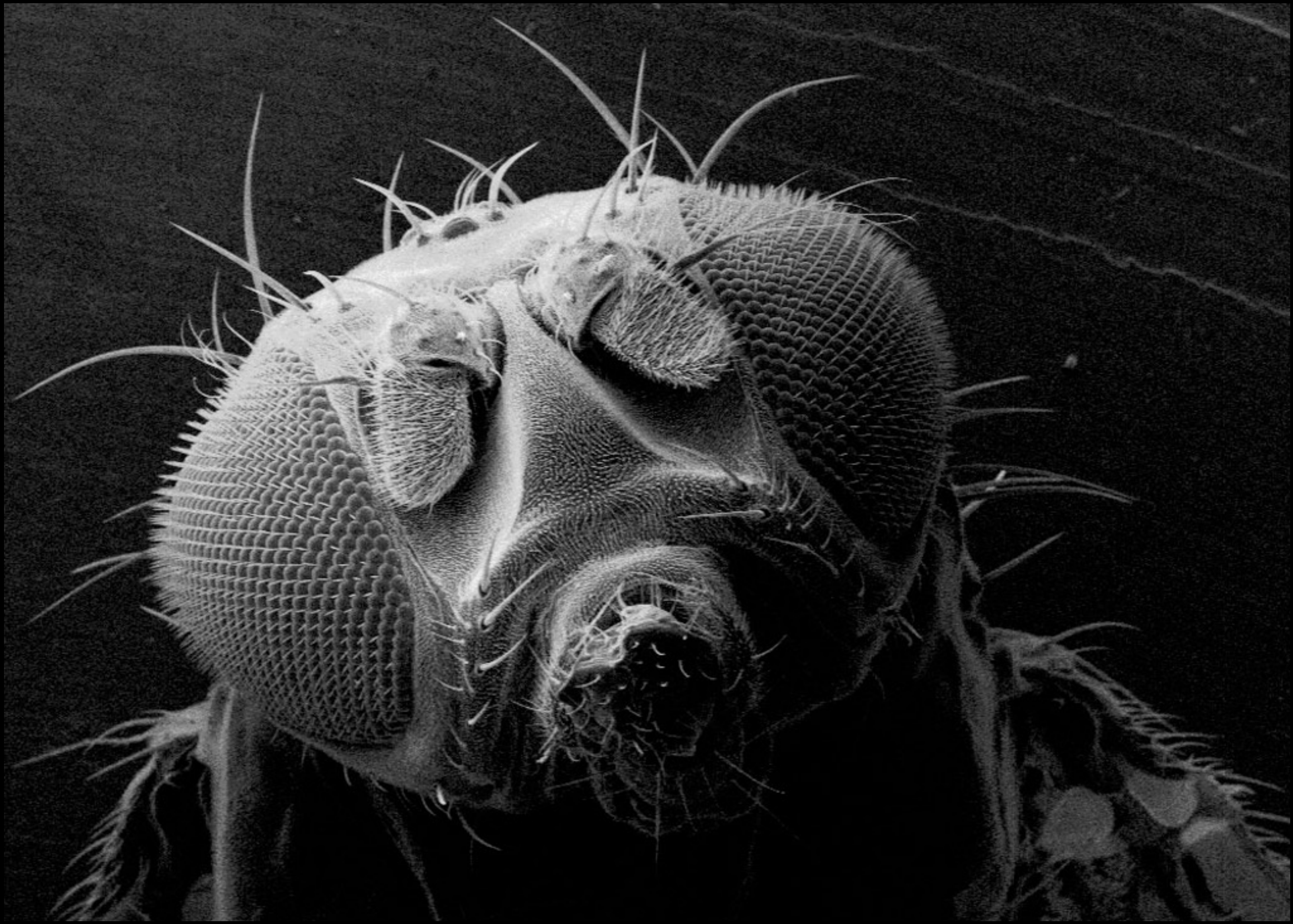
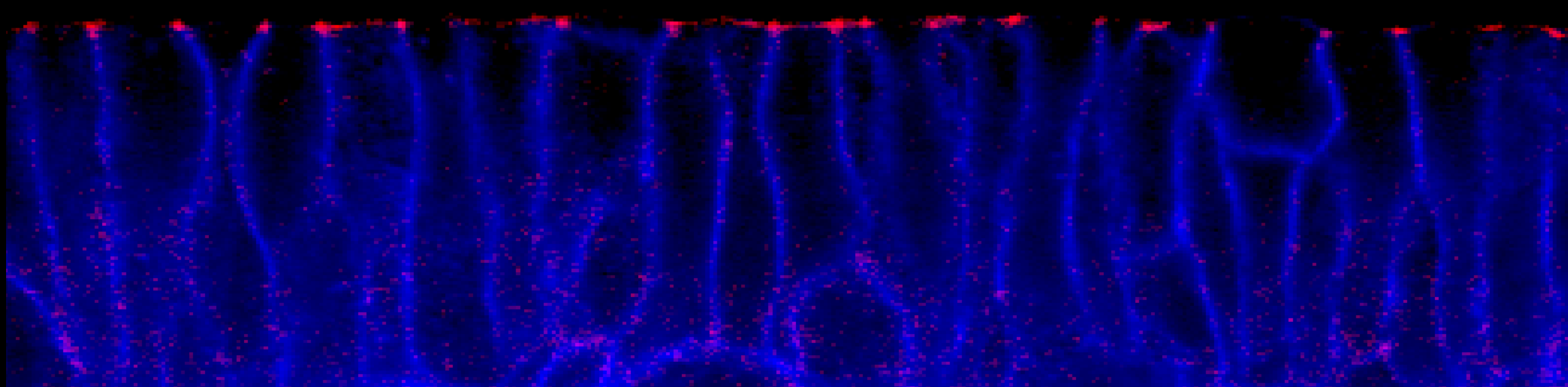
Building multicellular structures during development



neurons

mesenchymal cells

epithelial cells



Outline of lecture

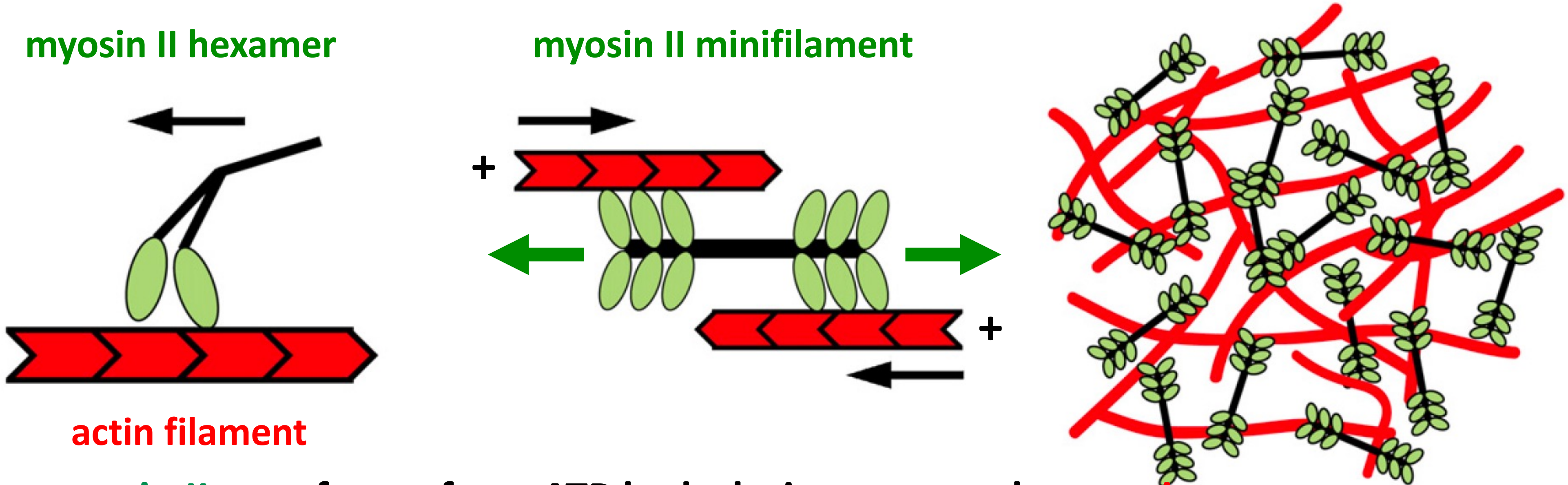
1. How do cells generate force?

2. How do cells respond to force?

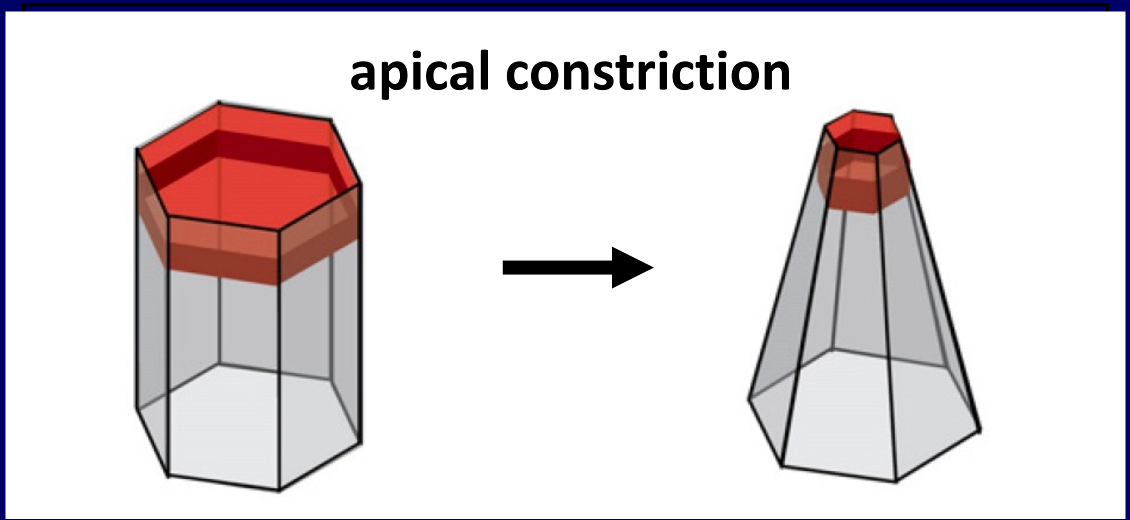
3. Roles of mechanical forces in tissue morphogenesis

4. Open questions and challenges in the field

Actomyosin networks generate contractile force



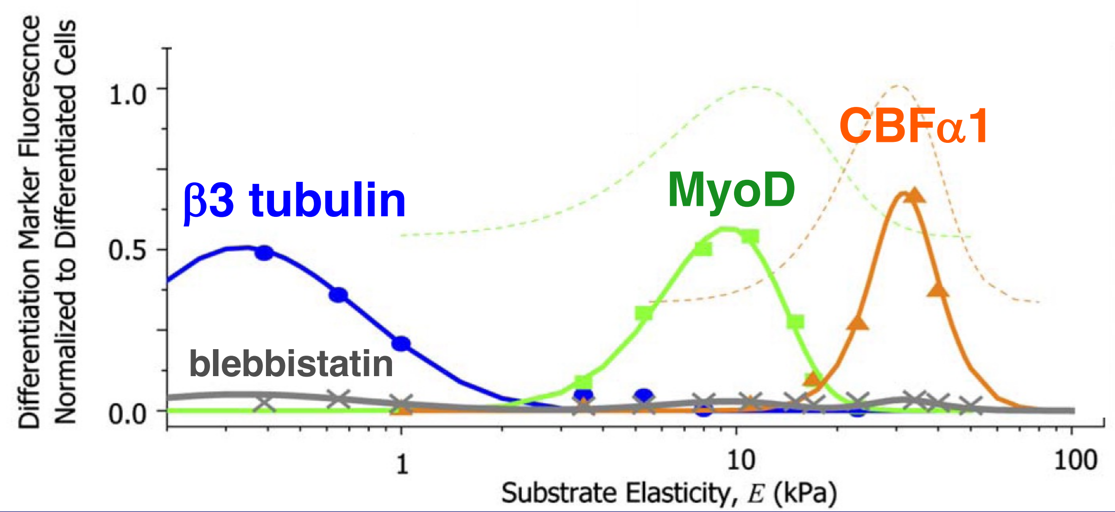
myosin II uses forces from ATP hydrolysis to move along actin



Kasza et al. (2011)
PMID 21130639

How do mechanical signals influence cell behavior?

substrate elasticity contols cell fate

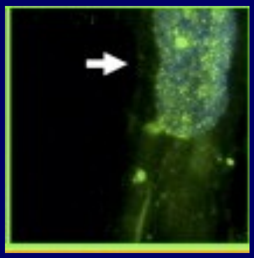


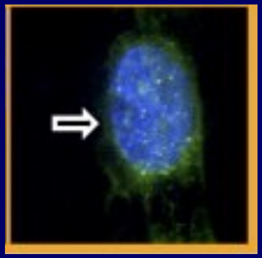
0.1 - 1 kPa
neurogenic

8 - 17 kPa
myogenic

25 - 40 kPa
osteogenic

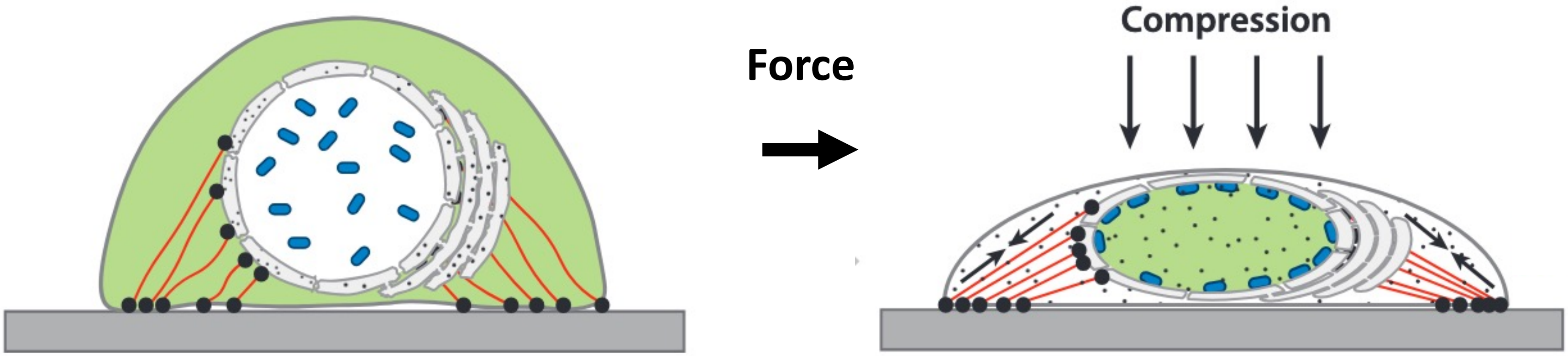
→ glass, plastic MPa





Engler et al. (2006), PMID 16923388

Force sensing by the nucleus



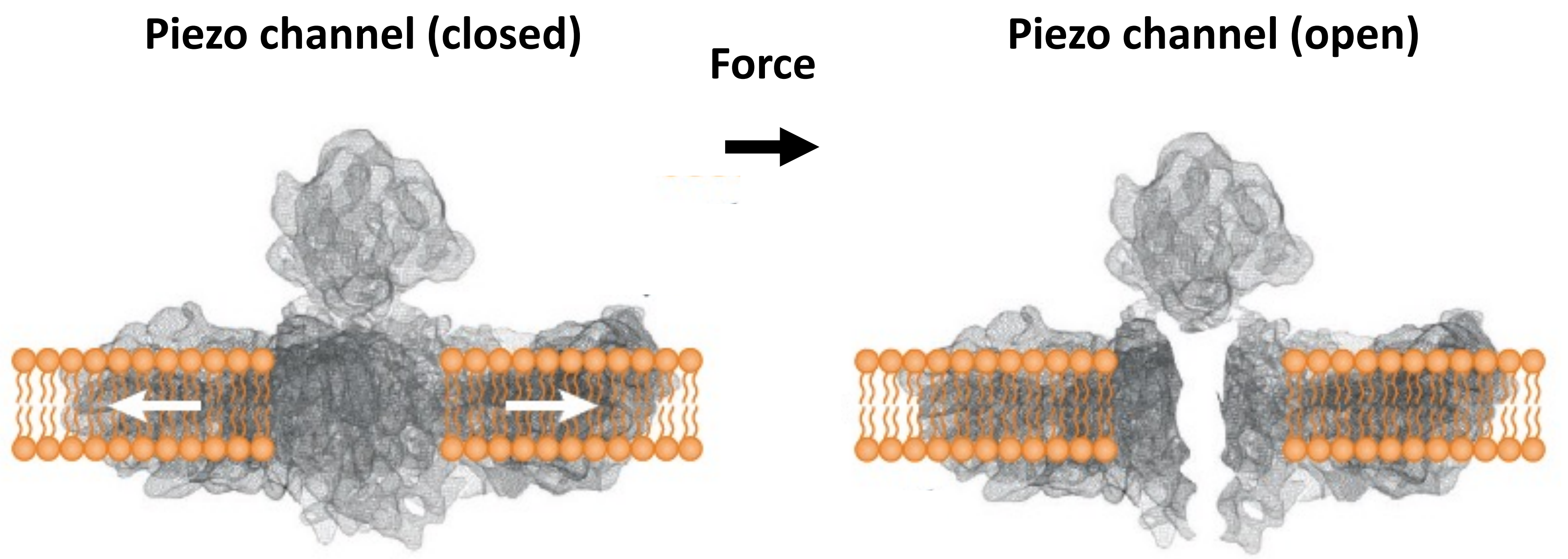
Transcriptional regulators can move into the nucleus

Lipid enzymes can localize to the inner nuclear membrane

Protein complexes link actomyosin networks to the membrane

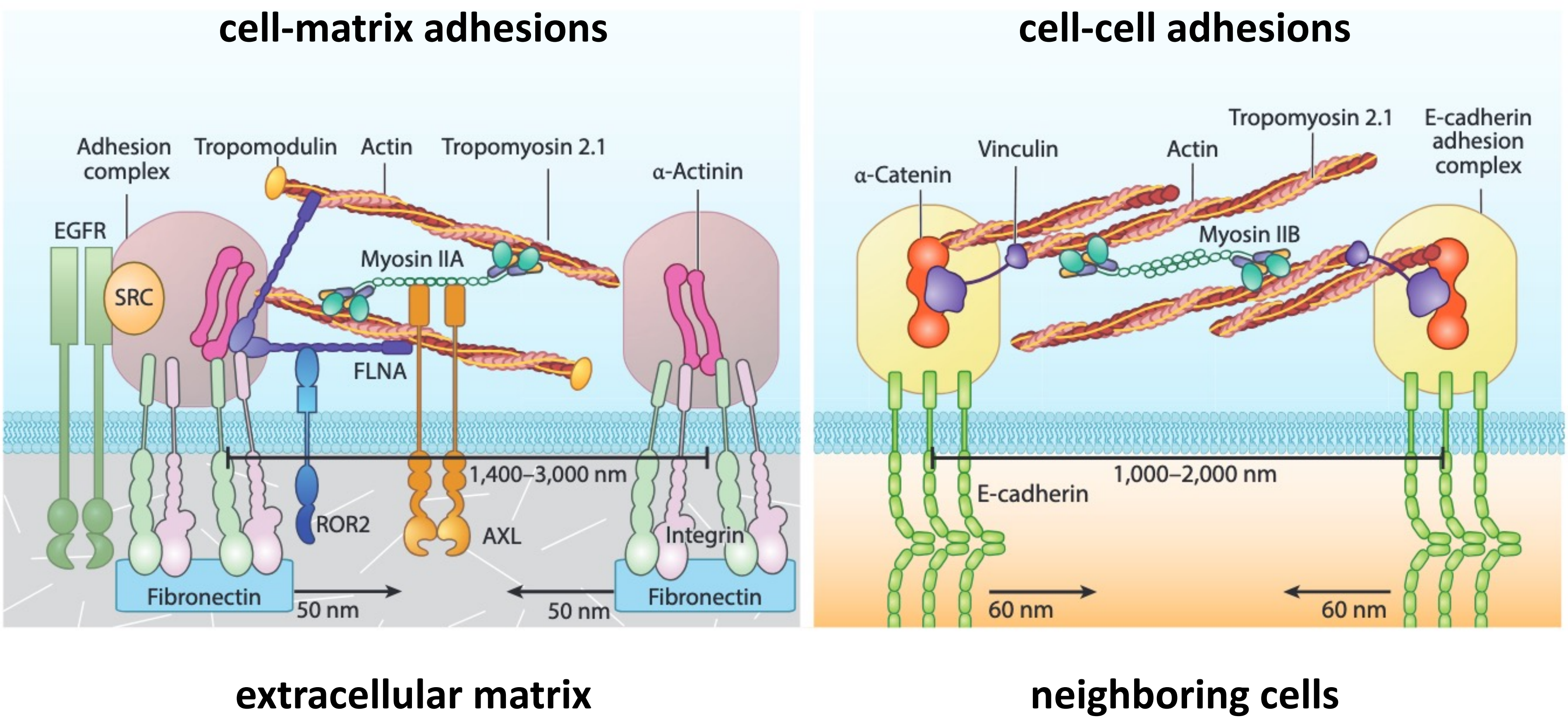
Niethammer (2021), PMID: 34213953

Force sensing at the plasma membrane



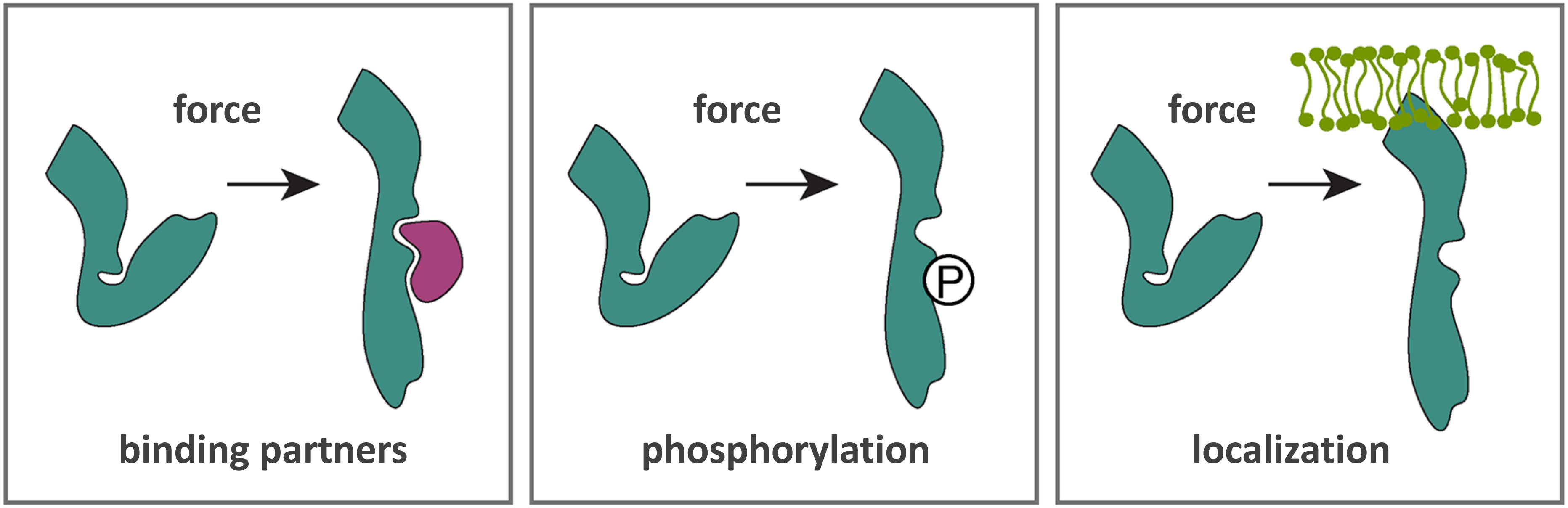
Murthy et al. (2017), PMID: 28974772

Force sensing at cell-matrix and cell-cell adhesions



Sheetz (2019), PMID: 31412209

How cells respond to force: Insights from *in vitro* studies



How do cells respond to physiological forces *in vivo*?

How do these force responses influence cell behavior?

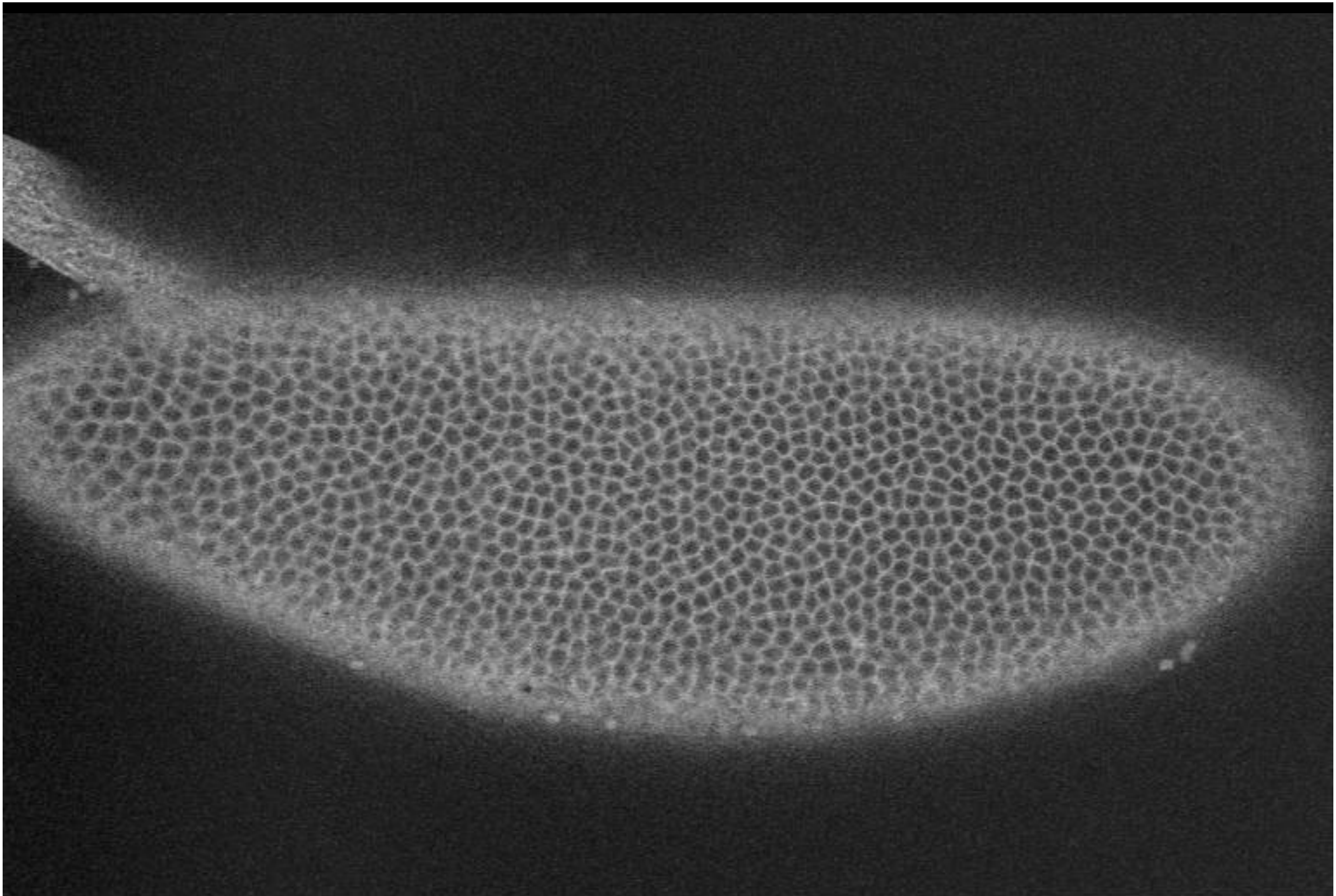
Outline of lecture

1. How do cells generate force?

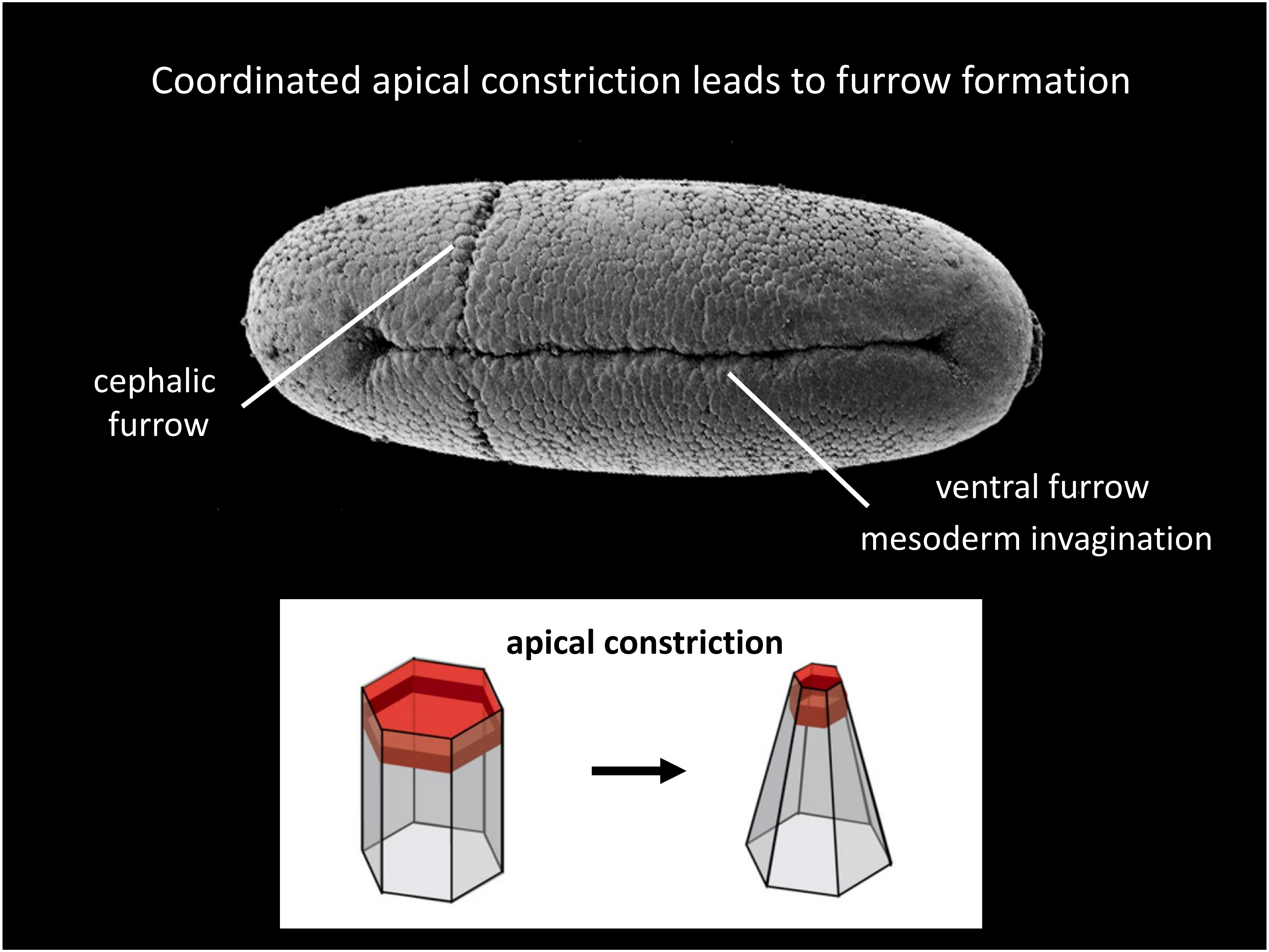
2. How do cells respond to force?

3. Roles of mechanical forces in tissue morphogenesis

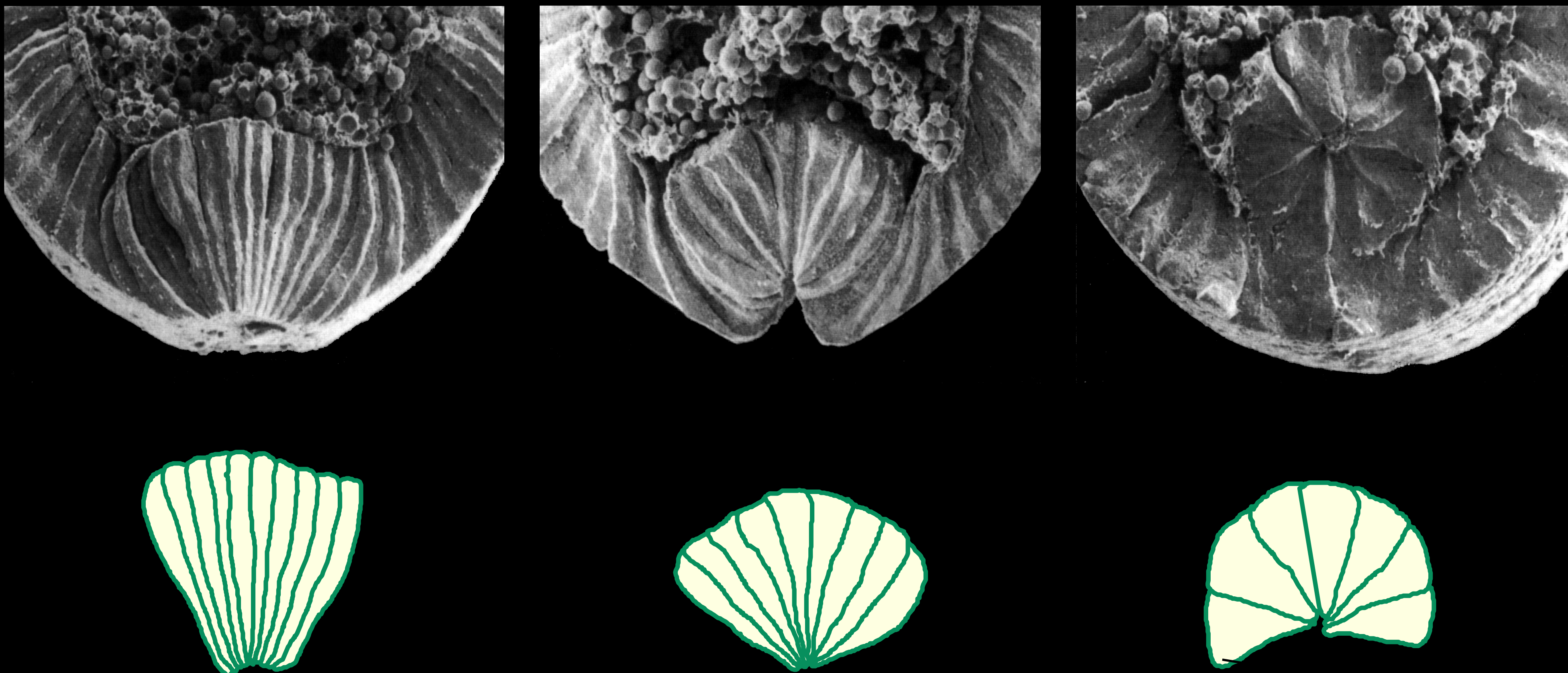
4. Open questions and challenges in the field



Movie of embryo expressing myristylated GFP by Eric Wieschaus


Coordinated apical constriction leads to furrow formation
cephalic furrow
ventral furrow
mesoderm invagination
apical constriction

Coordinated apical constriction leads to furrow formation

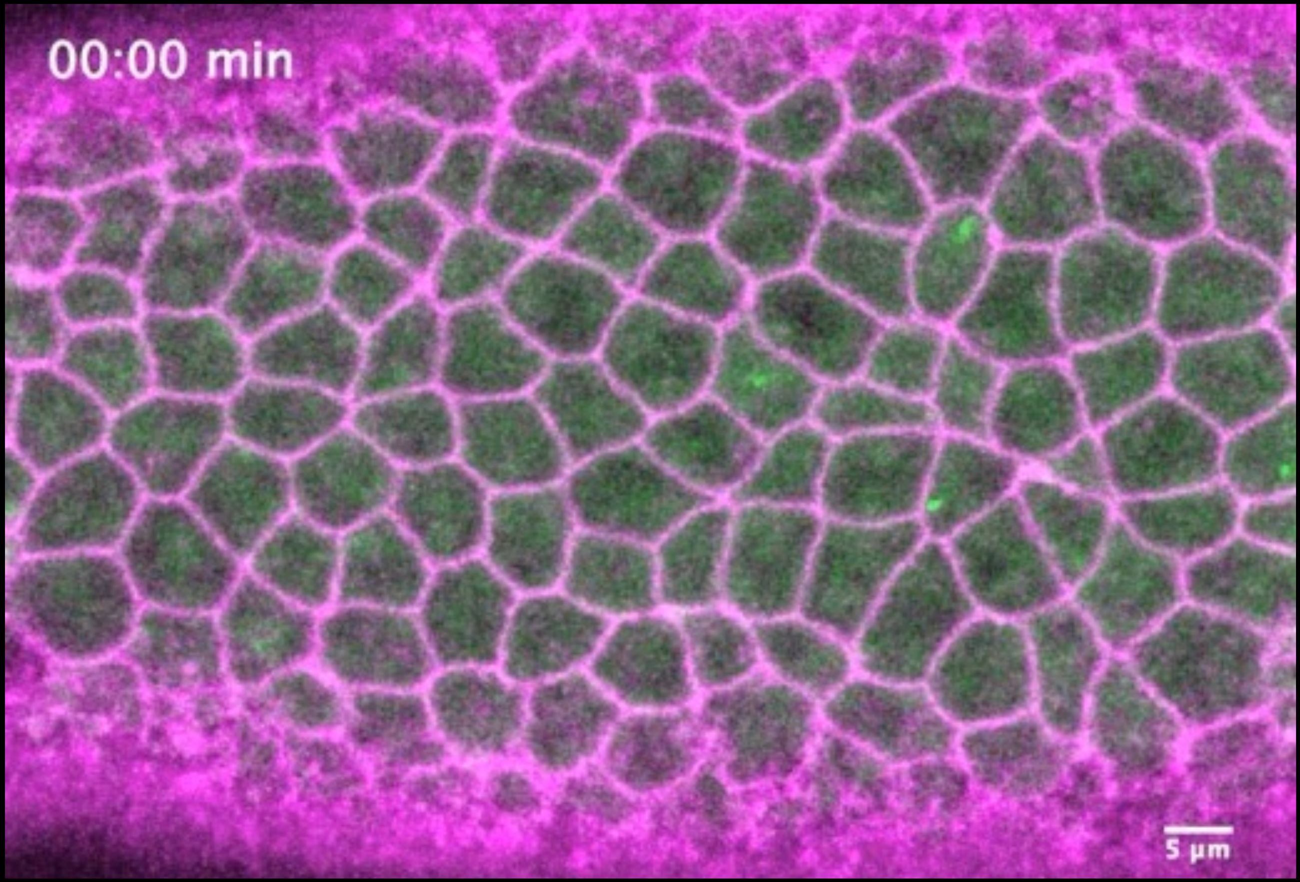


apical constriction

apical-basal shortening

Apical actomyosin contractility drives mesoderm invagination

Wild-type embryo

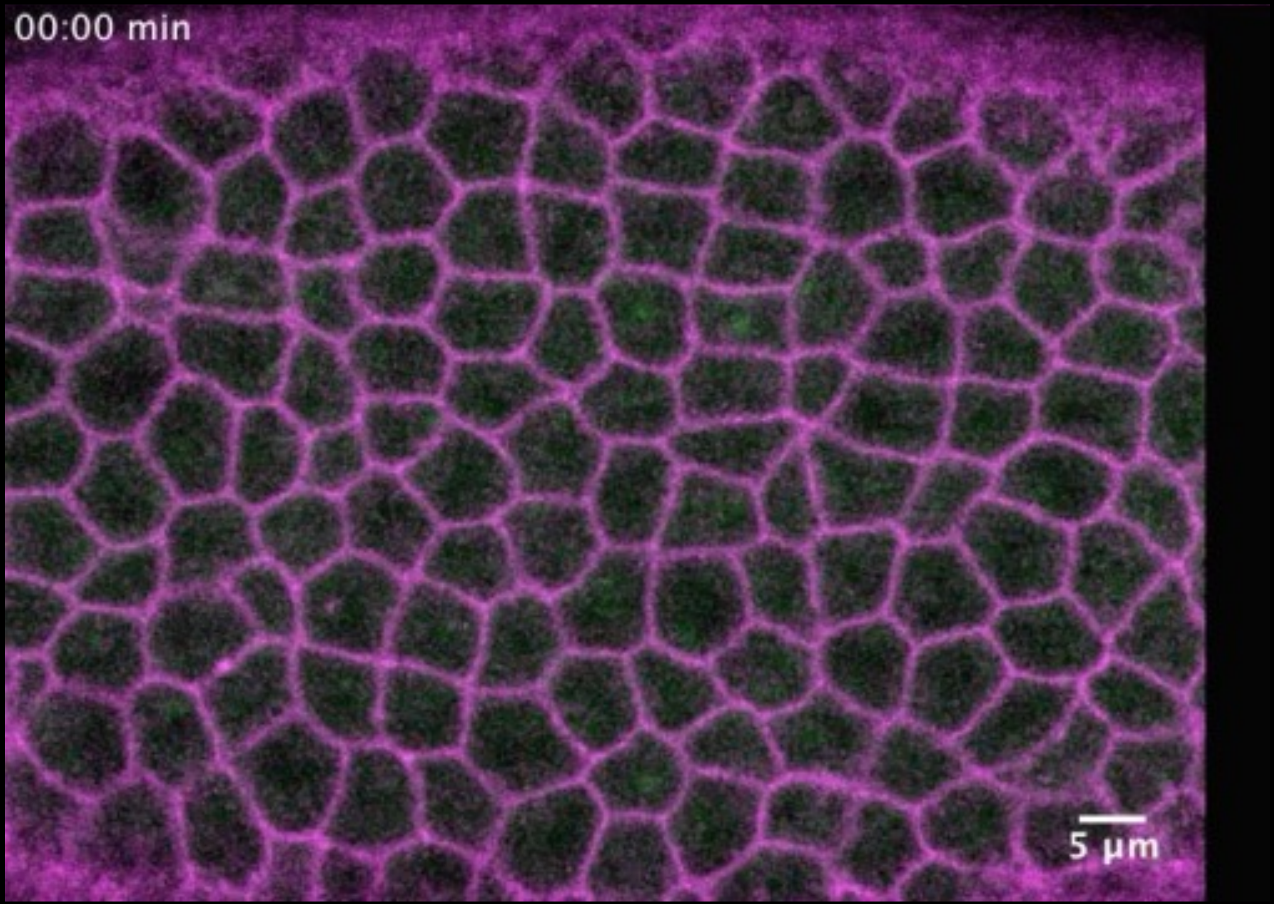


Rho-kinase-GFP cell membrane

Coravos and Martin (2016), PMID: 27773487

Apical actomyosin contractility drives mesoderm invagination

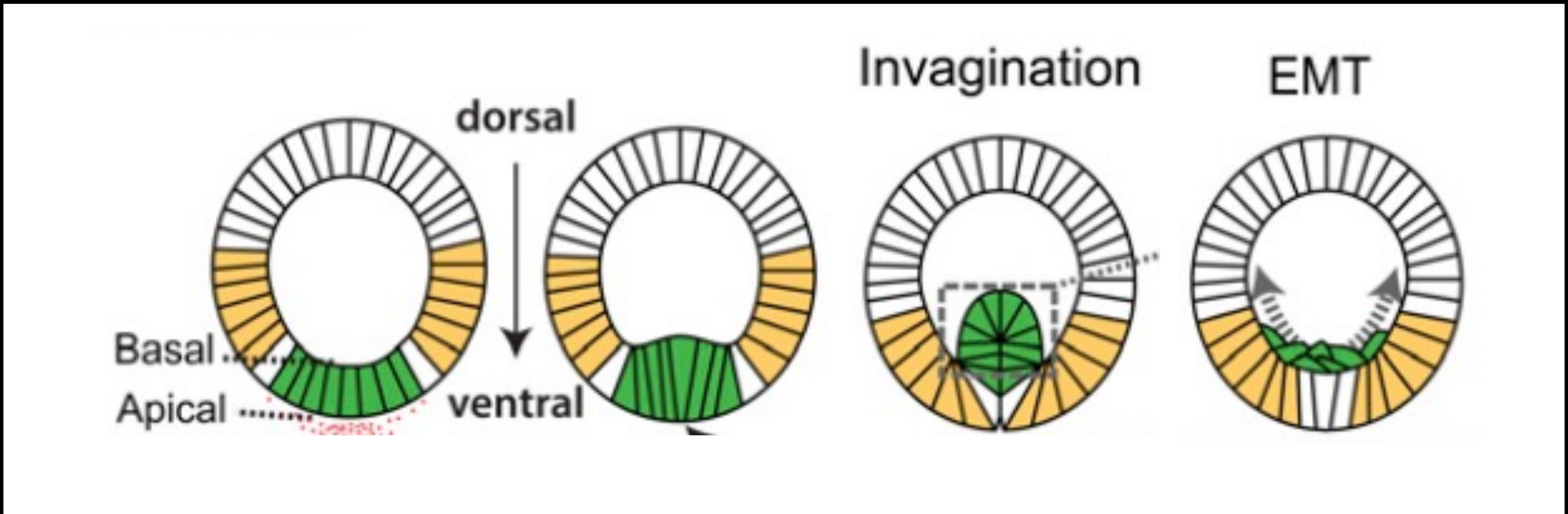
Inject Rho-kinase inhibitor partway through movie



Rho-kinase-GFP cell membrane

Coravos and Martin (2016), PMID: 27773487

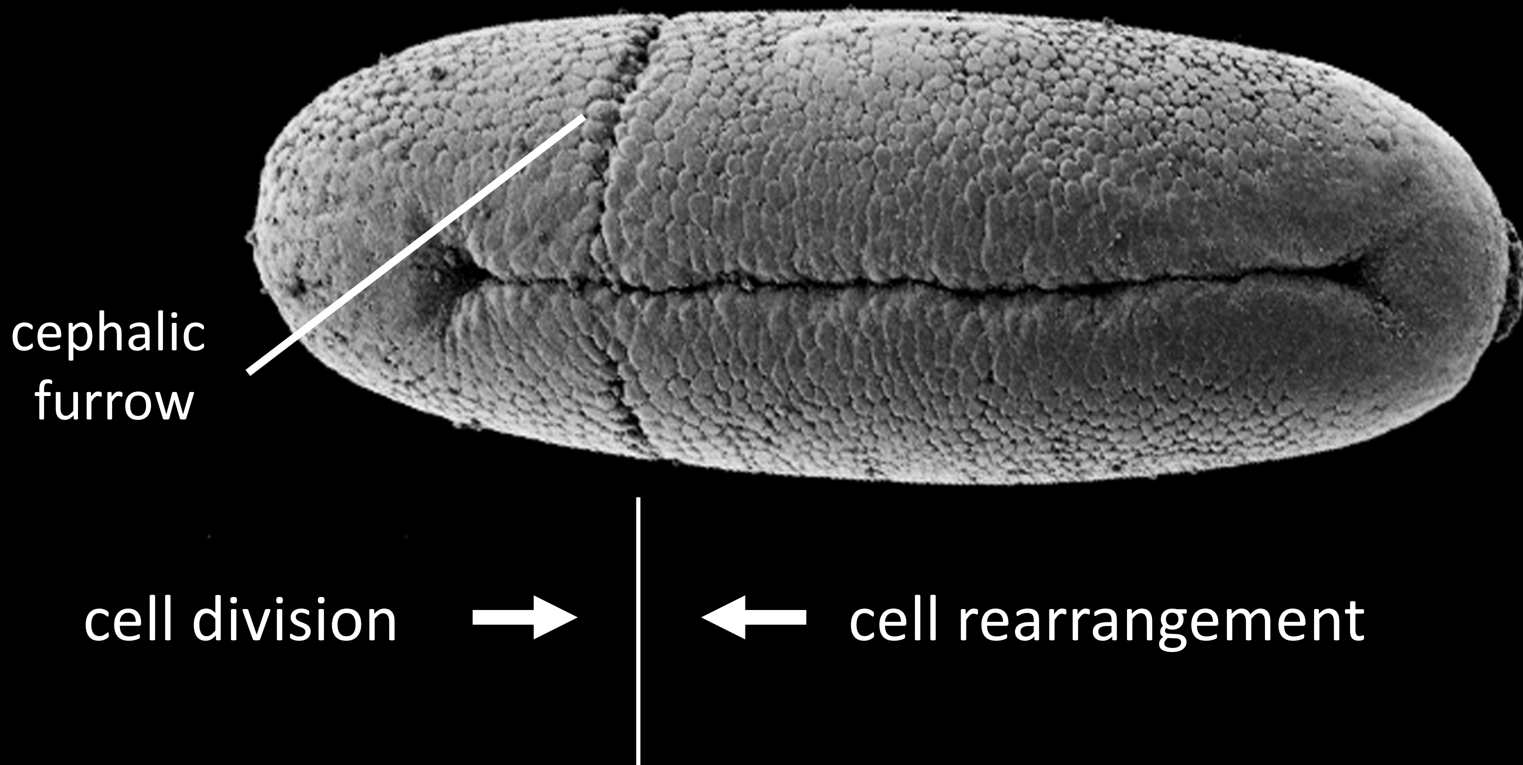
Genetic studies have identified key regulators of cell behavior



Transcriptional regulators	Signaling molecules	Force-generating proteins
Twist	GPCR	myosin II
Snail	G α	F-actin
	Rho GTPase	

Martin (2020), PMID: 32132154

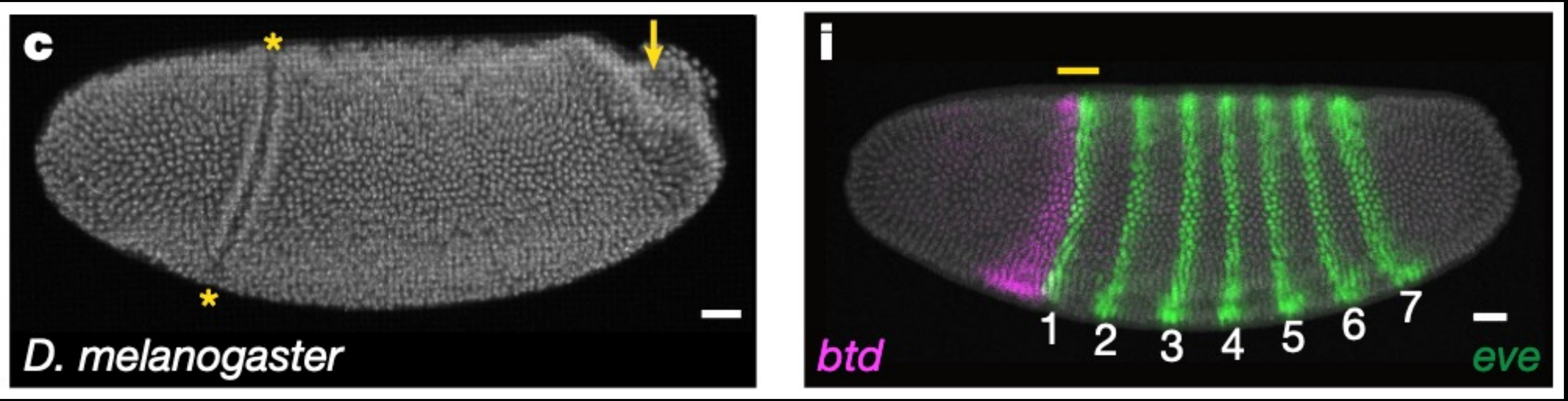
The cephalic furrow is a transient structure in the embryo



The ventral furrow leads to the permanent internalization of mesoderm cells

The cephalic furrow is transient, lasting only around 1.5 hours

What is the function of the cephalic furrow?



buttonhead (cephalic furrow)

Eve (cephalic furrow and axis elongation)

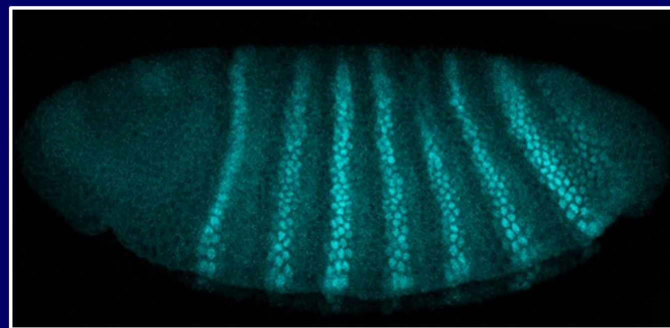
Dey et al. (2025), PMID: 40903584

Optogenetic ablation of the Cephalic furrow

Interpretation: the cephalic furrow is a mechanical sink that releases compressive stress

Dey et al. (2025), PMID: 40903584

Patterned spatial cues generate planar polarized forces

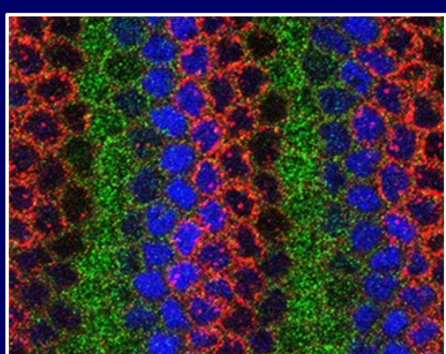


Eve, Runt

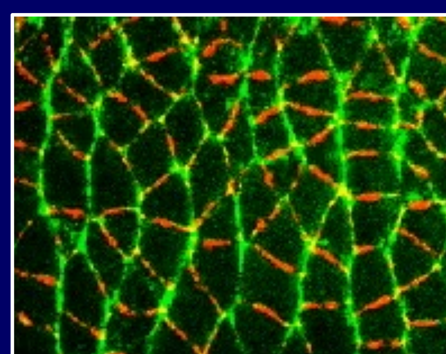
transcription factors

Eve and Runt target genes

Cell fate

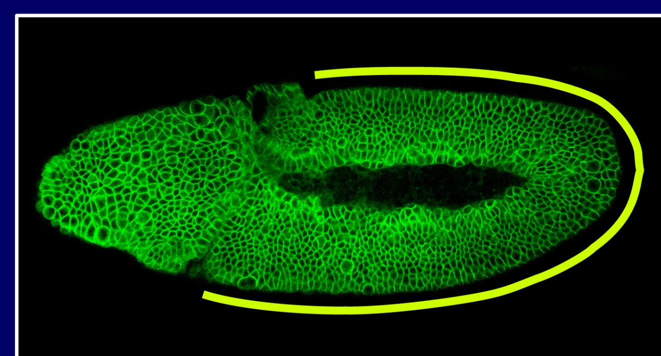


Planar polarized forces

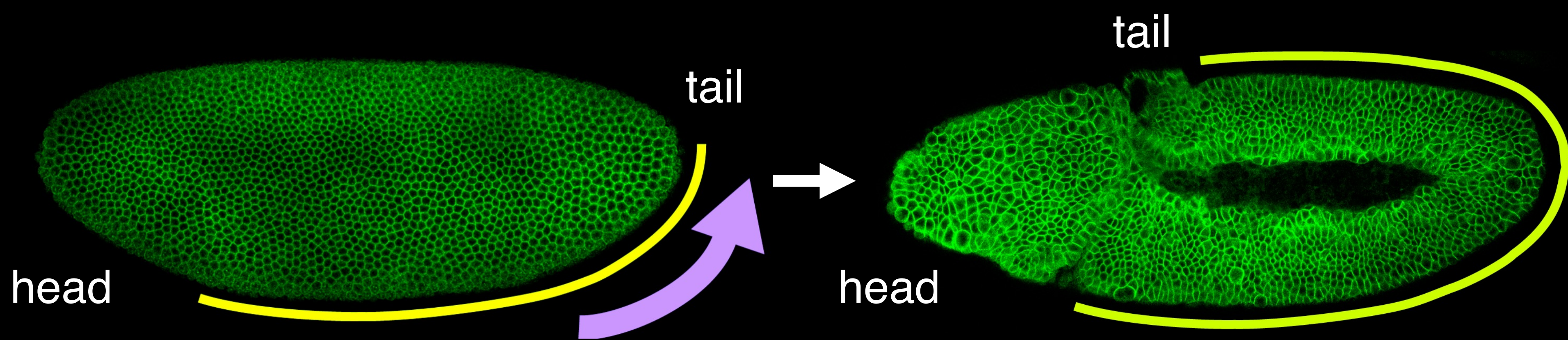


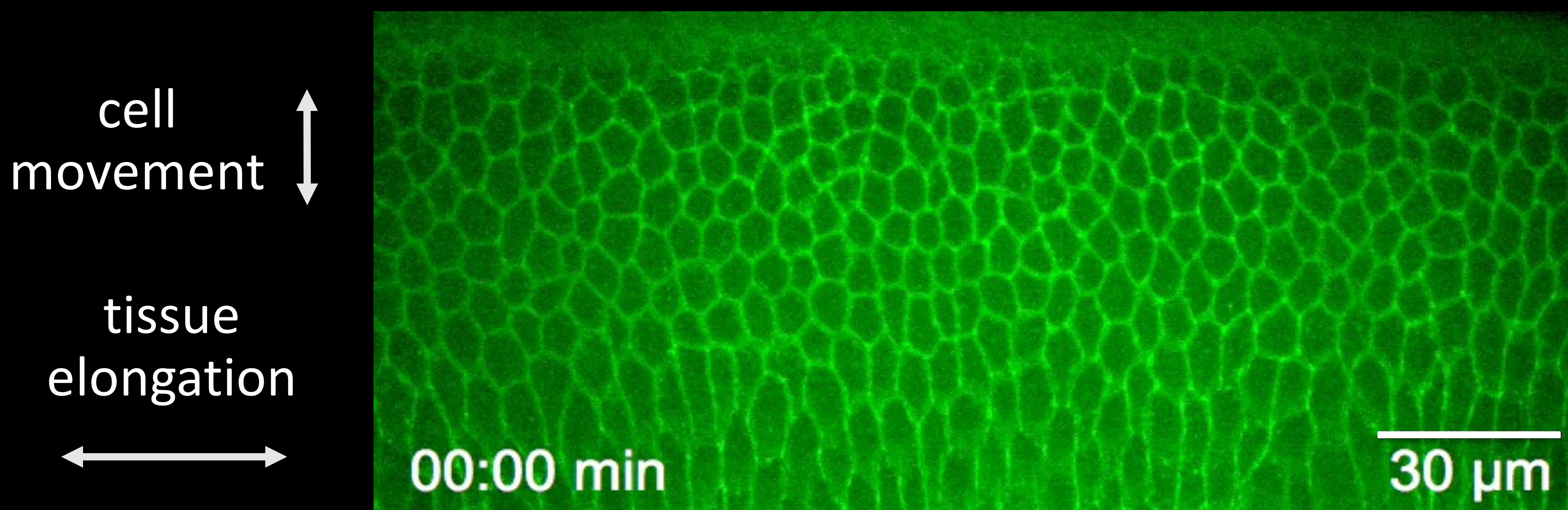
myosin II

Tissue elongation



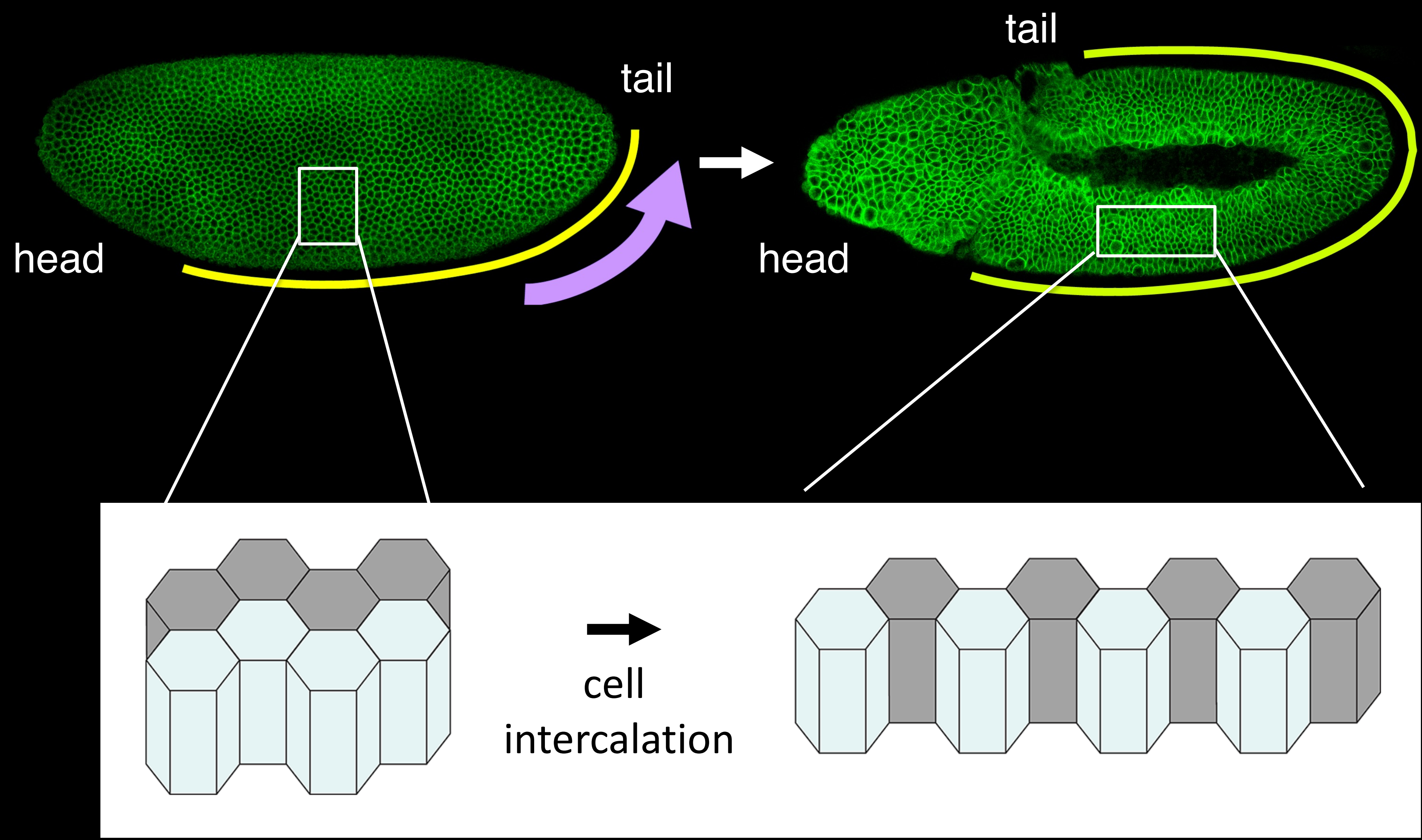
Cell rearrangements elongate the *Drosophila* body axis





Adam Paré

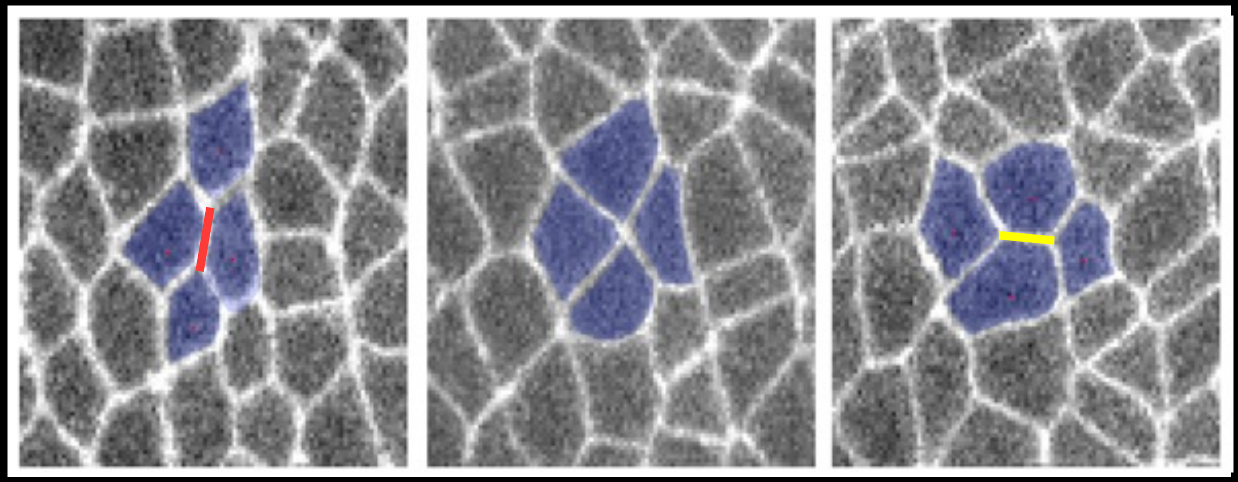
Cell rearrangements elongate the *Drosophila* body axis



Cell rearrangements elongate the *Drosophila* body axis

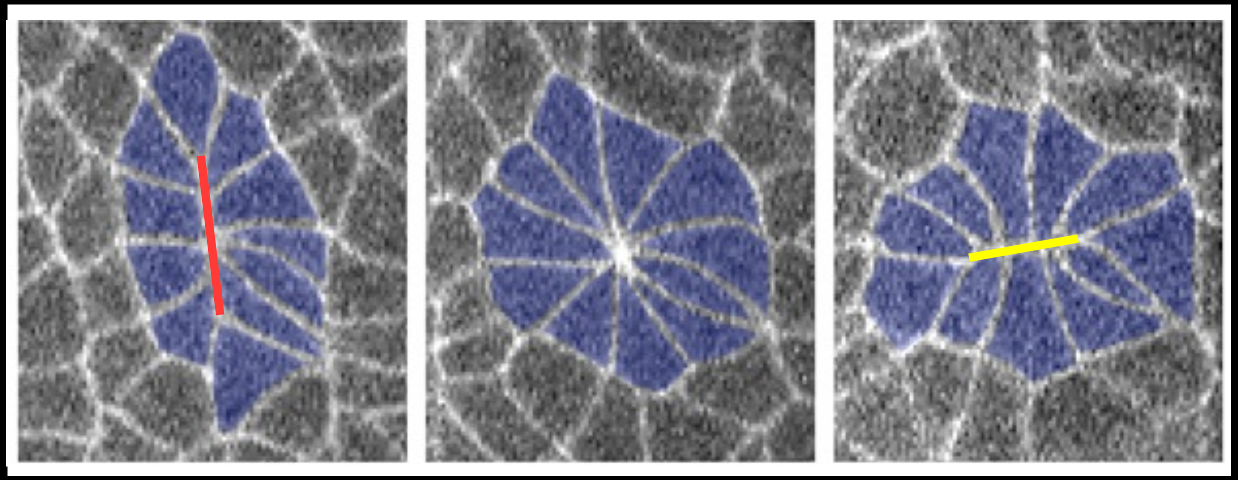
time →

neighbor exchange



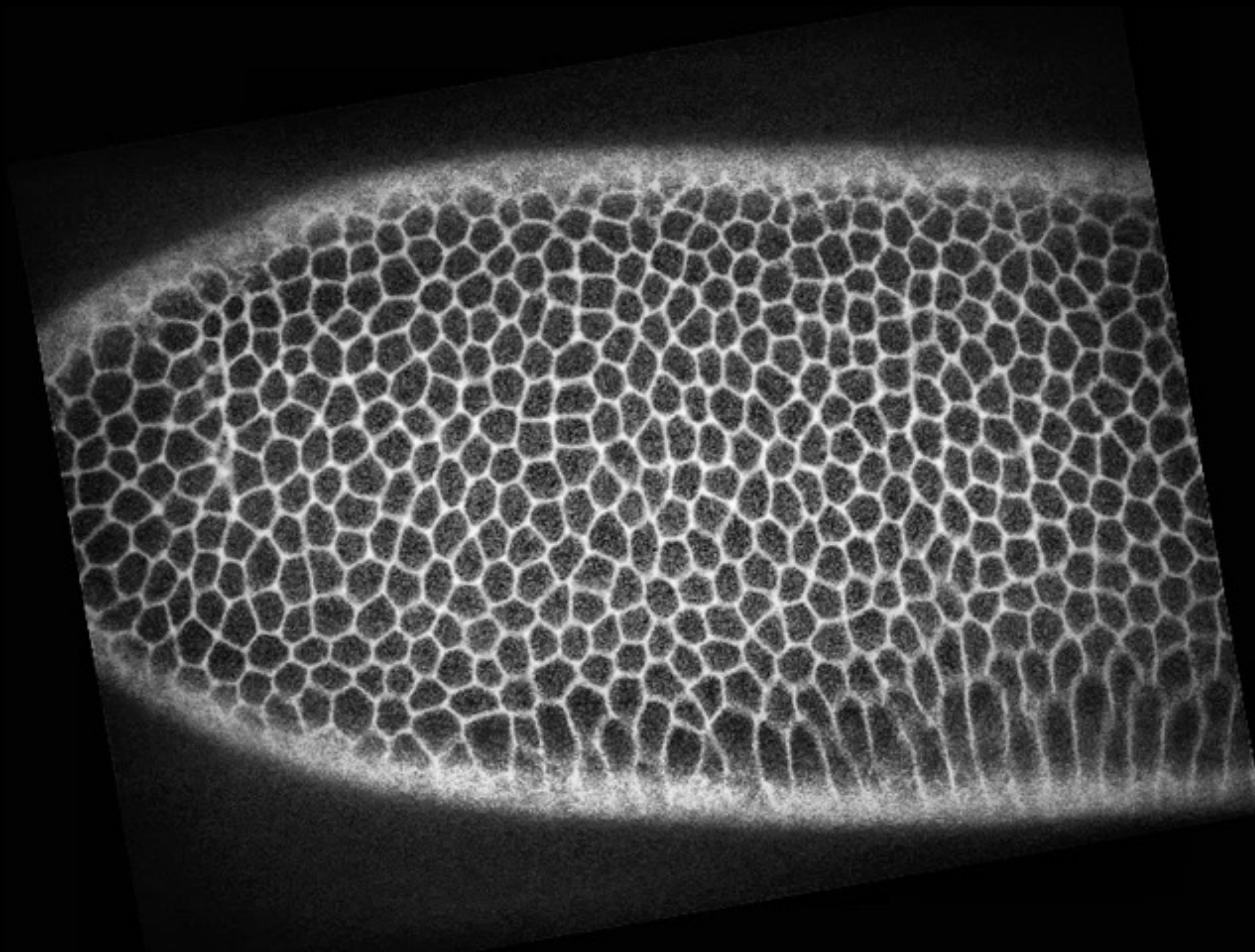
Bertet et al. PMID: 15190355

rosette formation

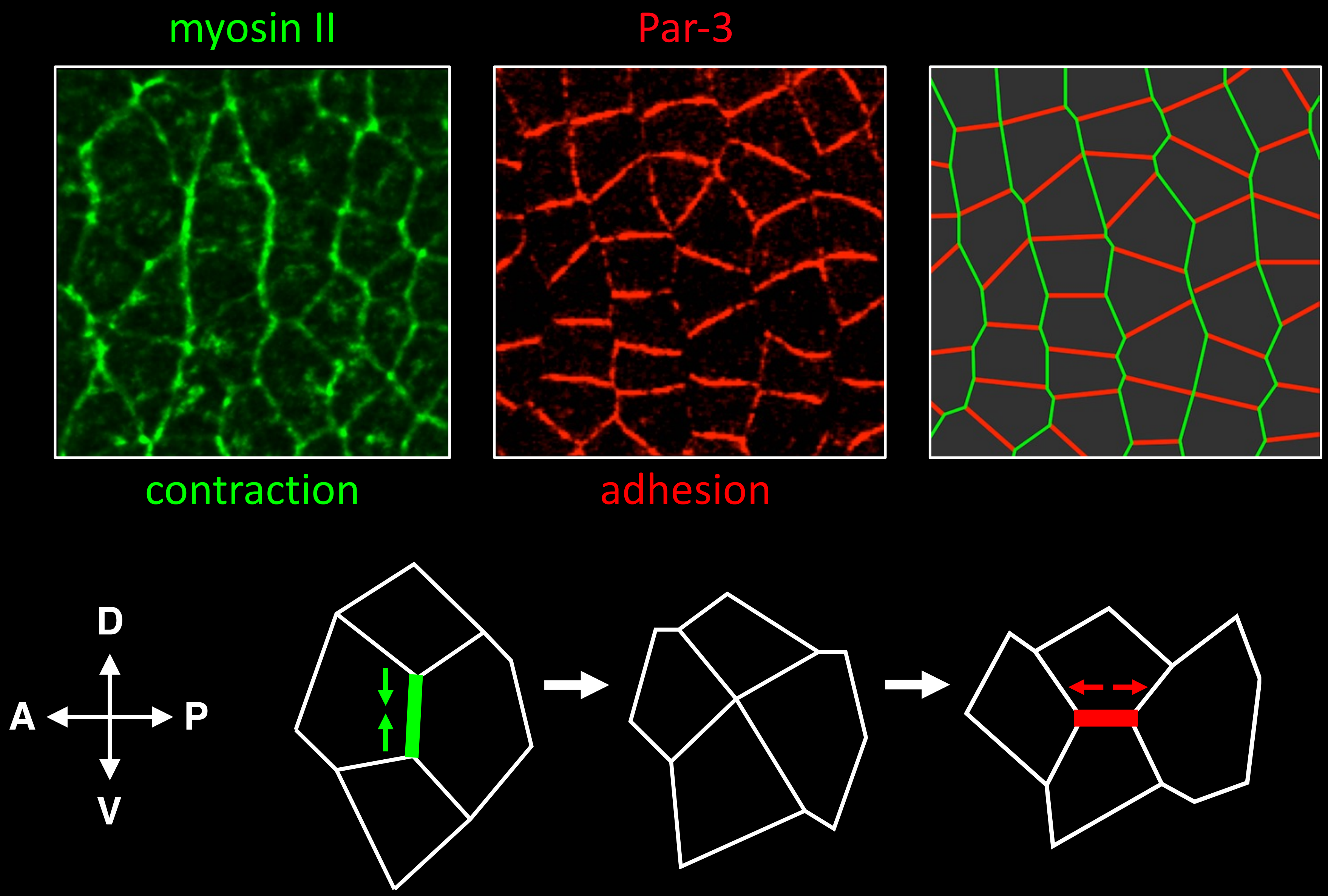


Blankenship et al. PMID: 17011486

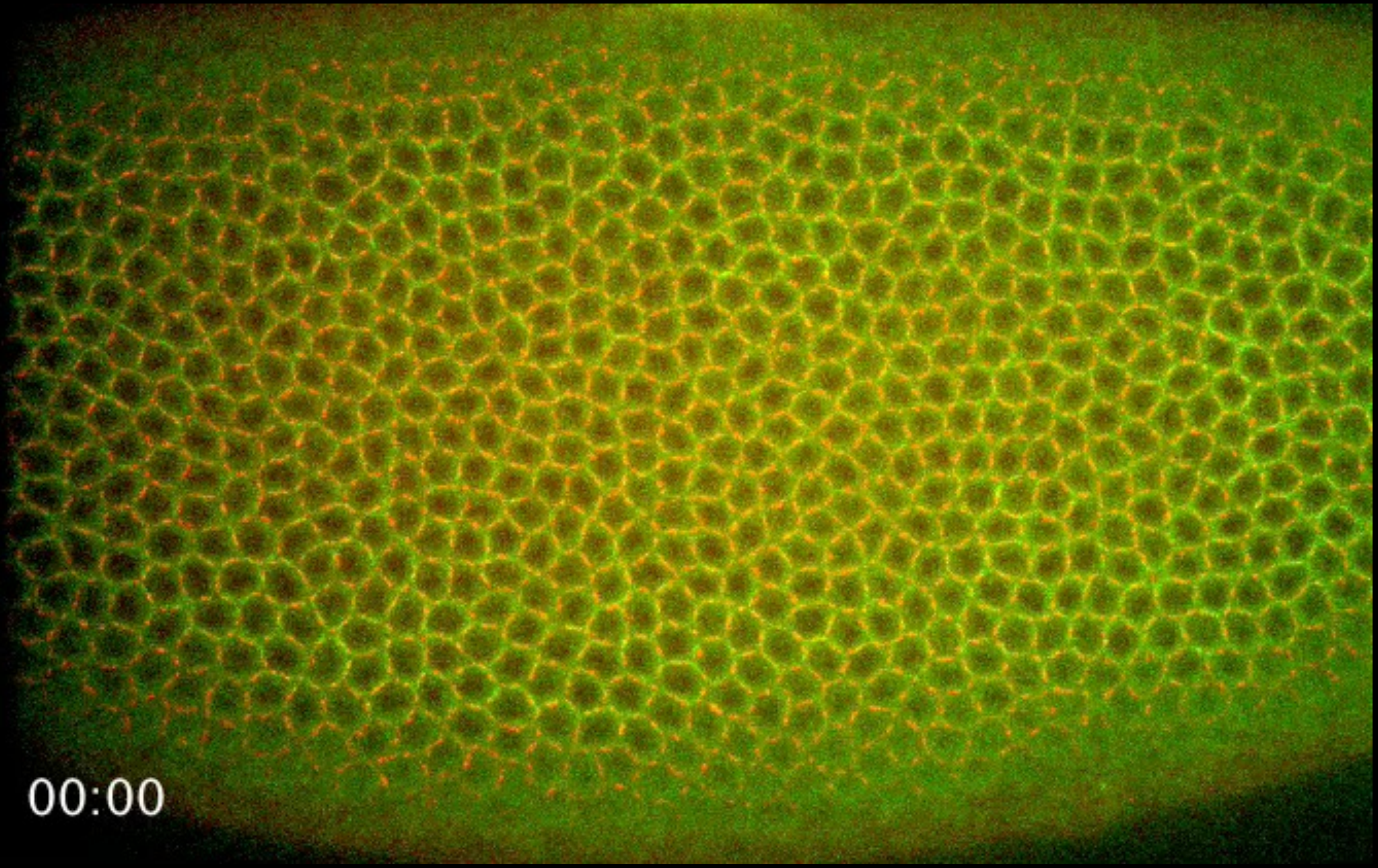
Cell rearrangements elongate the *Drosophila* body axis



Localized contractile and adhesive forces drive axis elongation



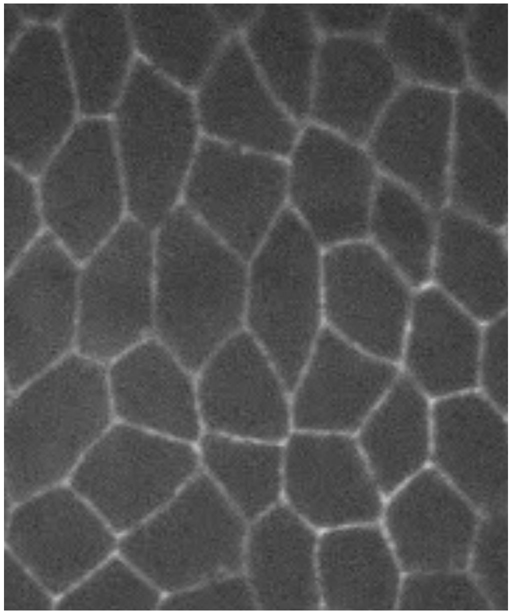
Localized contractile and adhesive forces drive axis elongation



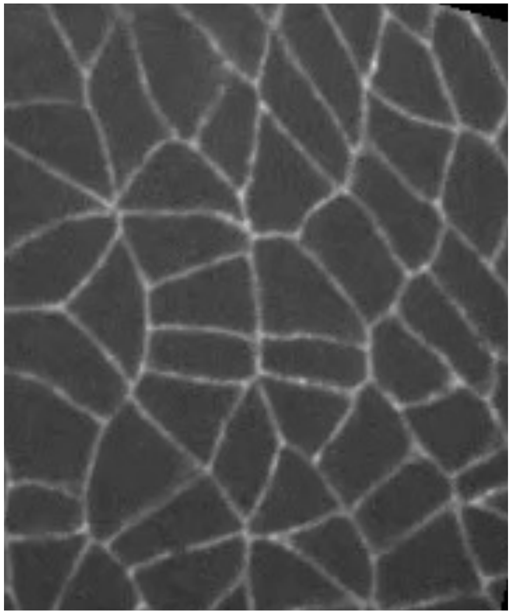
myosin II Par-3

Sergio Simoes

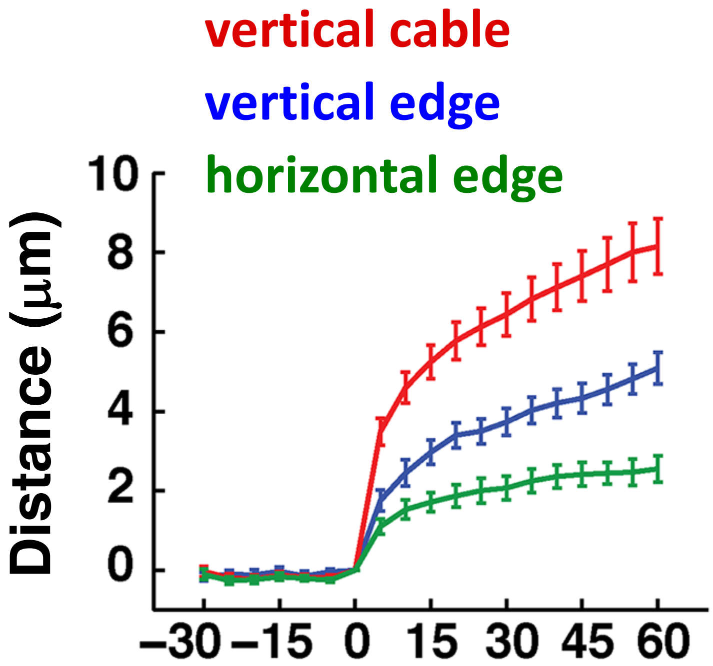
Analyzing the distribution of forces in the embryo



single edge
neighbor exchange



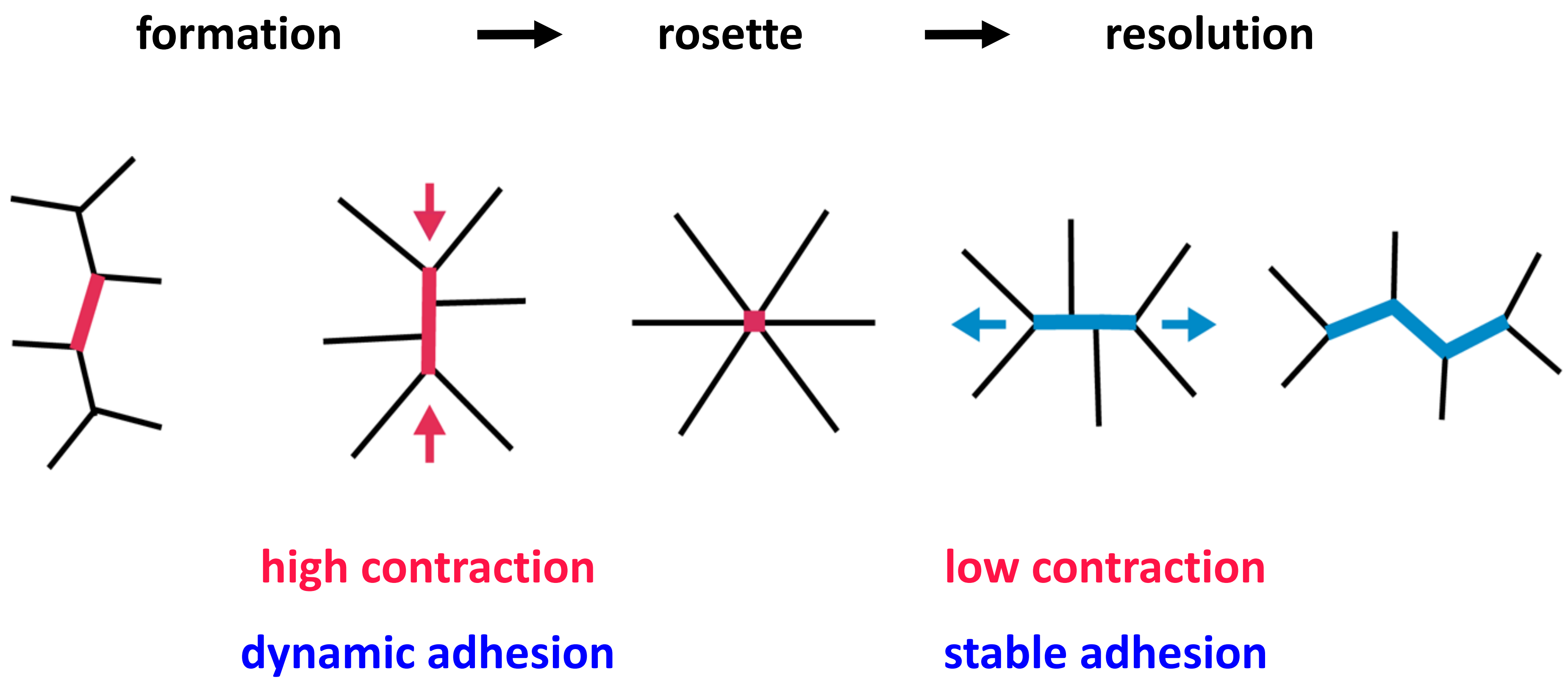
multicellular cable
rosette formation



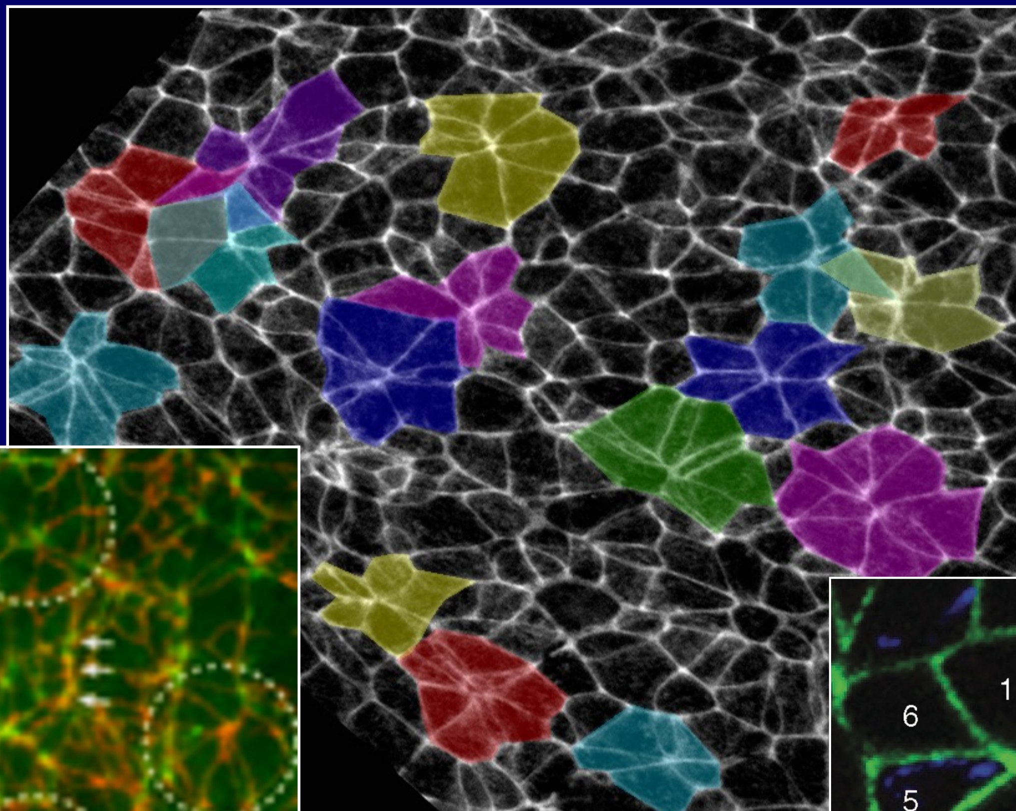
time (seconds)

Fernandez-Gonzalez et al. PMID: 19879198

Actomyosin cables drive cell rearrangement

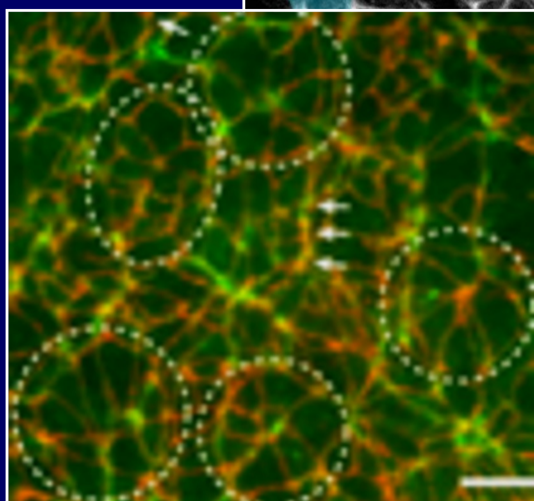


Rosettes as a general mechanism for epithelial elongation



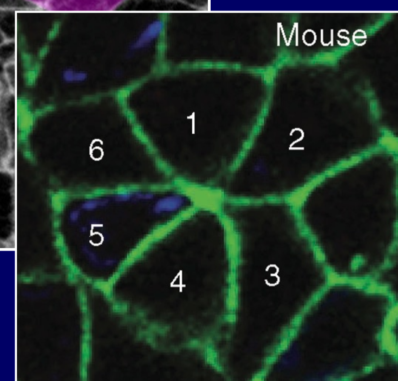
mouse
neural plate

Jamie Mahaffey
Kathryn Anderson
MSKCC
Sutherland,
Hildebrand labs



chick neural plate

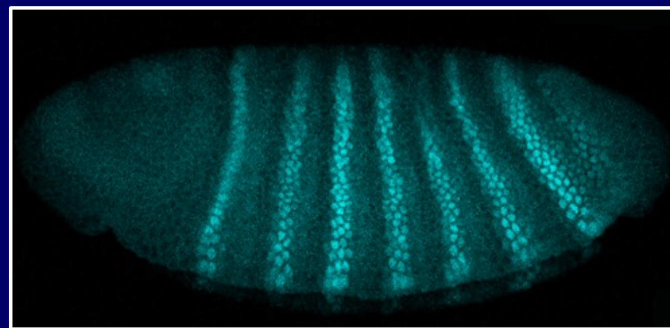
Takeichi, Weijer labs



mouse and frog kidney

Walz, Wallingford labs

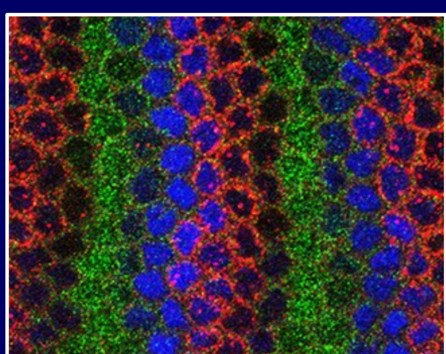
Patterned spatial cues generate planar polarized forces



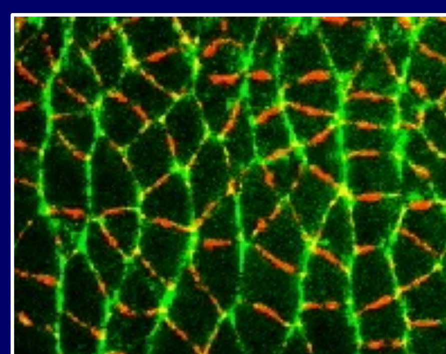
Eve, Runt
transcription factors

Eve and Runt target genes

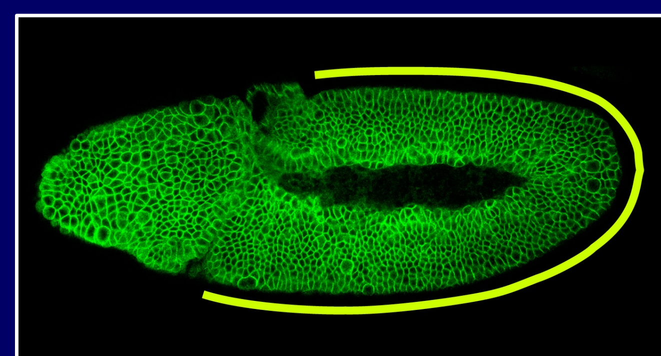
Cell fate



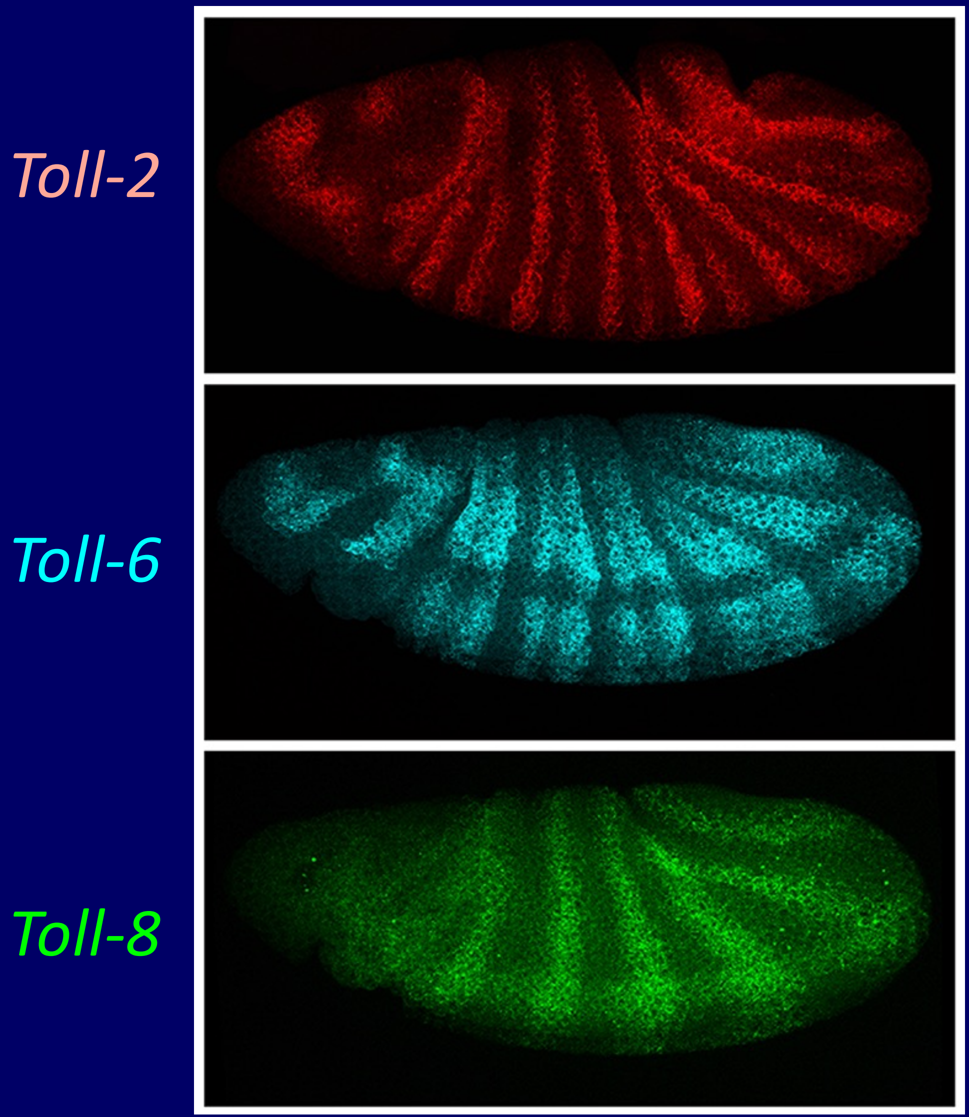
Planar polarized forces

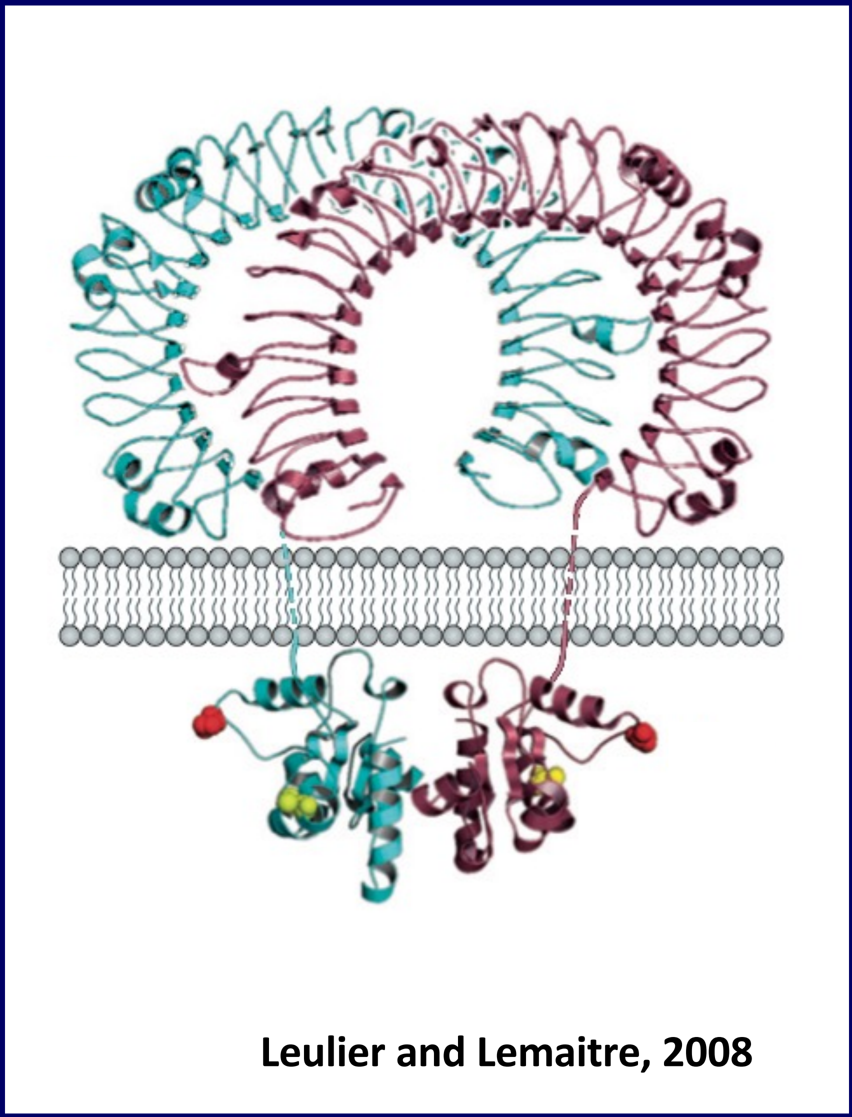


Tissue elongation



A positional Toll receptor code directs cell movements





Paré et al. (2014) PMID 25363762

# of neighbors lost

0

↓

1

↓

2

↓

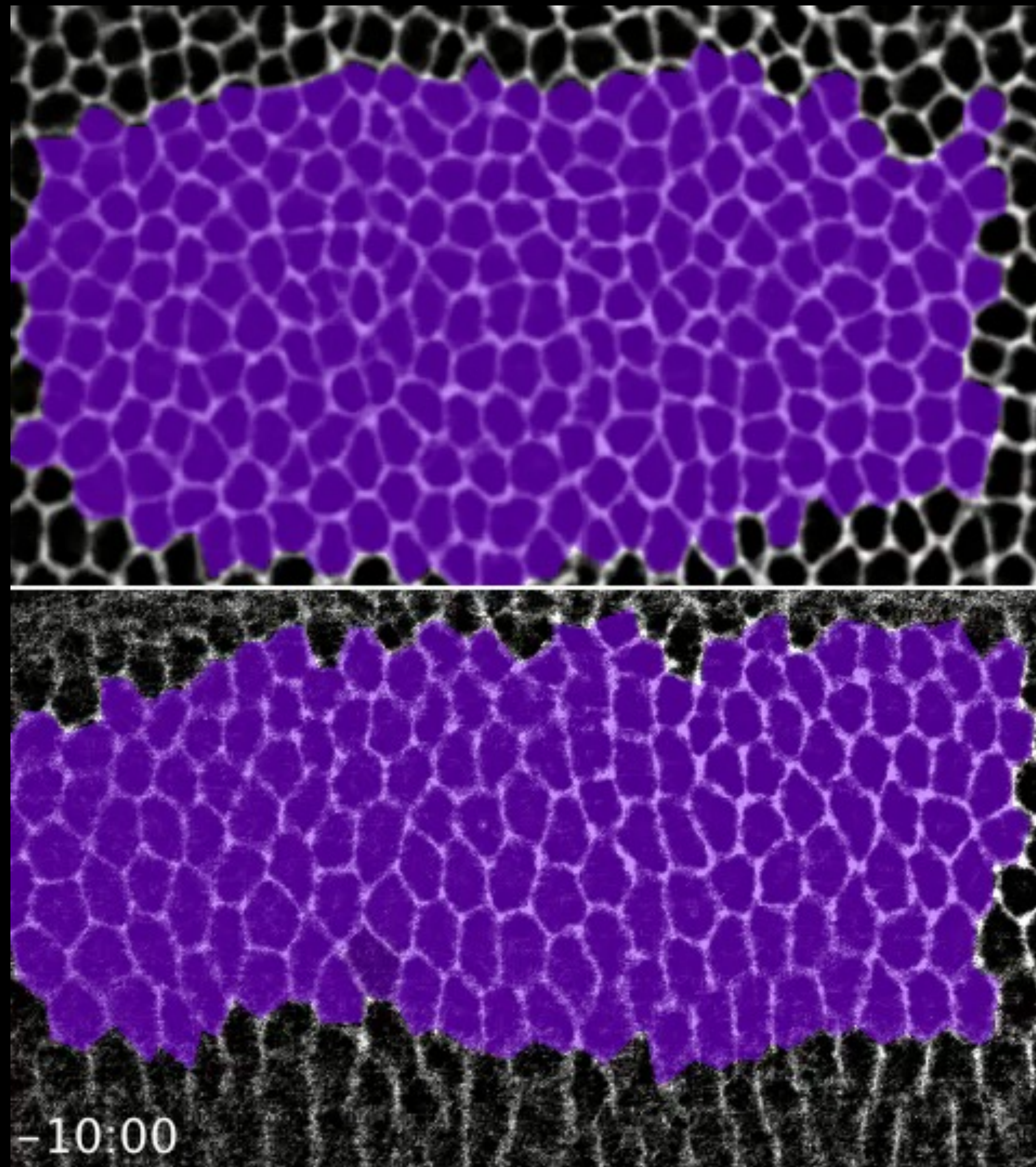
3

↓

4

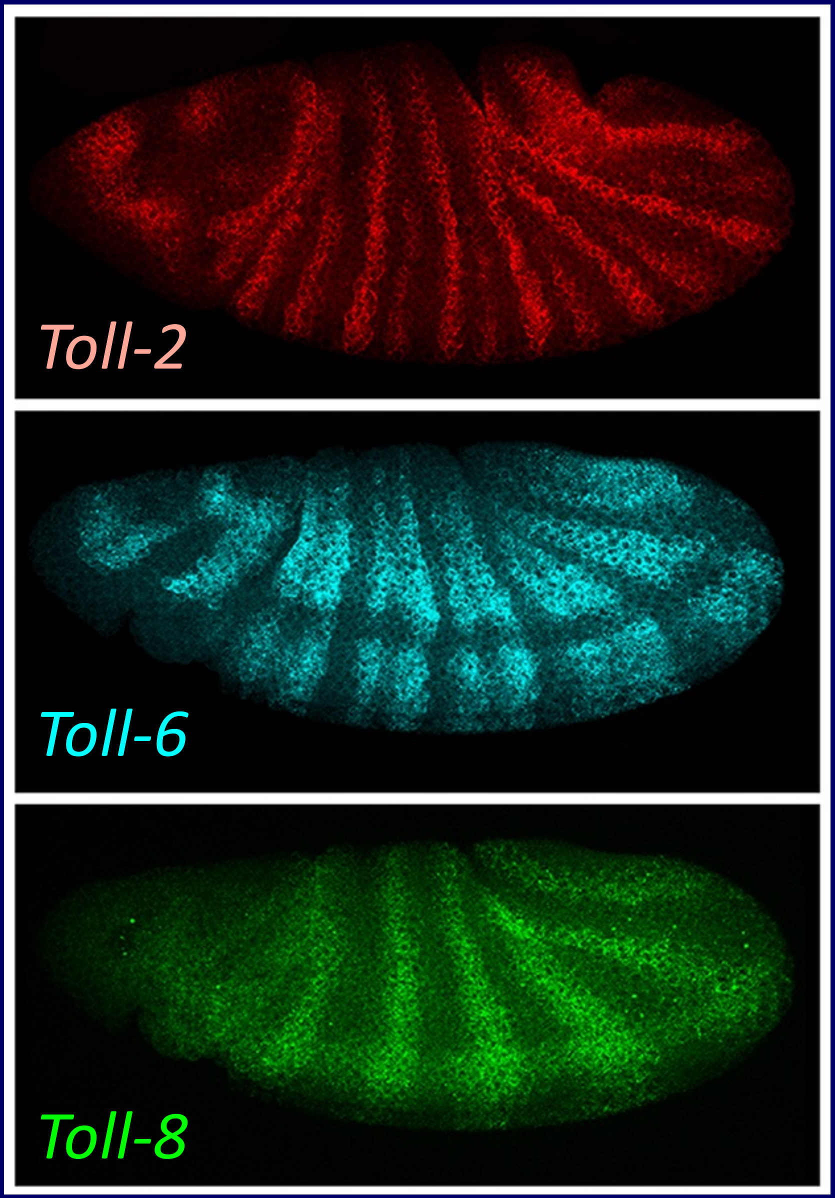
Wild type

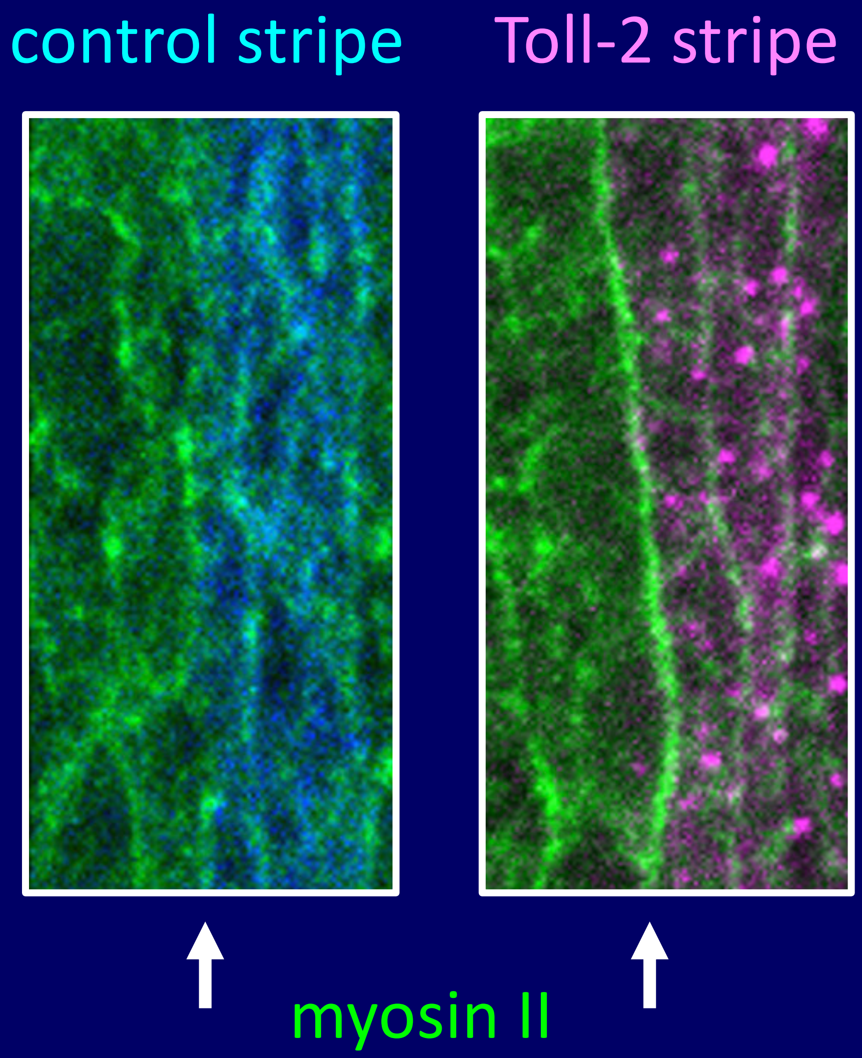
Toll-2,6,8 triple mutant



Zack Mirman, Adam Paré and Dene Farrell

Toll receptors are sufficient to generate myosin cables

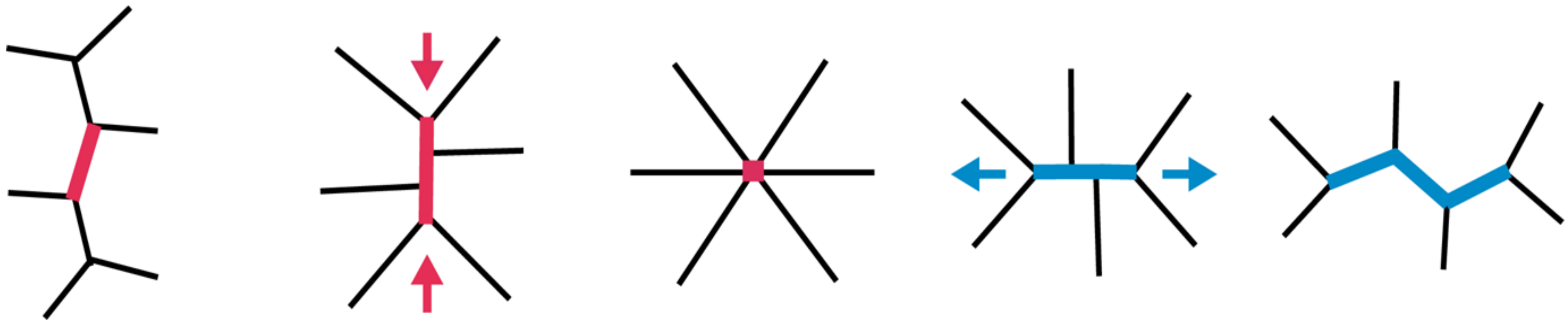




Adam Paré

Actomyosin cables drive cell rearrangement

formation → rosette → resolution



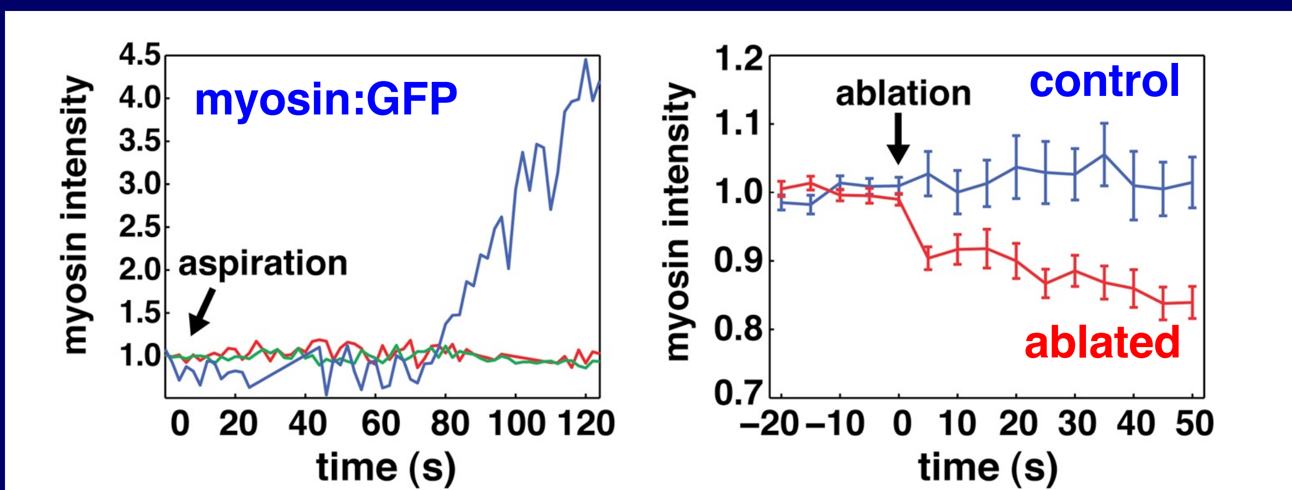
high contraction

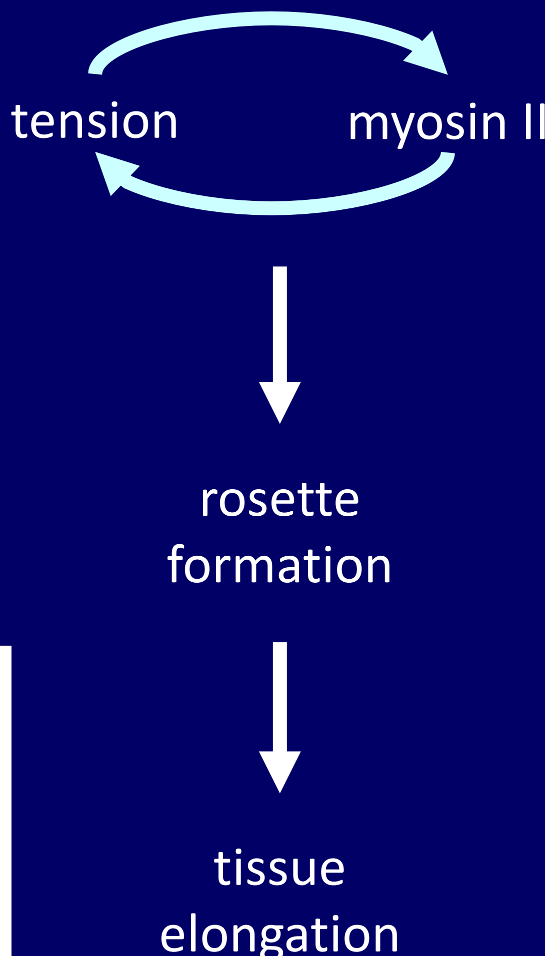
dynamic adhesion

low contraction

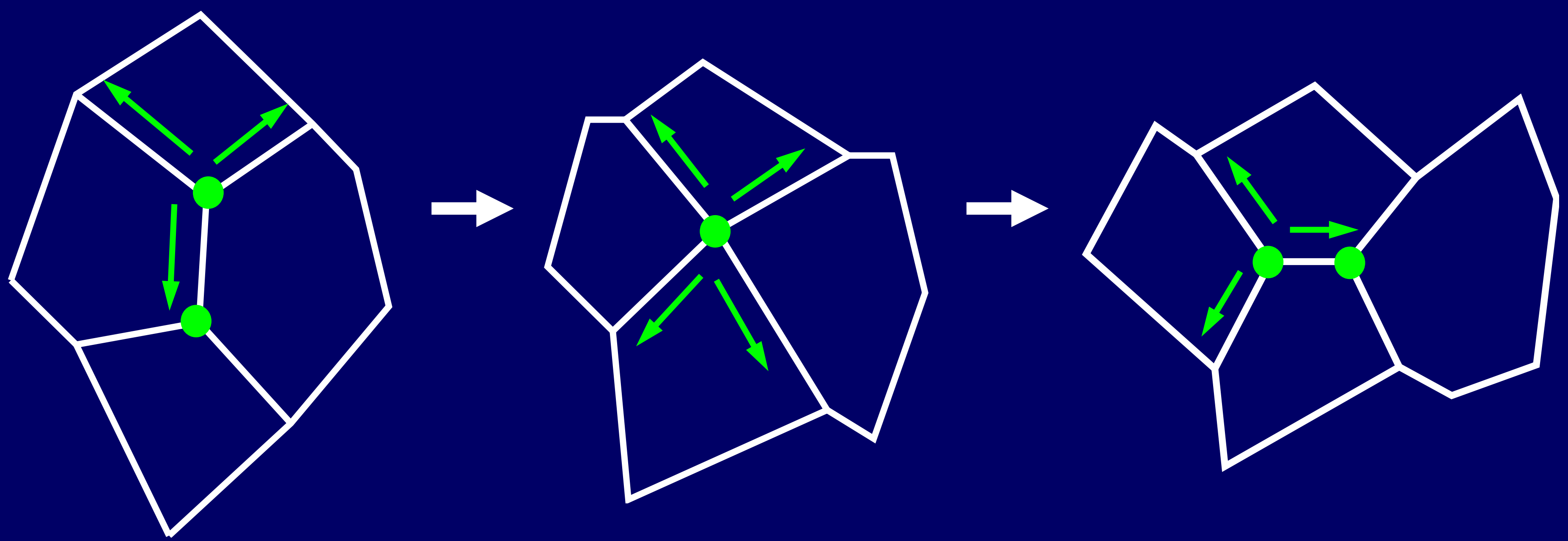
stable adhesion

Mechanical feedback stabilizes myosin II at the cortex





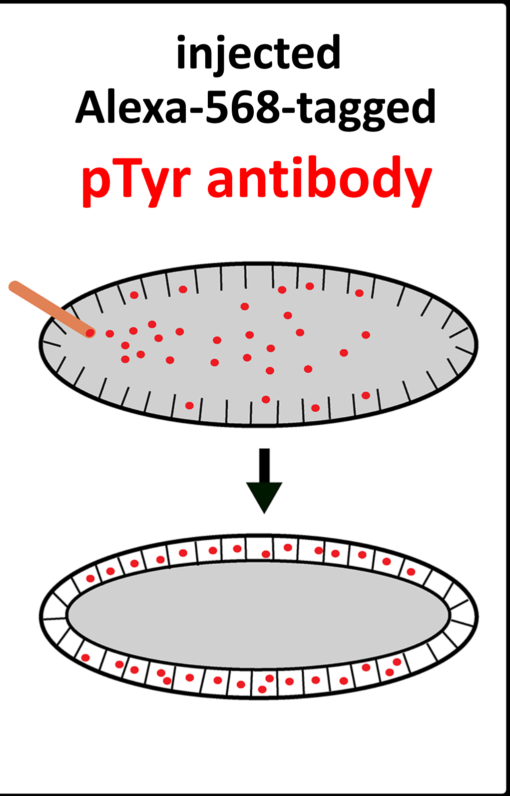
Epithelial tissues experience the strongest forces at tricellular junctions

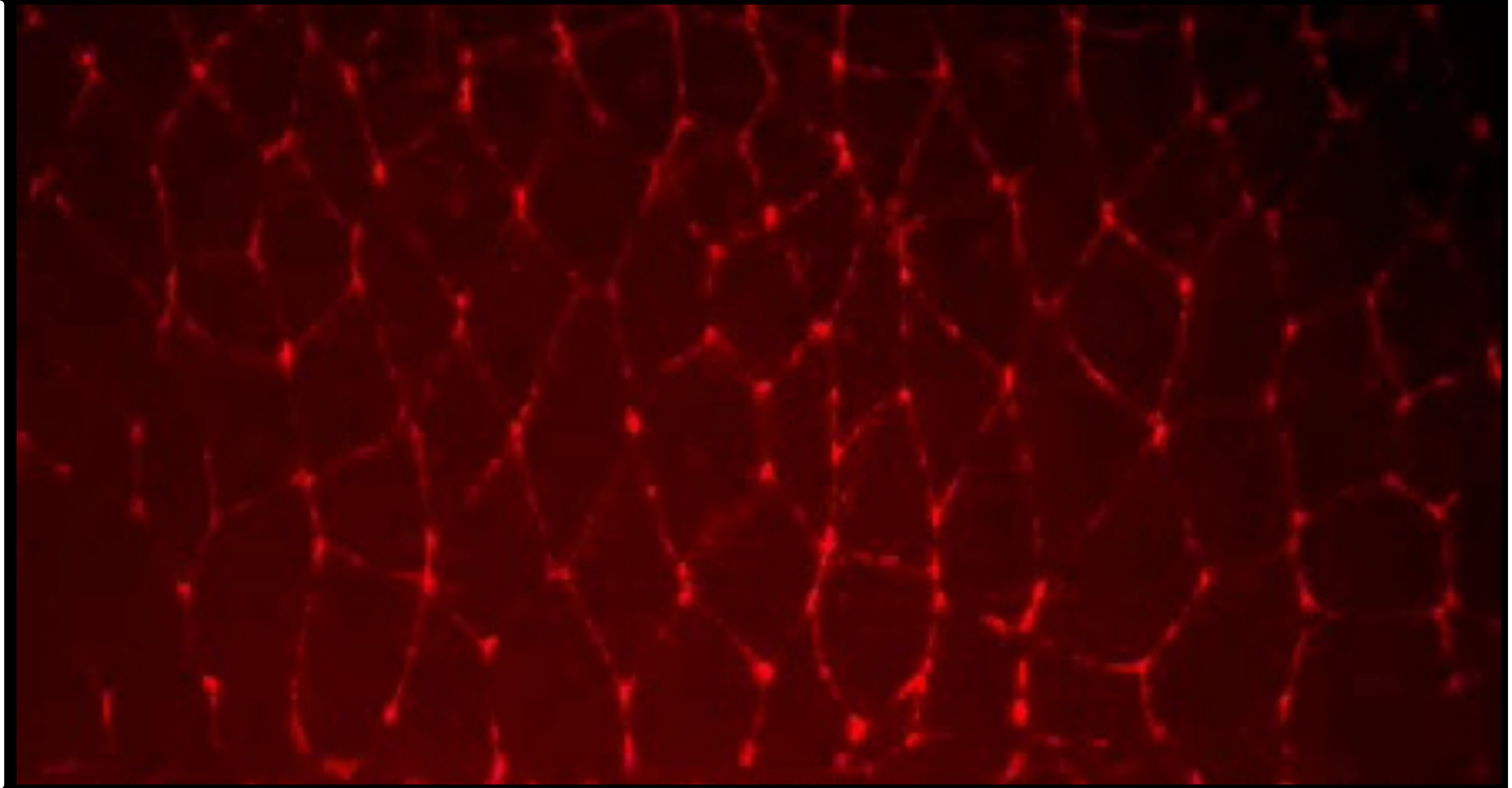


bicellular junctions (low tension)

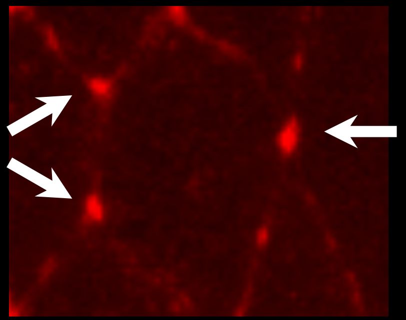
tricellular and multicellular junctions (high tension)

Tyrosine phosphorylation is increased at tricellular junctions



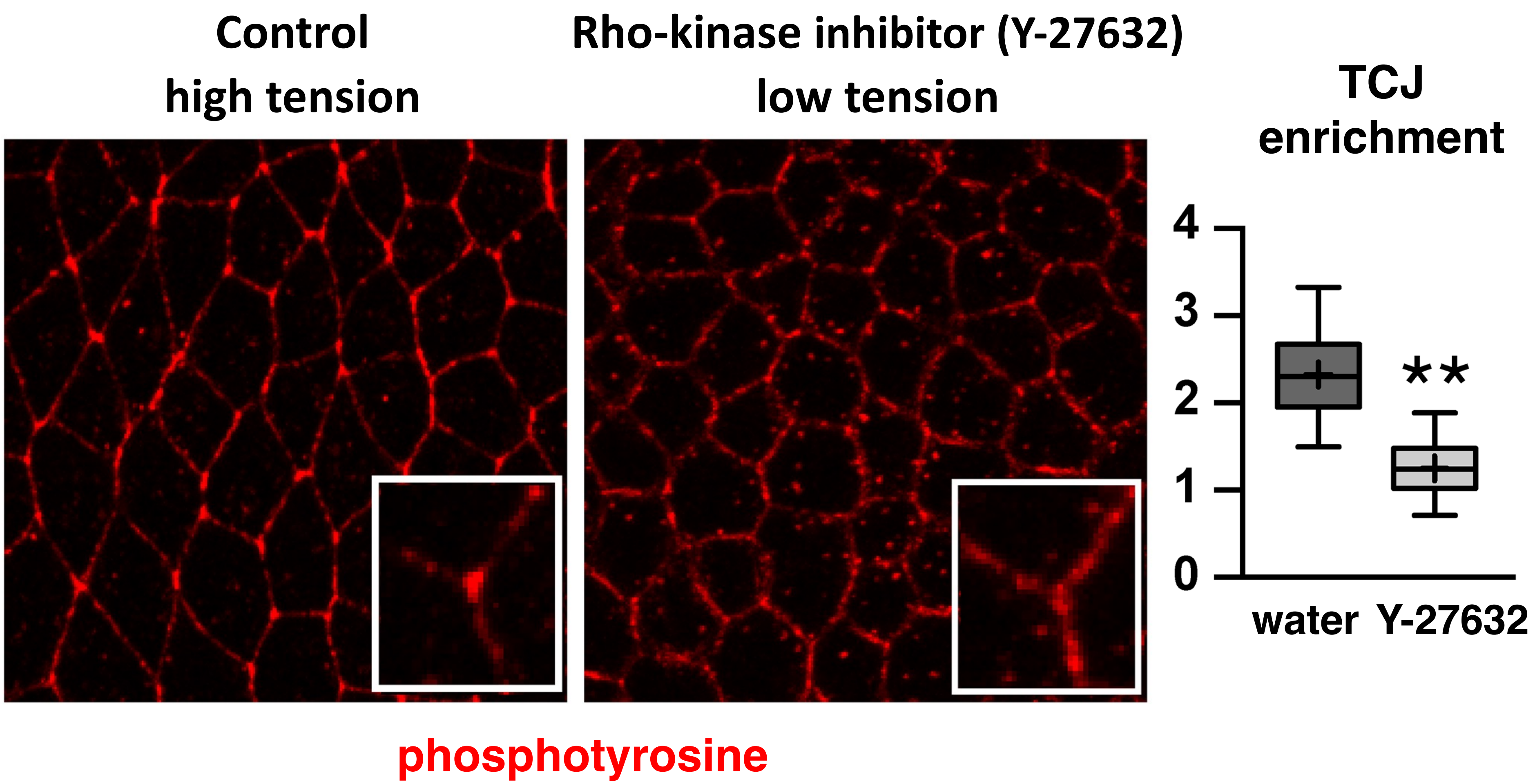


tricellular junctions

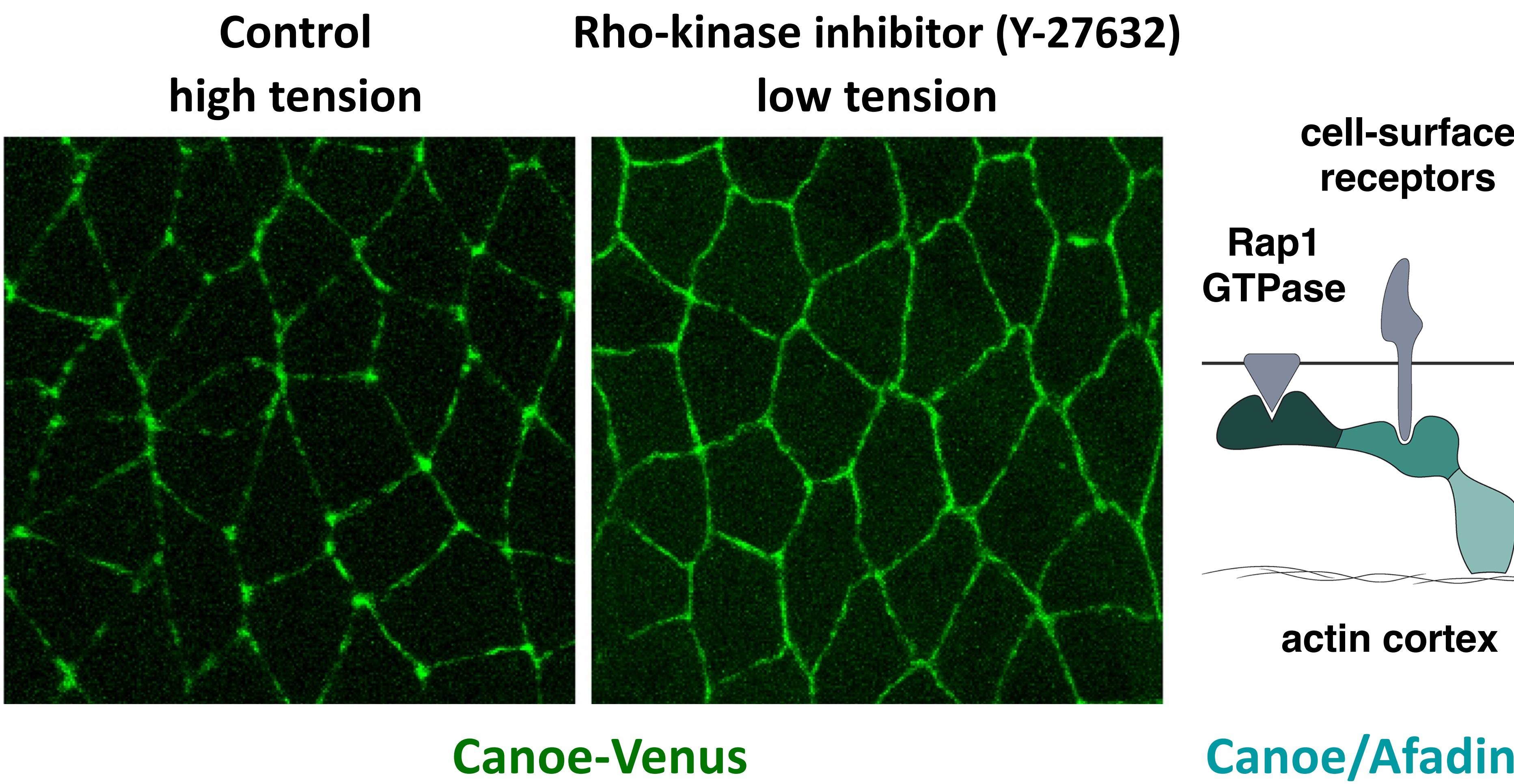


multicellular junction

Localized tyrosine phosphorylation requires myosin activity

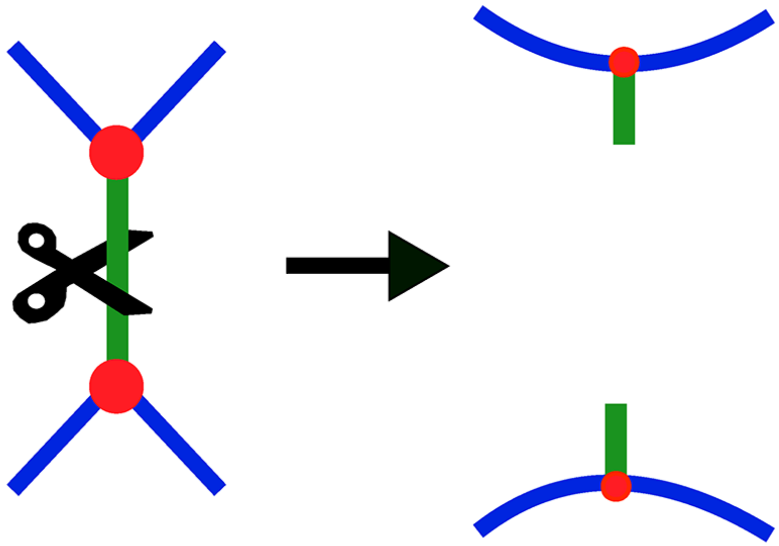


Canoe/Afadin localizes to tricellular junctions under tension

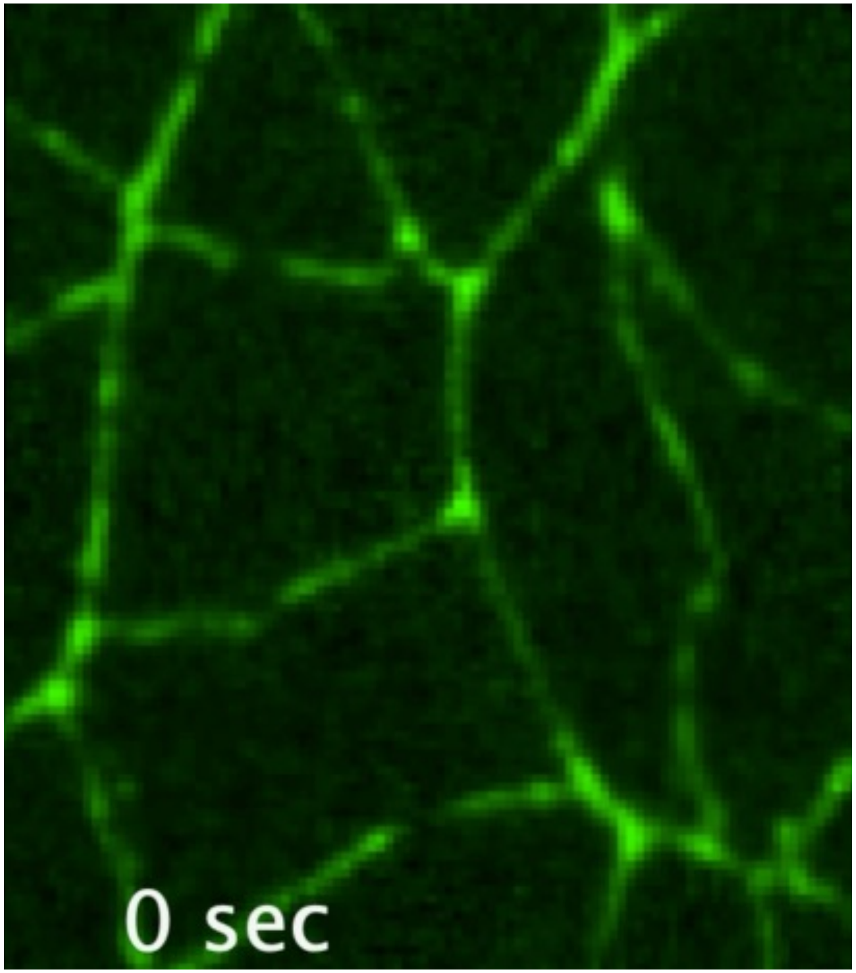


Yu and Zallen (2020), PMID: 33243859

Canoe/Afadin localization requires mechanical force

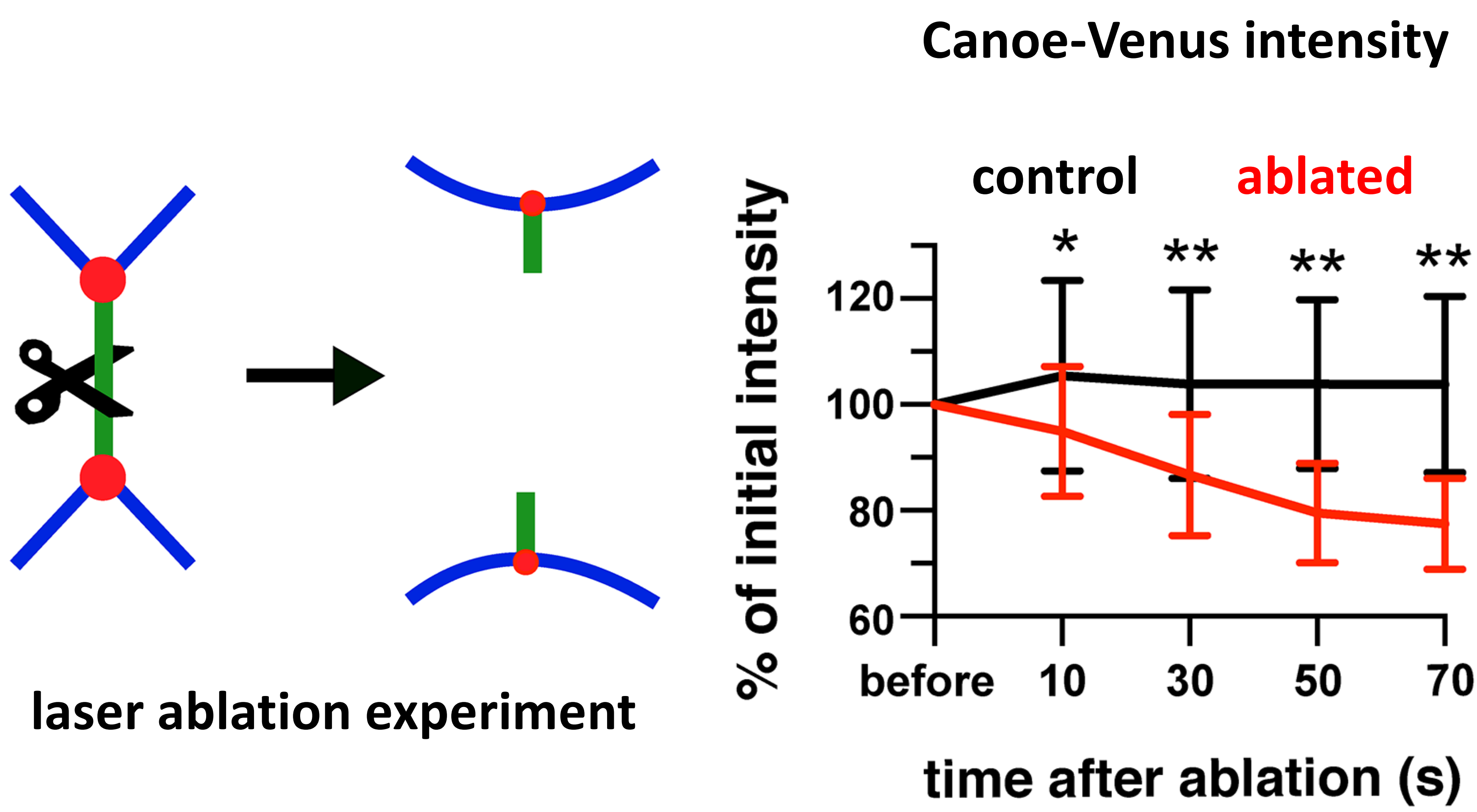


laser ablation experiment

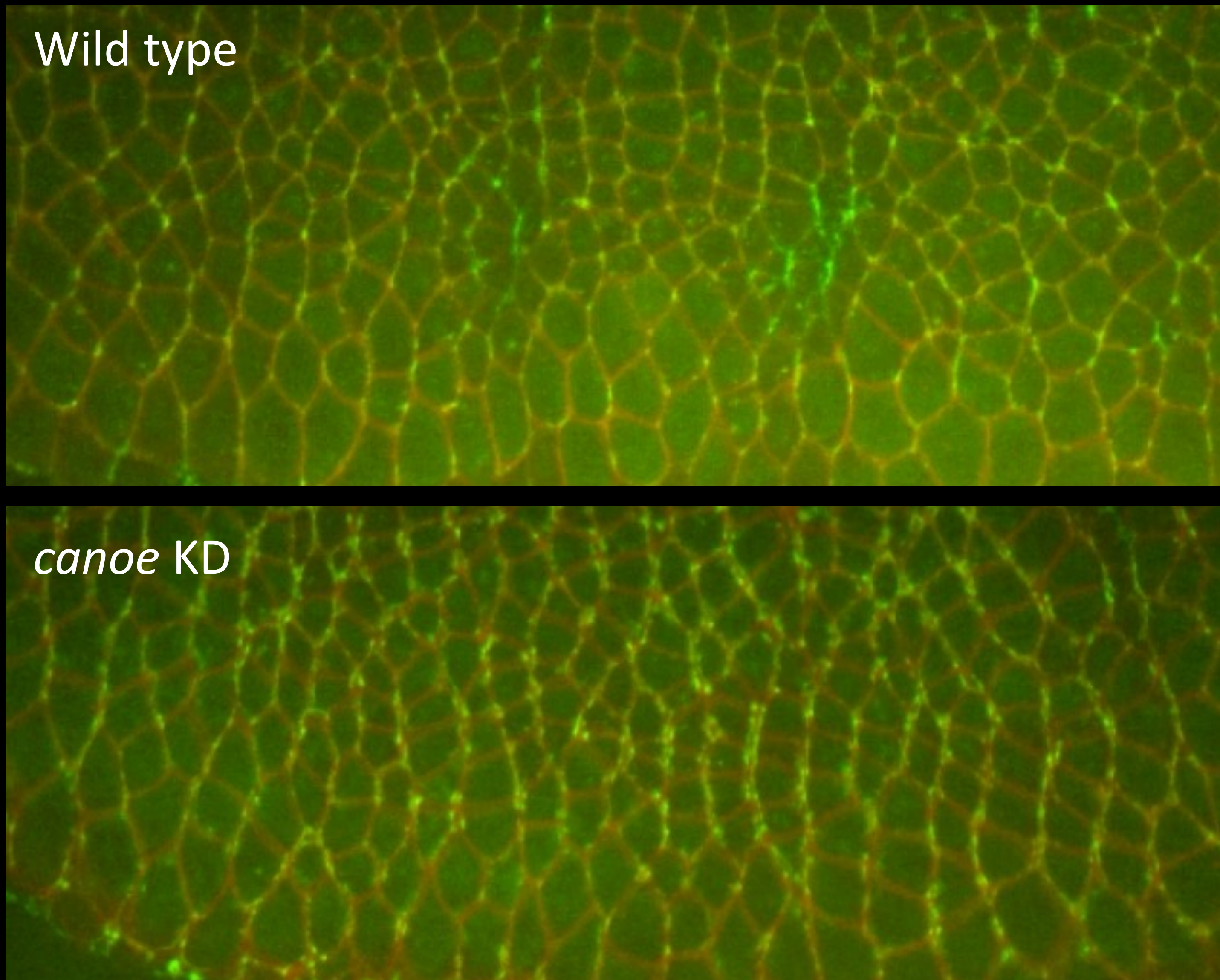


Canoe-Venus

Canoe/Afadin localization requires mechanical force



Canoe is required to maintain cell adhesion under tension

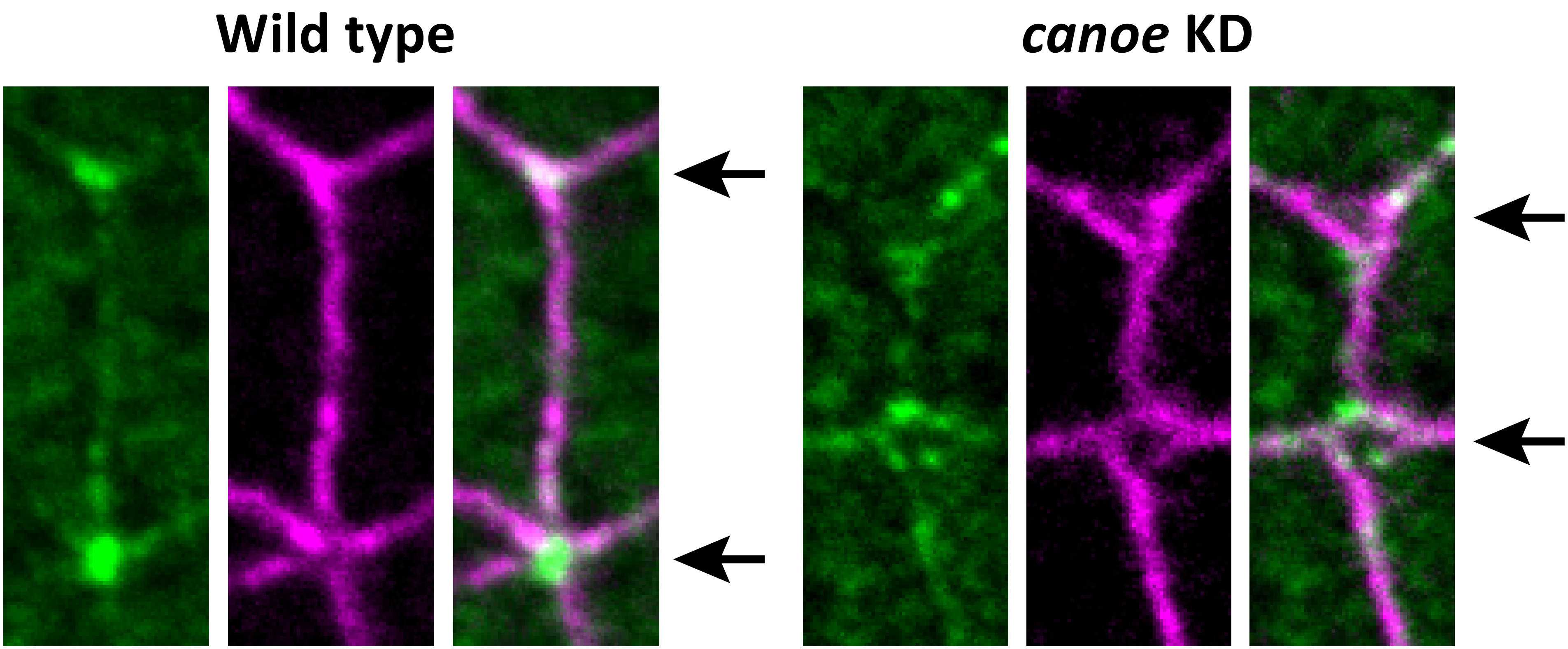


myosin-GFP

Gap43-mCherry

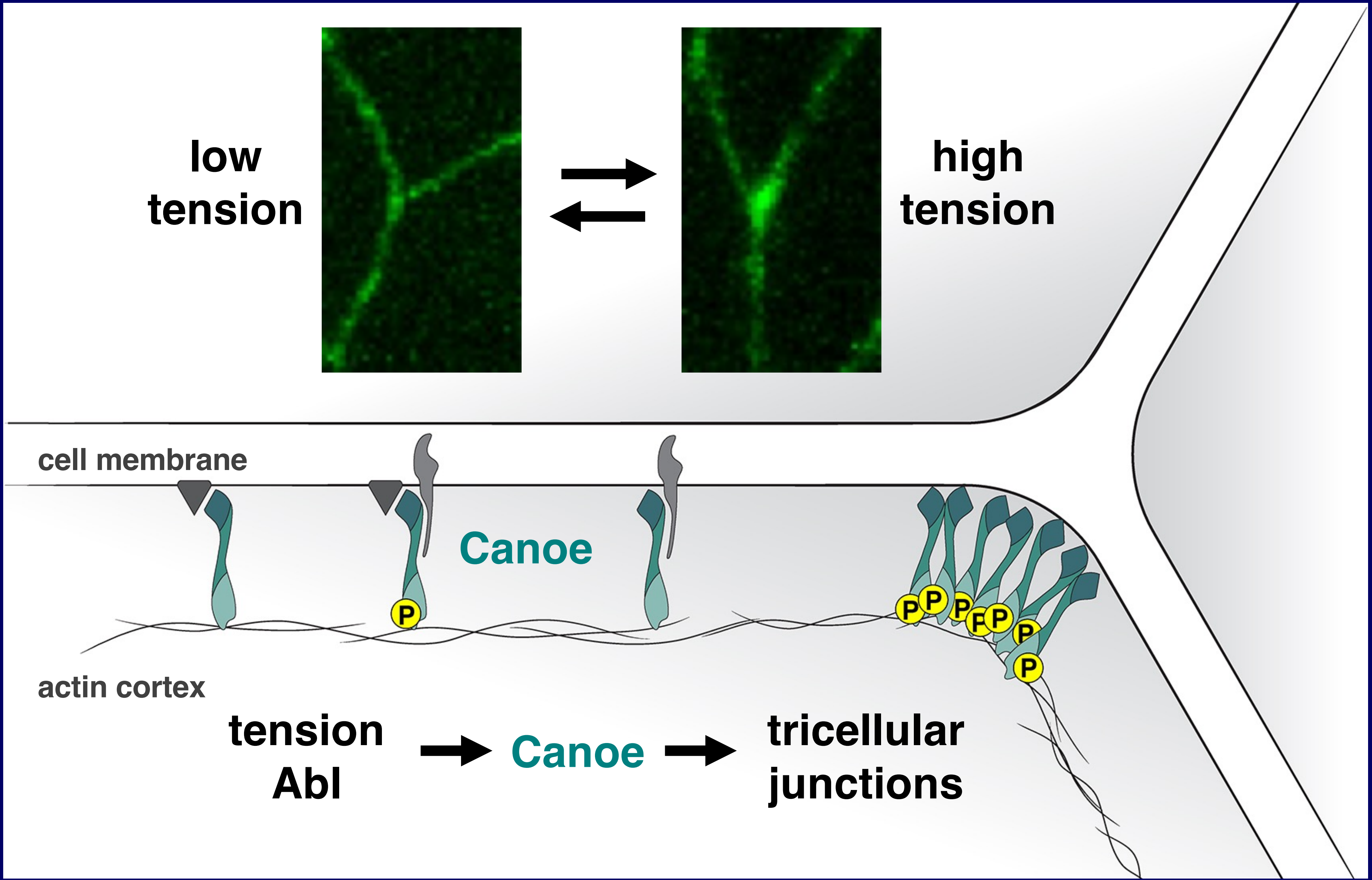
Sawyer et al. PMID 21613546

Canoe reinforces cell adhesion at tricellular junctions

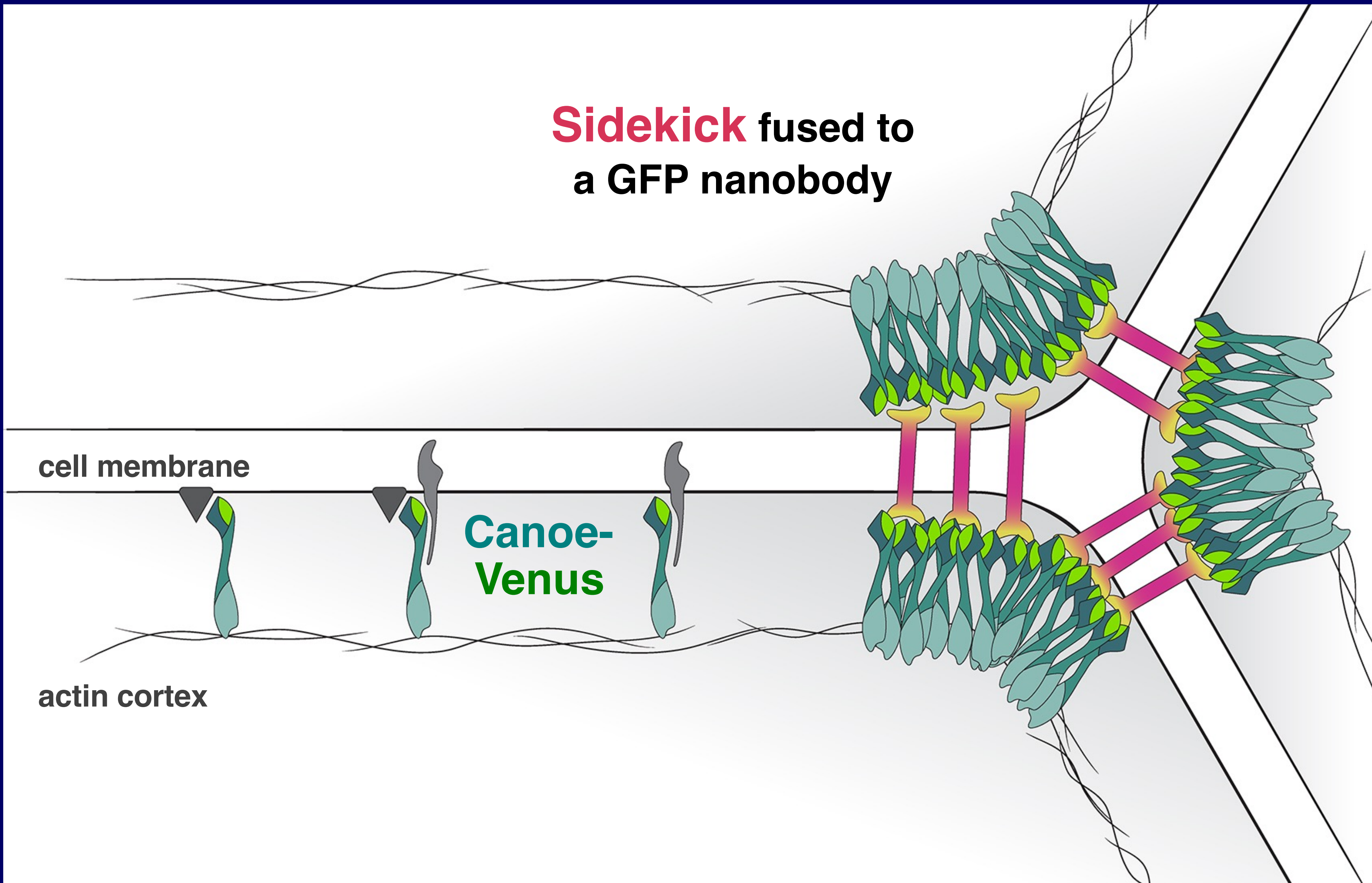


E-cadherin (all adherens junctions)
Sidekick (tricellular junctions)

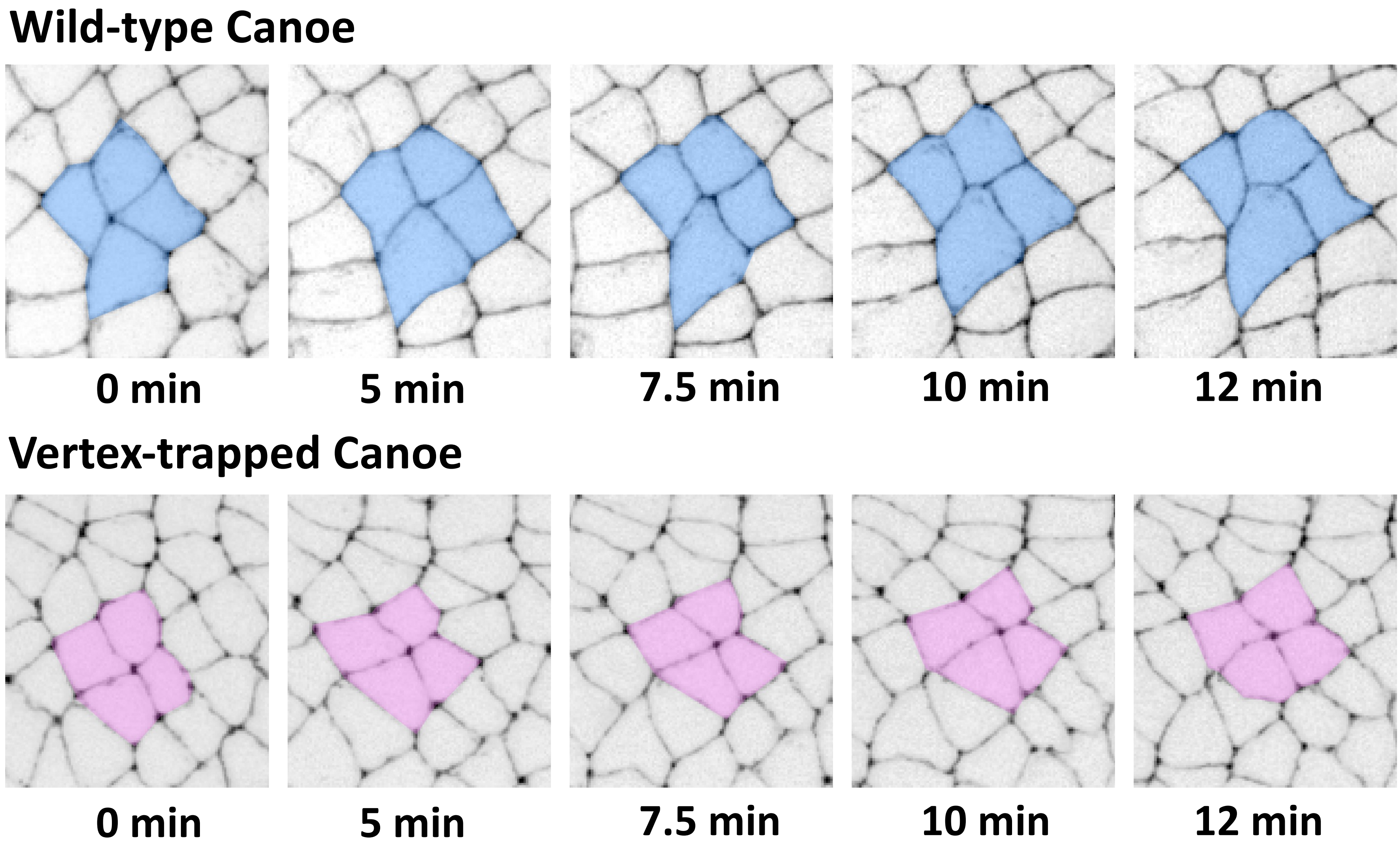
Canoe reinforces adhesion under tension at tricellular junctions



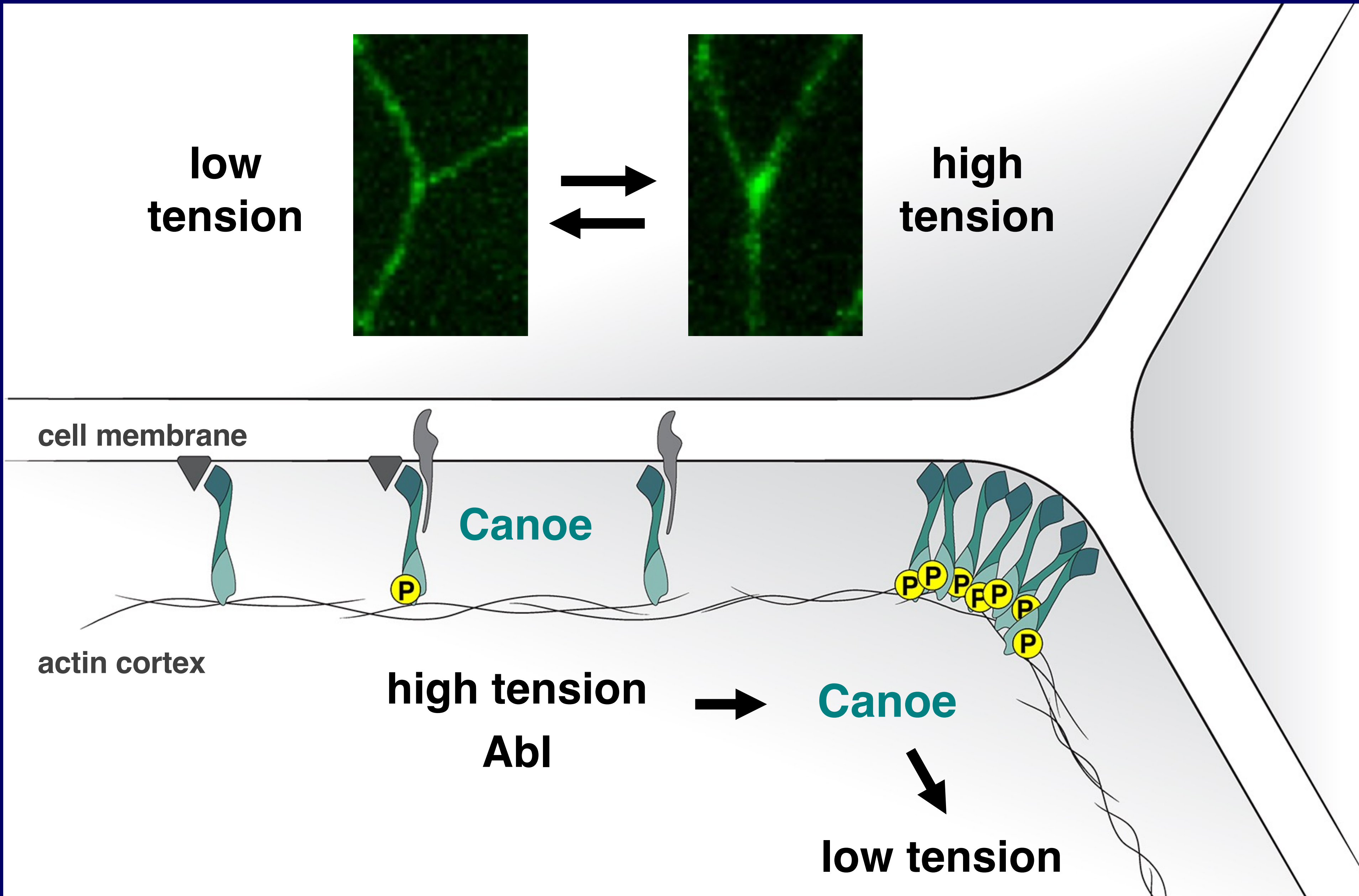
A vertex trap method to disrupt Canoe localization



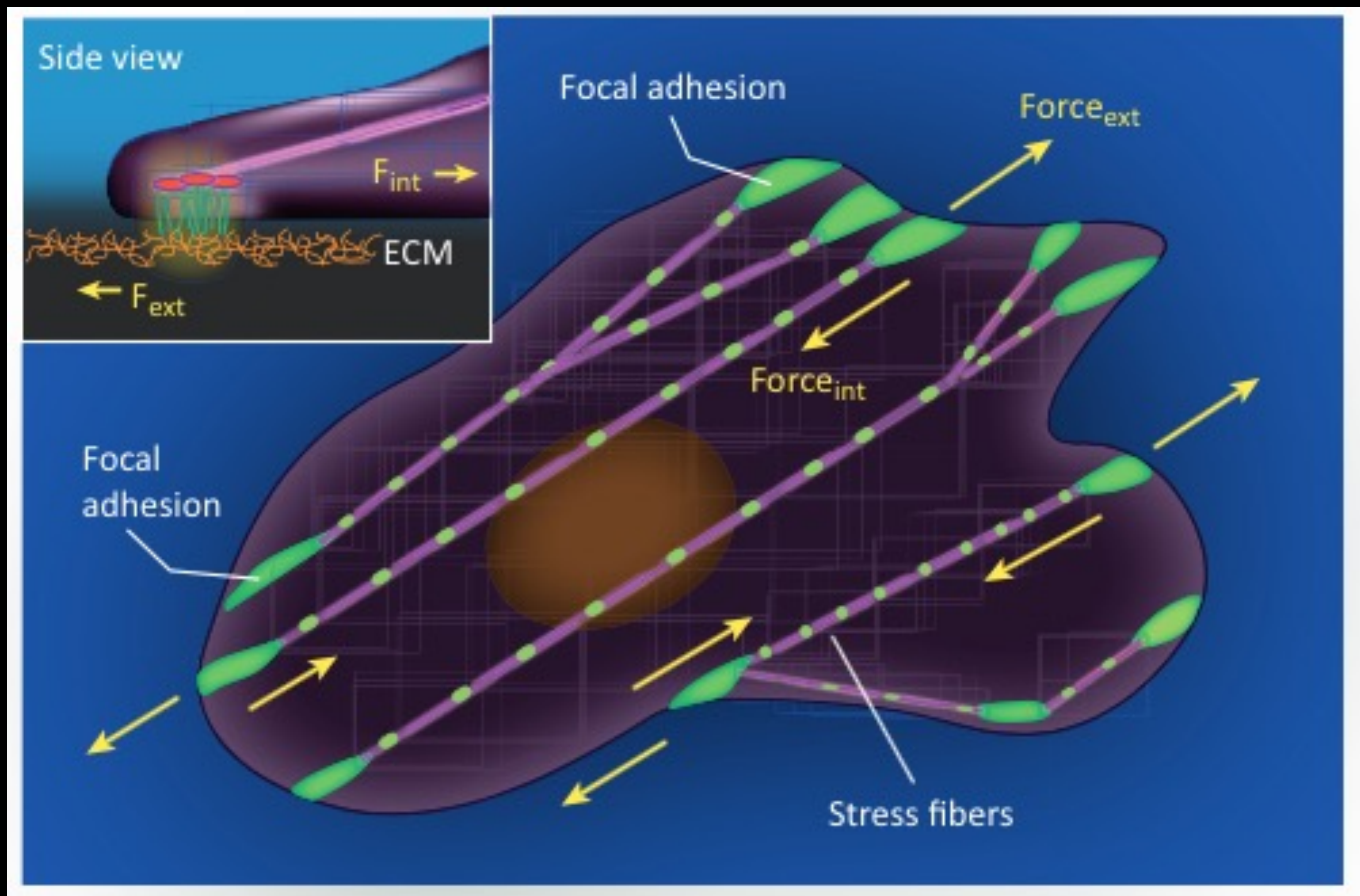
Trapping Canoe at multicellular junctions arrests rearrangement



A mechanism for generating dynamic adhesion under force



LIM domain proteins bind to cell-cell contacts, cell-matrix contacts, and actin stress fibers under tension

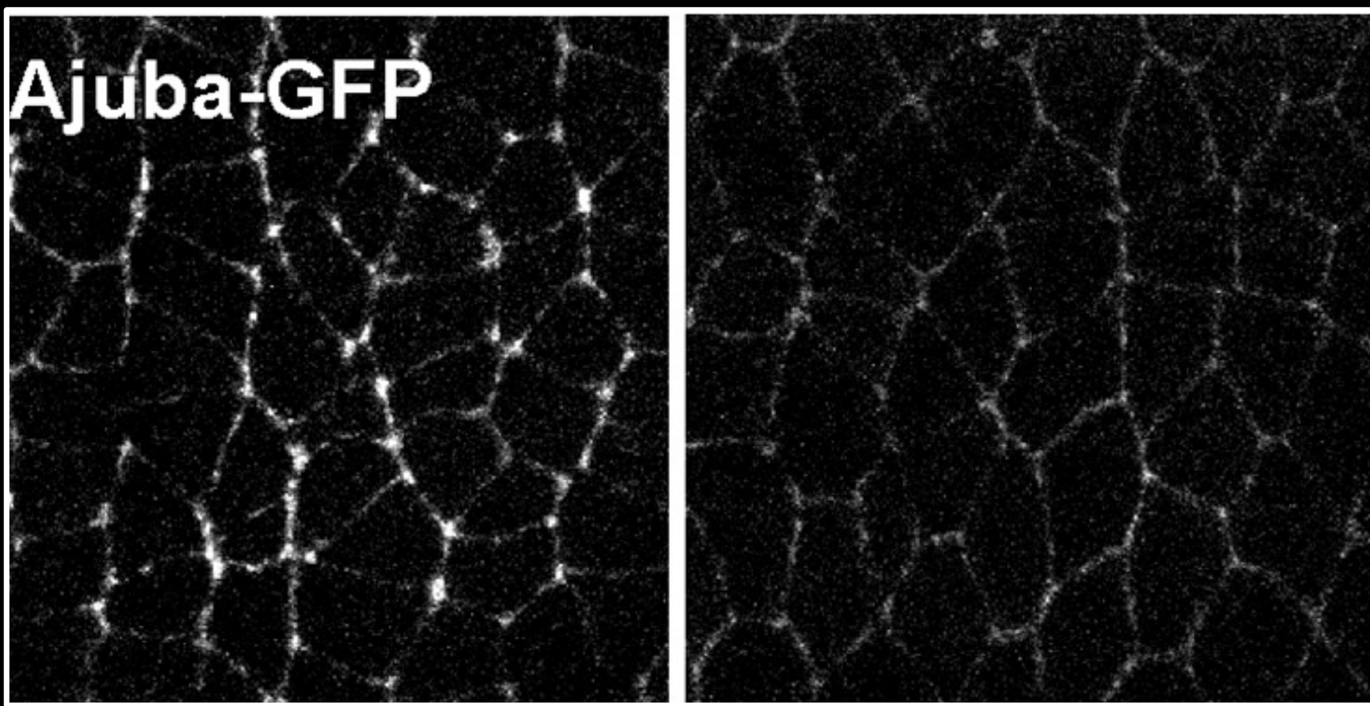


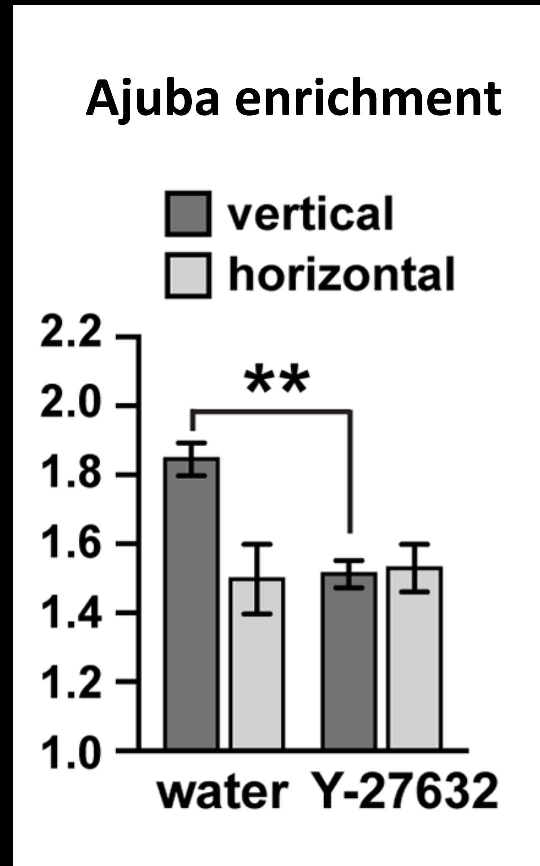
Smith et al. PMID: 24933506

The LIM domain protein Ajuba is regulated by mechanical force

Control
high tension

Rho-kinase inhibitor
low tension



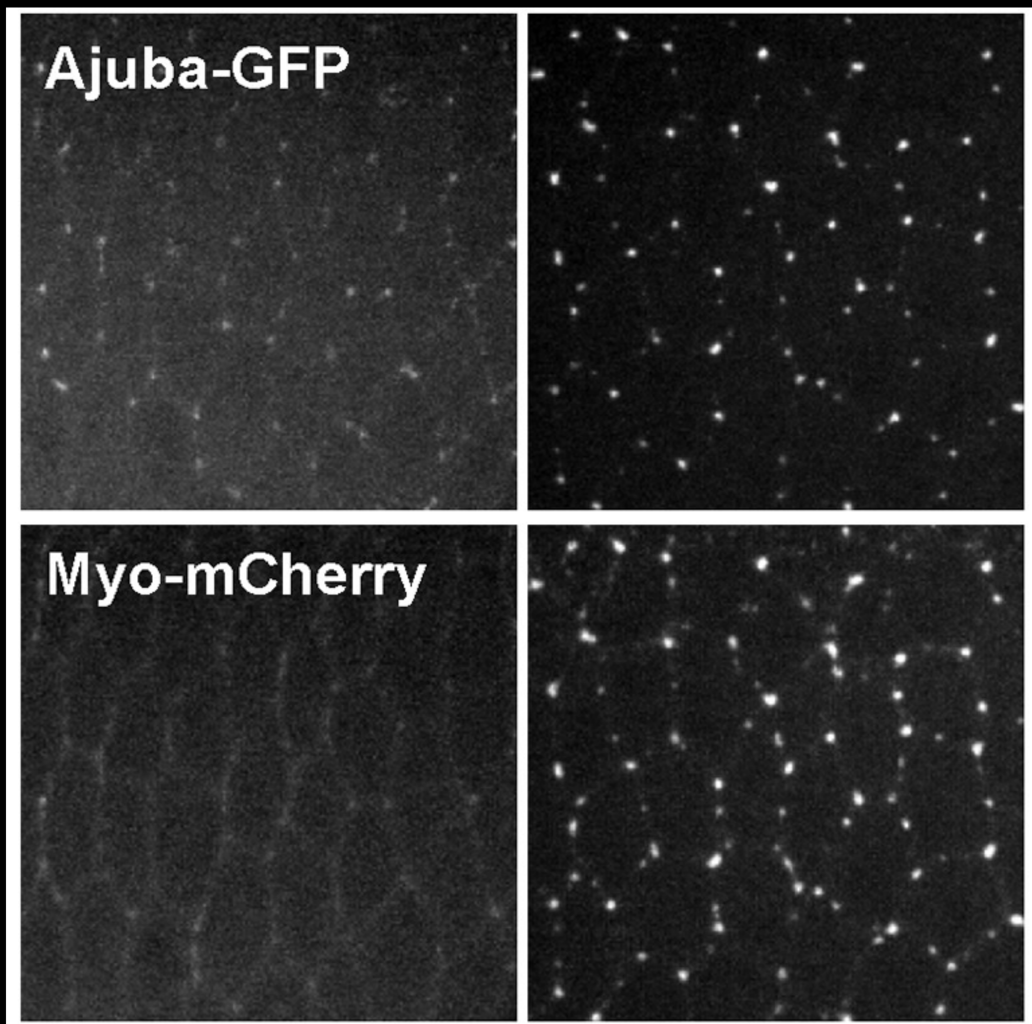


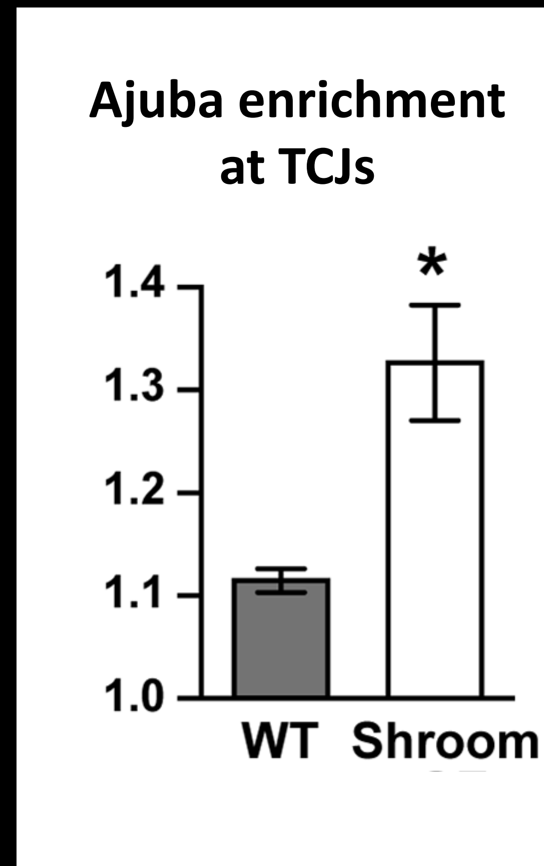
Razzell et al. PMID: 30006462

The LIM domain protein Ajuba is regulated by mechanical force

Wild type

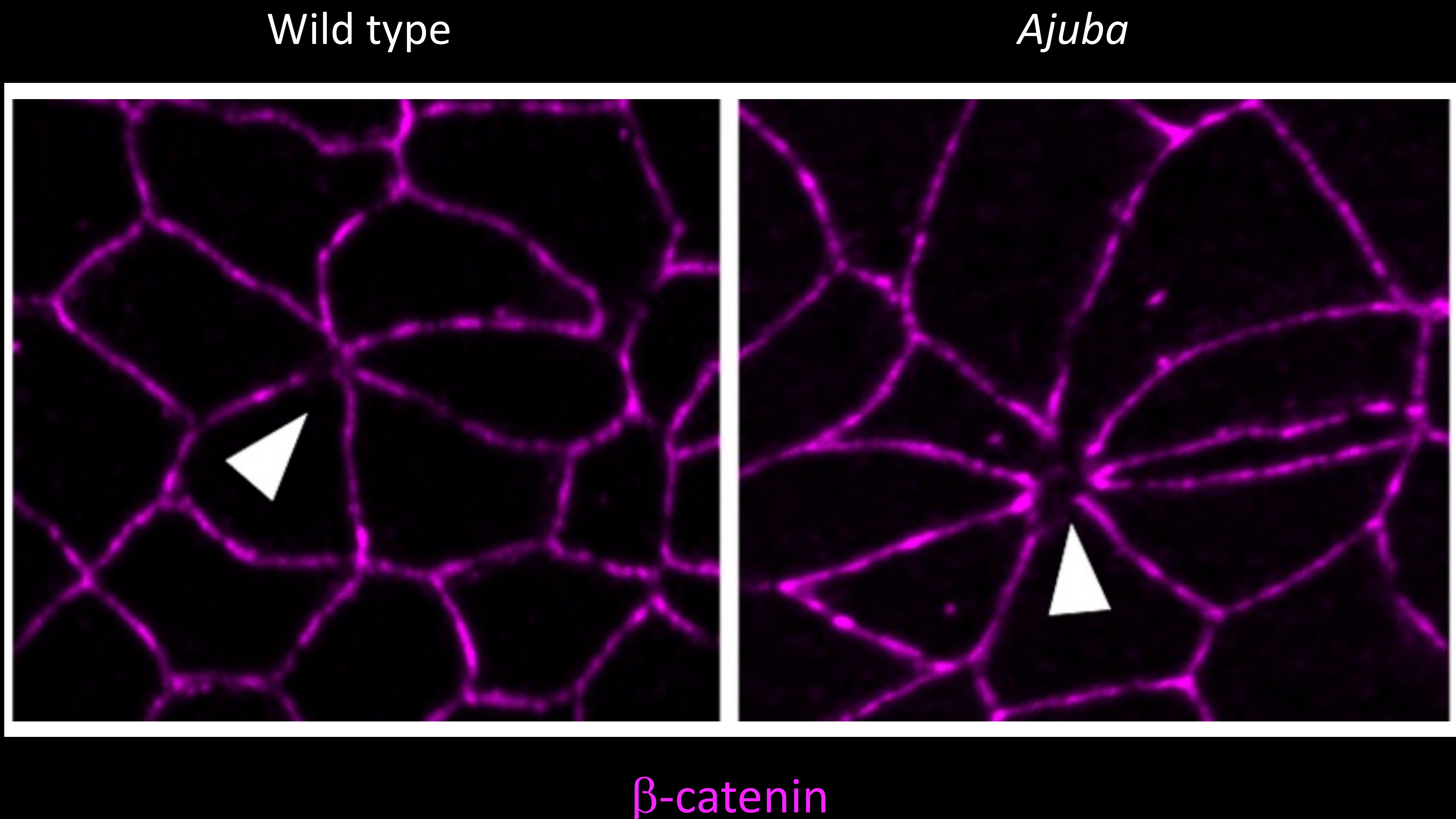
high tension
(Shroom expression)



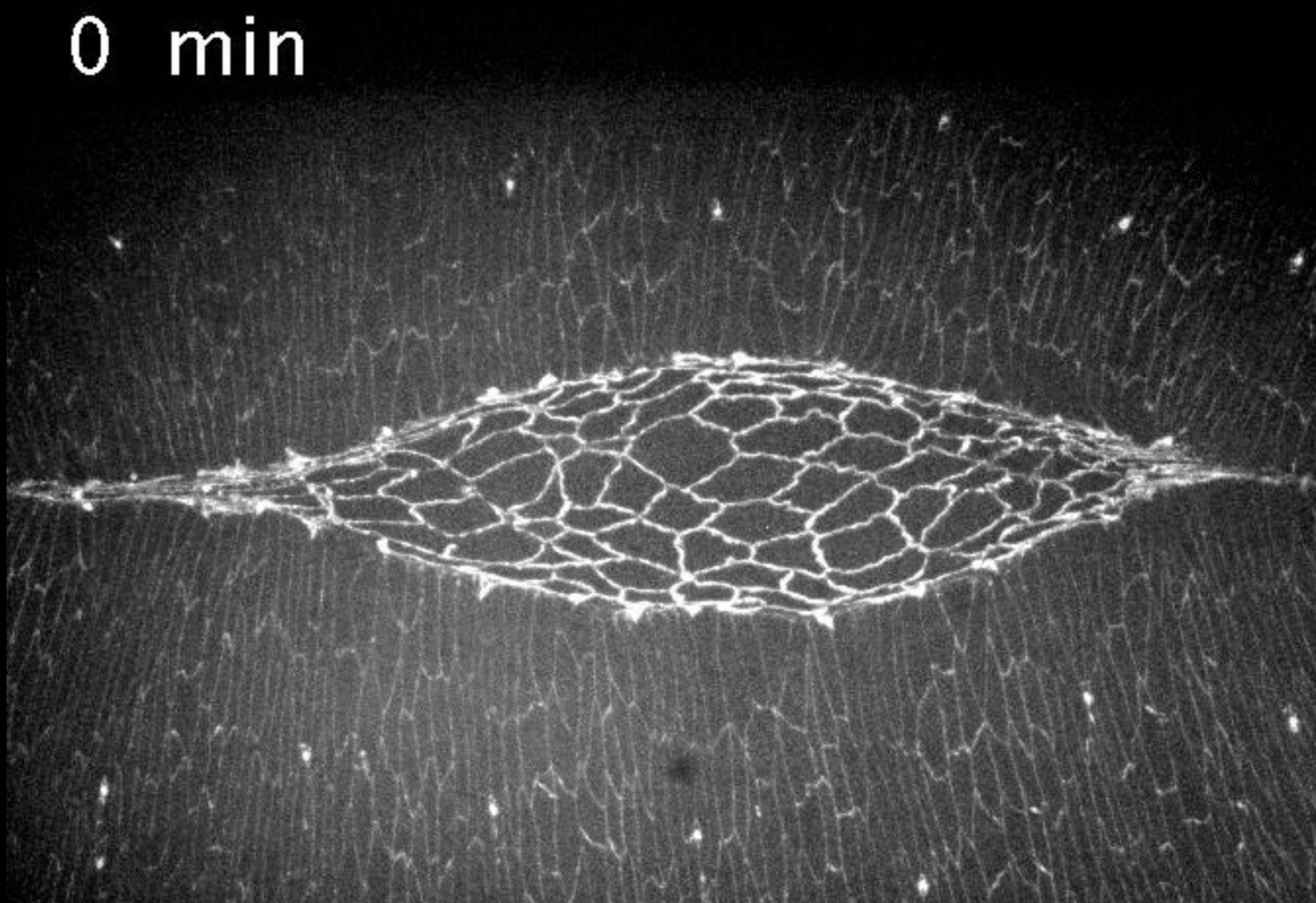


Razzell et al. PMID: 30006462

Ajuba stabilizes adhesion in regions of high tension

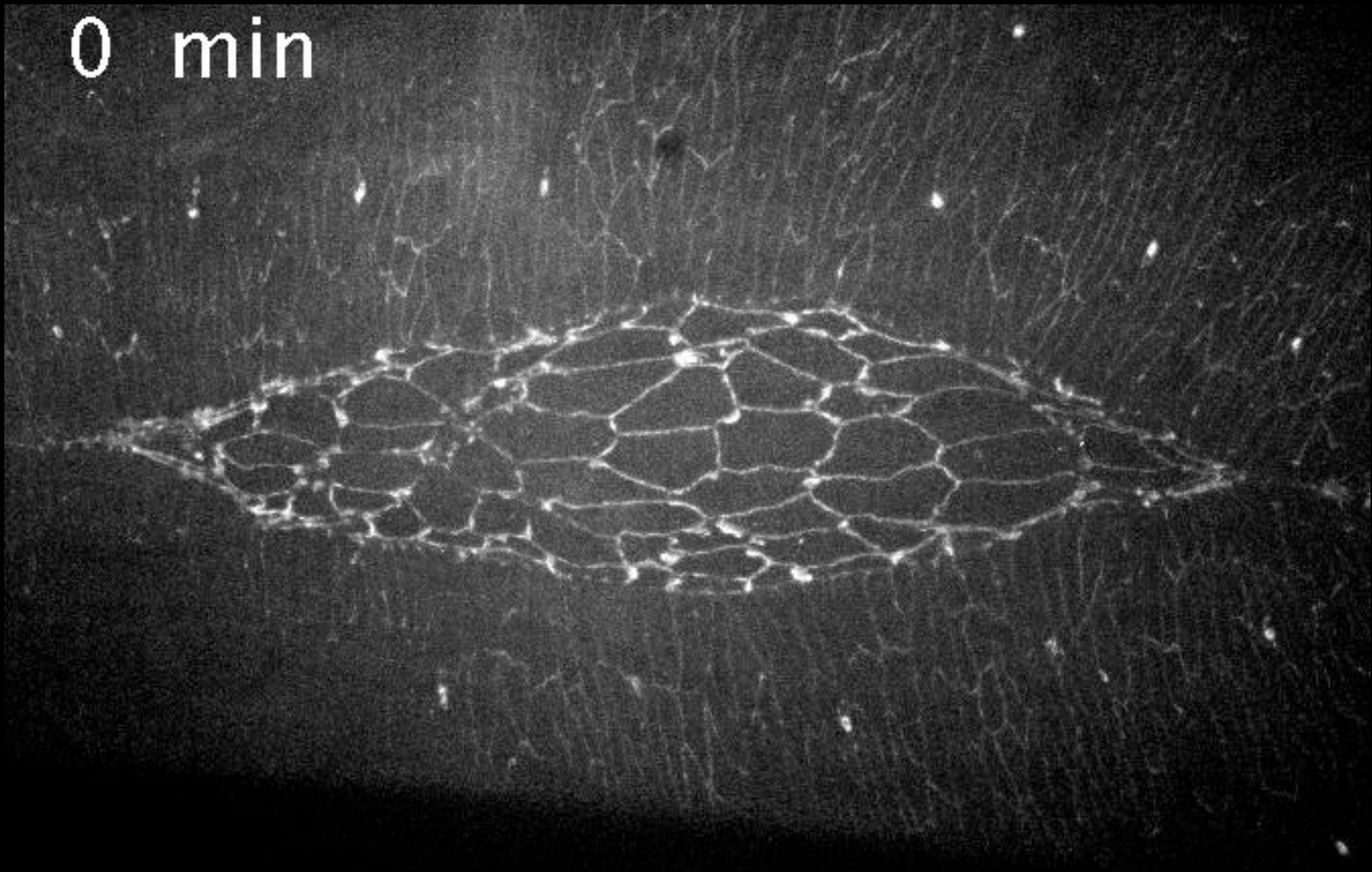


Mechanical forces at the leading edge are required for dorsal closure



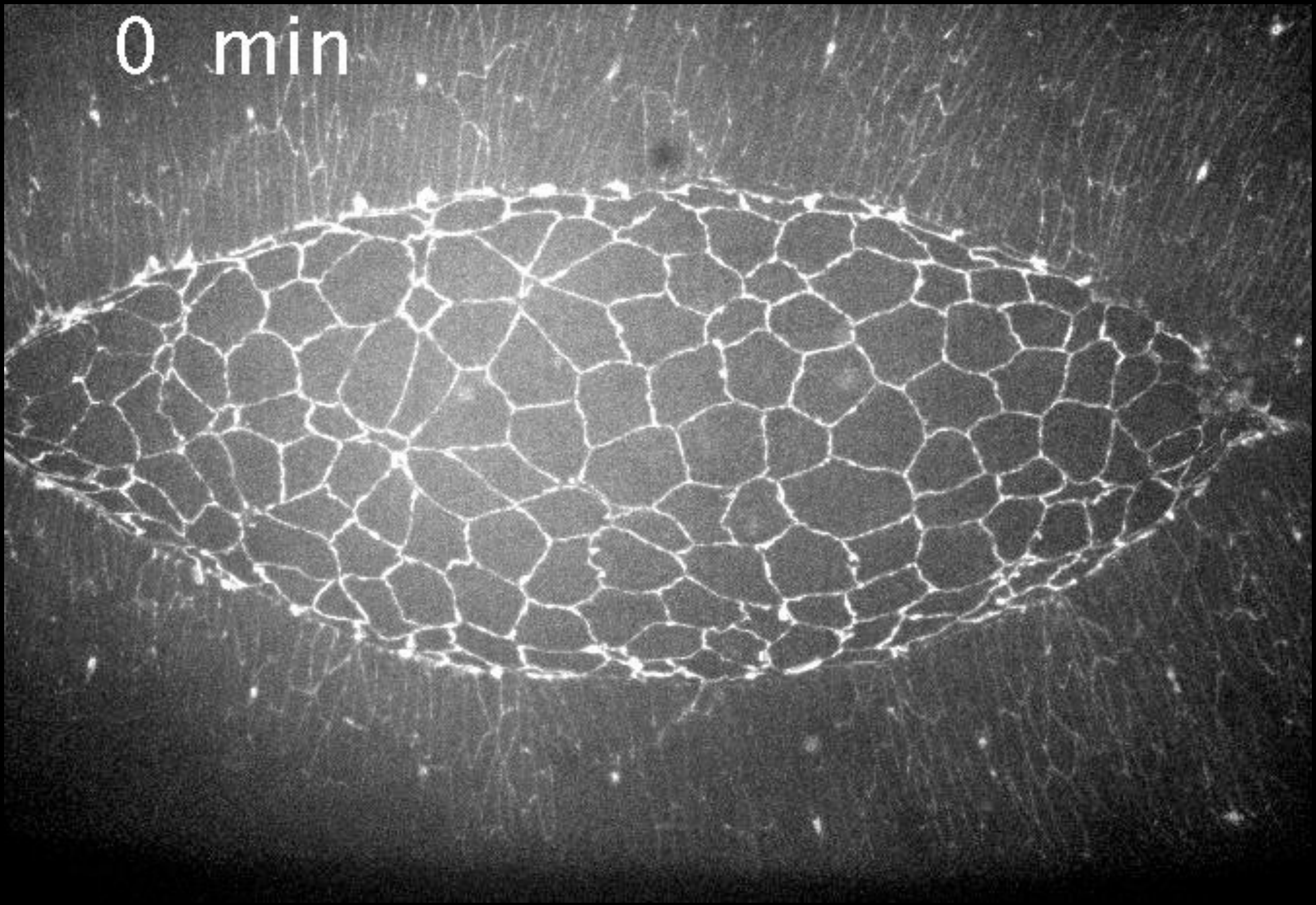
Wild type

Ajuba mutants develop small, transient gaps during dorsal closure



Ajuba mutant

Ajuba activity is essential when adhesion is reduced



Ajuba mutant; *E-cadherin*/+

Outline of lecture

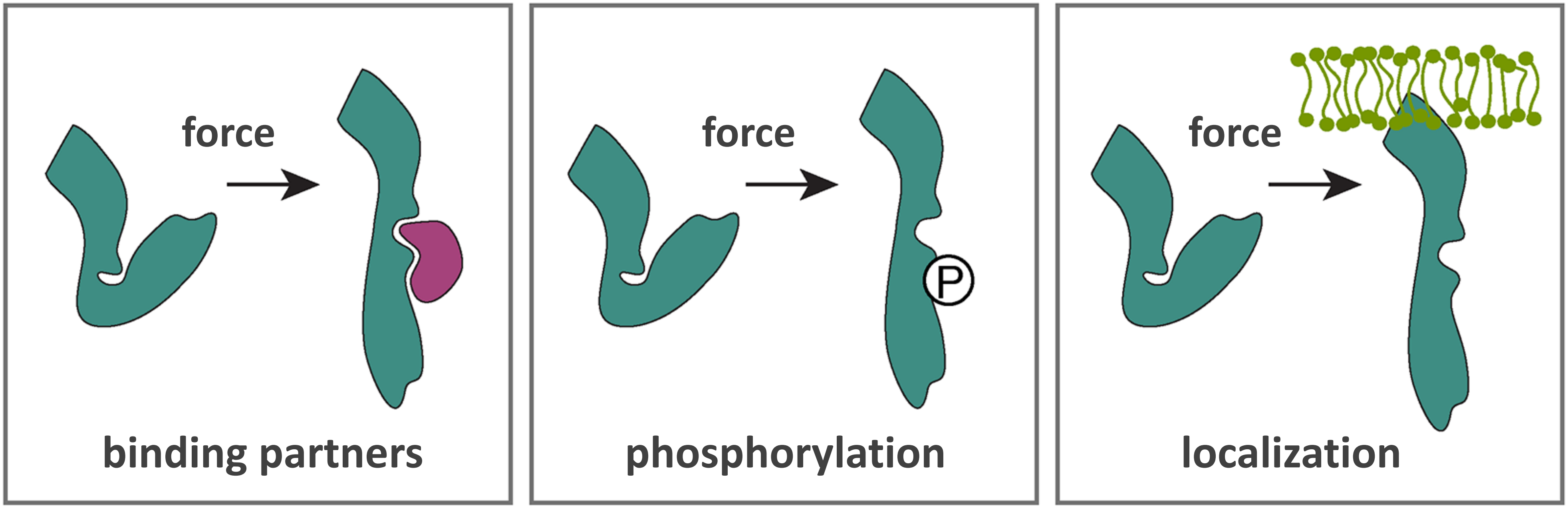
1. How do cells generate force?

2. How do cells respond to force?

3. Roles of mechanical forces in tissue morphogenesis

4. Open questions and challenges in the field

How do cells sense and respond to mechanical force?



What are the mechanosensors that detect mechanical forces in cells?

Are proposed *in vitro* mechanisms relevant *in vivo*?

How do mechanical signals influence cell behavior?