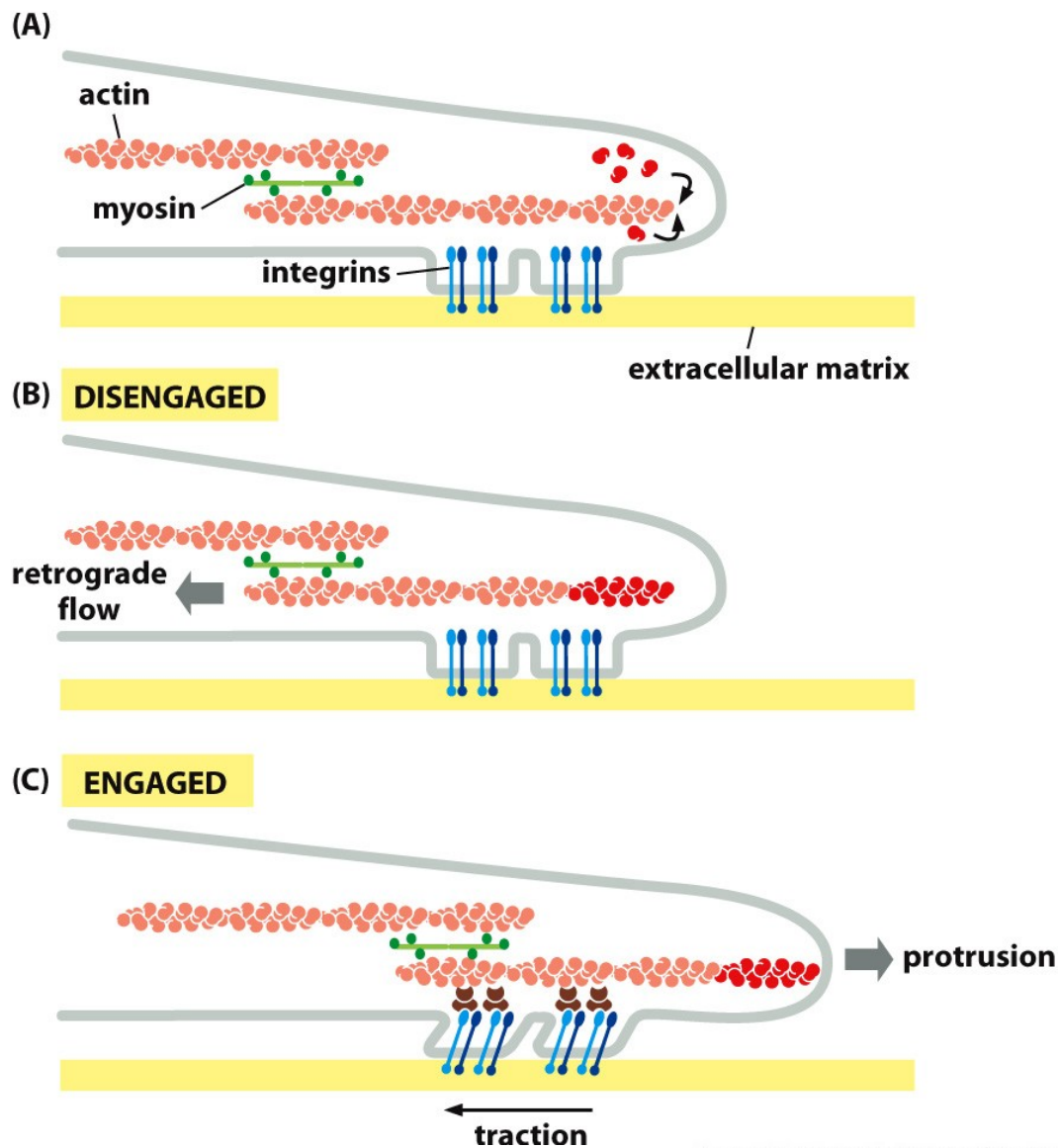
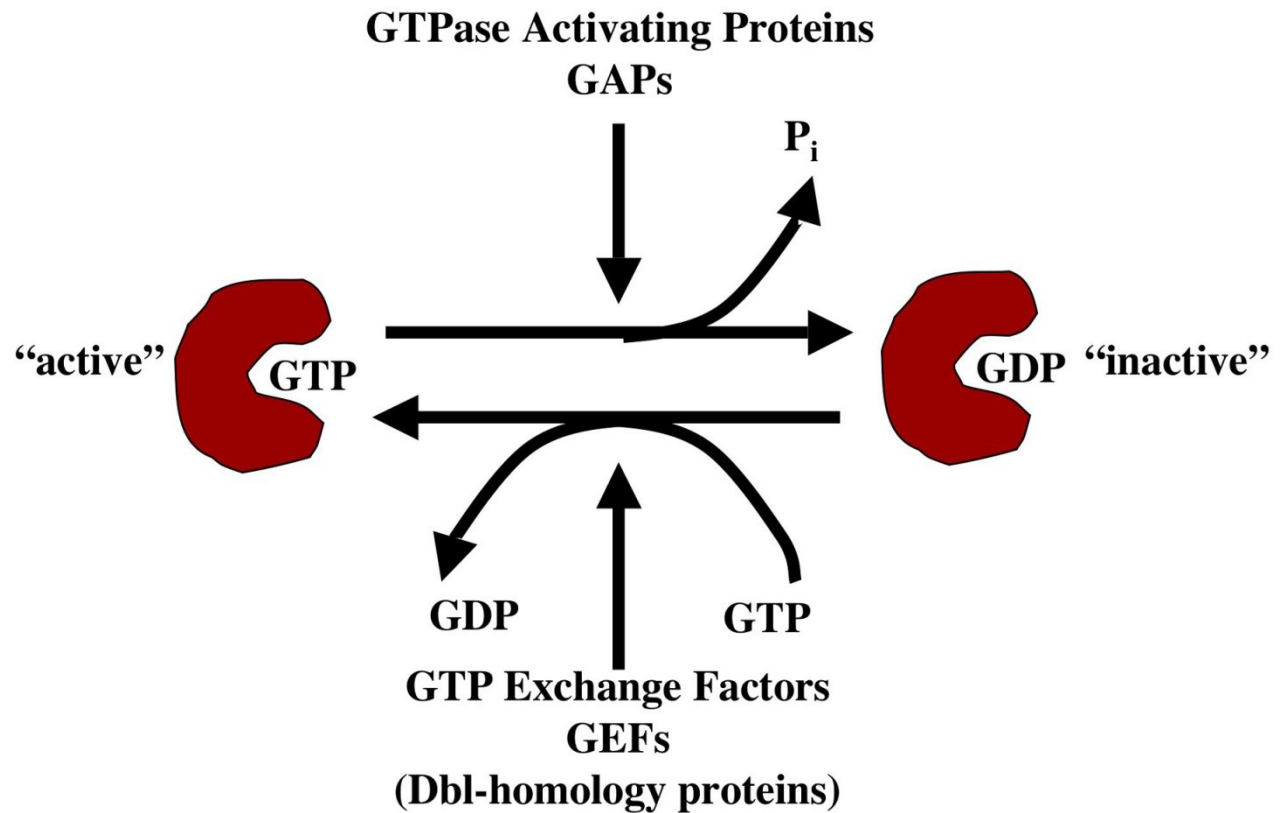
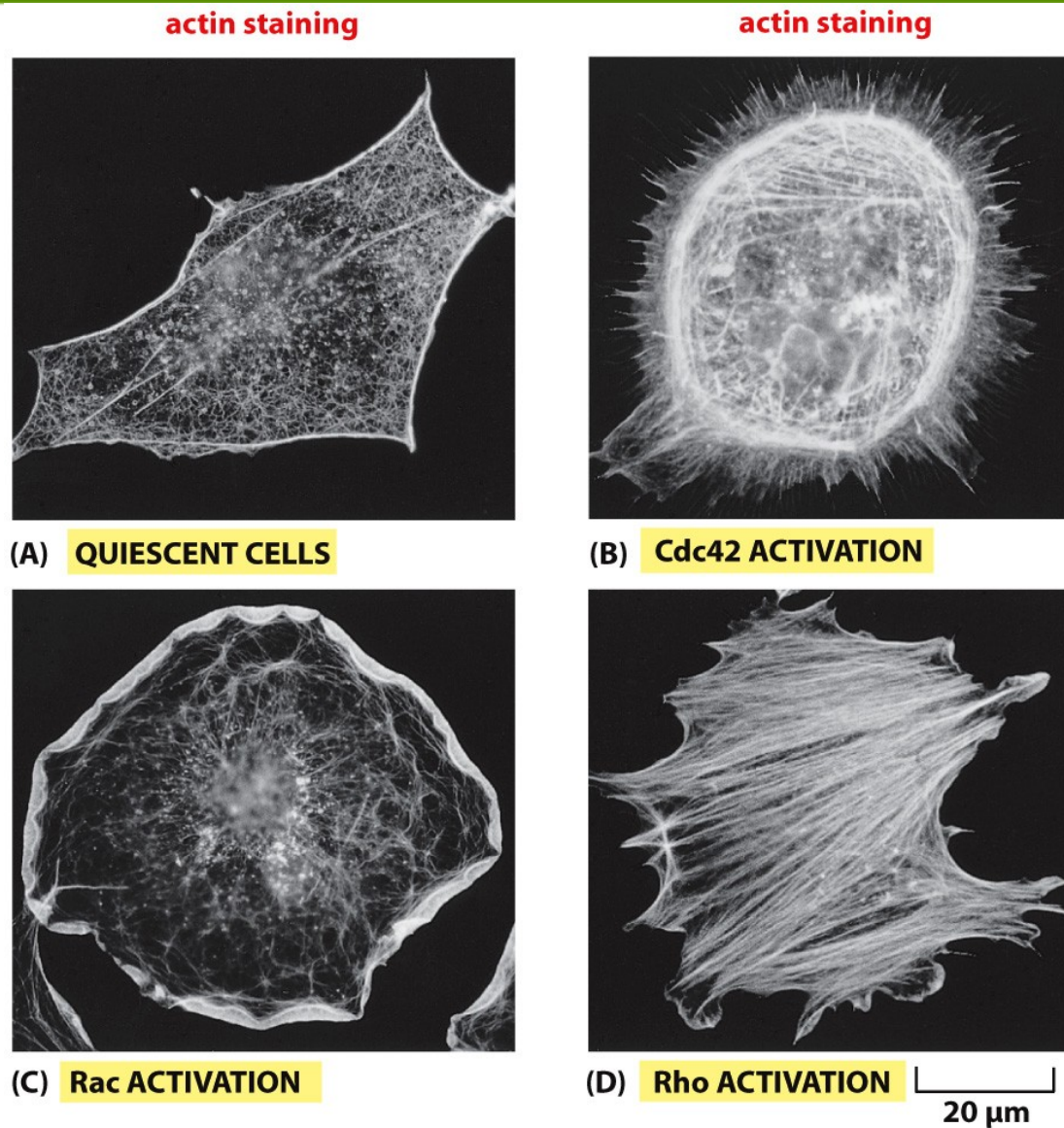


Figure 16-82 Molecular Biology of the Cell 6e (© Garland Science 2015)

# Malé GTPázy z Rho rodiny jsou klíčové regulátory cytoskeletu



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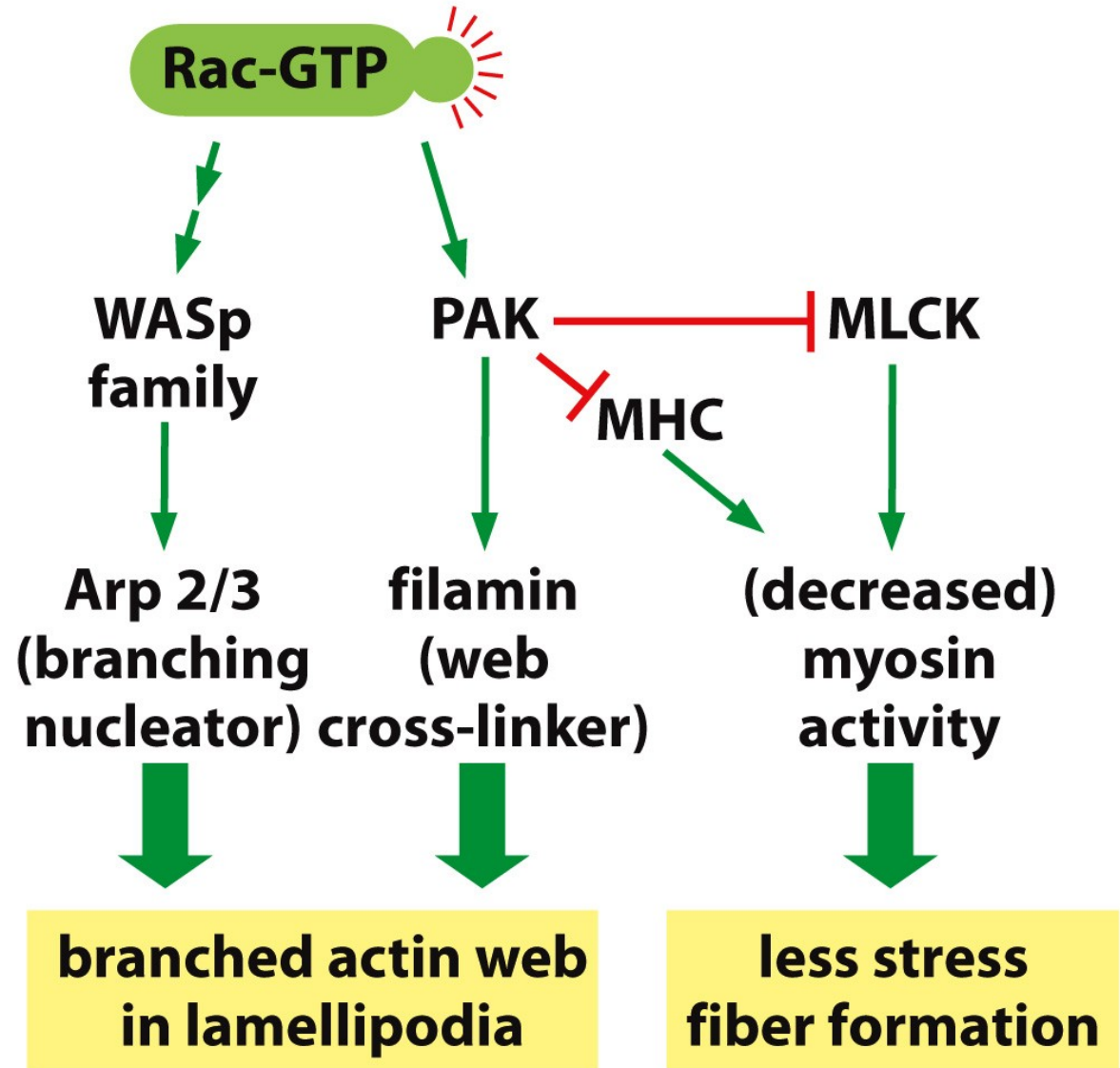


Figure 16-85a Molecular Biology of the Cell 6e (© Garland Science 2015)

# Pohyb buňky po substrátu

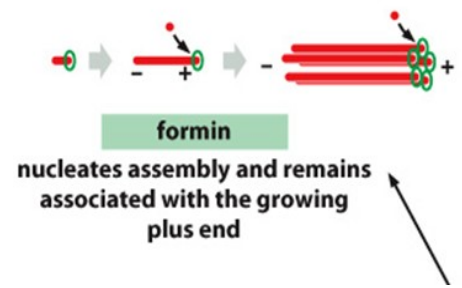
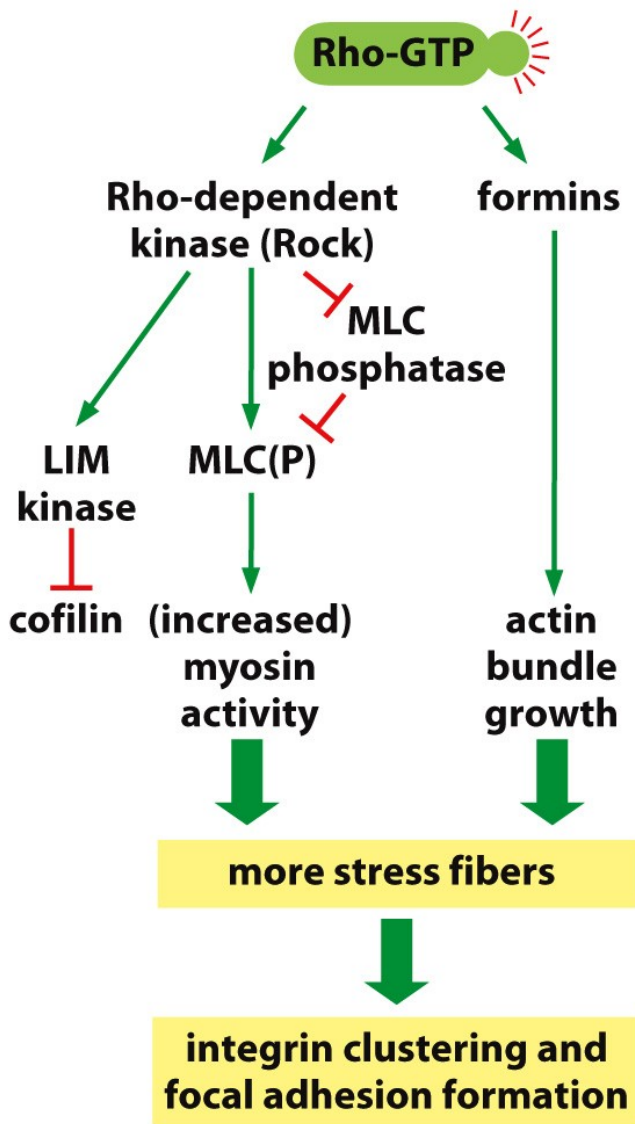


Figure 16-85b Molecular Biology of the Cell 6e (© Garland Science 2015)



# Pohyb buňky po substrátu – primární určení polarity

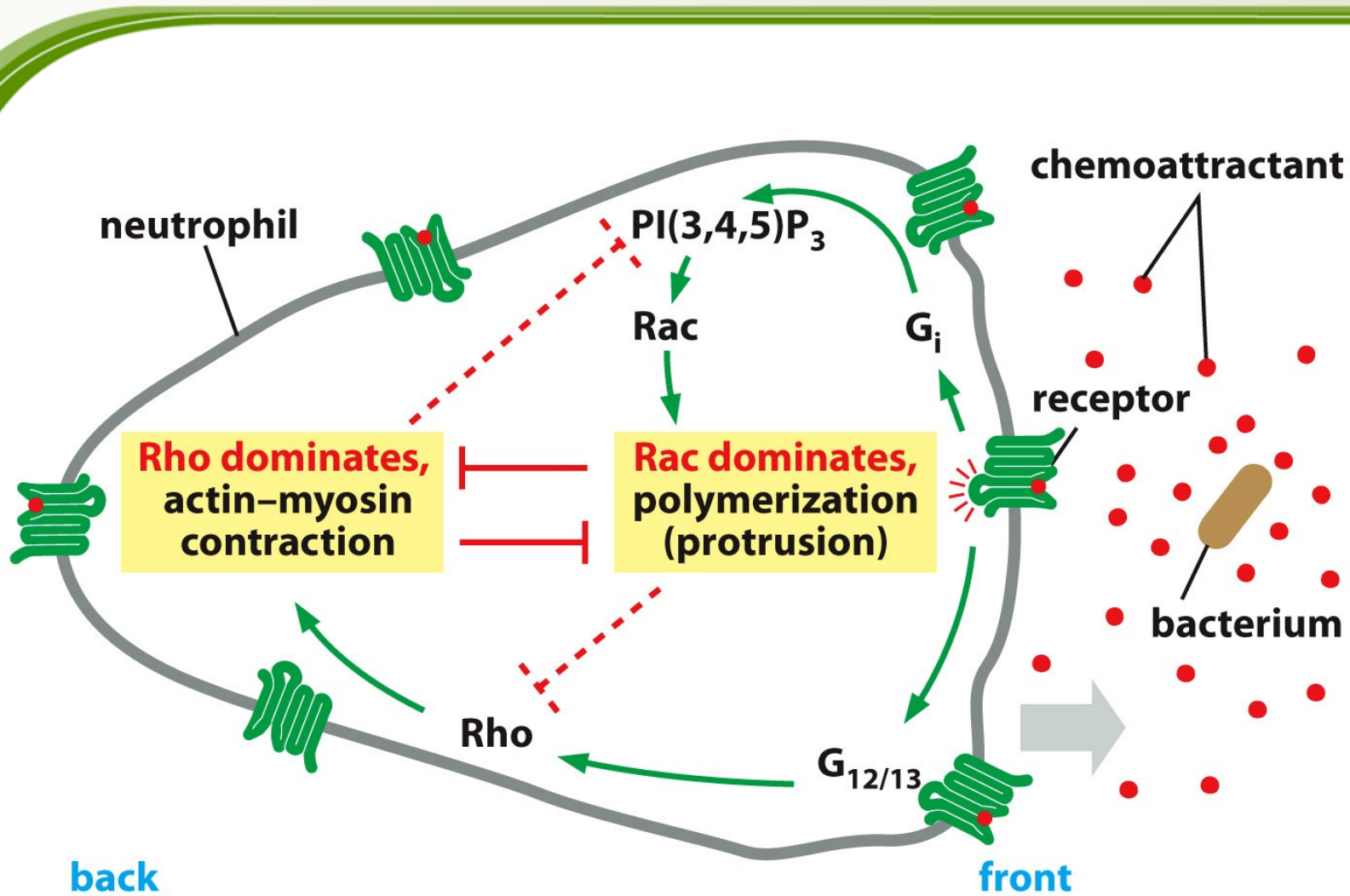


Figure 16-86b Molecular Biology of the Cell 6e (© Garland Science 2015)



# Rac1-RhoA v migraci (nejen) buněk neurální lišty

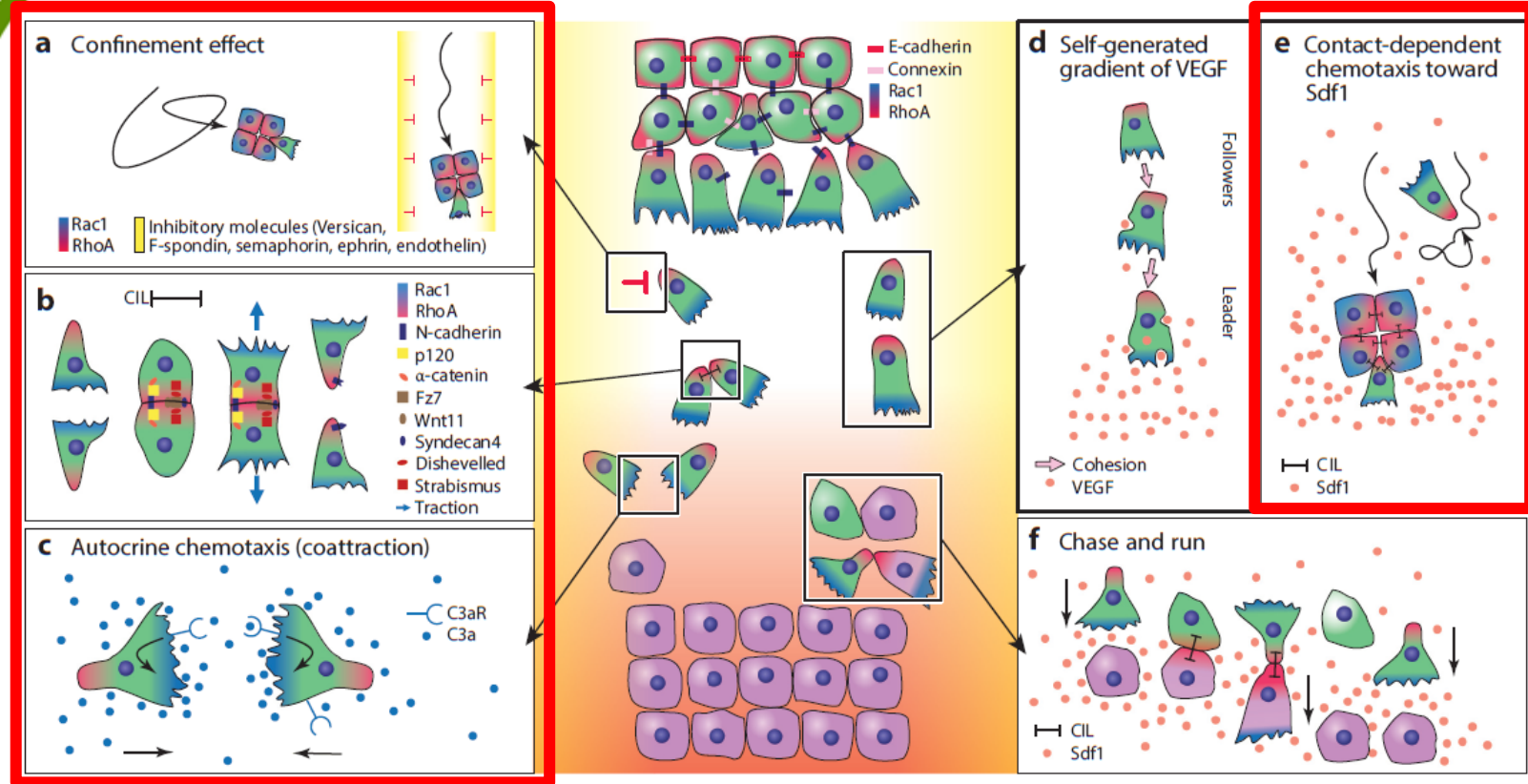


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# Vývojová biologie živočichů

