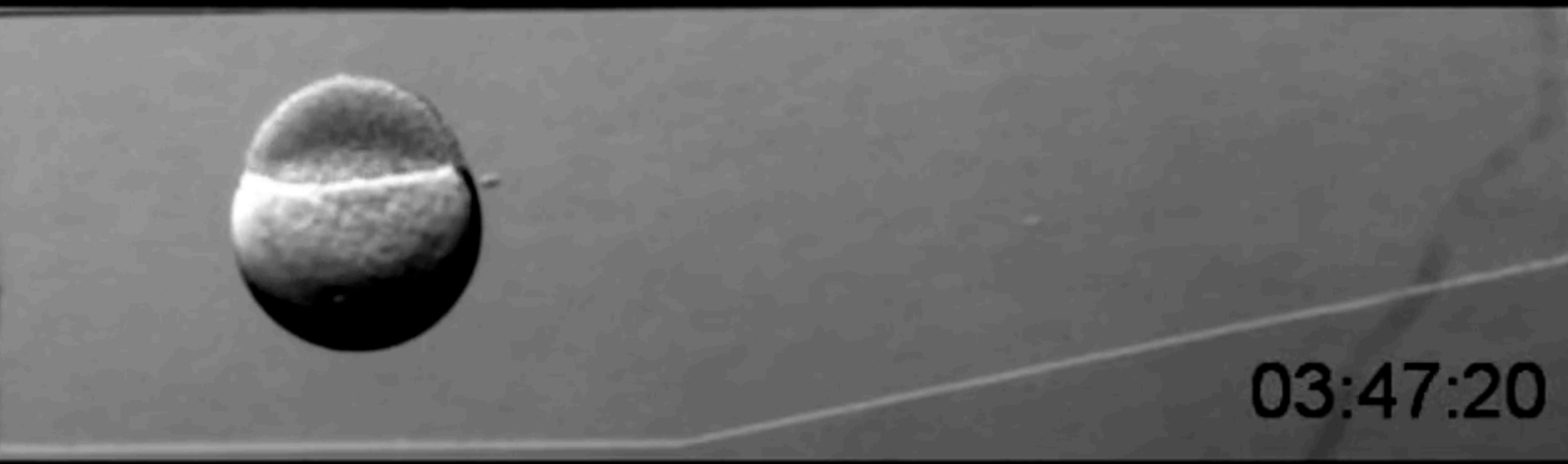
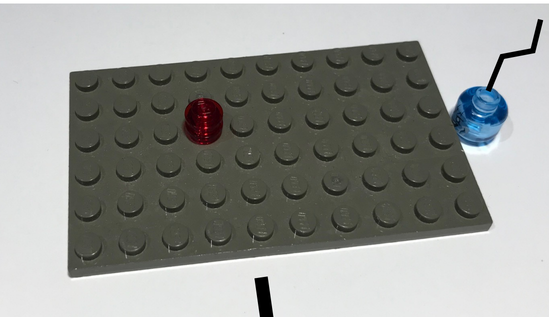
Big questions

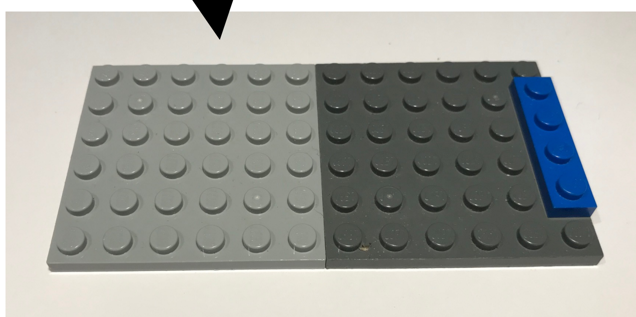


LEGO embryo - where are we?

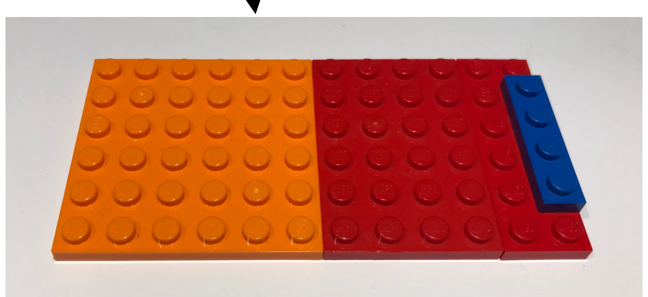
Morphogenesis: Gastrulation and folding



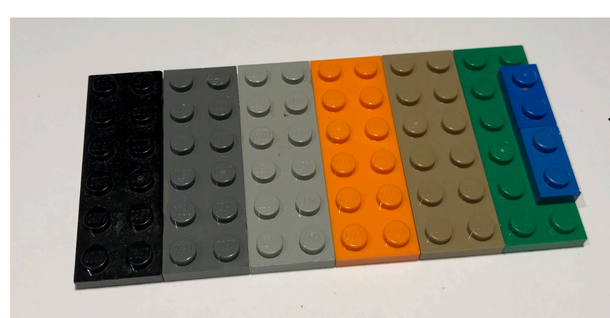
Fertilisation



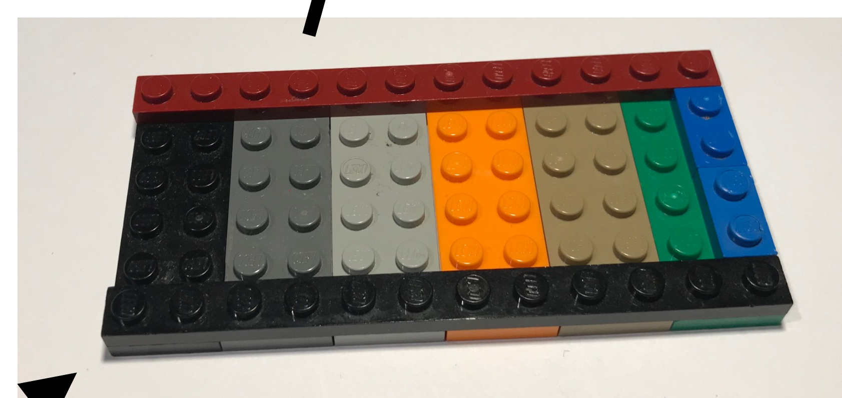
Symmetry breaking Zygote



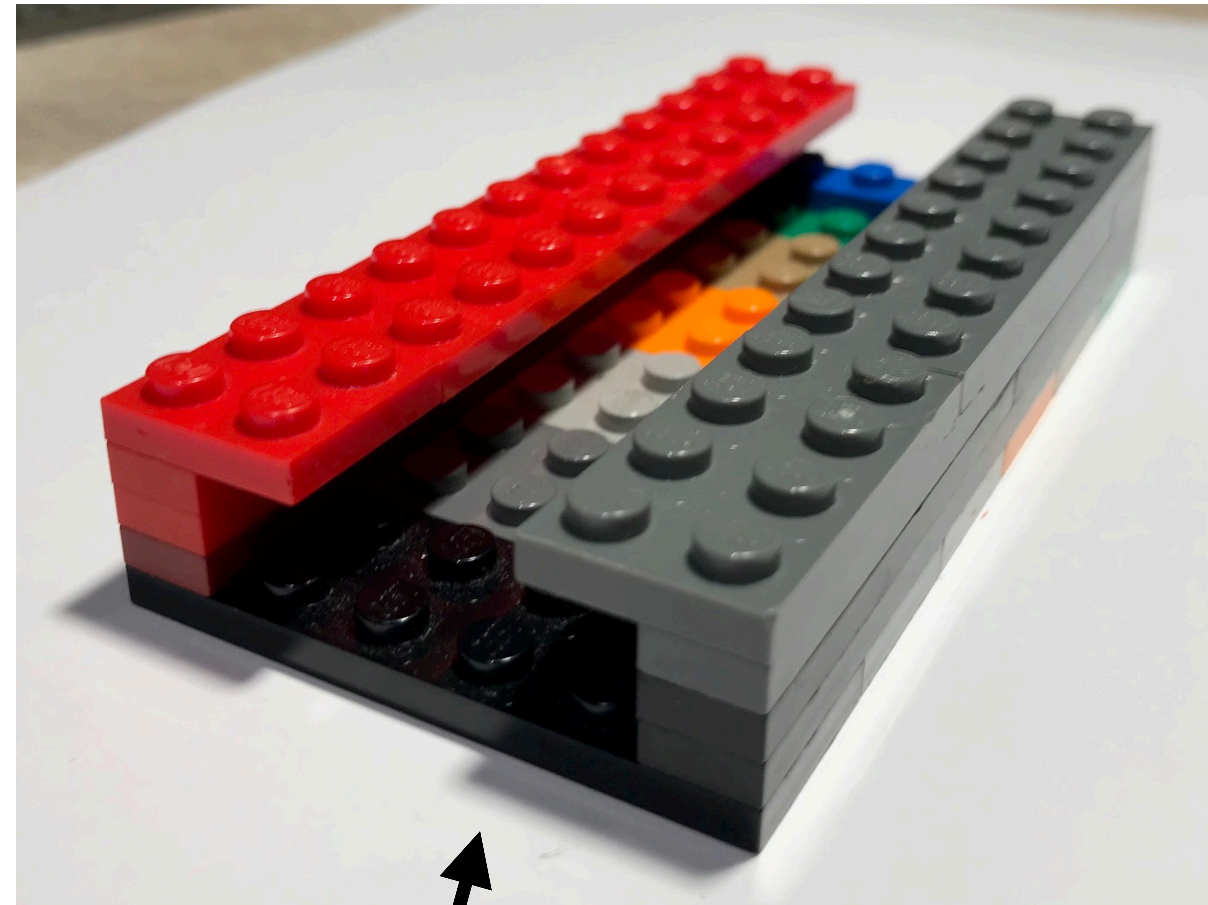
Maternal-to-Zygotic transition



Early patterning A-P axis



D-V and L-R axes

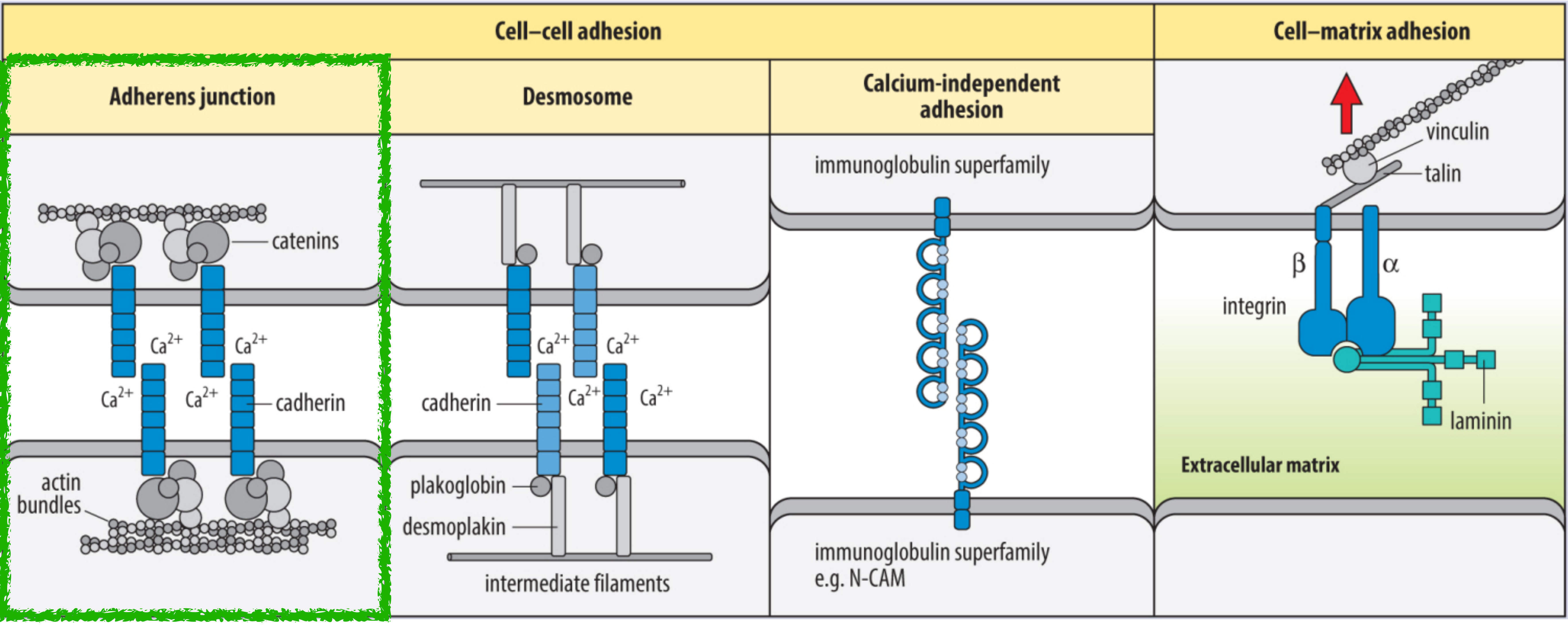


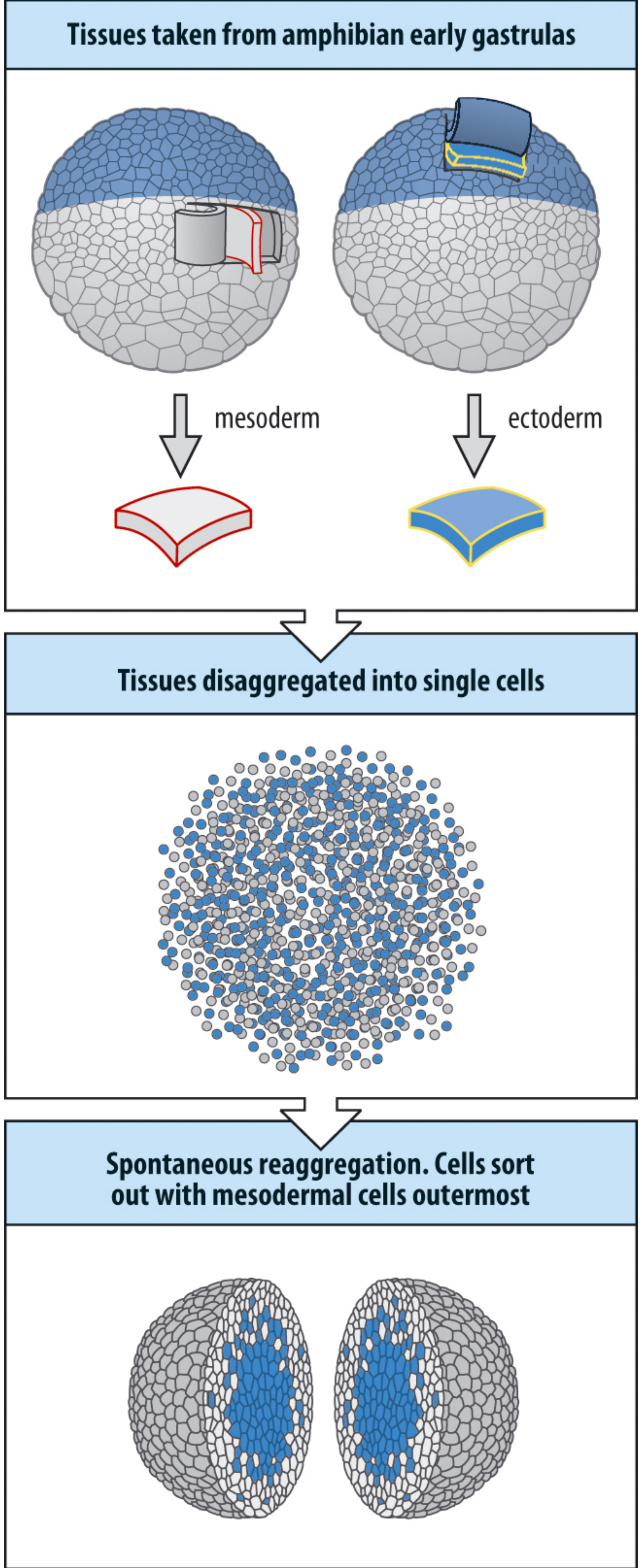
Today’s menu

- **Morphogenesis**
- Basic mechanisms
- Cell-cell Adhesion
- Actin and myosin
- Oriented cleavage and blastula

- **Gastrulation and folding**
- EMT, migration
- Bending the sheet
- Cell rearrangement in the sheet - convergent extension
- Other folding - brains and guts

Cell-cell and cell-matrix adhesion systems





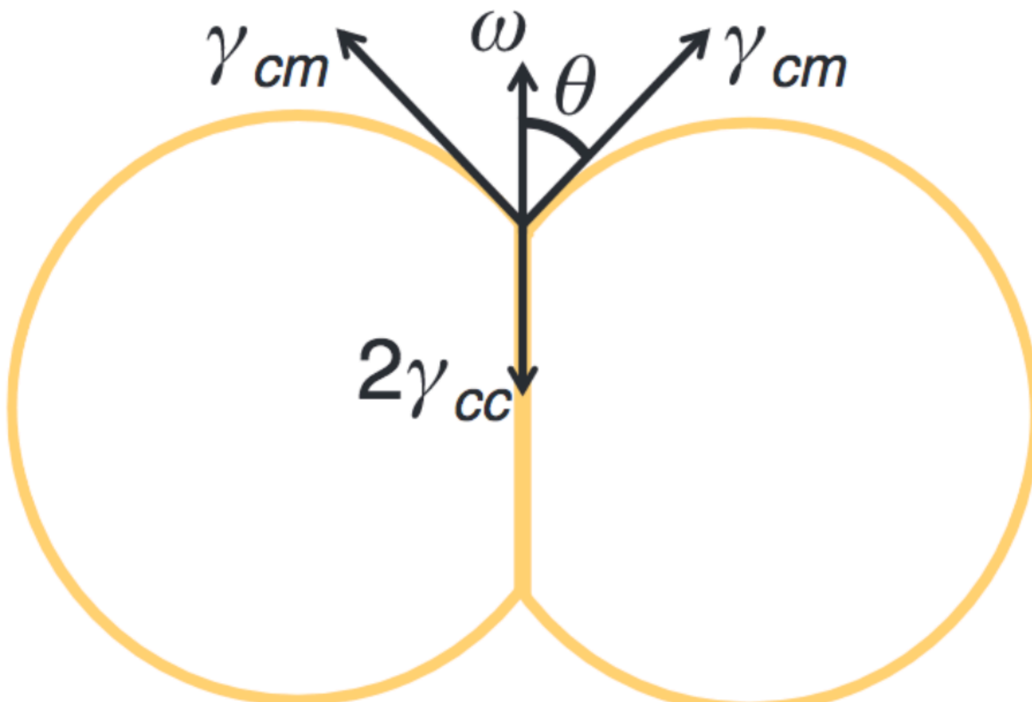
Cell sorting driven by differential surface tension and differential adhesion

N-cadherin

E-cadherin

- Surface tension: oil-water
- Surface tension modified by adhesion
- Cells with strongest interactions form inner layer

Balance of forces at contact point



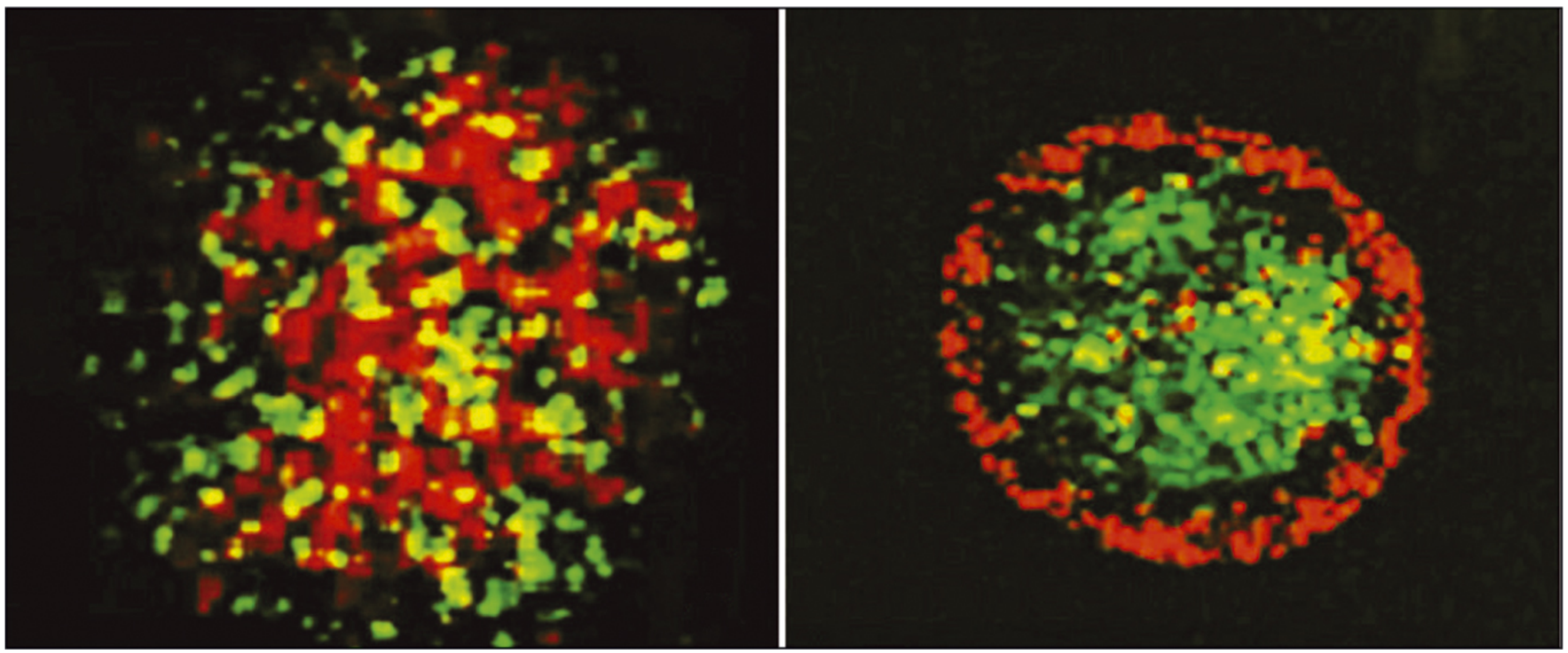
$$\cos\theta = \frac{2\gamma_{cc} - \omega}{2\gamma_{cm}}$$

- Tension from cortex contact with medium (γ_{cm})
- Tension from cortex contact with cell (γ_{cc})
- Tension from adhesion between cells (ω)

Maitre et al,. 2012

Individual puzzle

Cadherin *type* and *level* can drive cell sorting



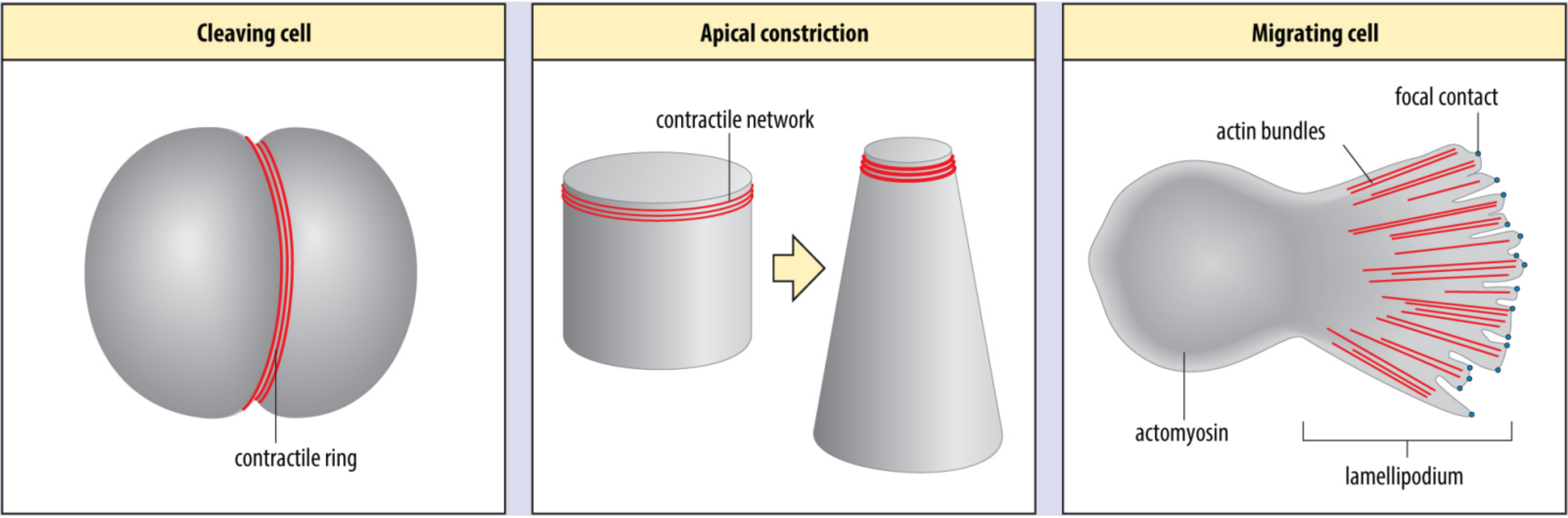
Early ⟶ **Late**

N-Cadherin

Cellular “building blocks” of morphogenesis

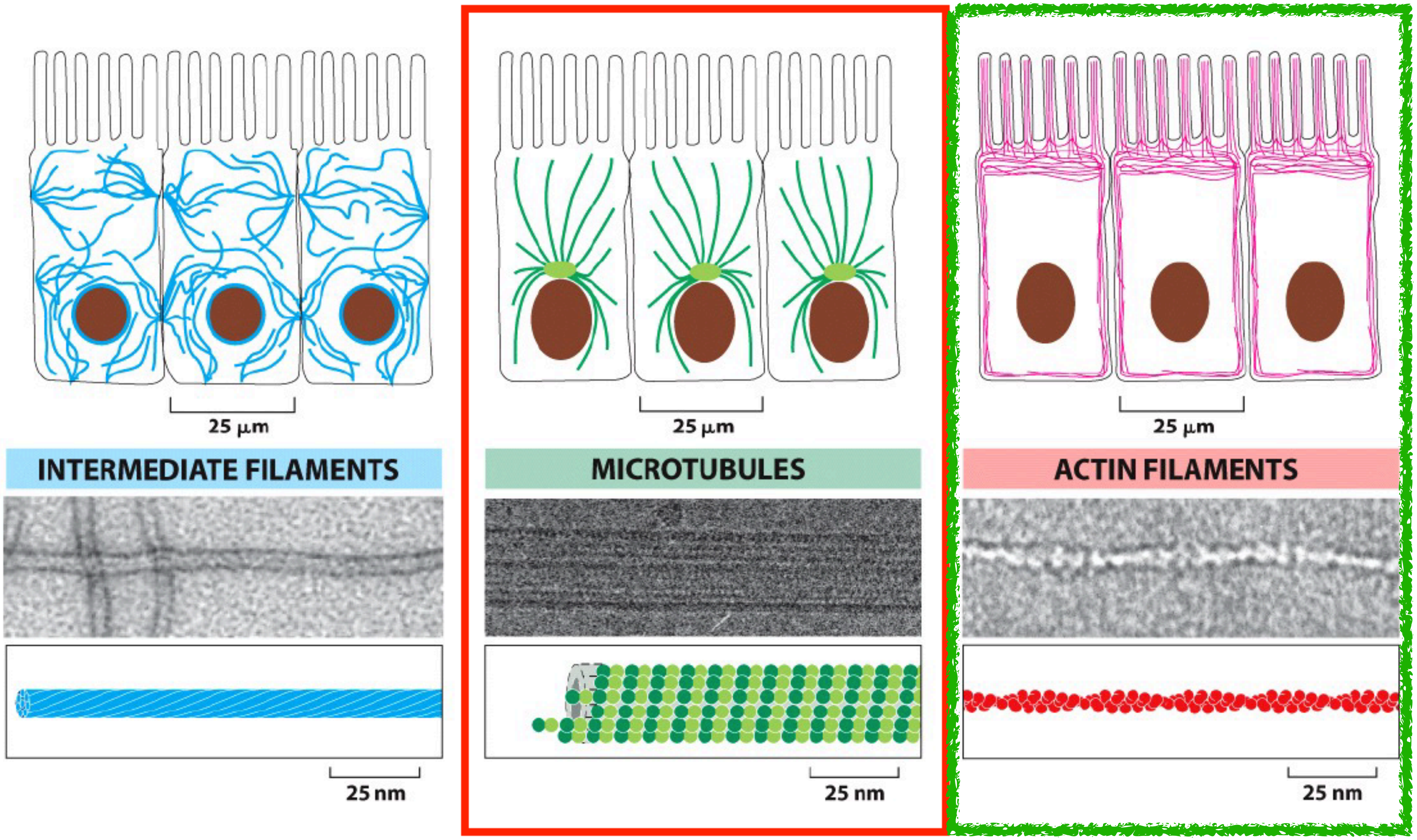
Oriented division | **Change in cell shape** | **Cell migration**

Death




KEEP
CALM
AND USE
THE
FORCE

Three principal cytoskeletal polymers



The actin polymer

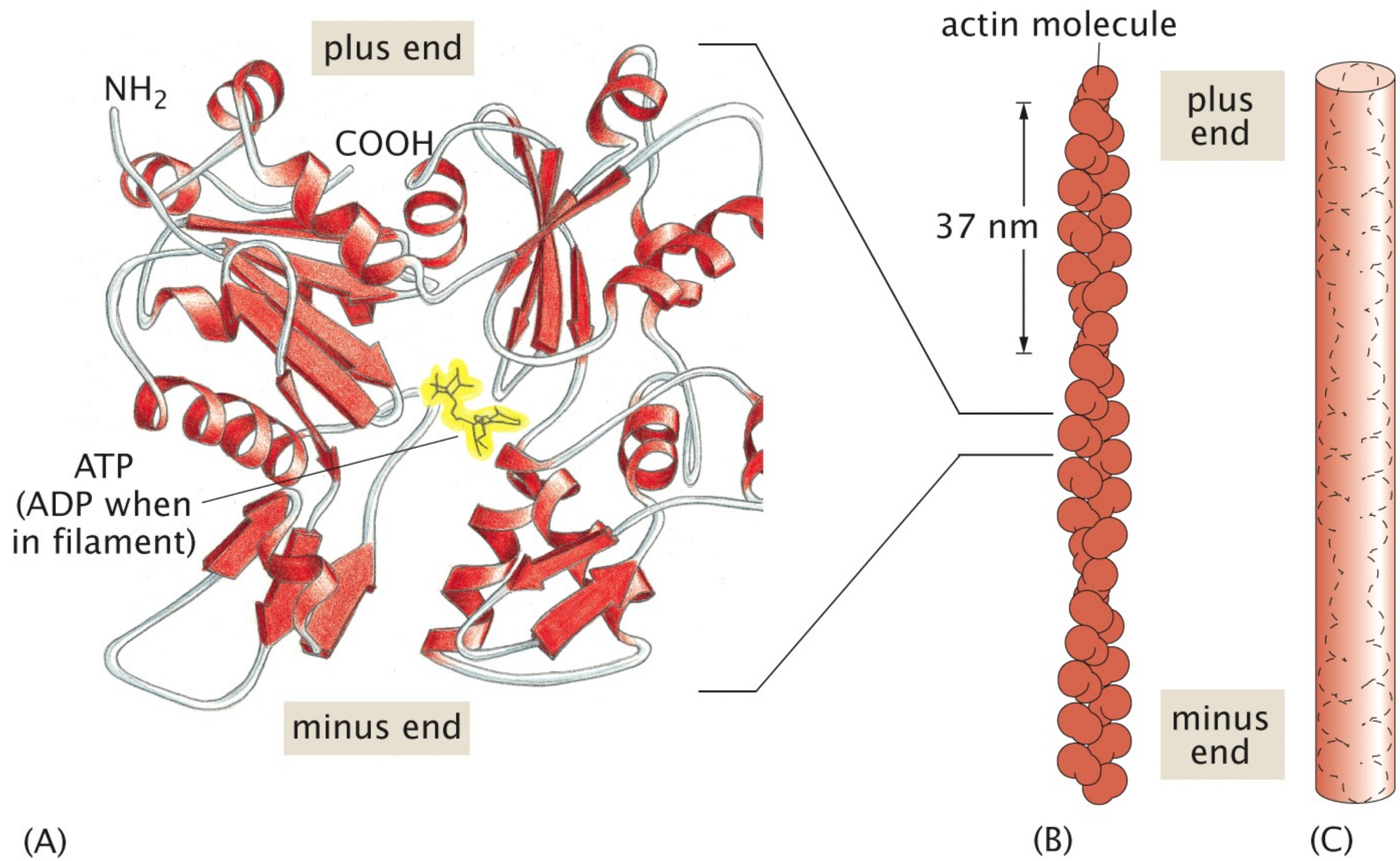


Figure 10.29 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Actin filaments are floppier than microtubules

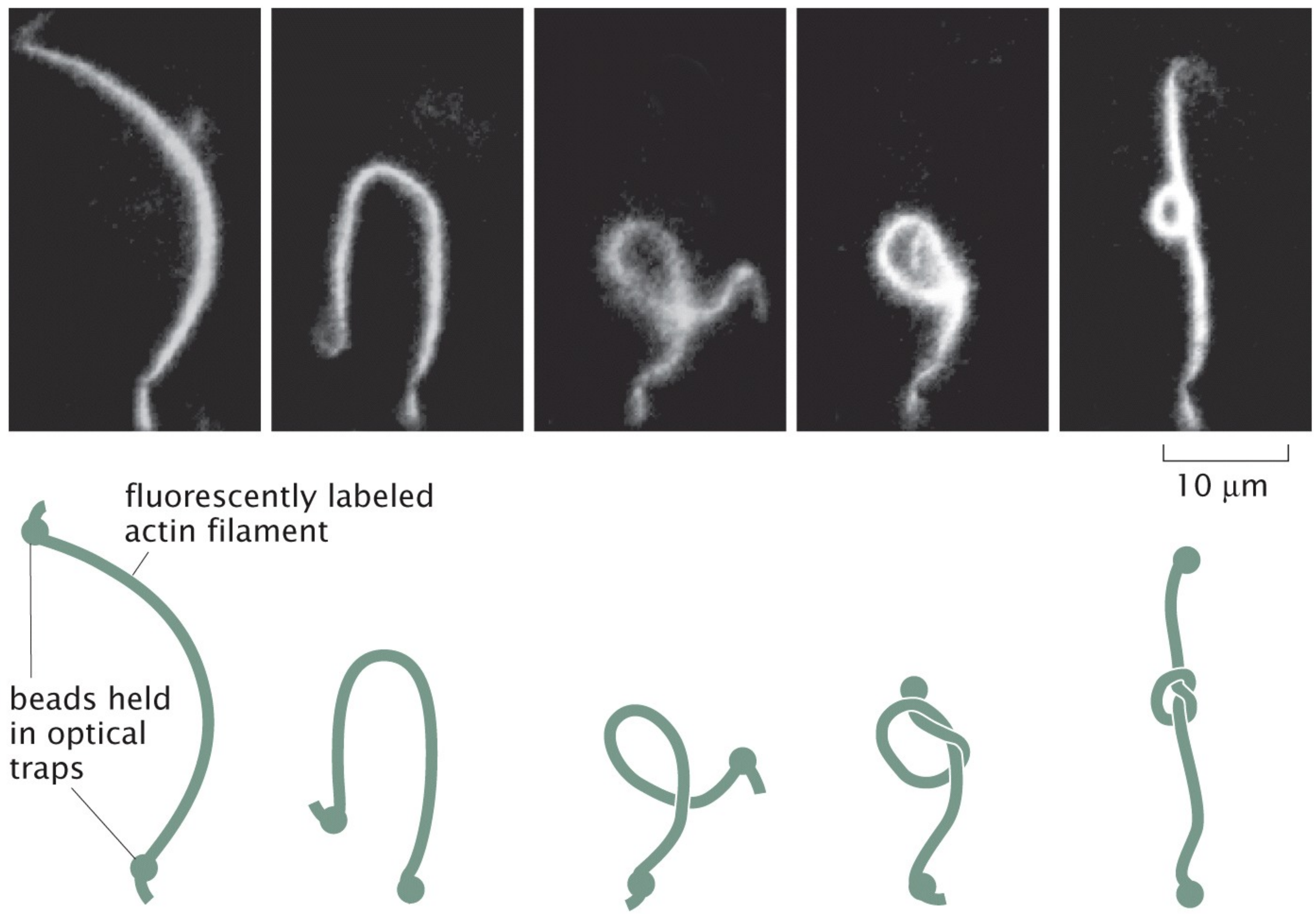


Figure 10.30 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Myosin motors walk along actin filaments

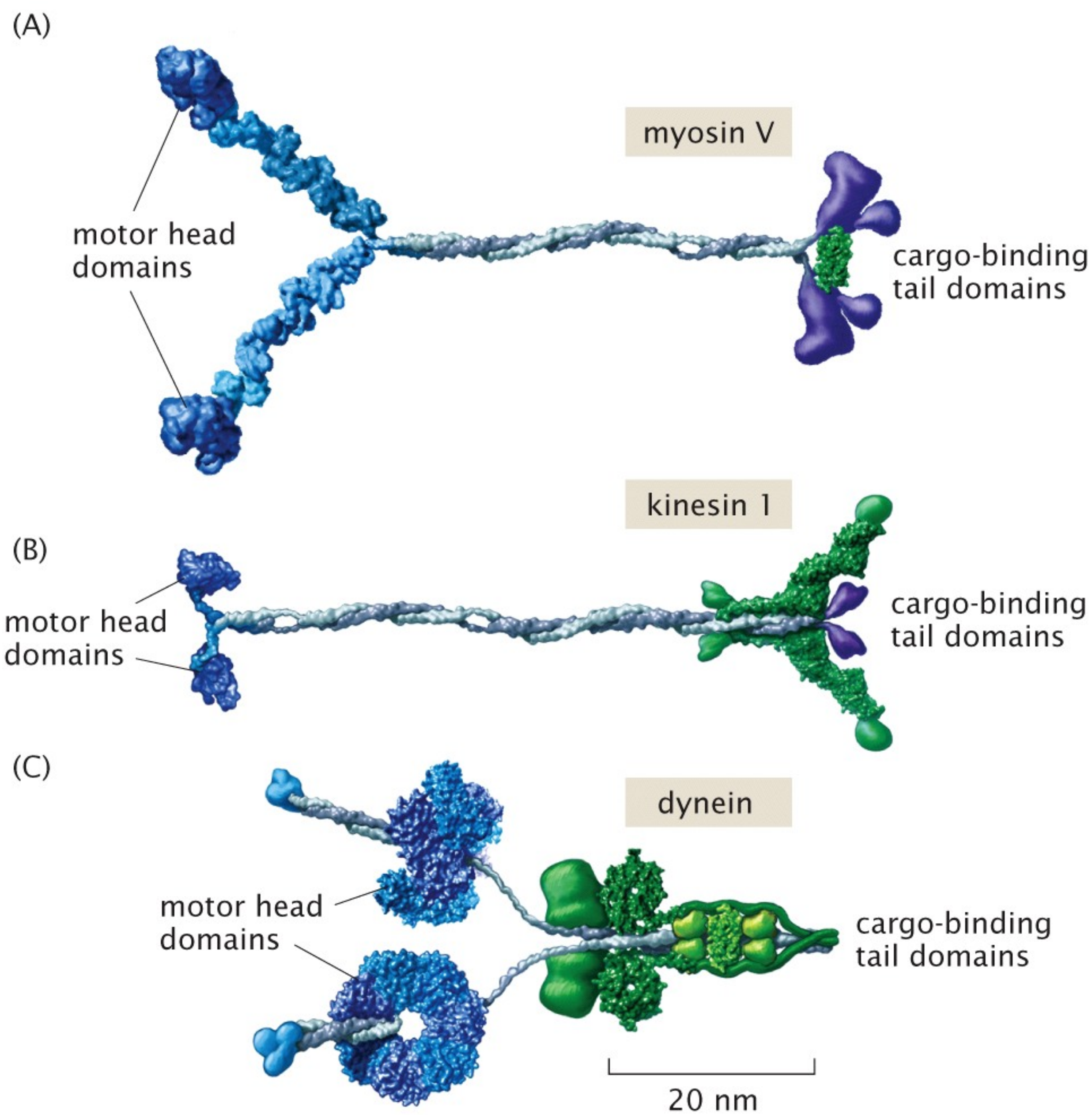


Figure 16.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Myosin II

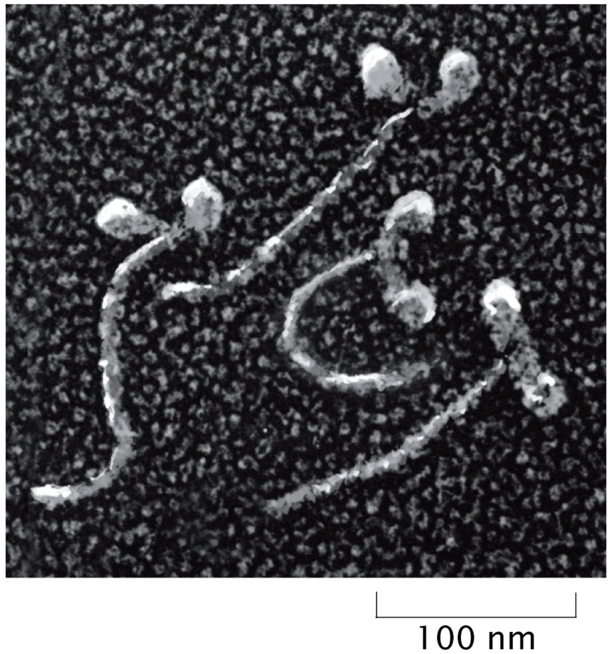
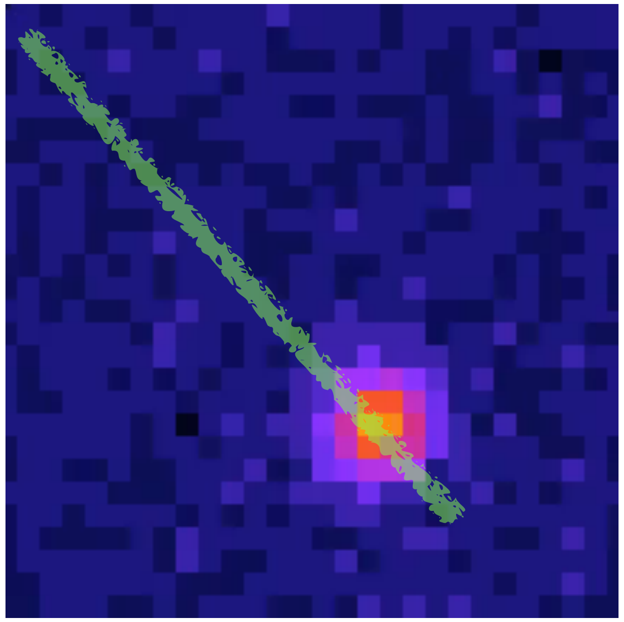


Figure 16.6b Physical Biology of the Cell, 2ed. (© Garland Science 2013)



Myosin II - Fluorescent bead

Myosin II *multimers* act to contract actin fibres

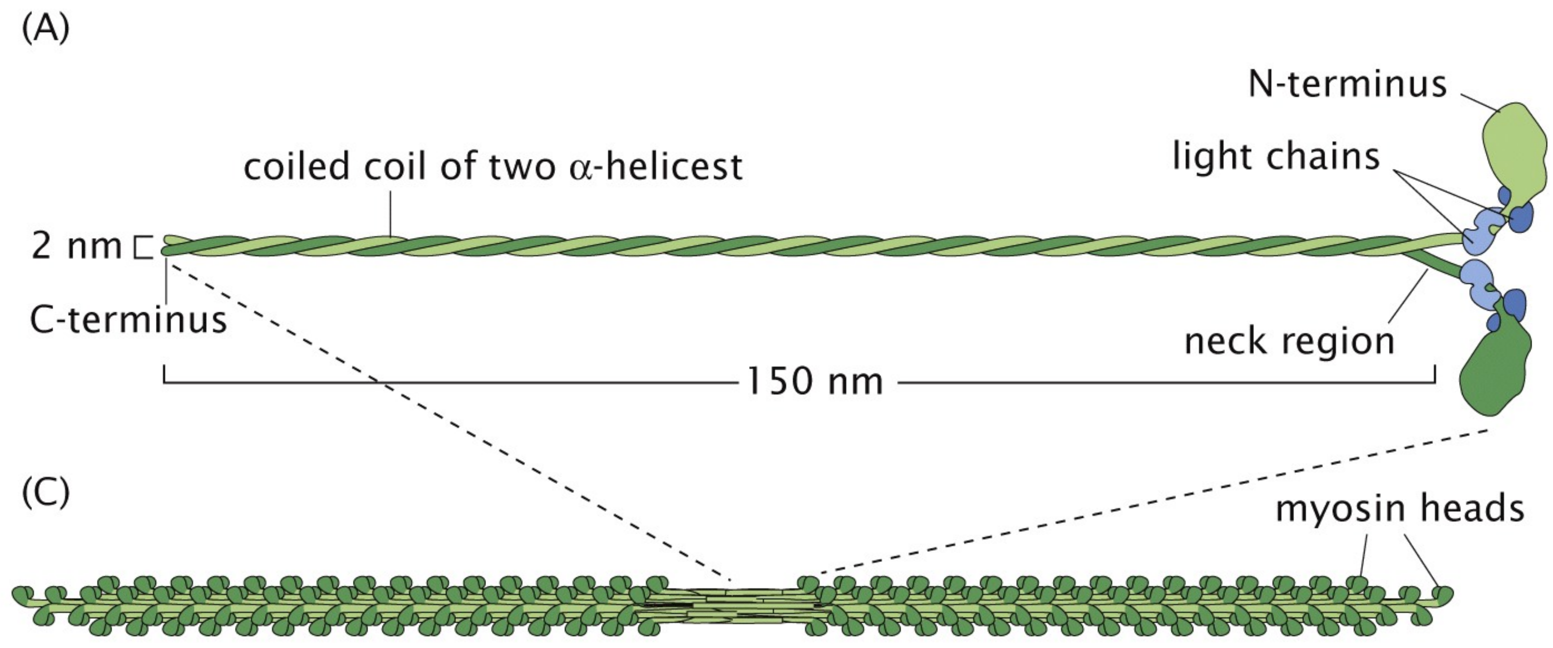


Figure 16.6ac Physical Biology of the Cell, 2ed. (© Garland Science 2013)

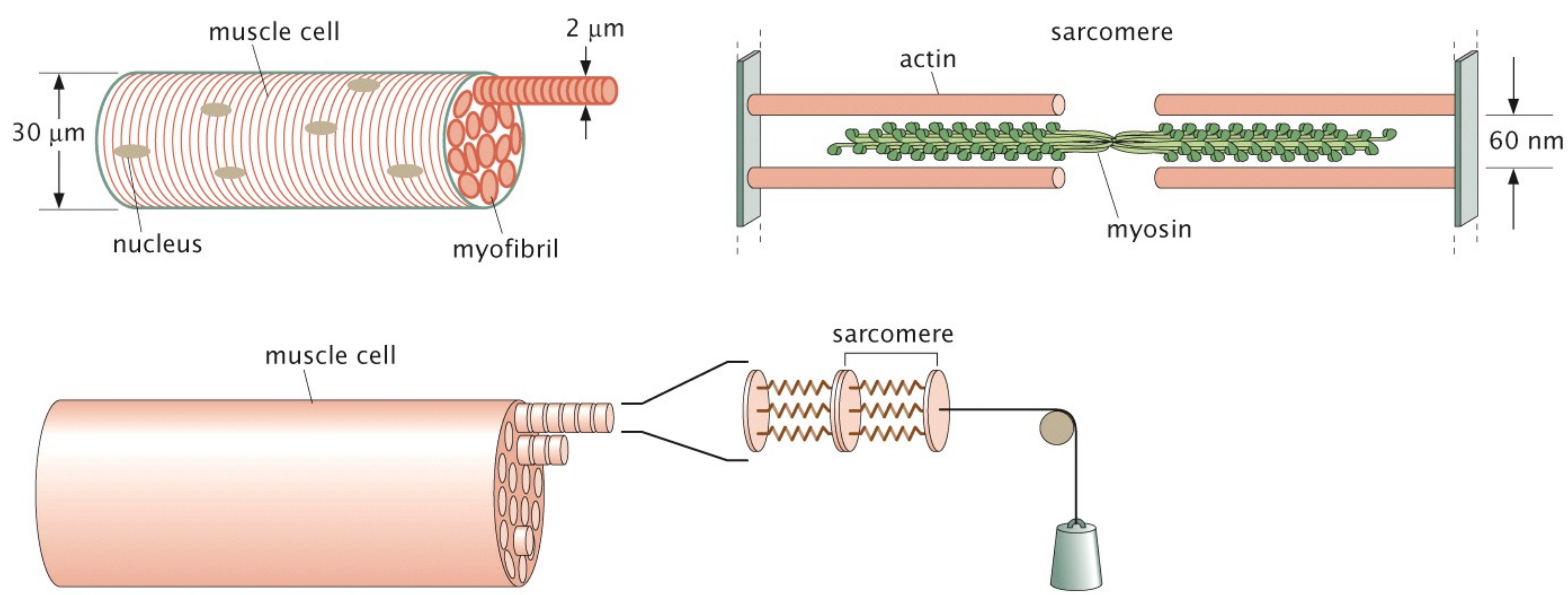
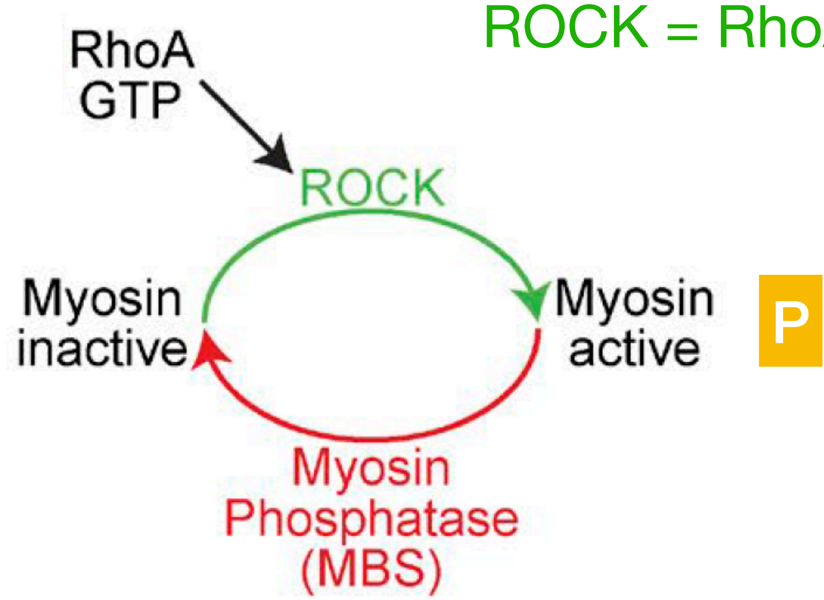


Figure 16.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Myosin II *activity* regulated by phosphorylation cycle

ROCK = RhoA-associated Kinase



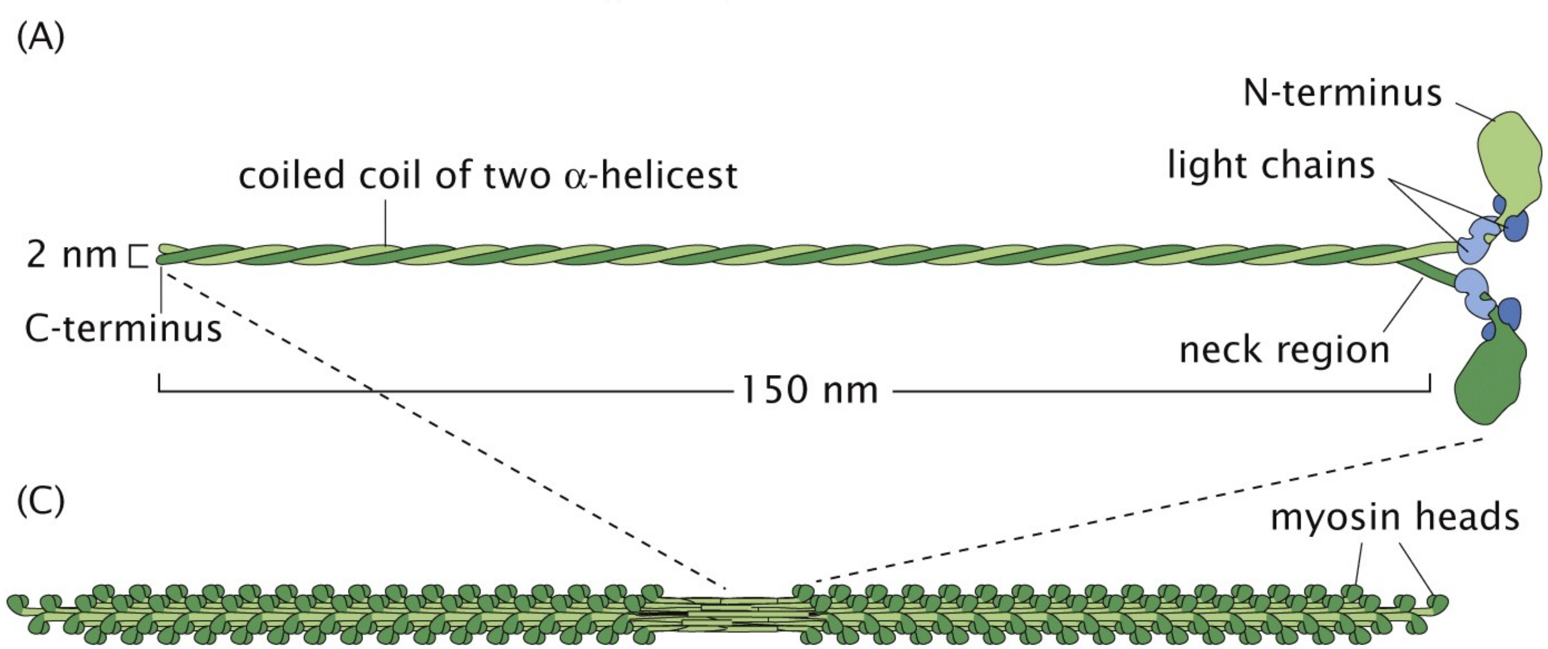
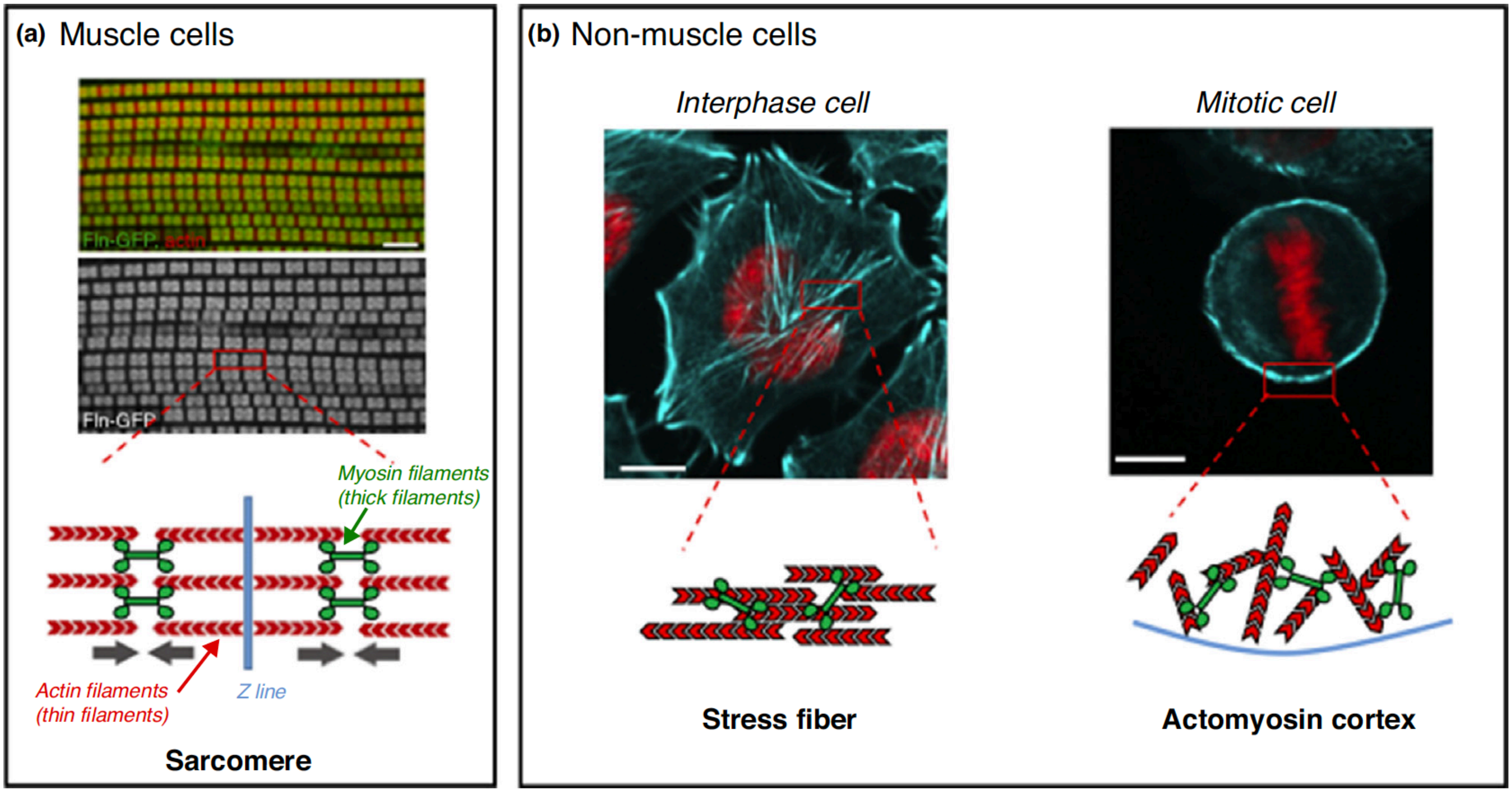


Figure 16.6ac Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Architecture of actomyosin shapes contractility

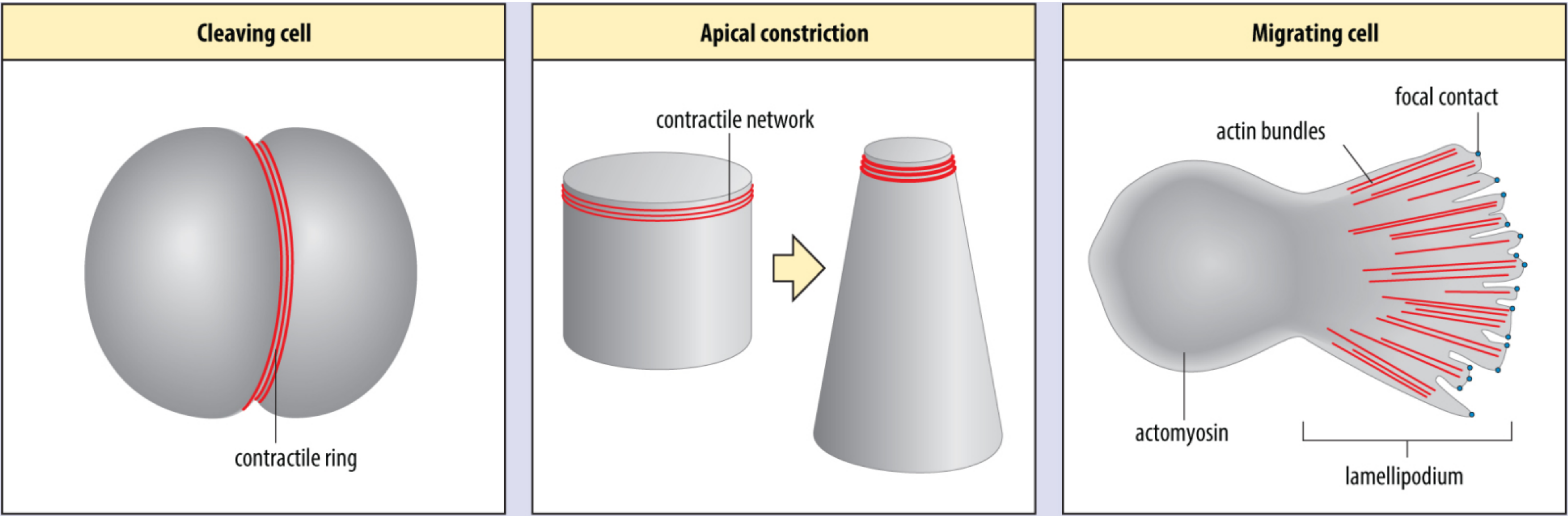


Current Opinion in Cell Biology

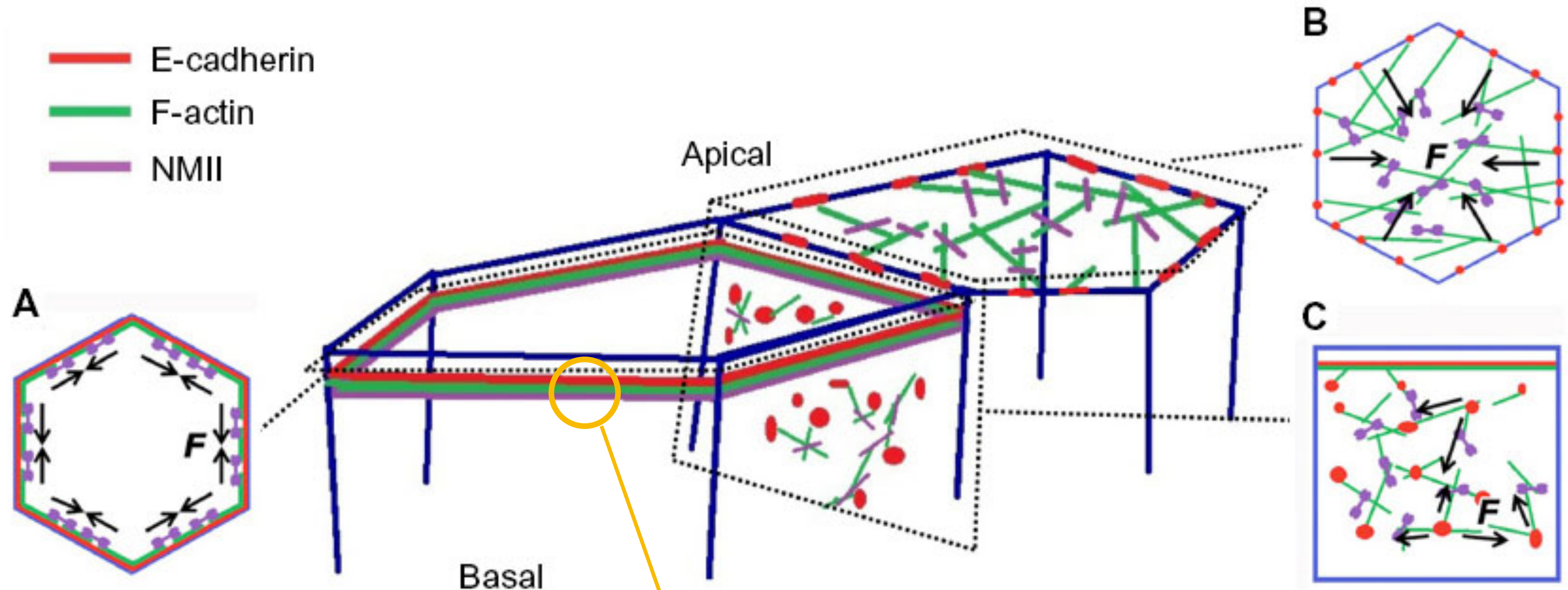
Cellular “building blocks” of morphogenesis

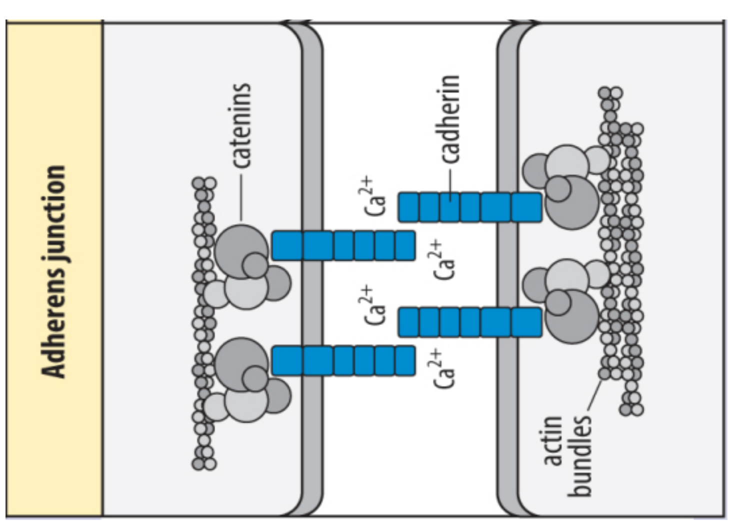
Oriented division | **Change in cell shape** | **Cell migration**

Death



Epithelial structure and actomyosin activity

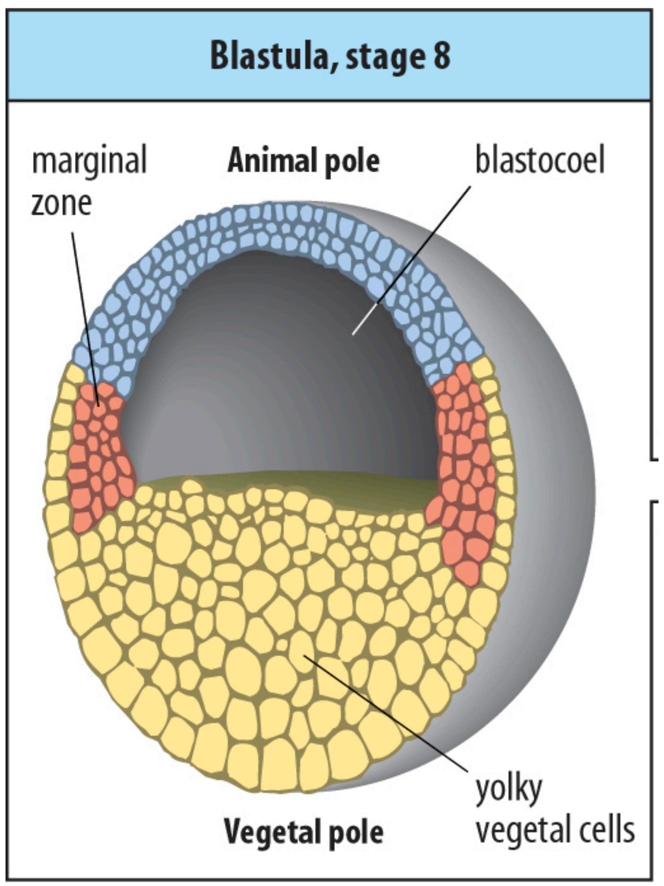


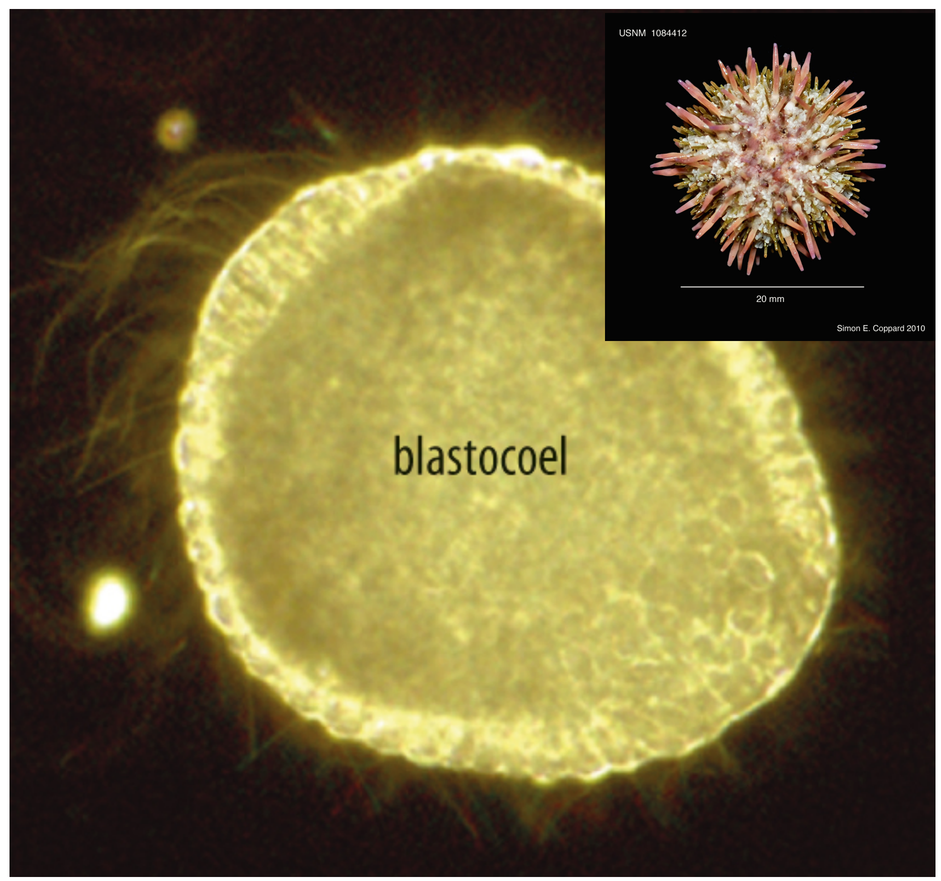


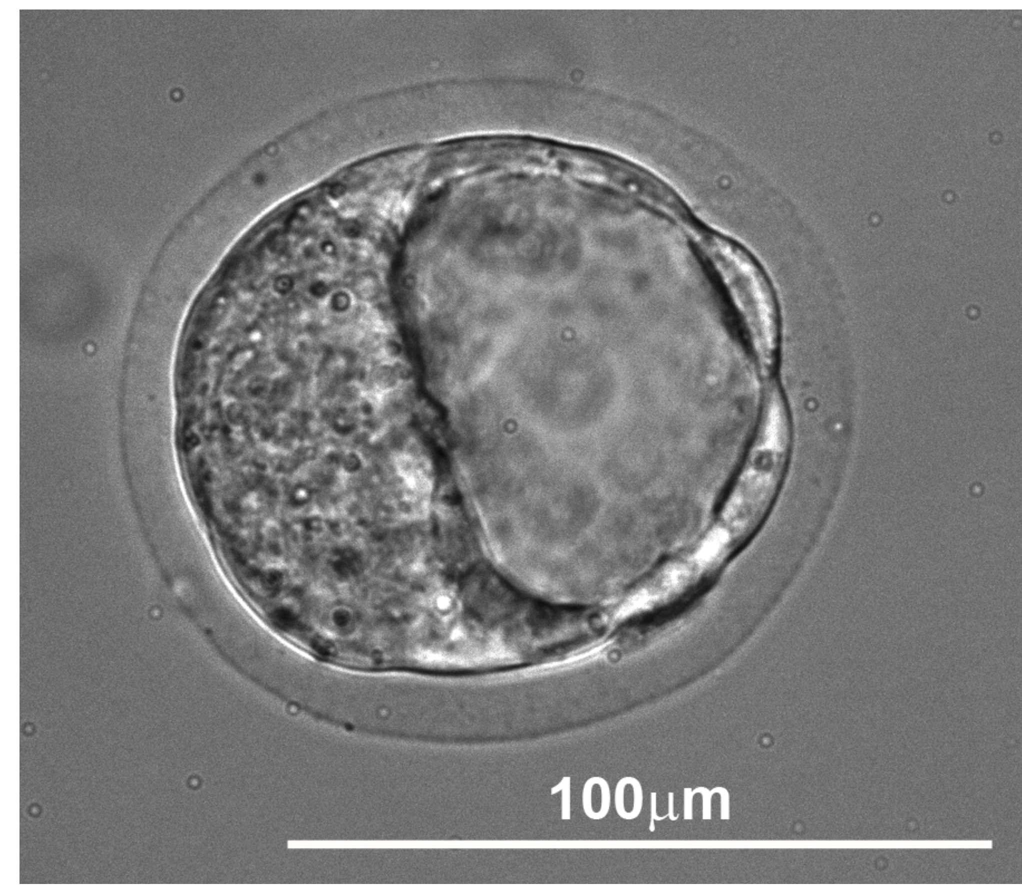
Epithelium often modelled as 2D network

Liang, Gomez, Yap 2014

Oriented cleavage and formation of the blastula







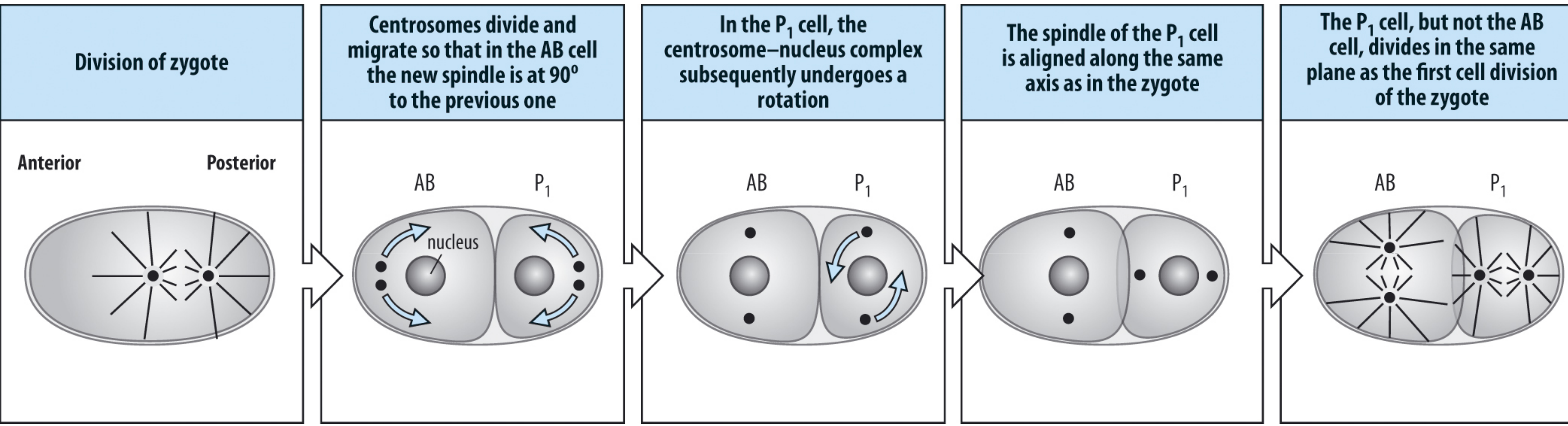
***Xenopus* embryo**

Sea-urchin embryo

50 microns

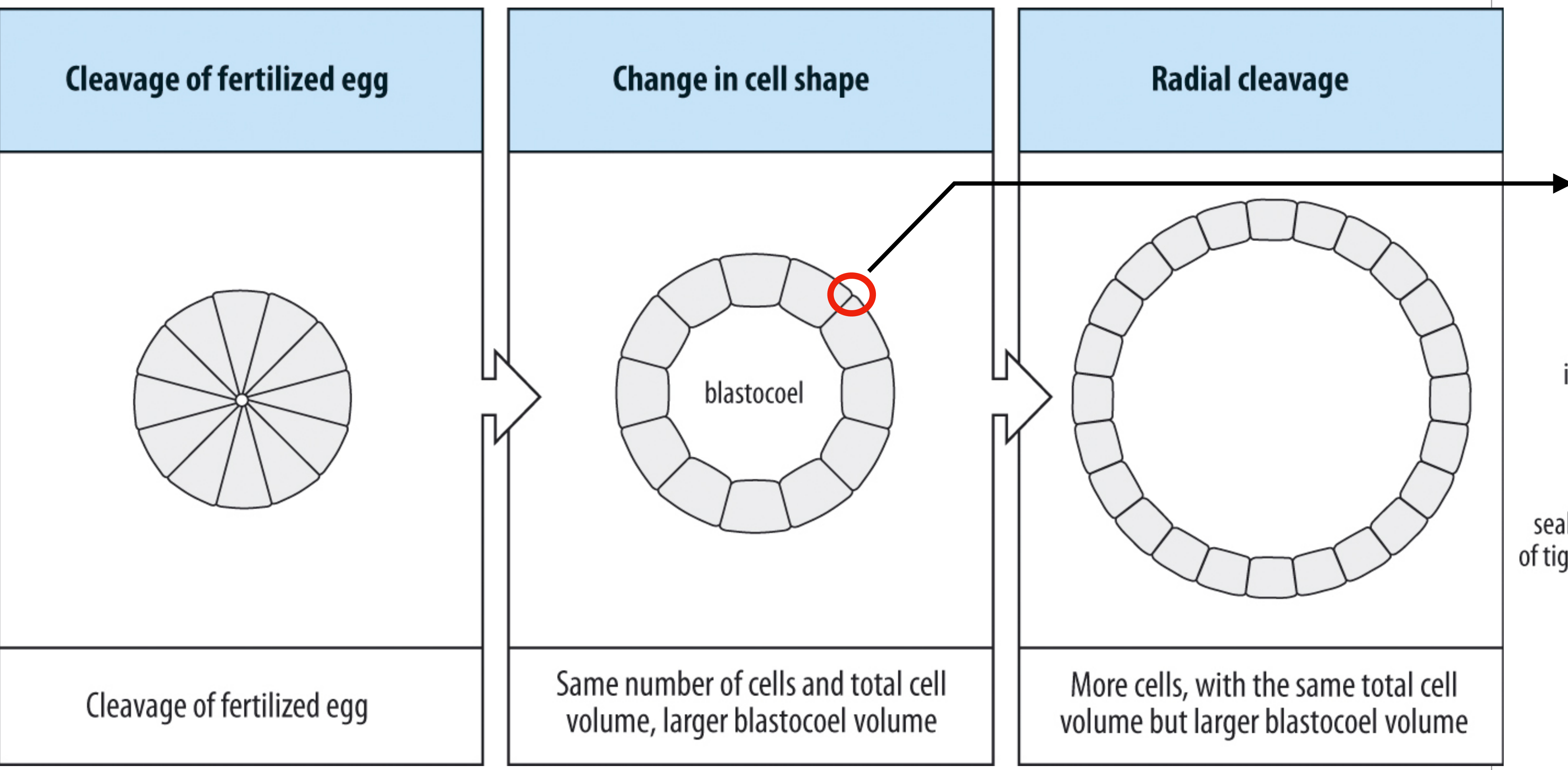
Mouse embryo

Reminder - Spindle position controls orientation of division

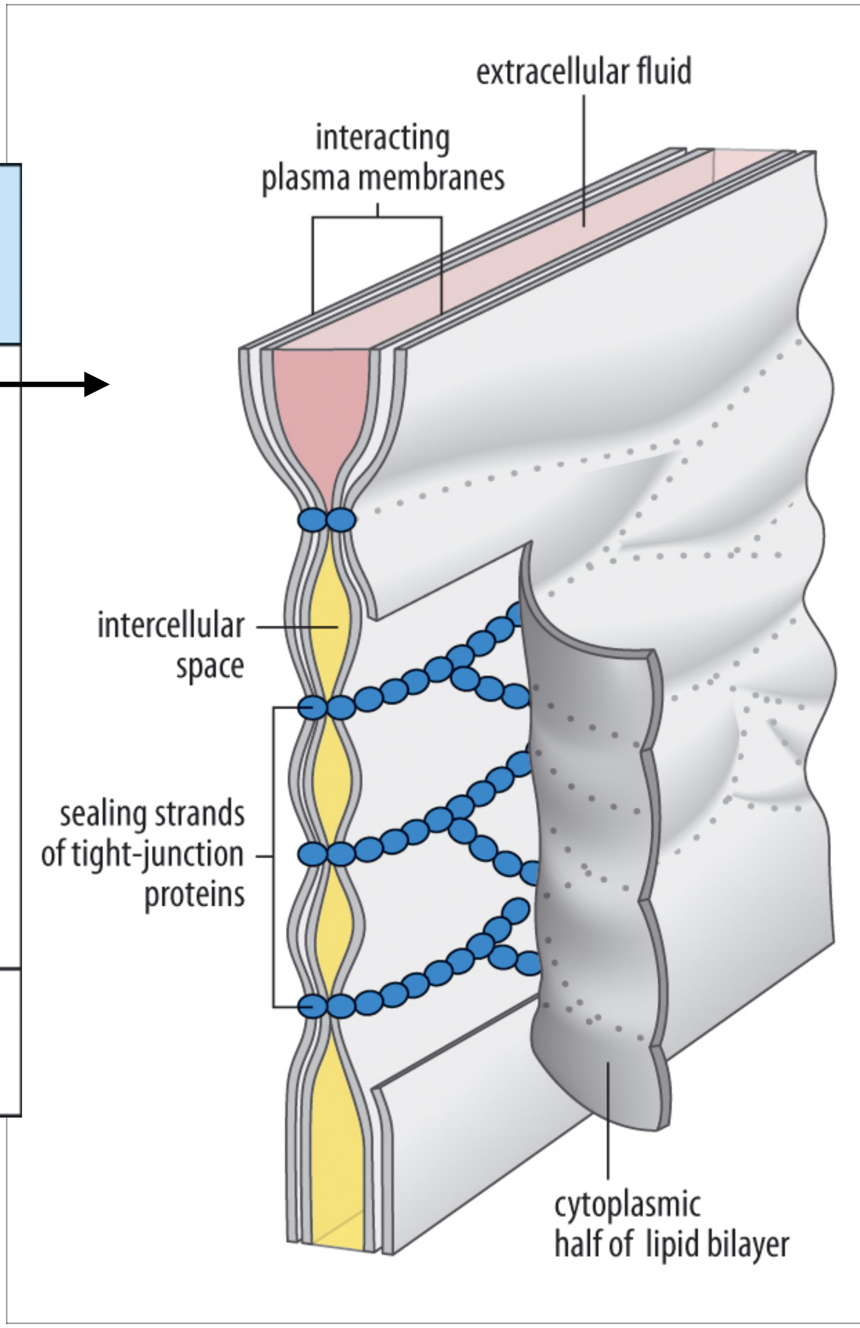


Signals for spindle positioning - interaction of cortex and spindle MT asters, +???

Version 1. Sea urchin



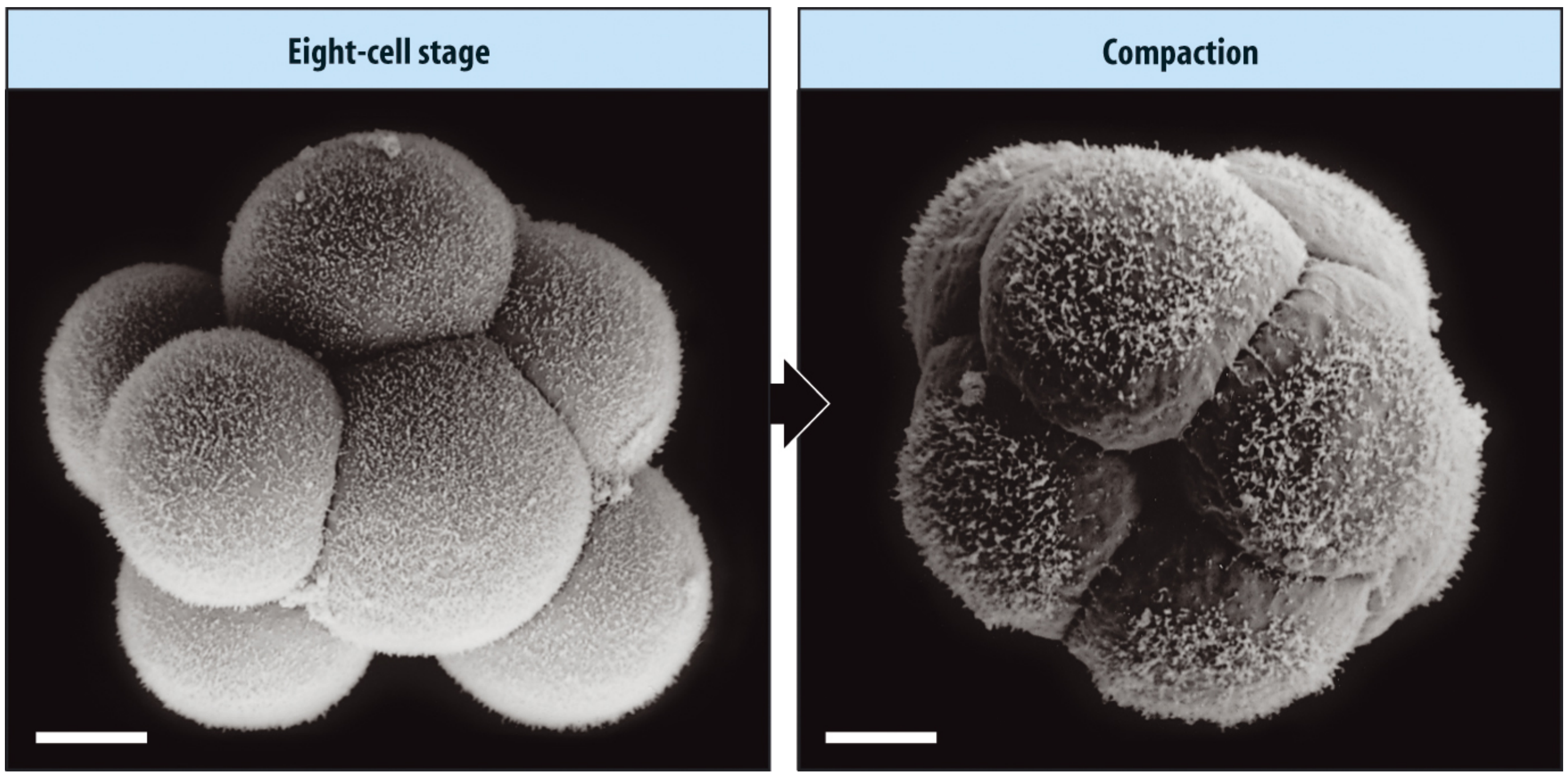
Septate junctions / Tight junctions

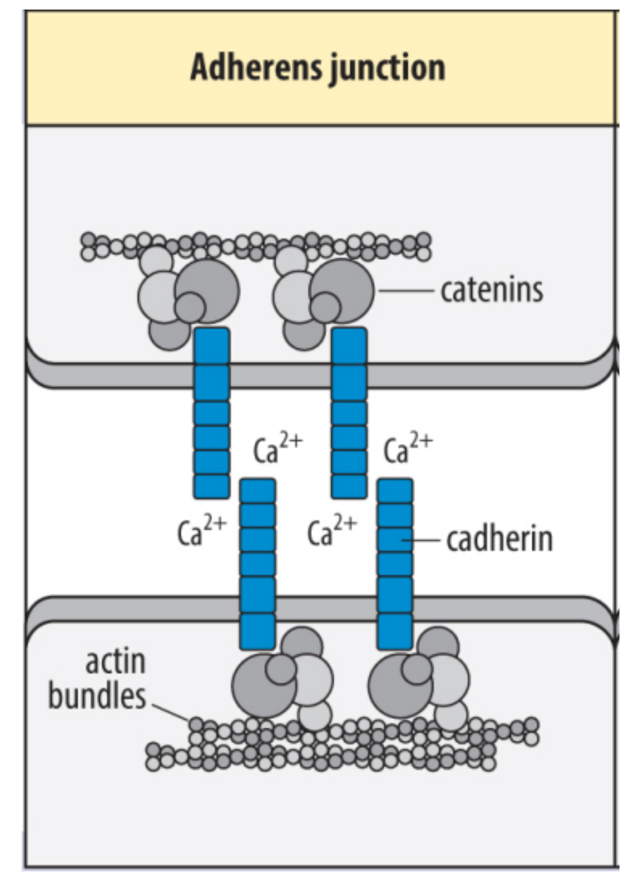


membrane-spanning:
E-cadherin
+ Claudin, Occludin

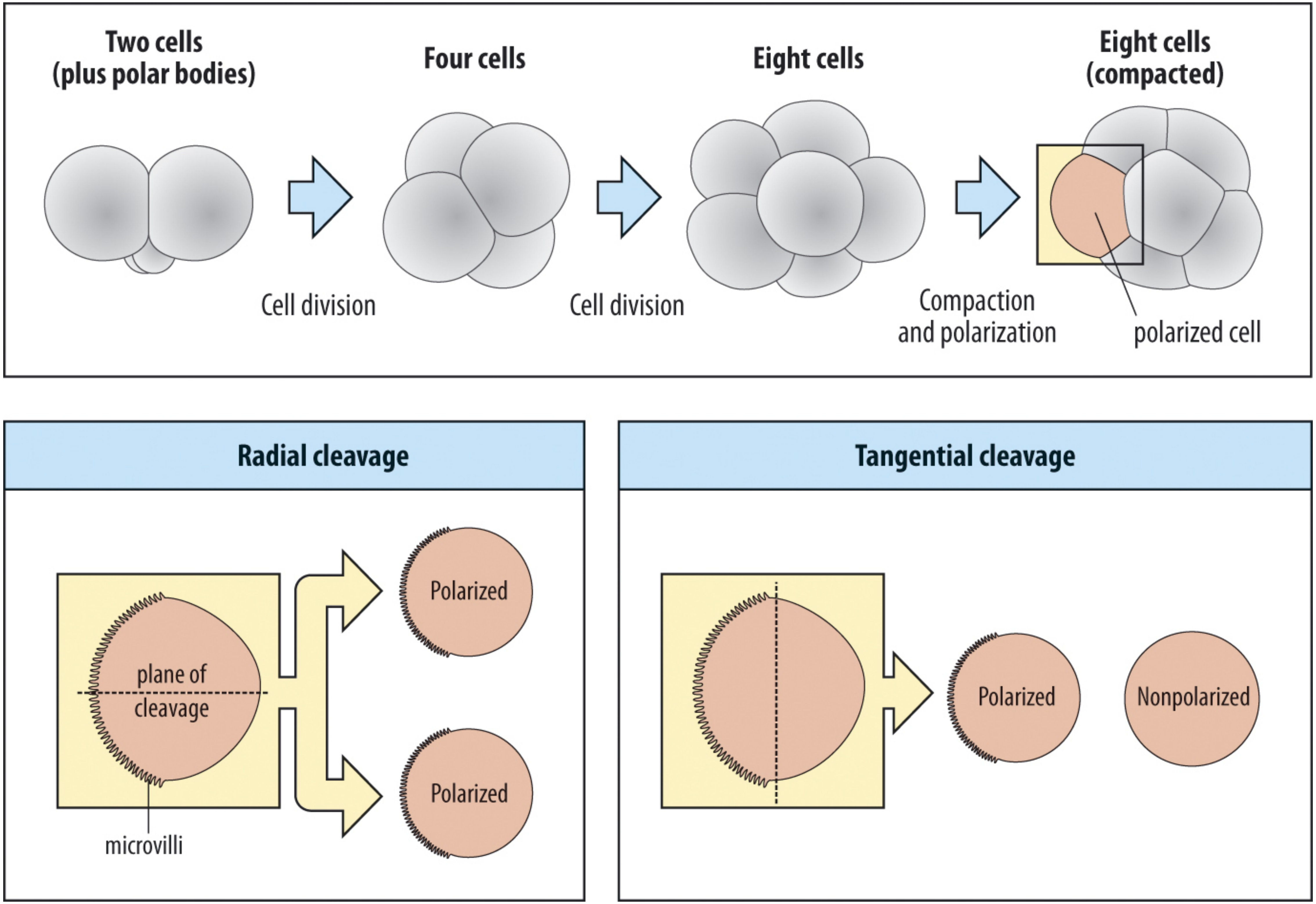
We will return to the sea urchin in part 2

Version 2. Mouse

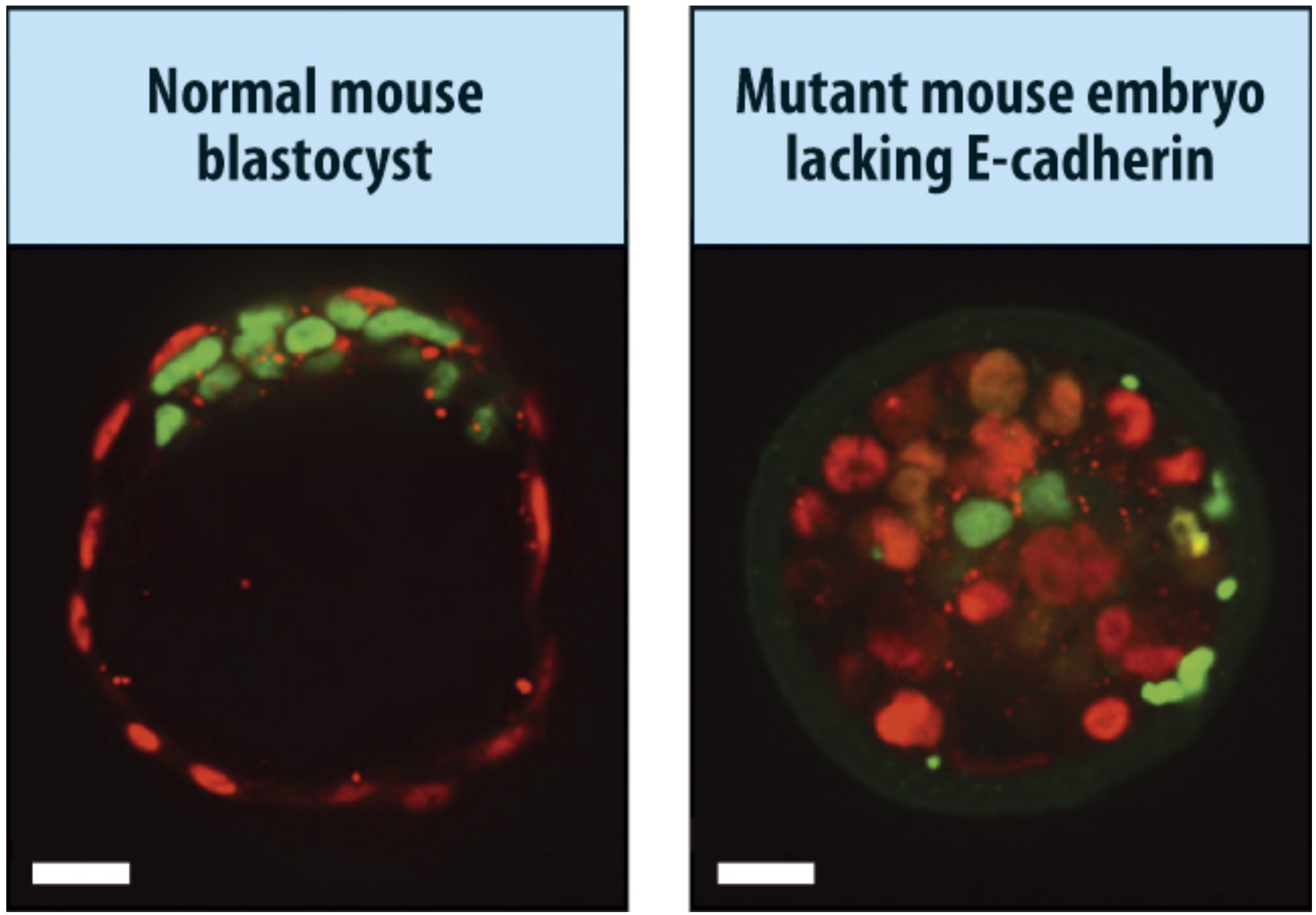




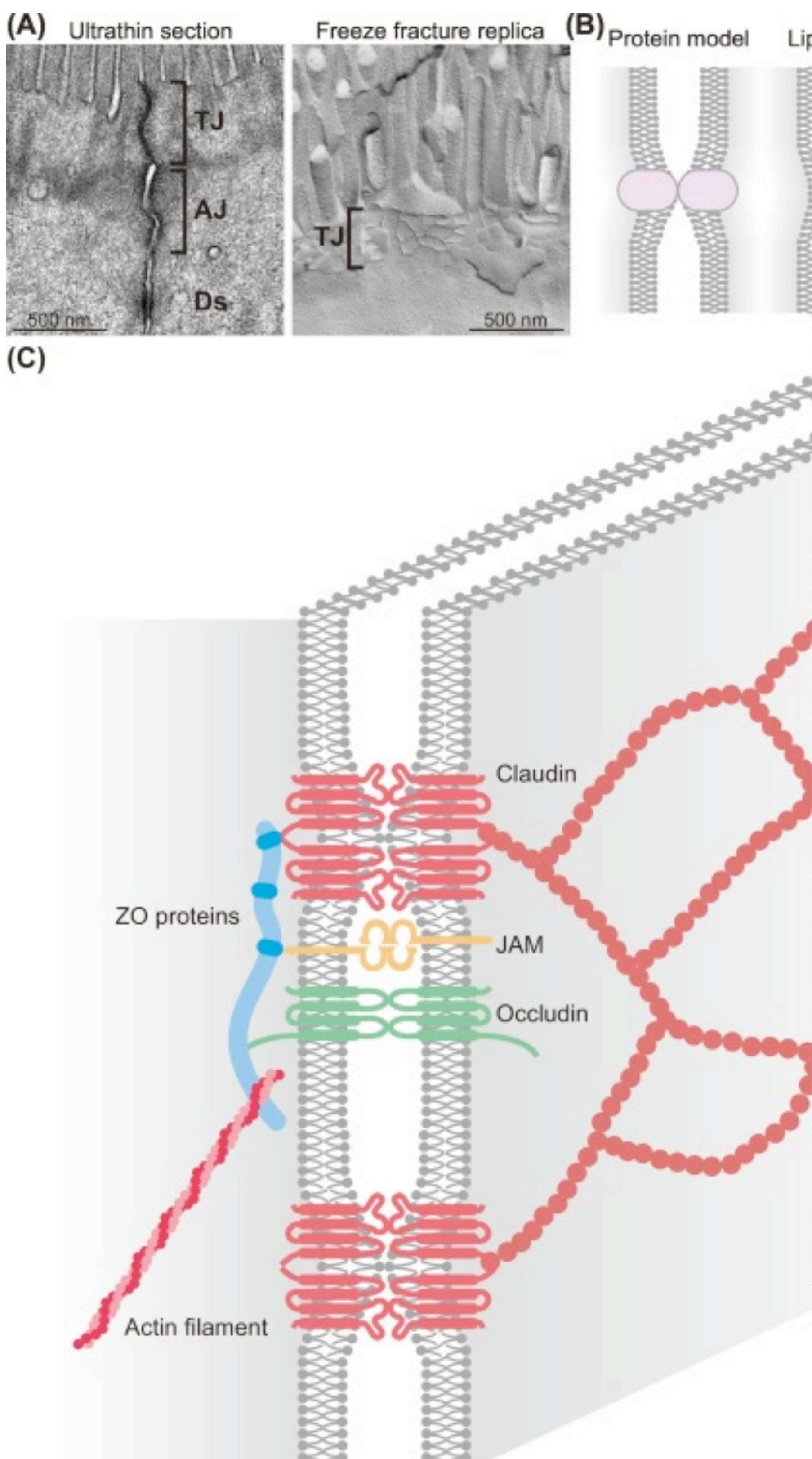
Consequence of changing cleavage orientation

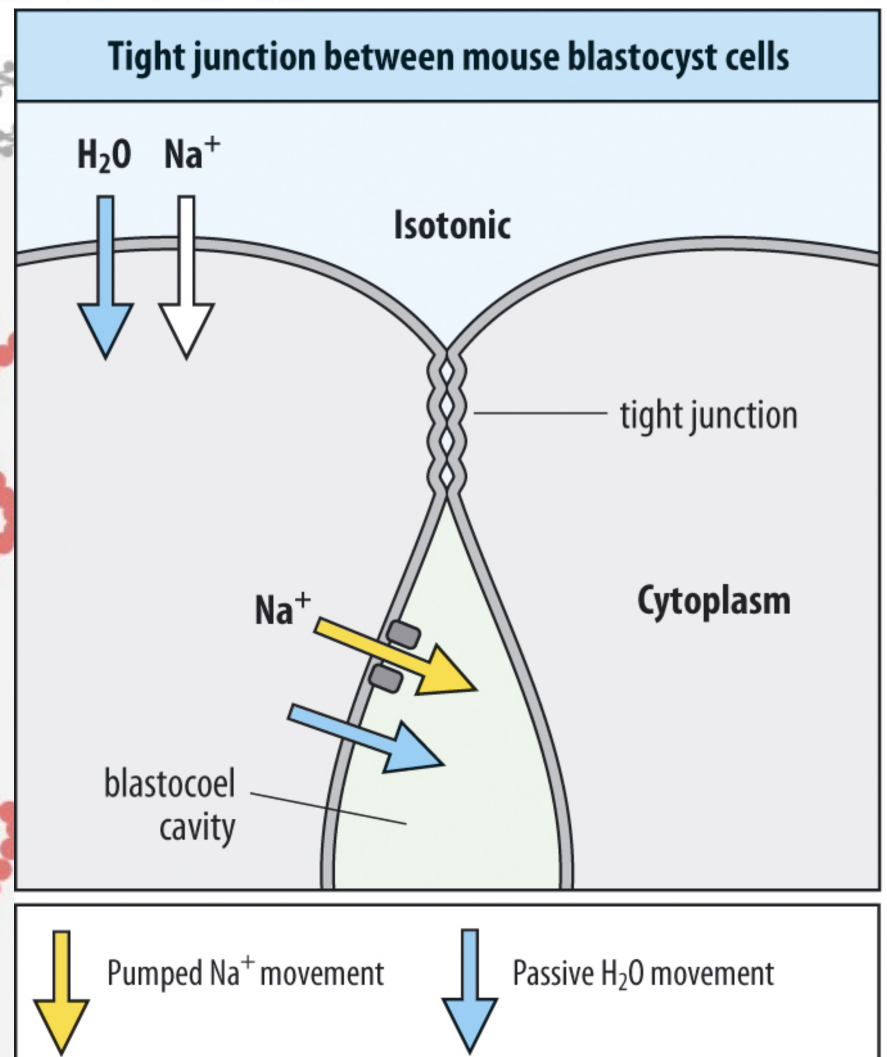


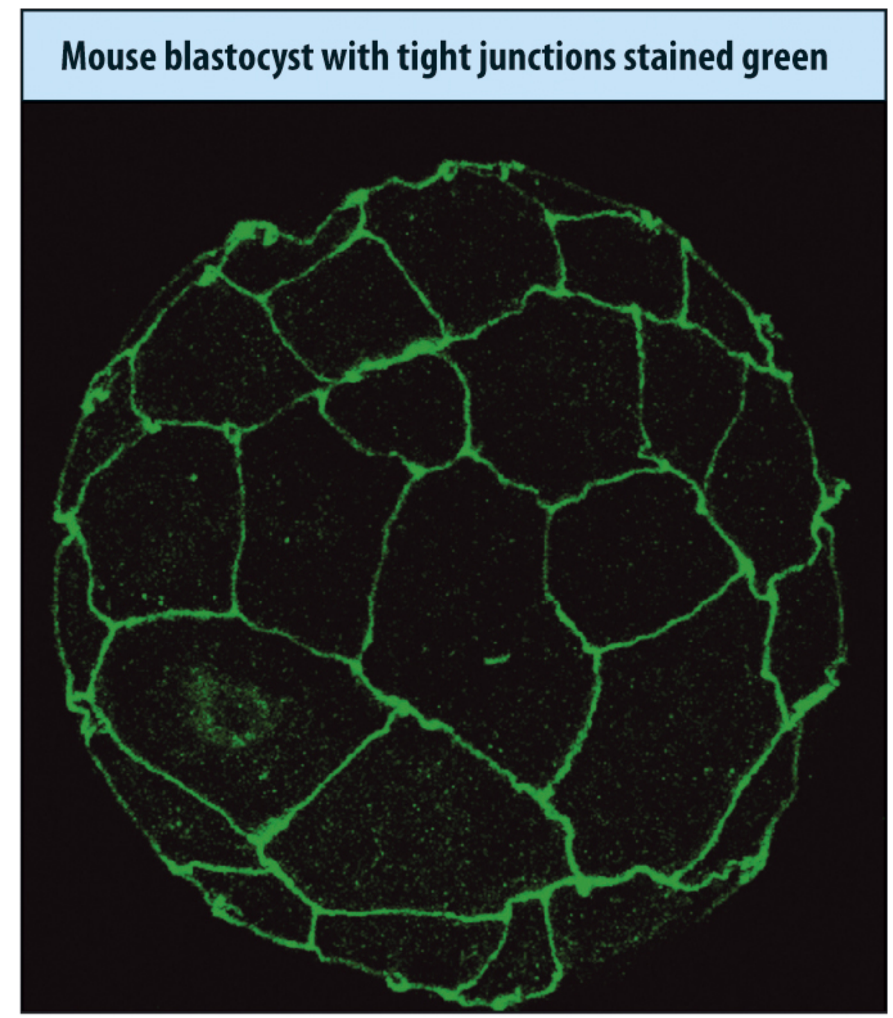
E-cadherin required for compaction and blastula formation



Tight junctions and Na+ pumps swell blastocoel

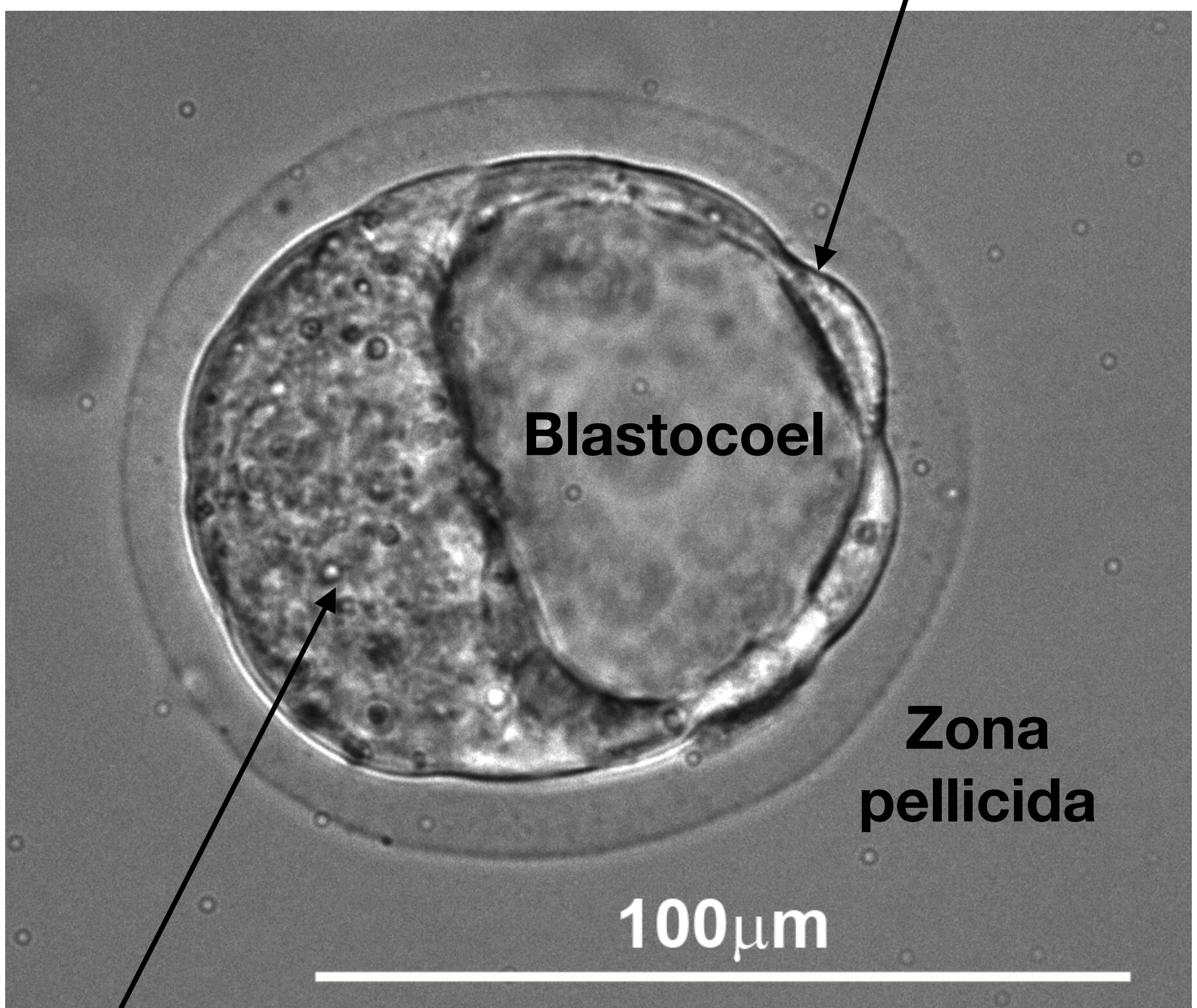




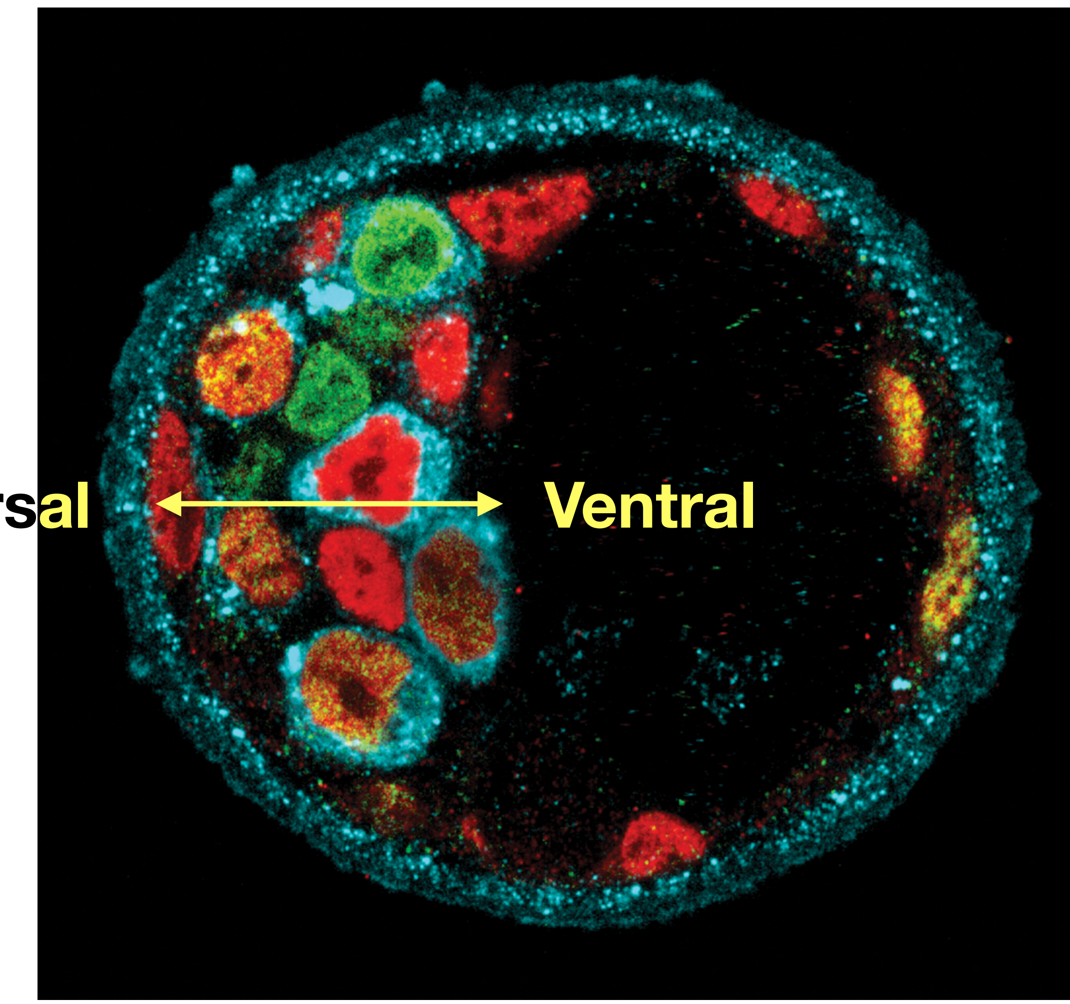


Generation of inner and outer cell layers (and an embryonic axis… D-V)

Trophectoderm



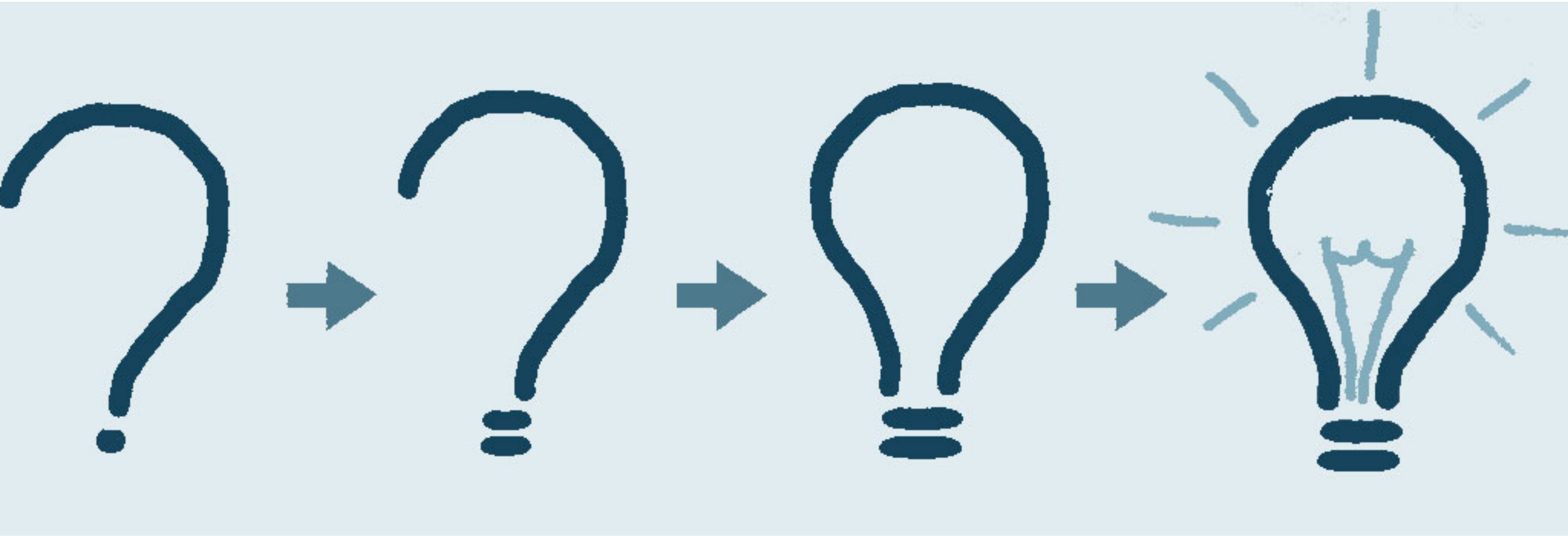
Inner cell mass (ICM)



Summary

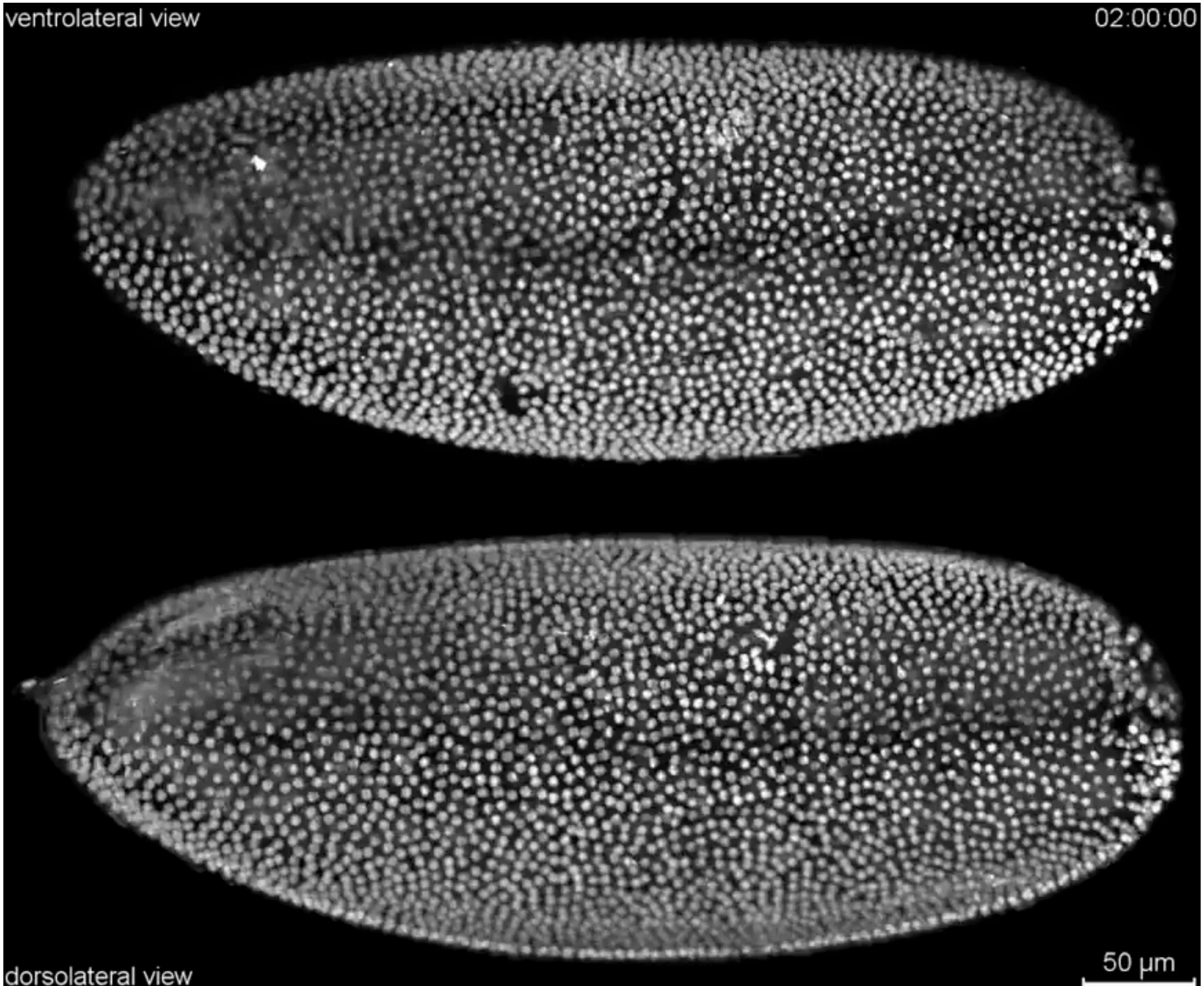
- **Morphogenesis**
- Cell adhesion - Cadherins
- Cell division - orientation
- Actin and myosin provide tissue-level forces through surface complexes
- Oriented cleavage and blastula in sea urchin and mouse

Questions?

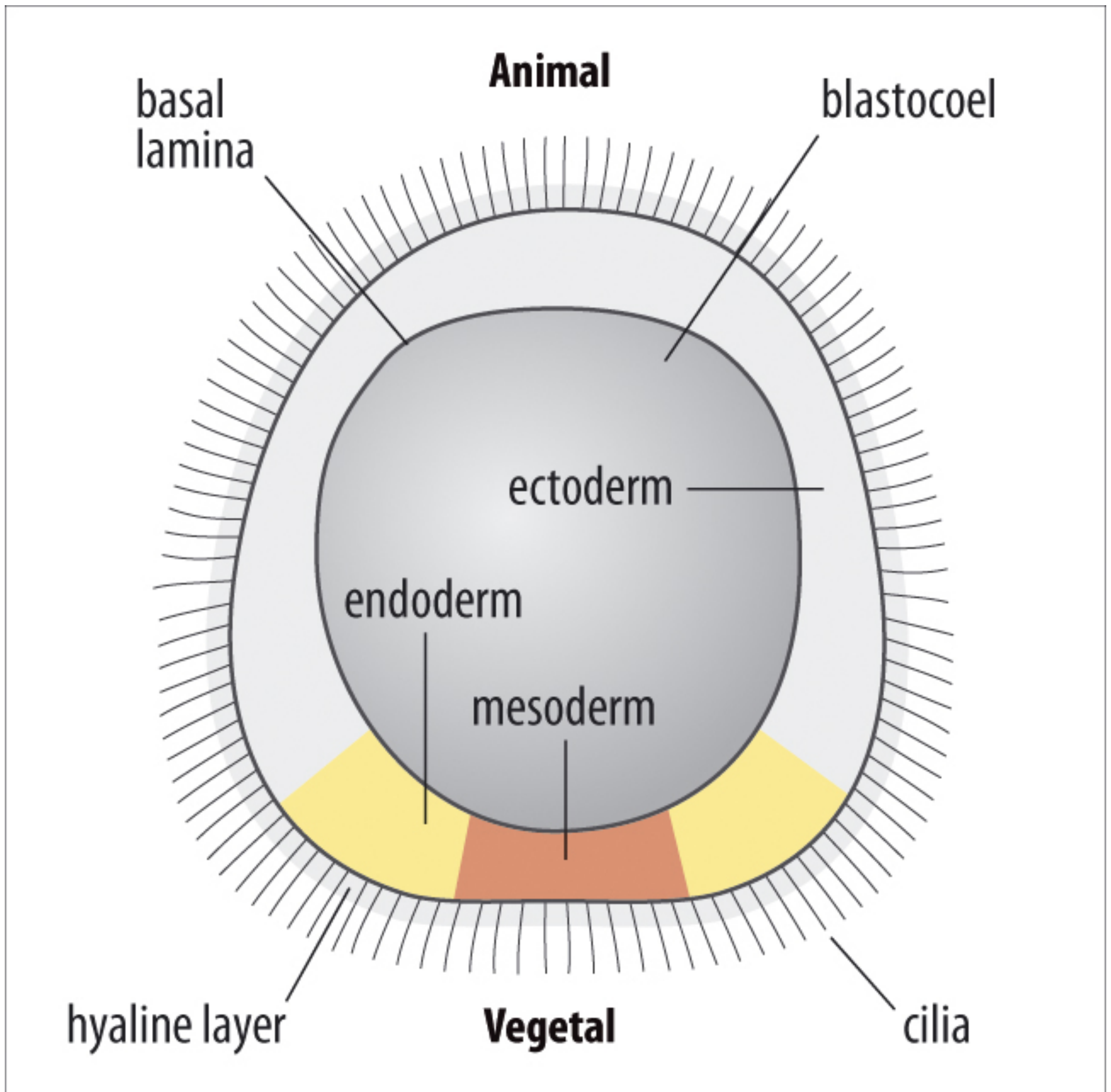


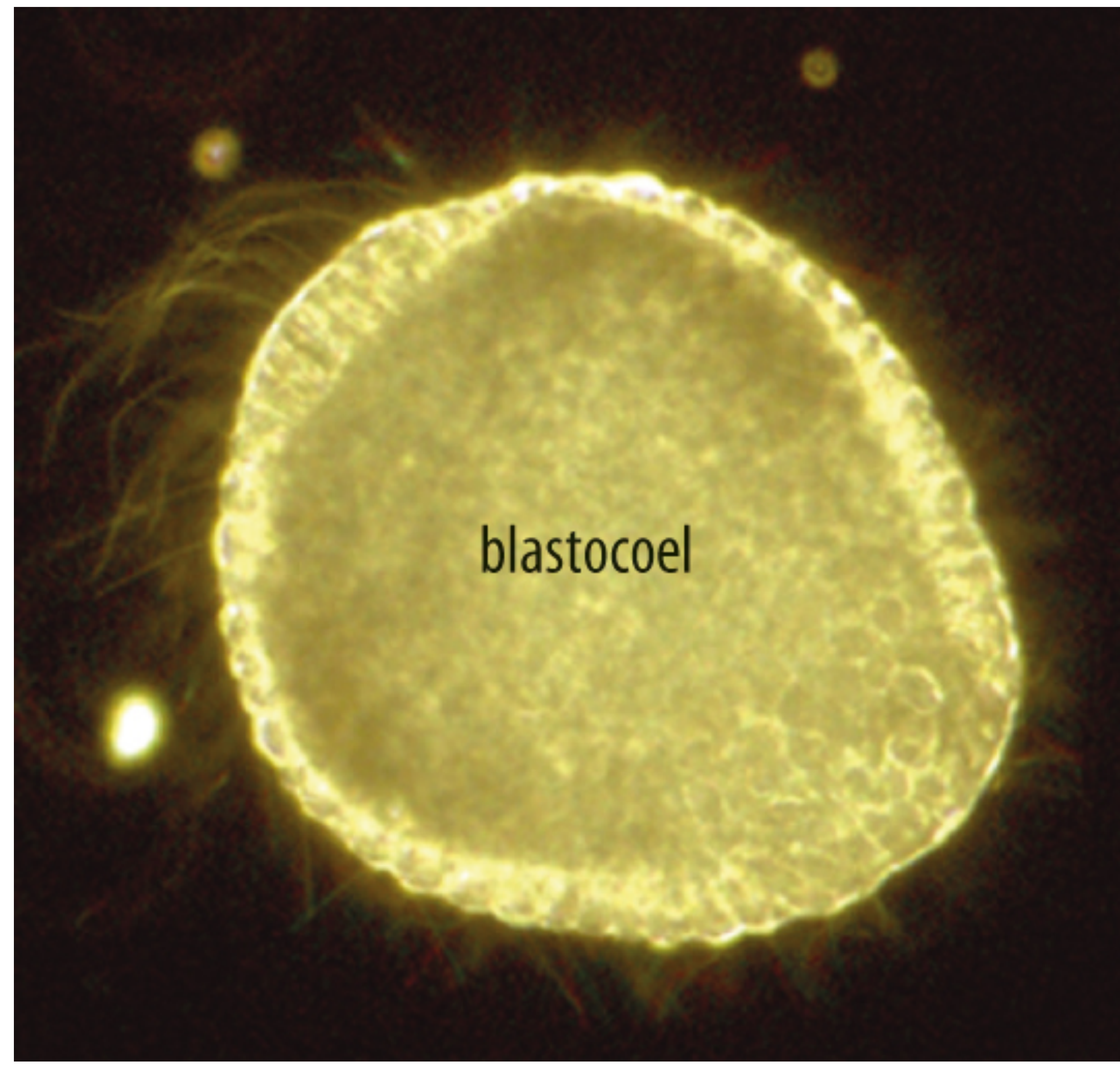
Take a break

Big questions

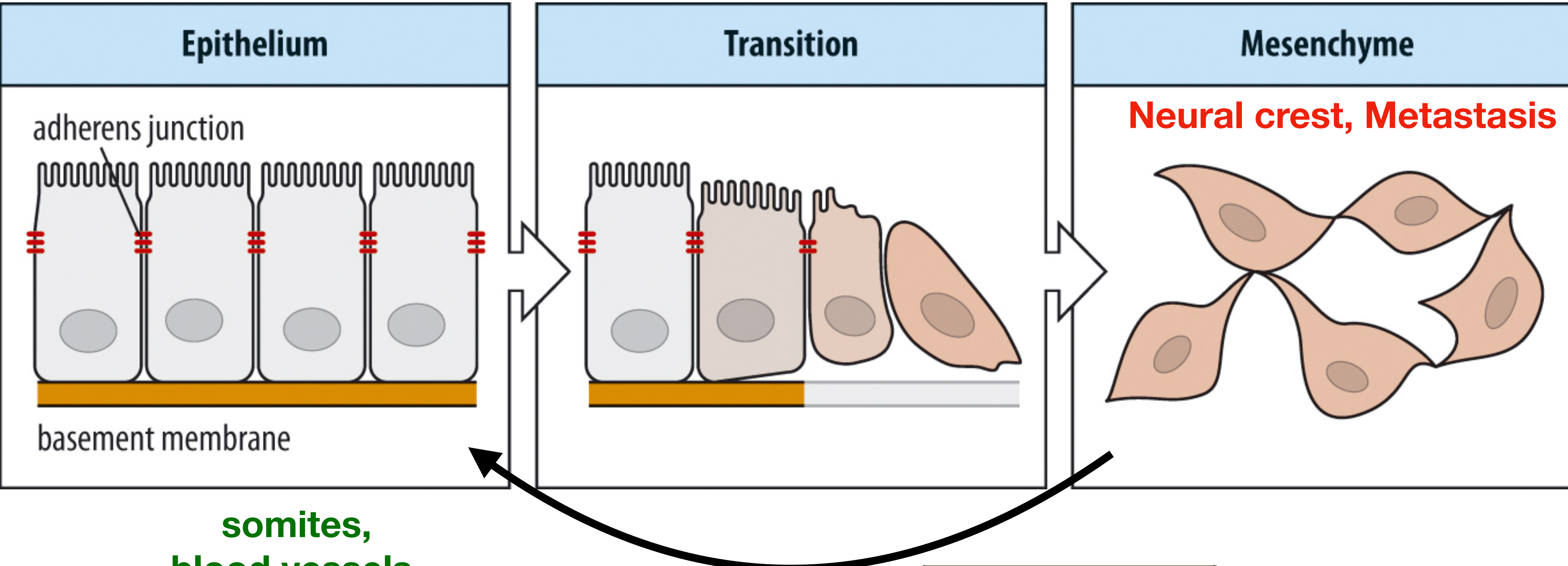


Sea urchin blastula





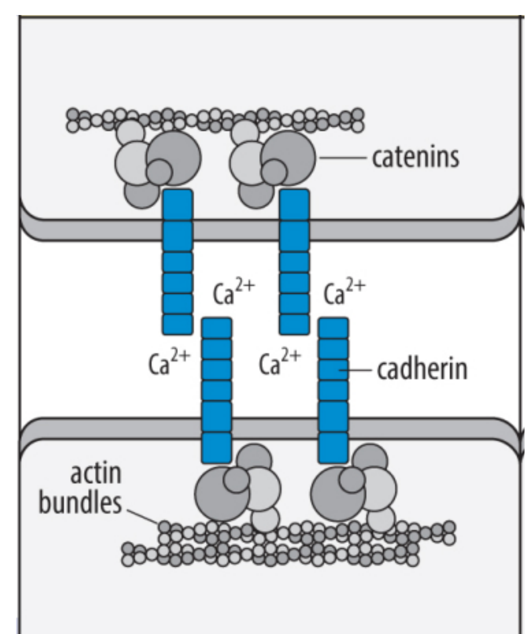
Epithelial - Mesenchymal Transition (EMT)



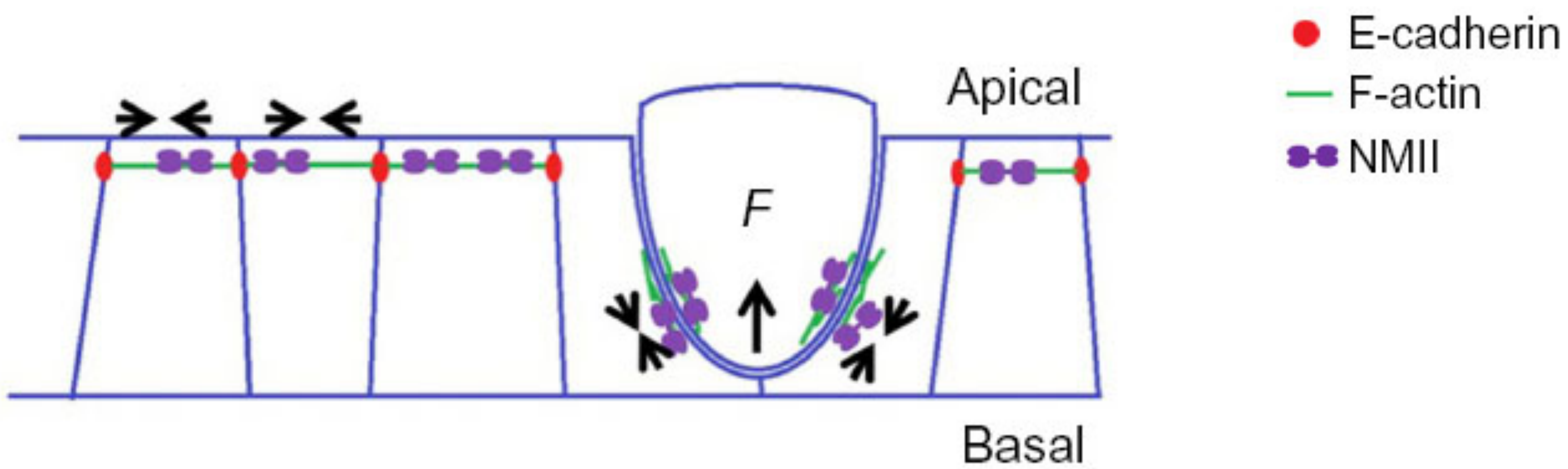
somites,
blood vessels,
kidney tubules

Snail ⬆

Cadherins, catenins ⬇

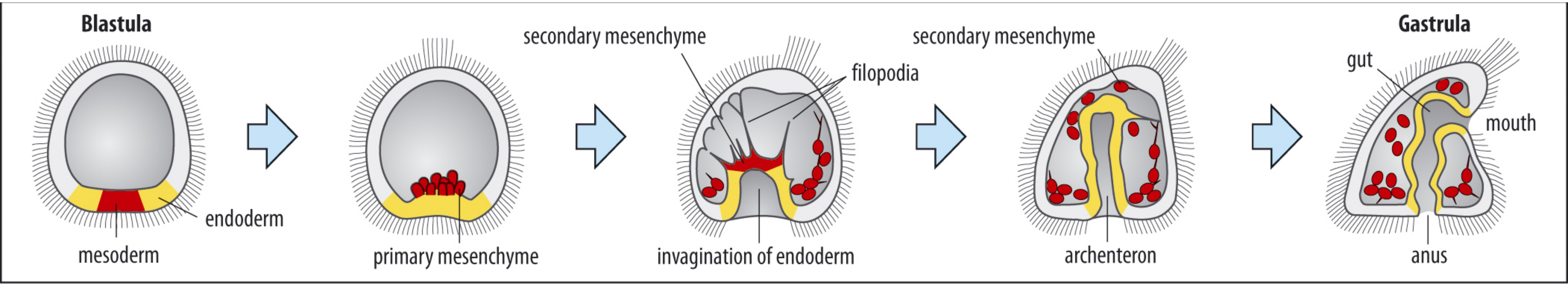


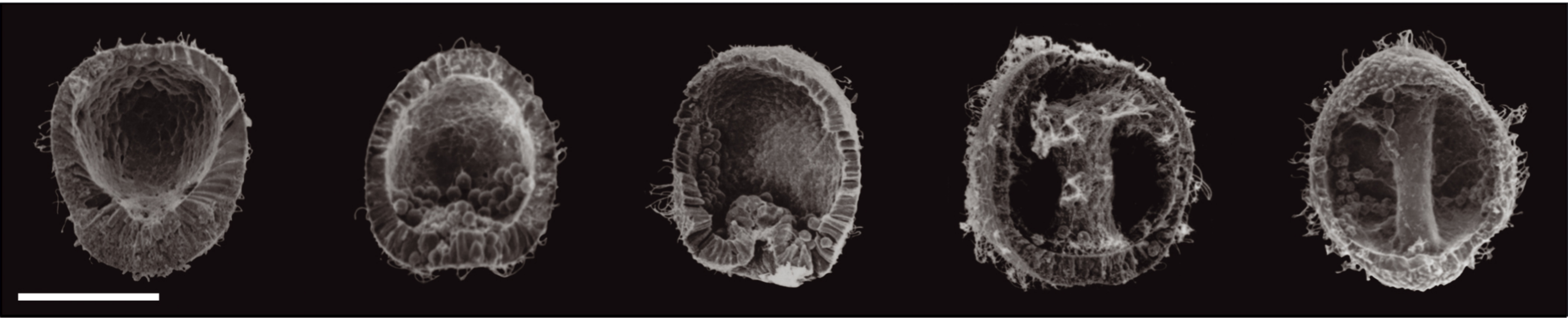
Delamination - cells leave an intact epithelium



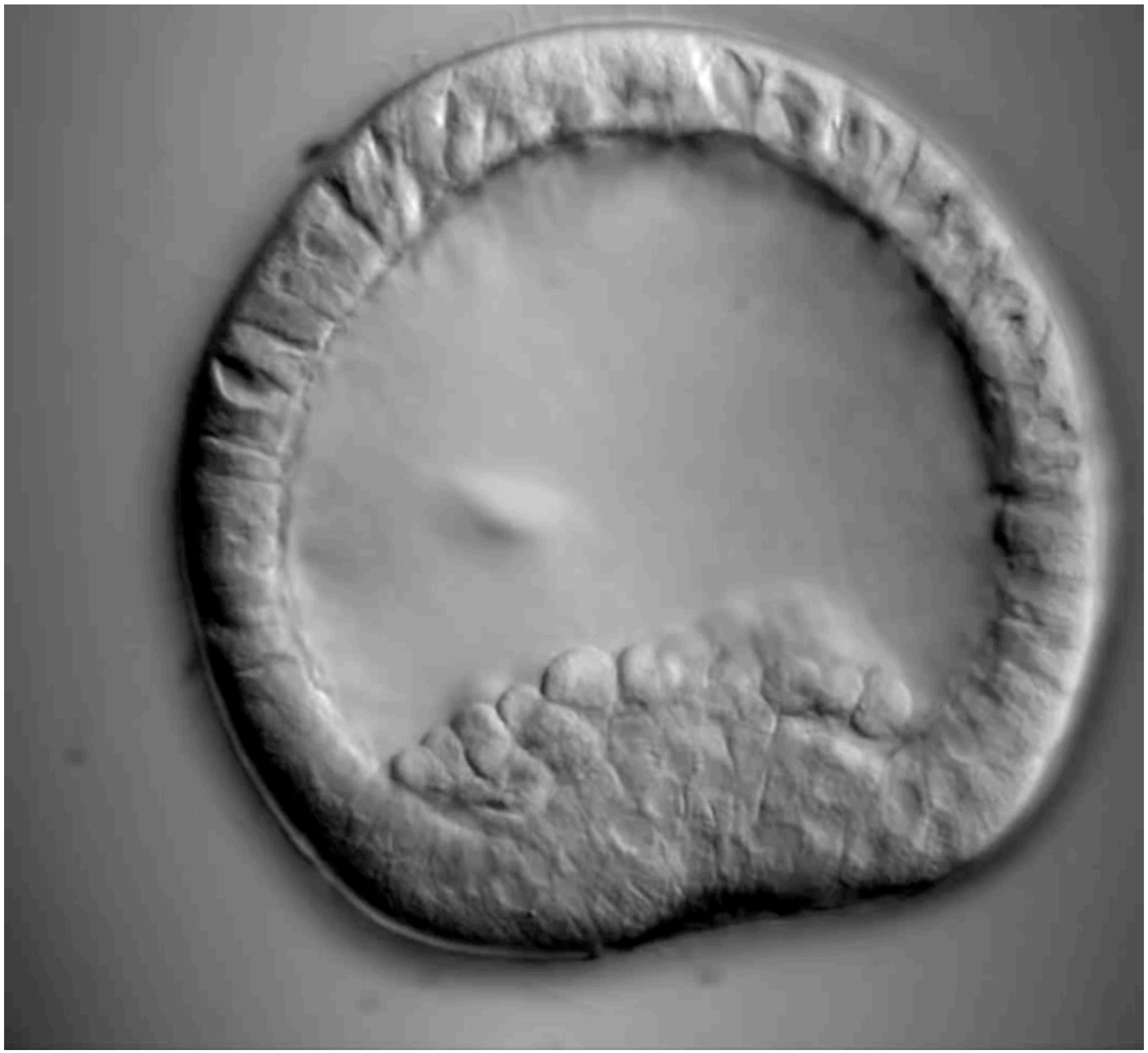
Seen also during neurogenesis (week 8 fine-grain patterns)

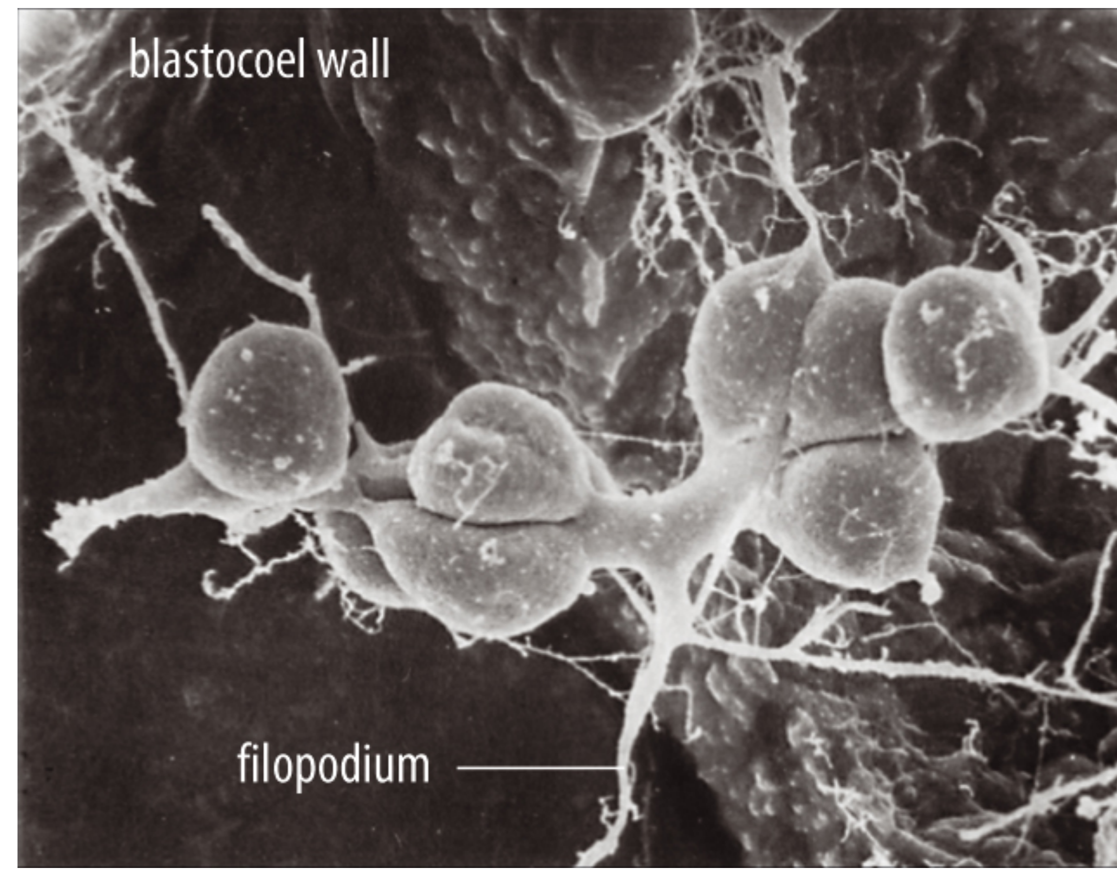
Sea-urchin gastrulation
EMT / delamination, then migration and invagination



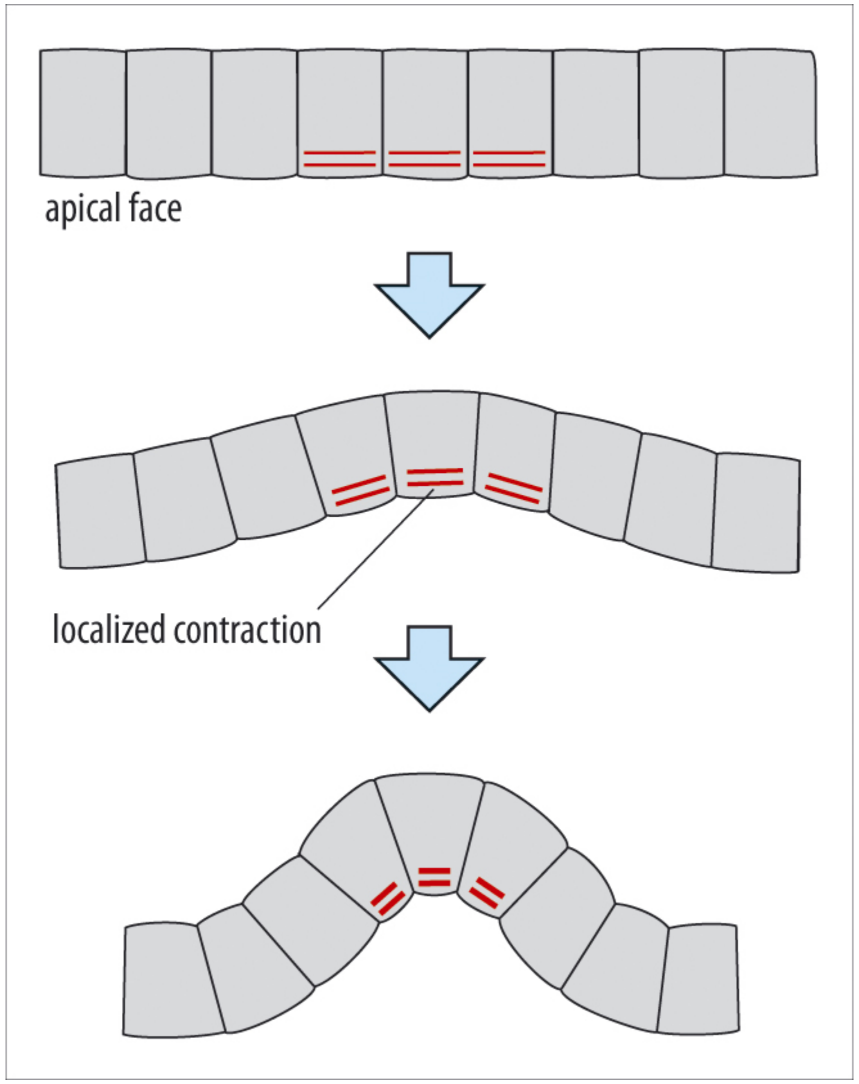


Apical constriction drives invagination
Secondary mesenchyme EMT

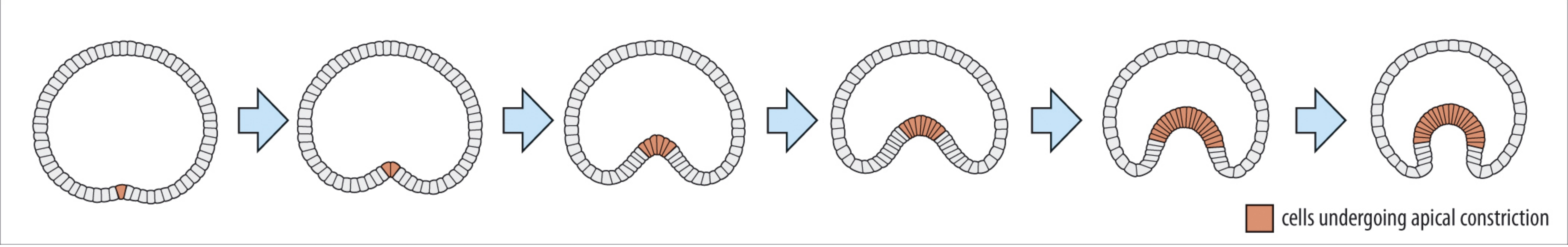




Apical constriction drives invagination



Actomyosin contractility

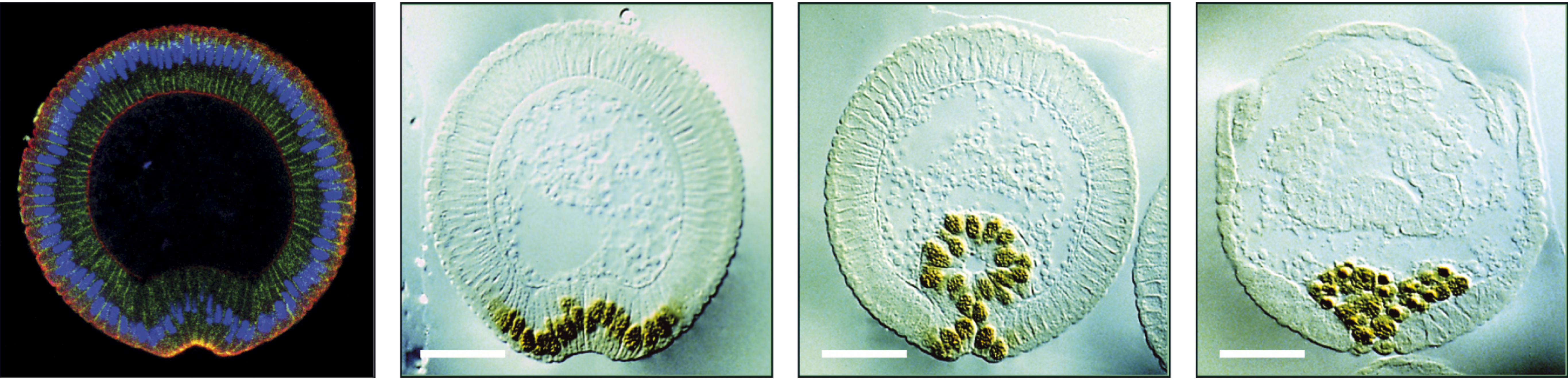


Odel et al., 1981

Drosophila gastrulation
Invagination, *then* EMT and migration

Posterior

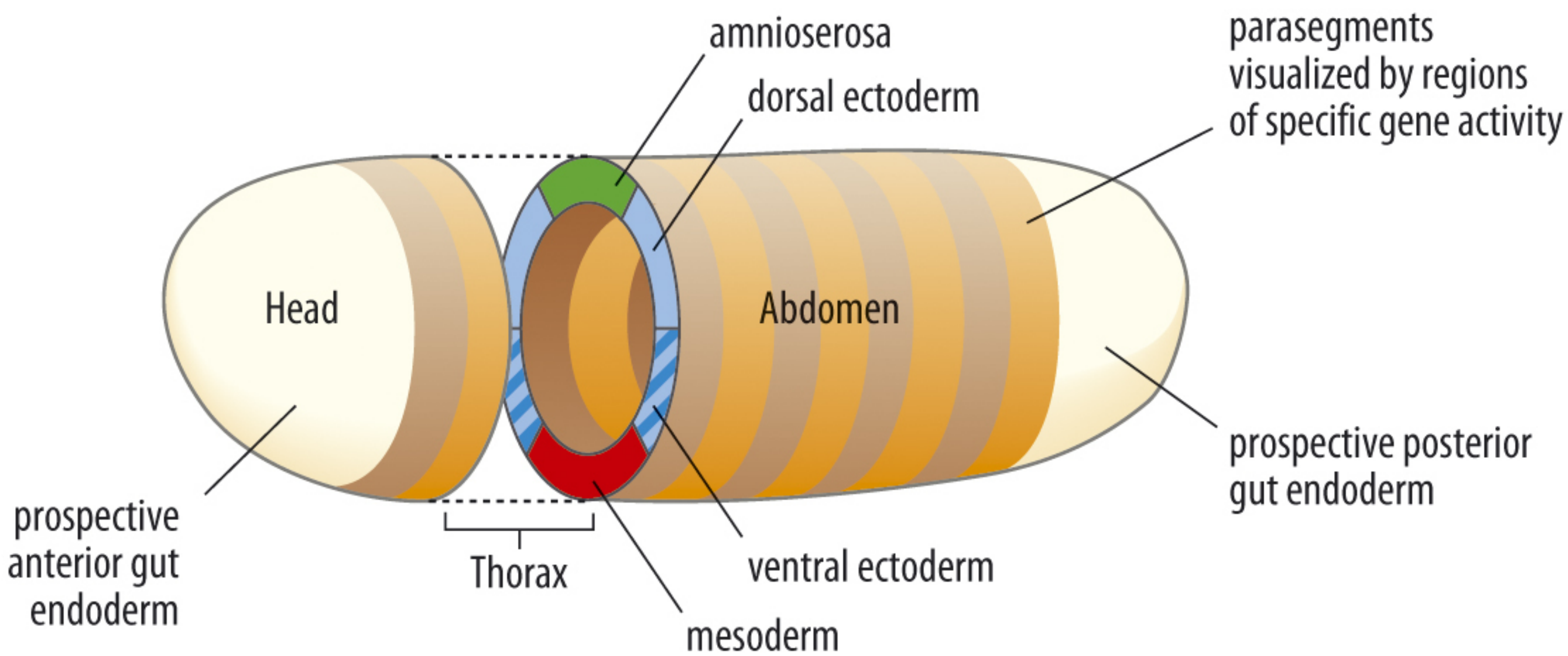
Anterior

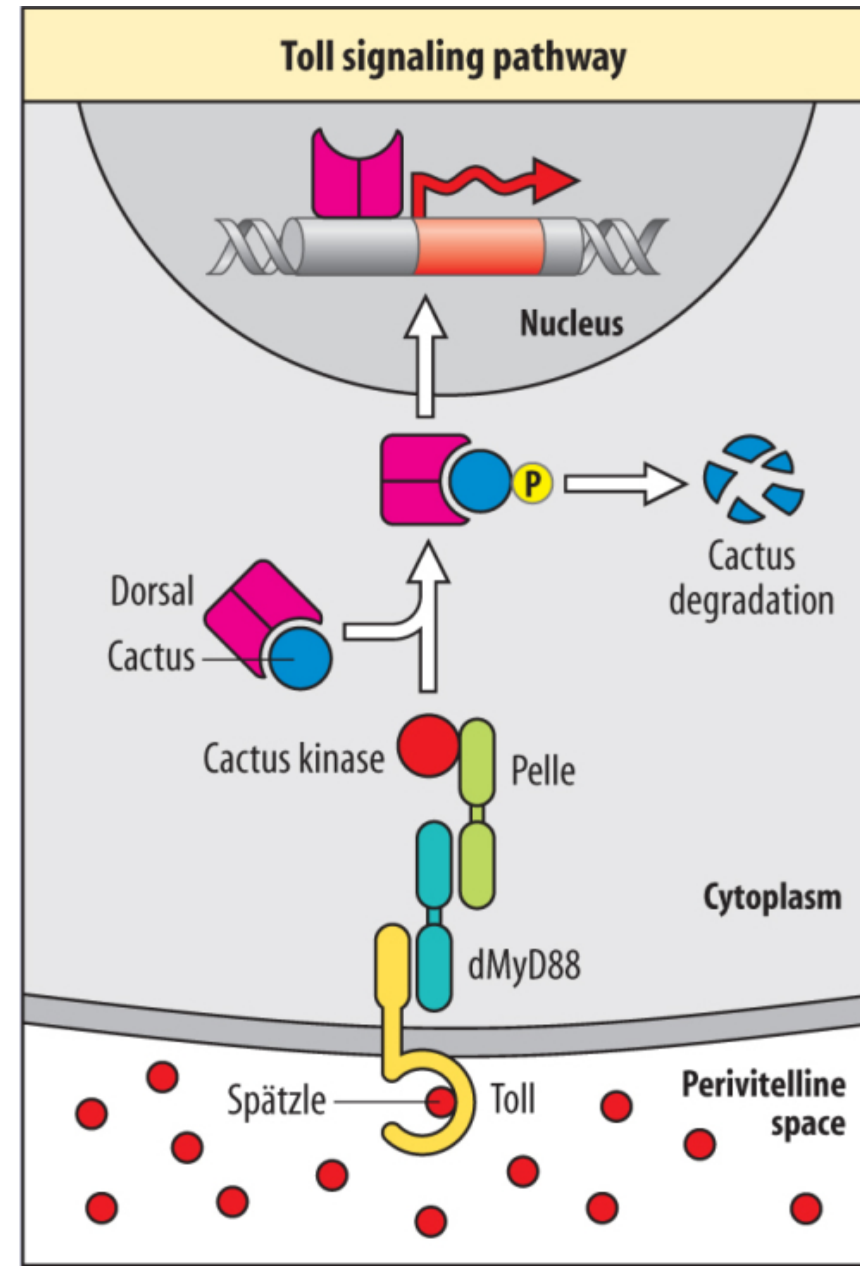


Myosin II

Twist

Genetic control of *Drosophila* gastrulation



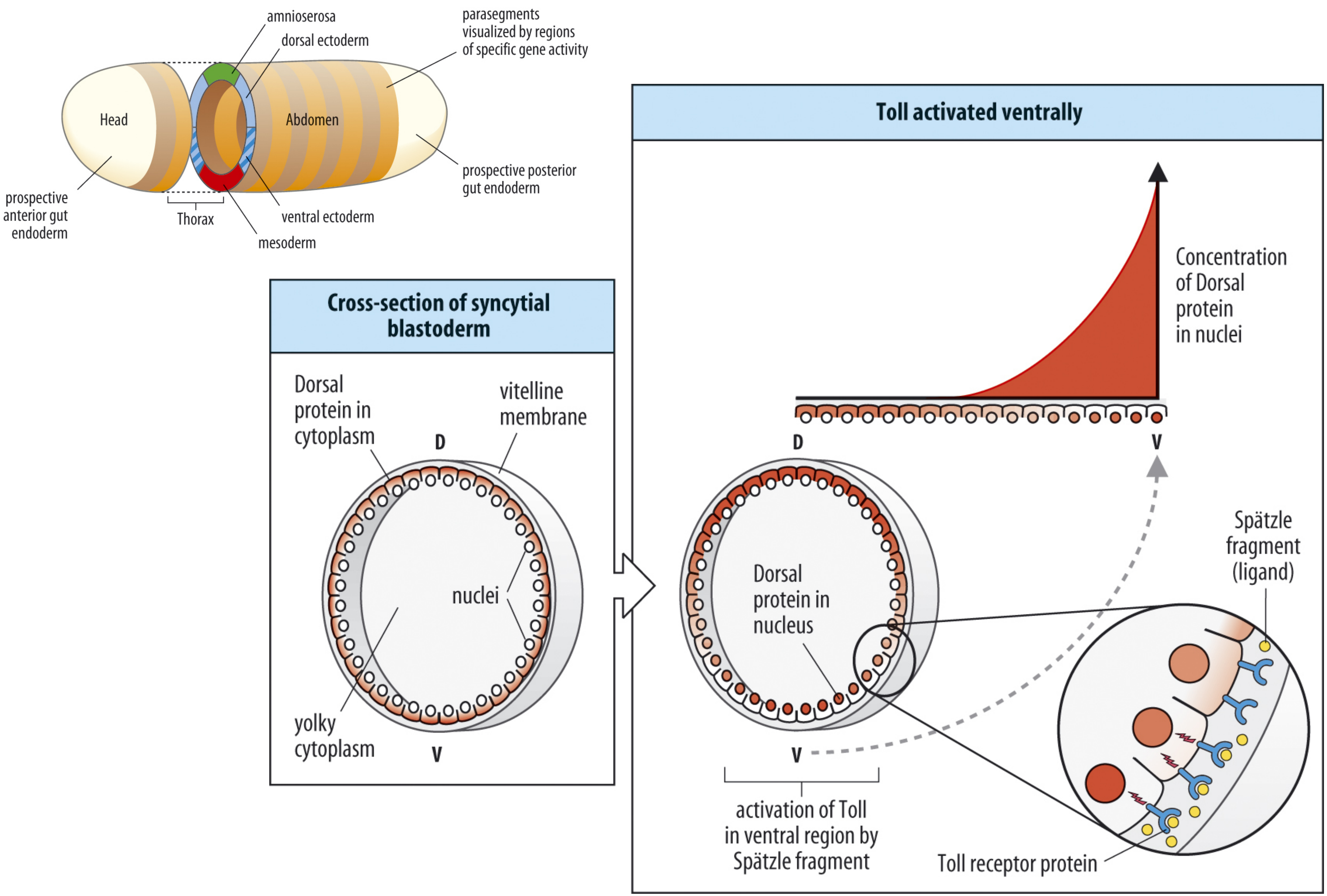


Toll receptor = human innate immunity receptor

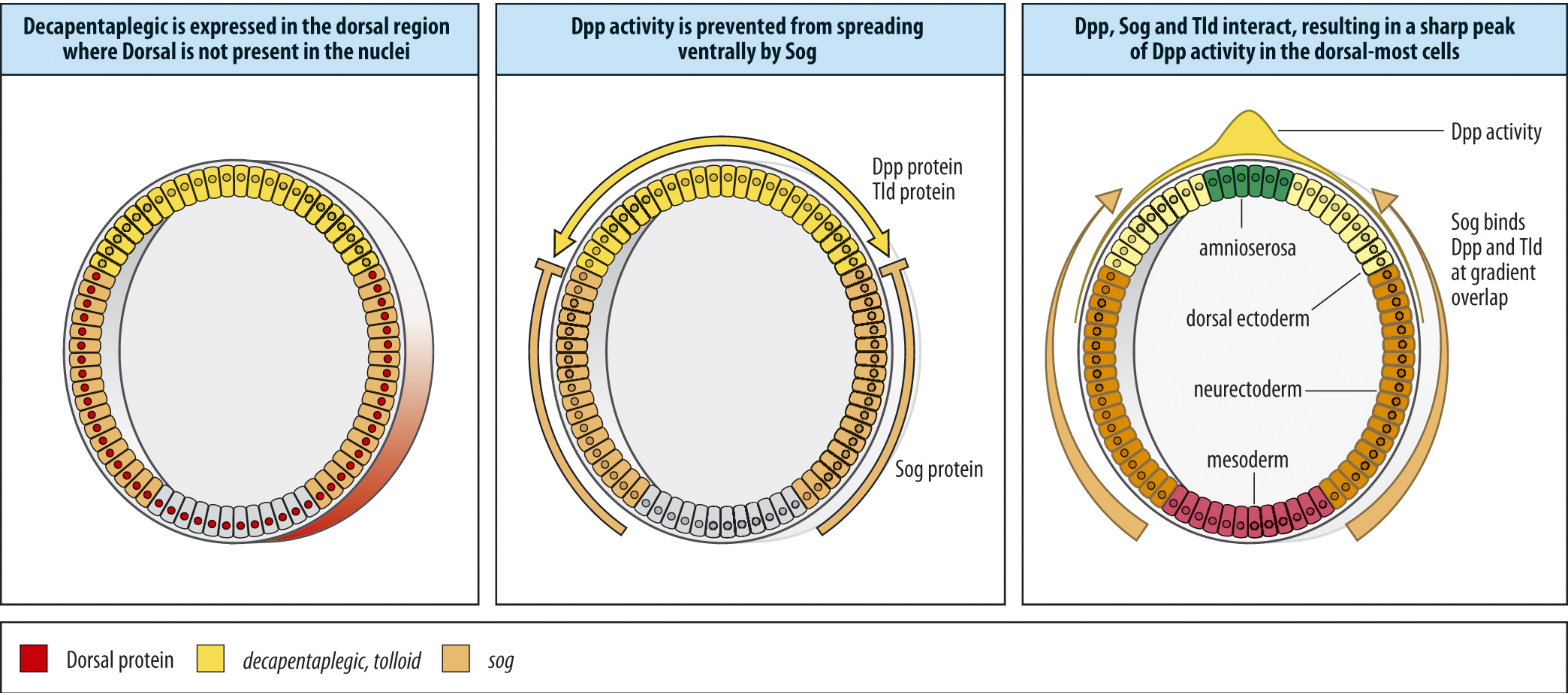
Nobel prize in Physiology and Medicine 2011
Bruce A. Beutler & Jules A. Hoffmann

Lemaitre B, Nicolas E, Michaut L, Reichhart JM, **Hoffmann JA**.
The dorsoventral regulatory gene cassette *spätzle/Toll/cactus* controls the potent antifungal response in *Drosophila* adults.
Cell 1996;86:973-983.

Genetic control of *Drosophila* gastrulation



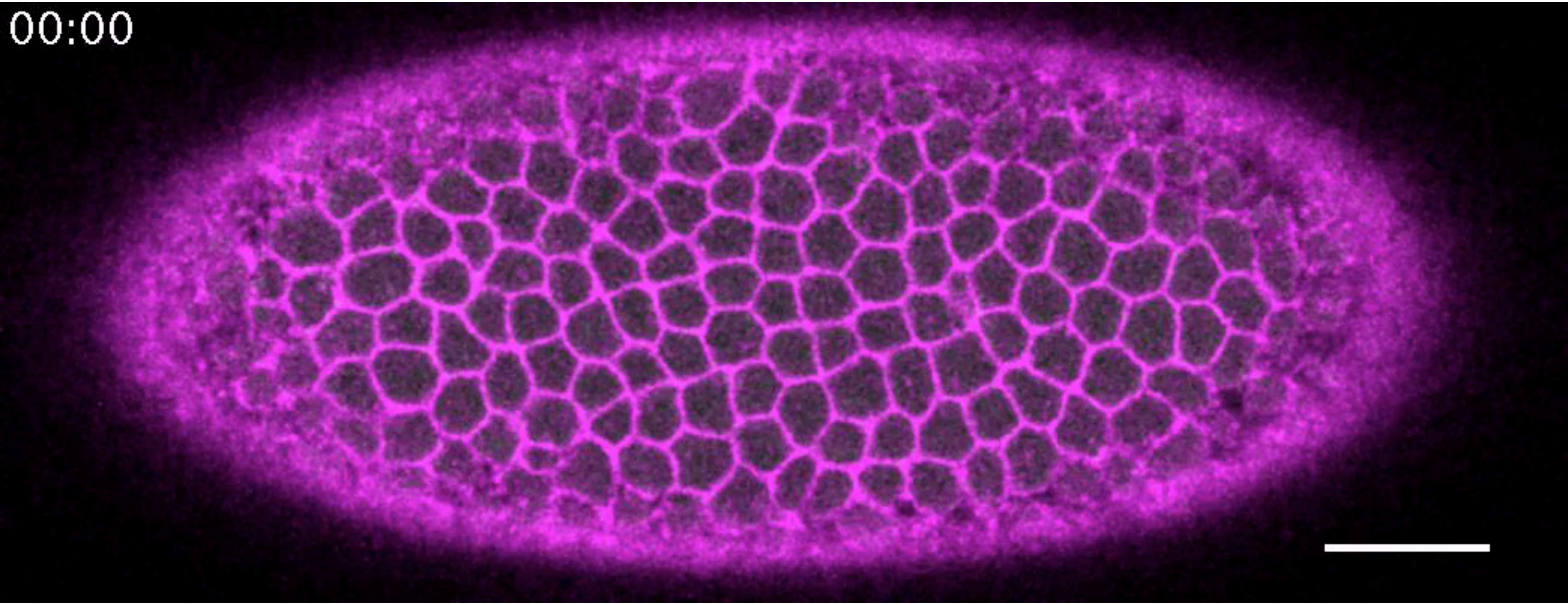
Genetic control of *Drosophila* gastrulation

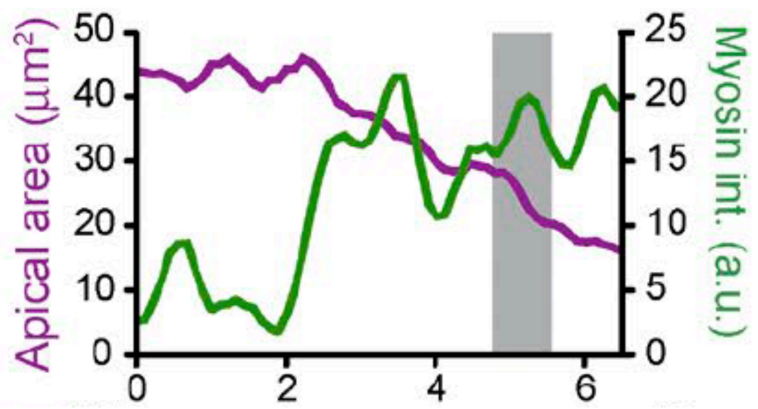


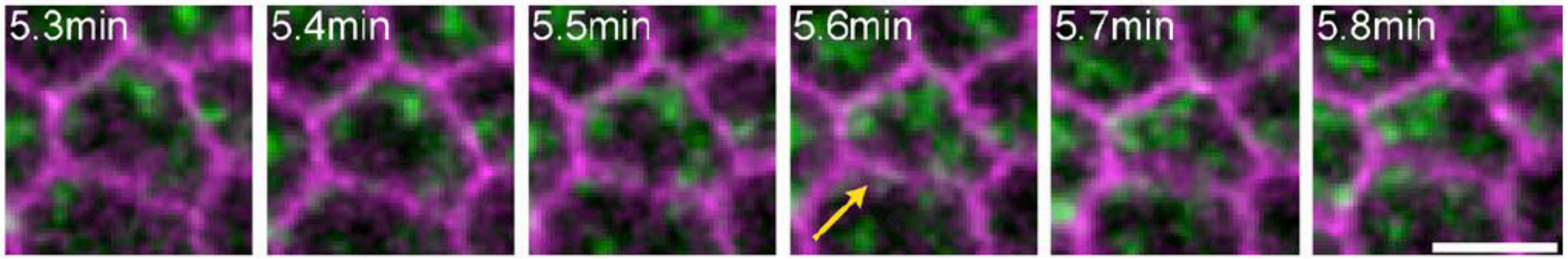
Decapentaplegic = BMP, Short gastrulation (sog) = Chordin

Actomyosin has pulsatile contractile cycles

Myosin II:GFP   Membrane:RFP



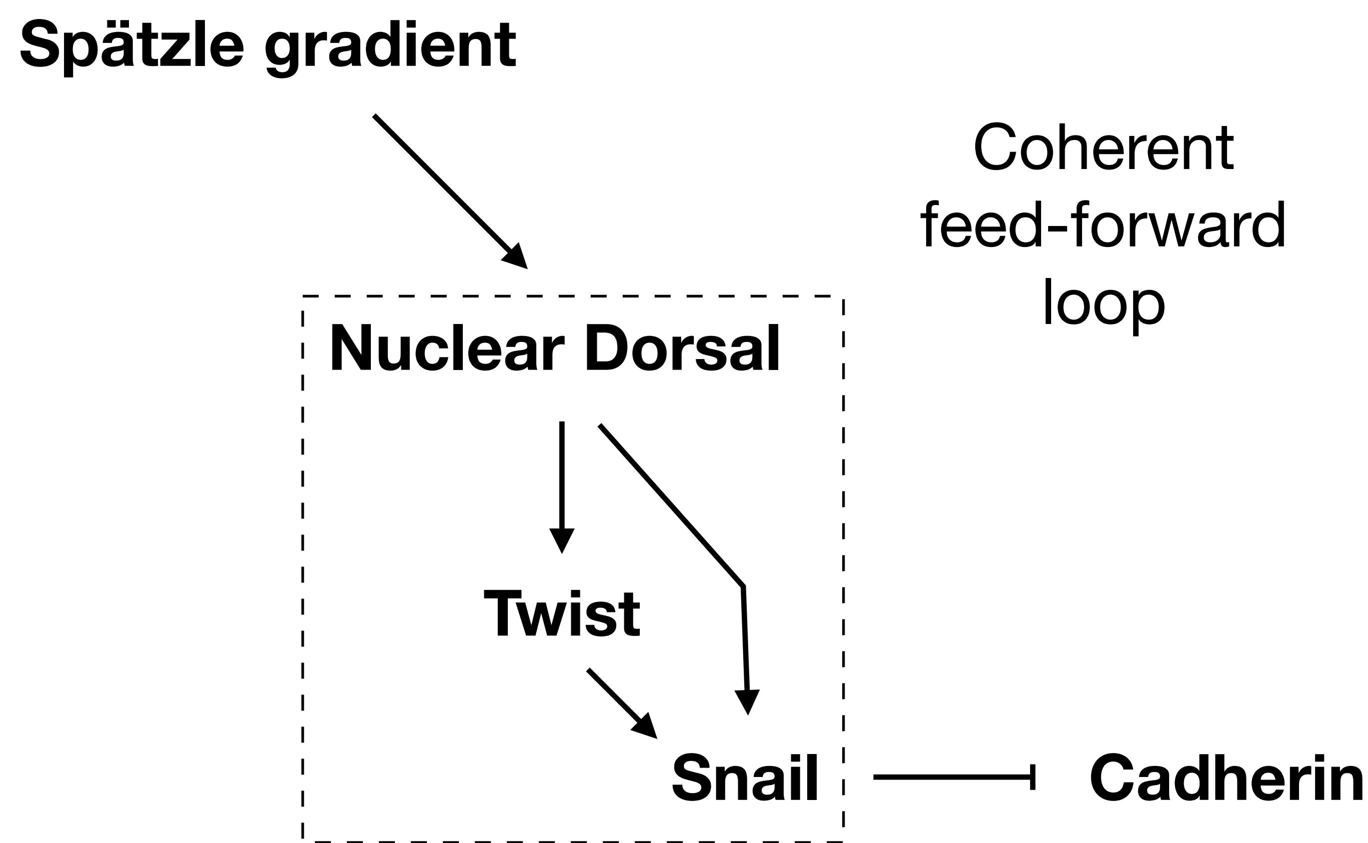




"Ratcheting" of apical area, gastrulation at 6 min

Mason et al., 2016

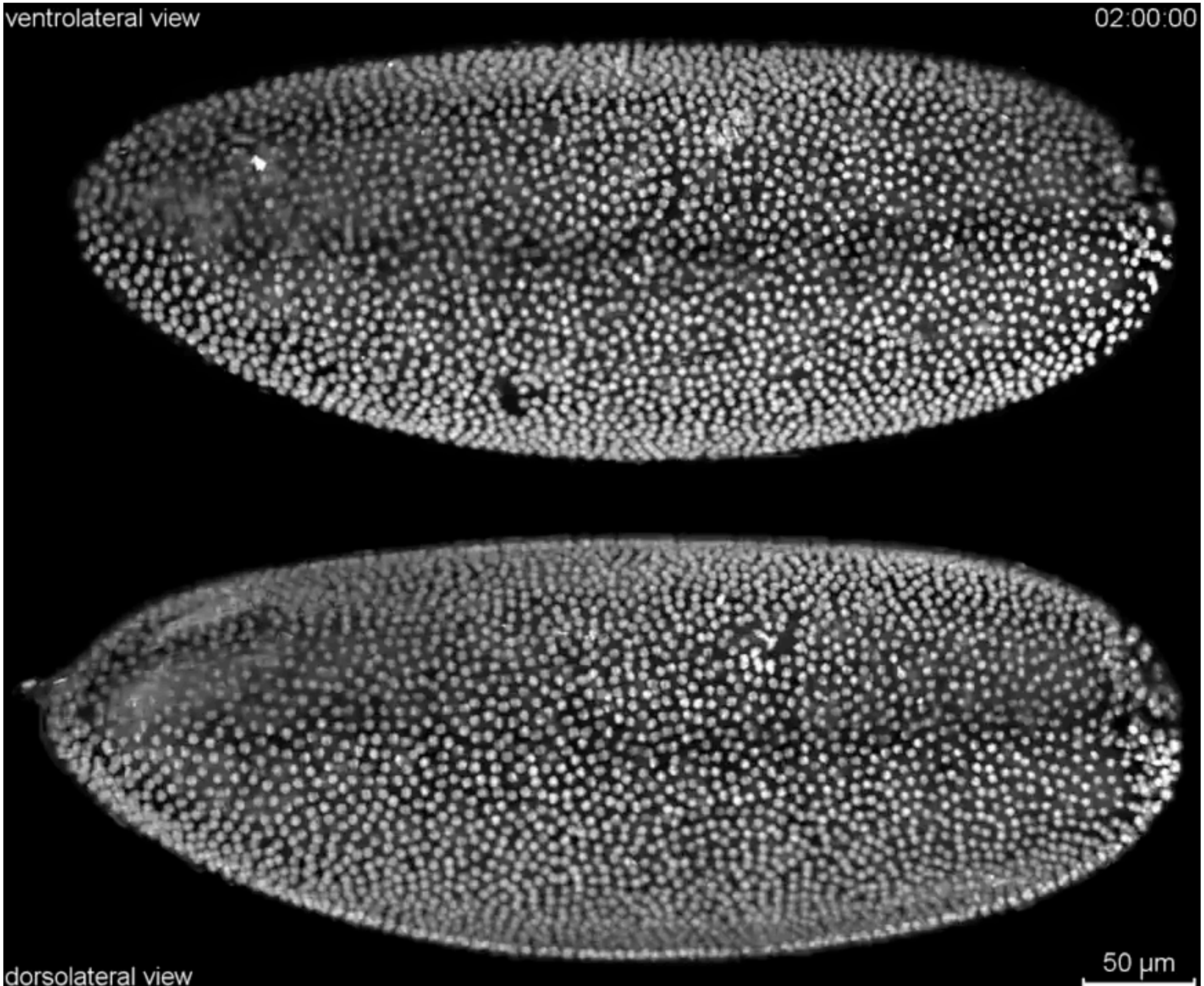
Timing and coordination of gastrulation?



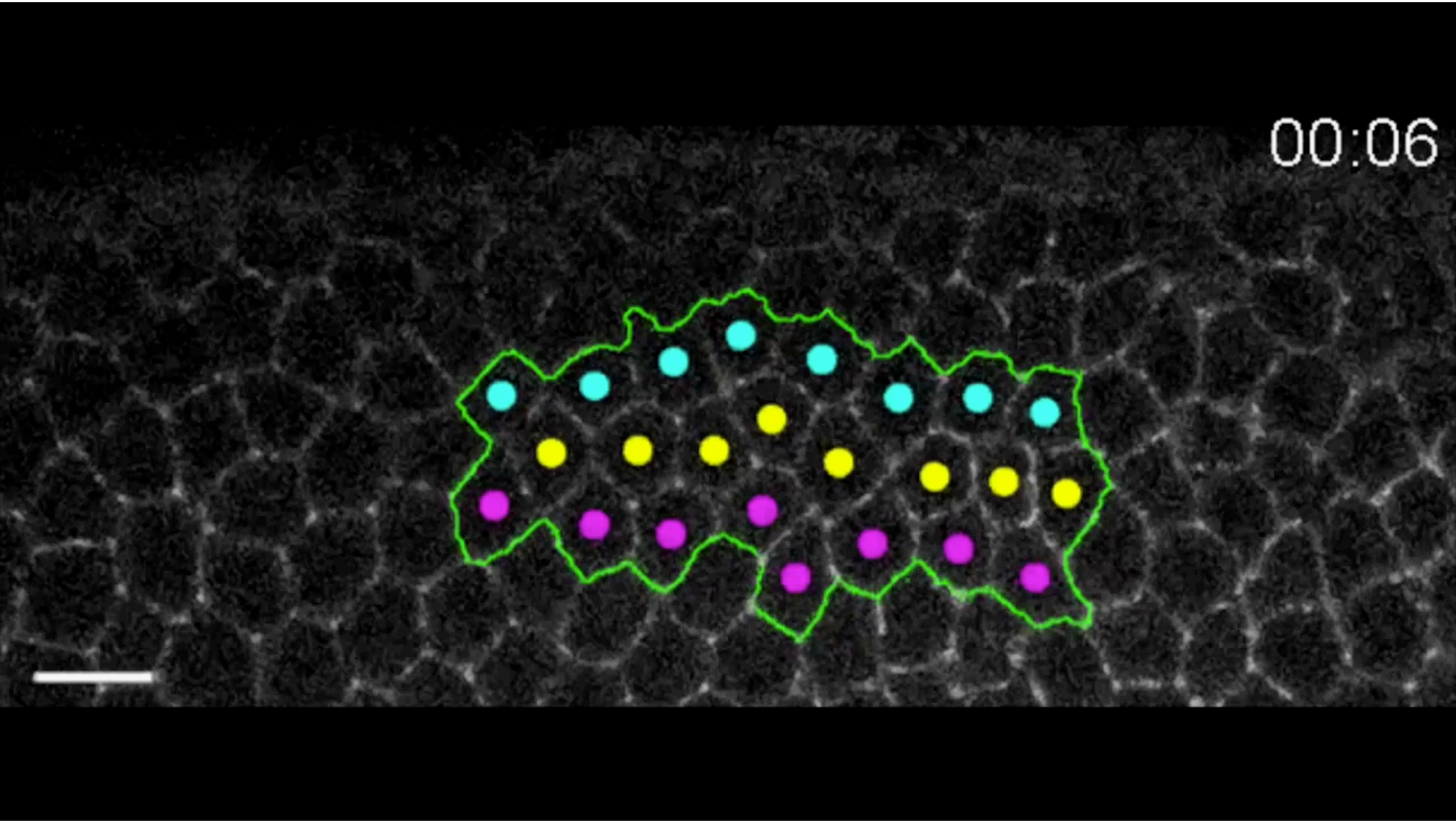
How could this pathway control the observed *rapid* change in cell shape?

Group puzzle

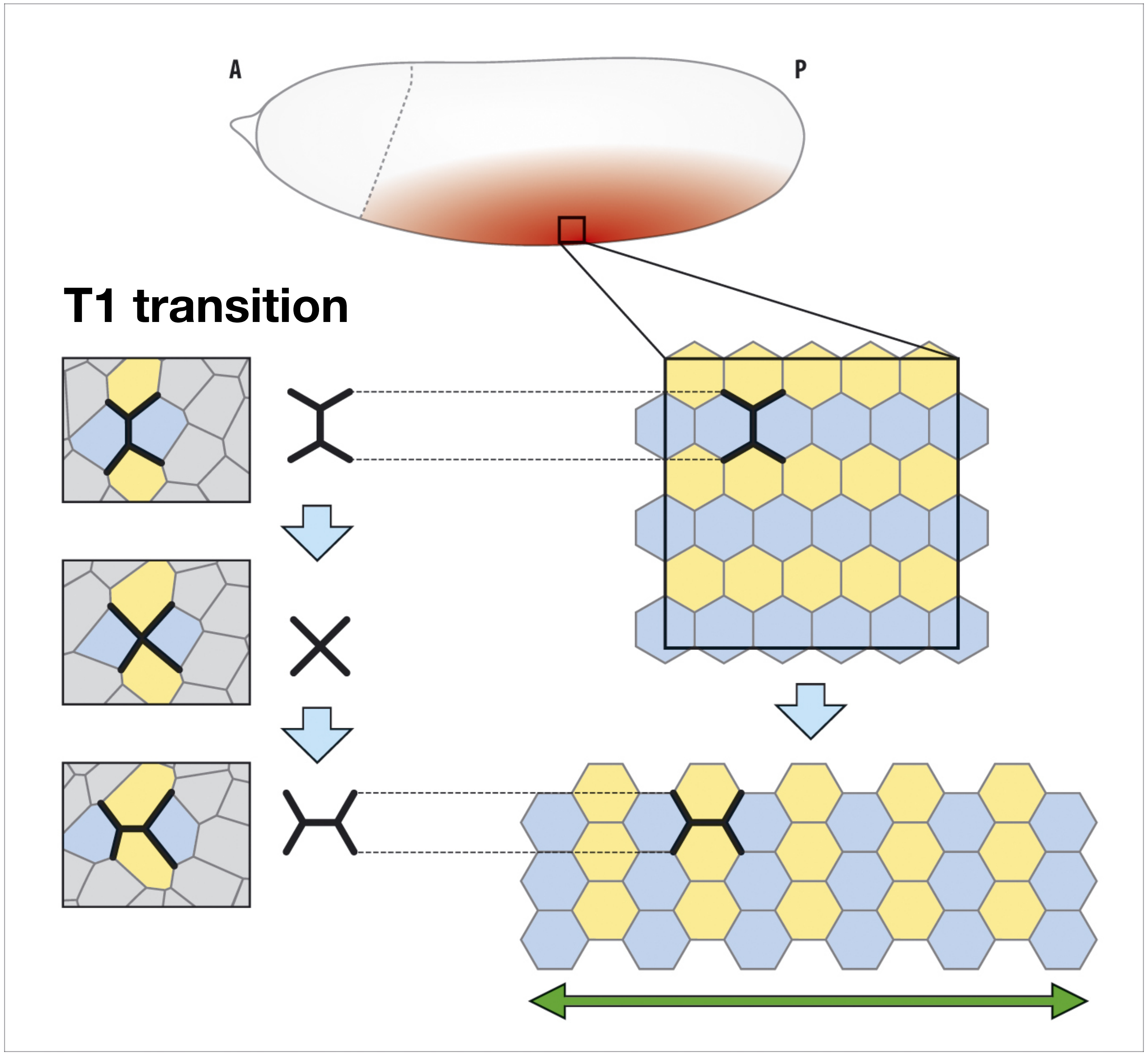
Extension of the body by “convergent extension”

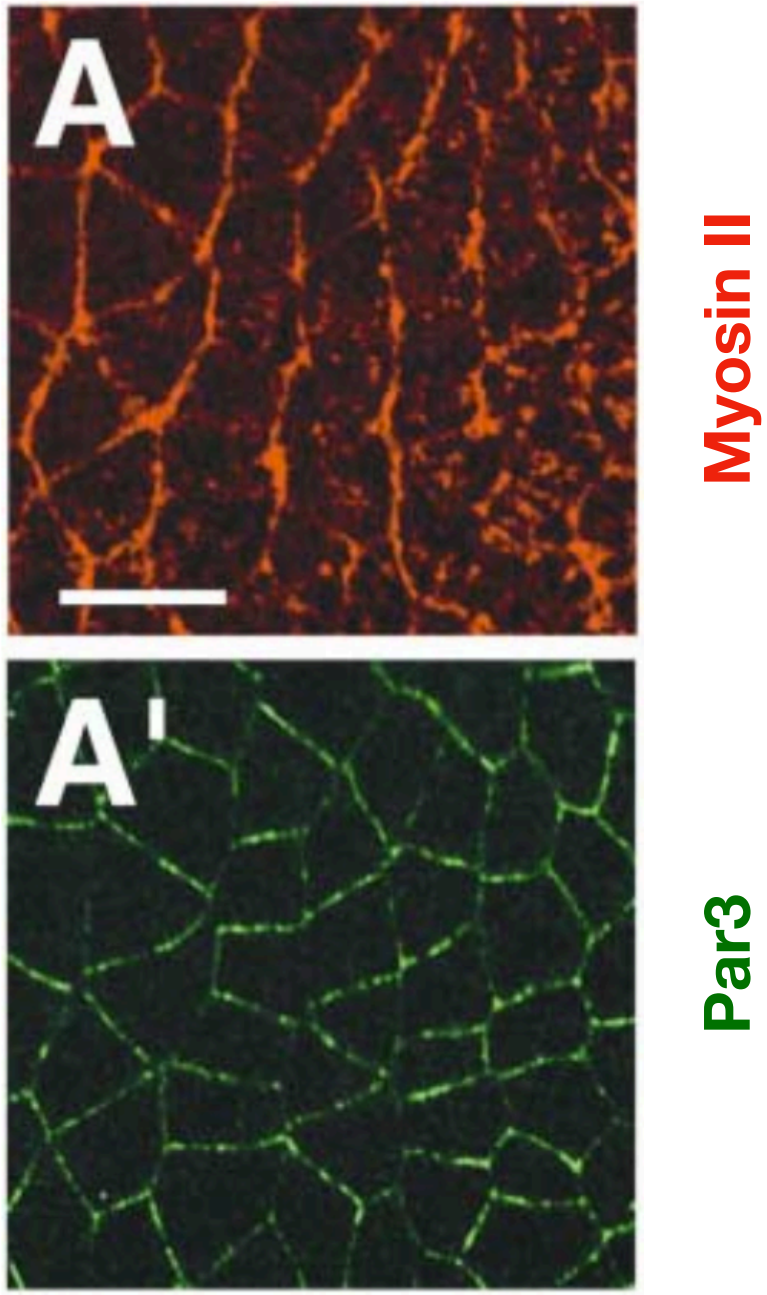


Extension of the body by “convergent extension”

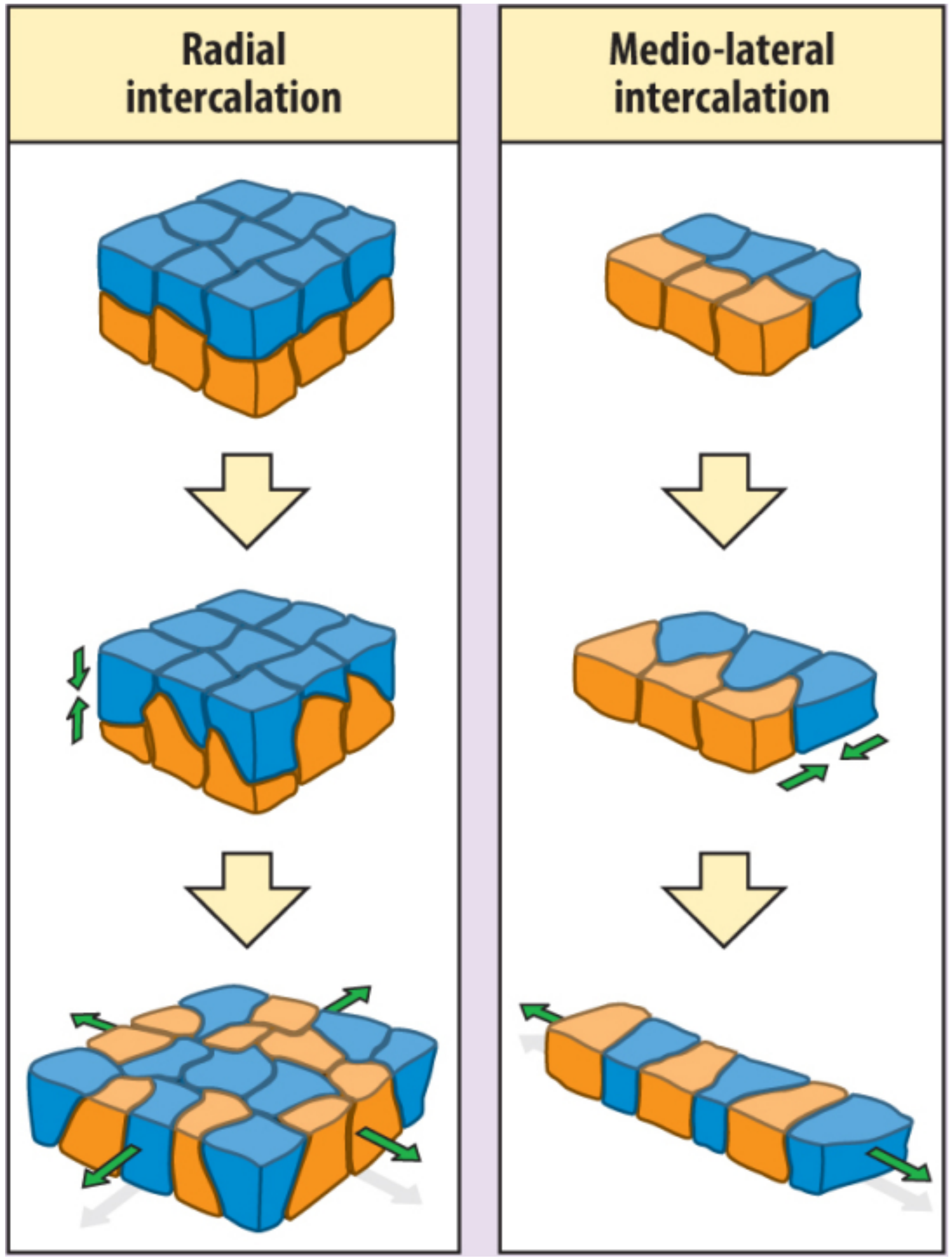


Convergent extension regulated by planar cell polarity and actomysion pulses



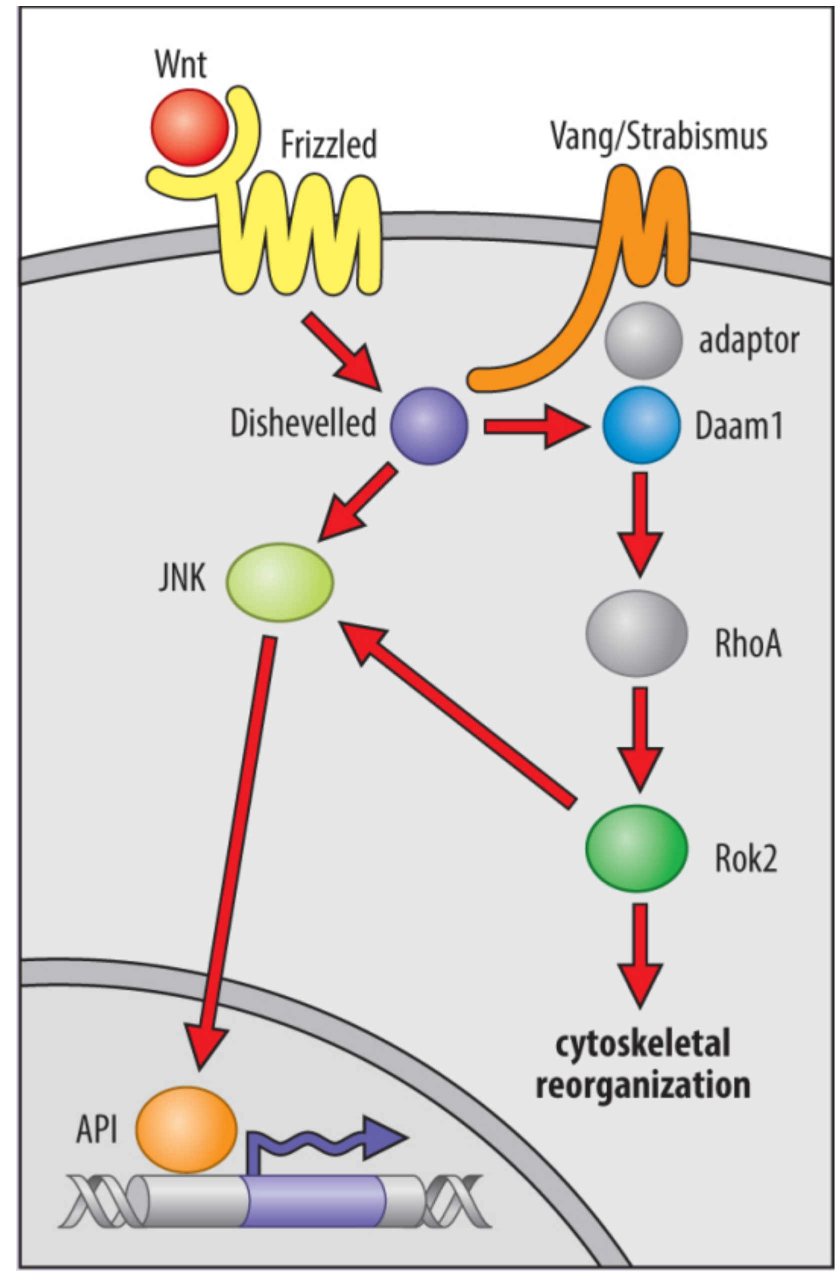


Convergent extension is regulated by planar cell polarity (PCP) pathway

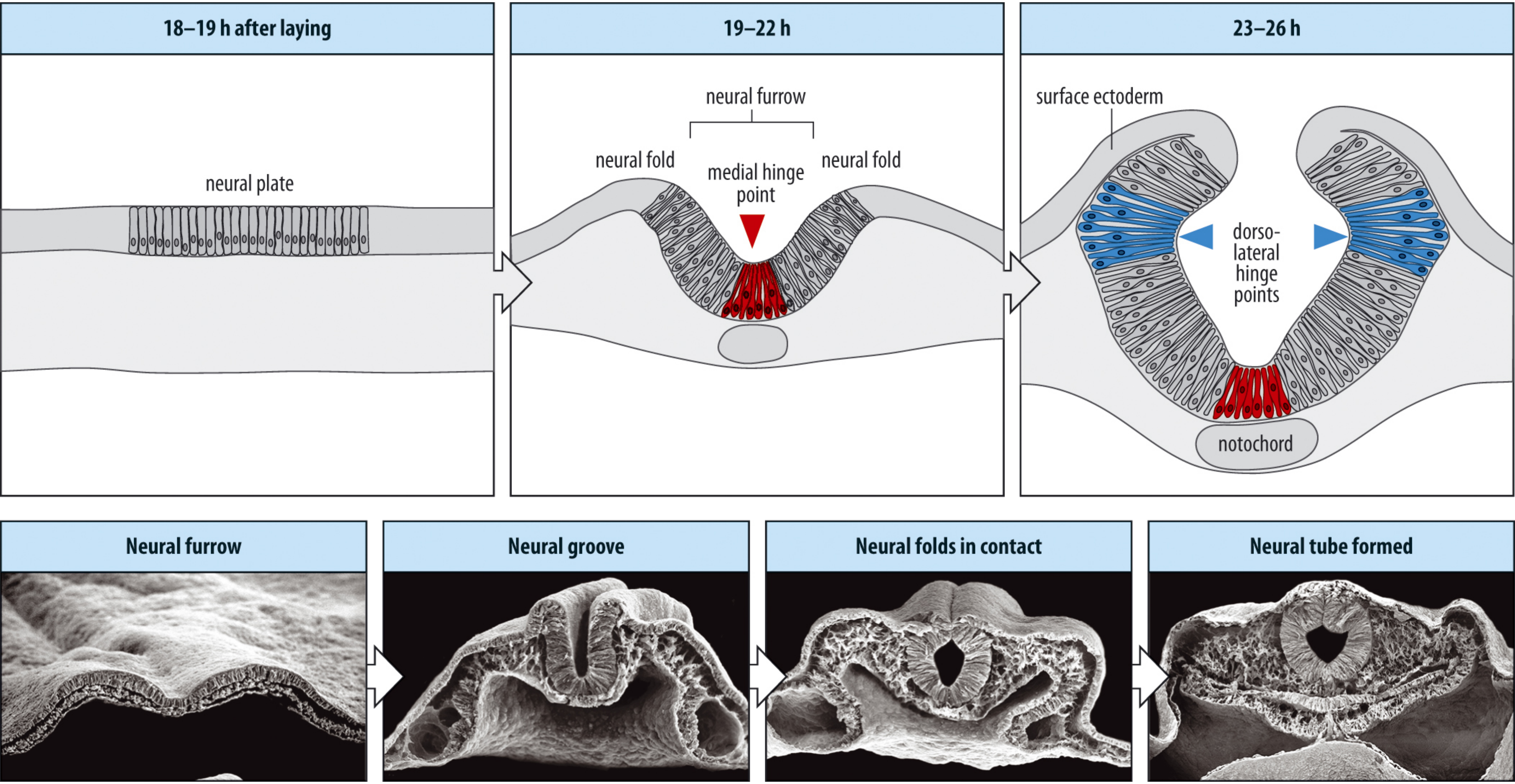


Animal cap **Notochord**

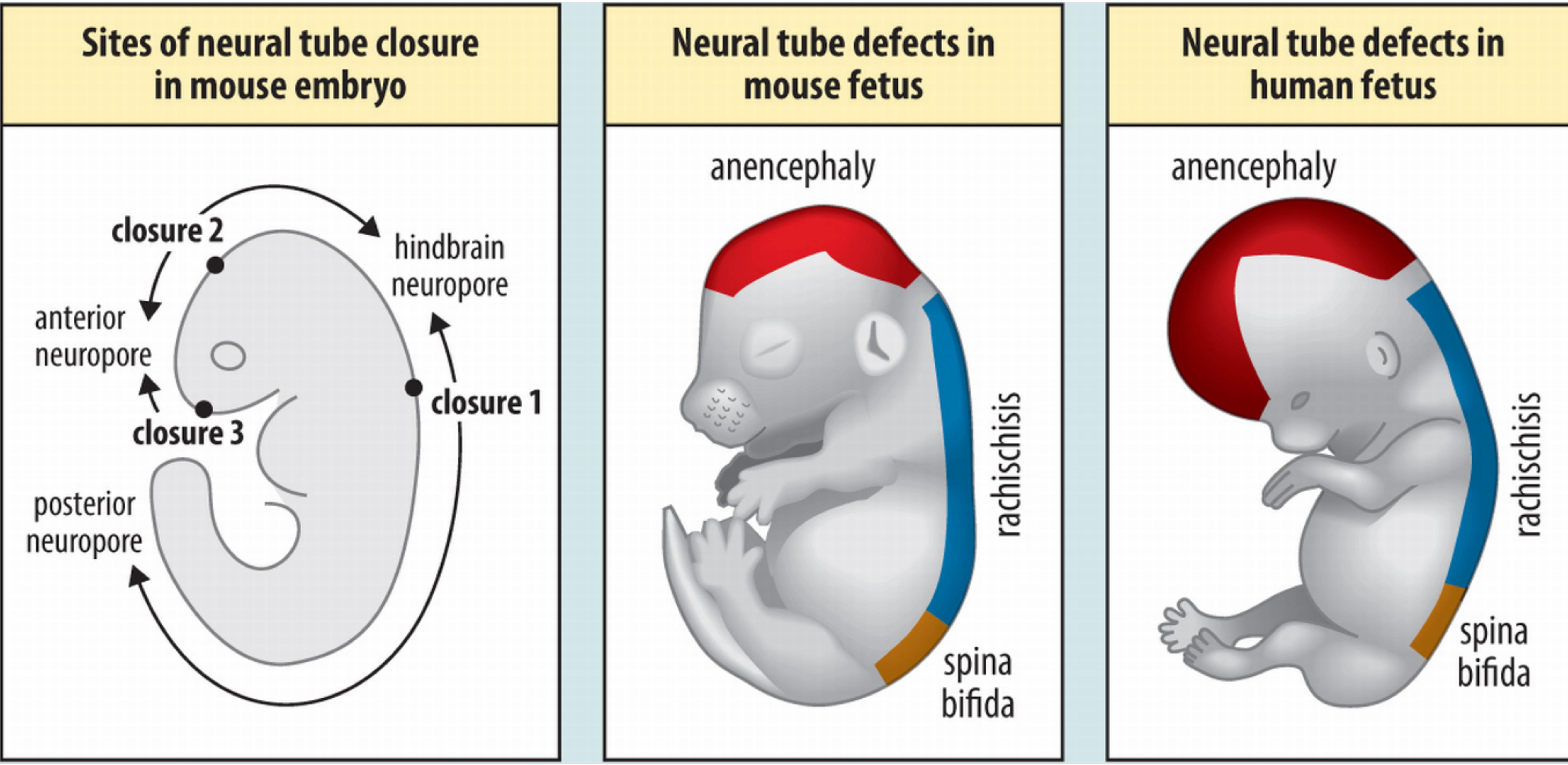
Xenopus and zebrafish



Neural tube formation



Neural tube defects



EphA7 splicing mutation

Vitamin B12, folic acid (Dorothy Hodgkin, Nobel Prize in Chemistry 1964)

Crispr (Doudna, Charpentier)

Summary

- **Gastrulation: folding and shear**
- Gastrulation occurs in a variety of ways involving EMT, invagination and migration
- Epithelia are bent by localised contractility
- Convergent extension involves cell intercalations
- Genetic regulation of both adhesion and contractility
- Other folding - neural tube, brains and guts

Questions?