Epithelial-Mesenchymal Transition during embryonic development

1) EMT: Definition?

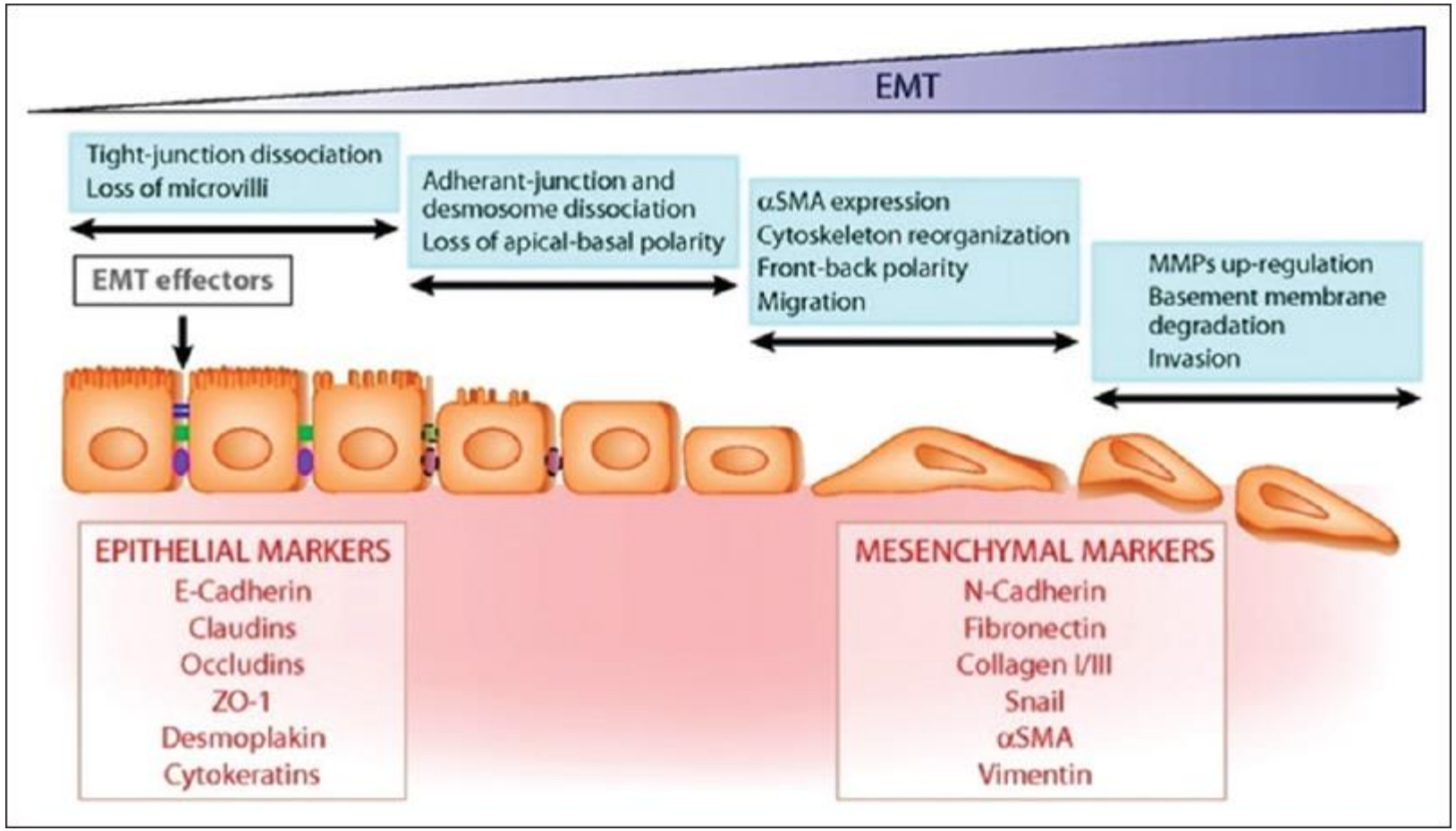
2) Gastrulation, the basic example of “EMT”

3) Neural crest cell migration

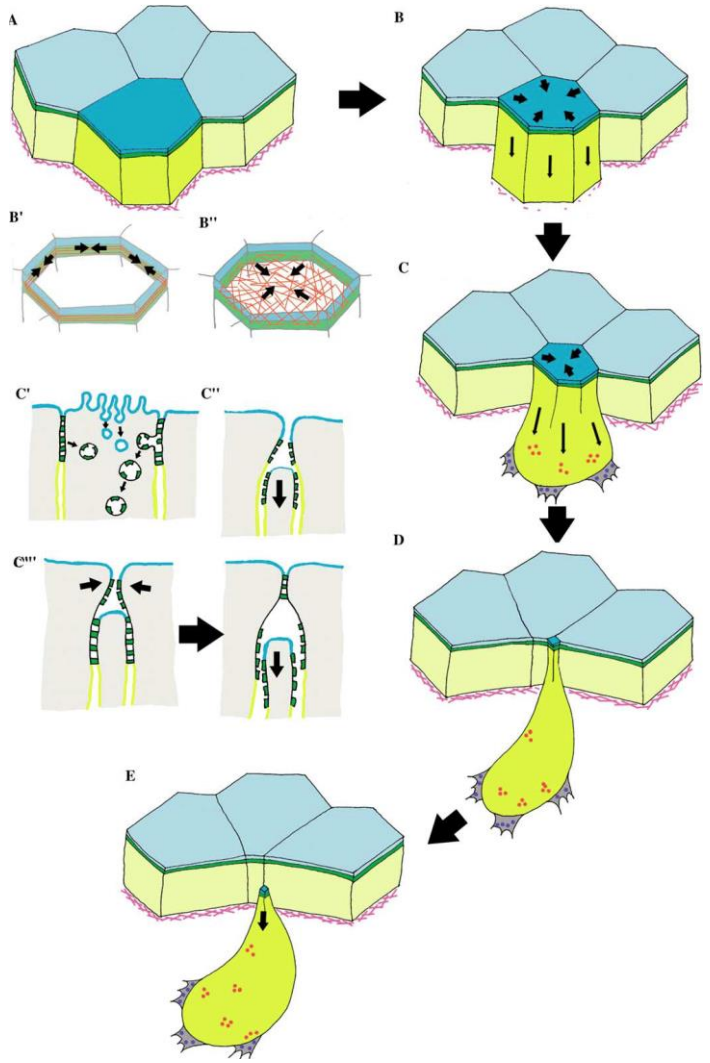
4) Other examples

Cadherin switch? Regulation of adhesion?

Classical view of EMT (cancer cell lines)



Classical view of EMT: cellular changes



Classical view of EMT: cellular changes

Apical constriction

Cell elongation

E-cadherin downregulation

Cadherin switch
(E- to N- ??)

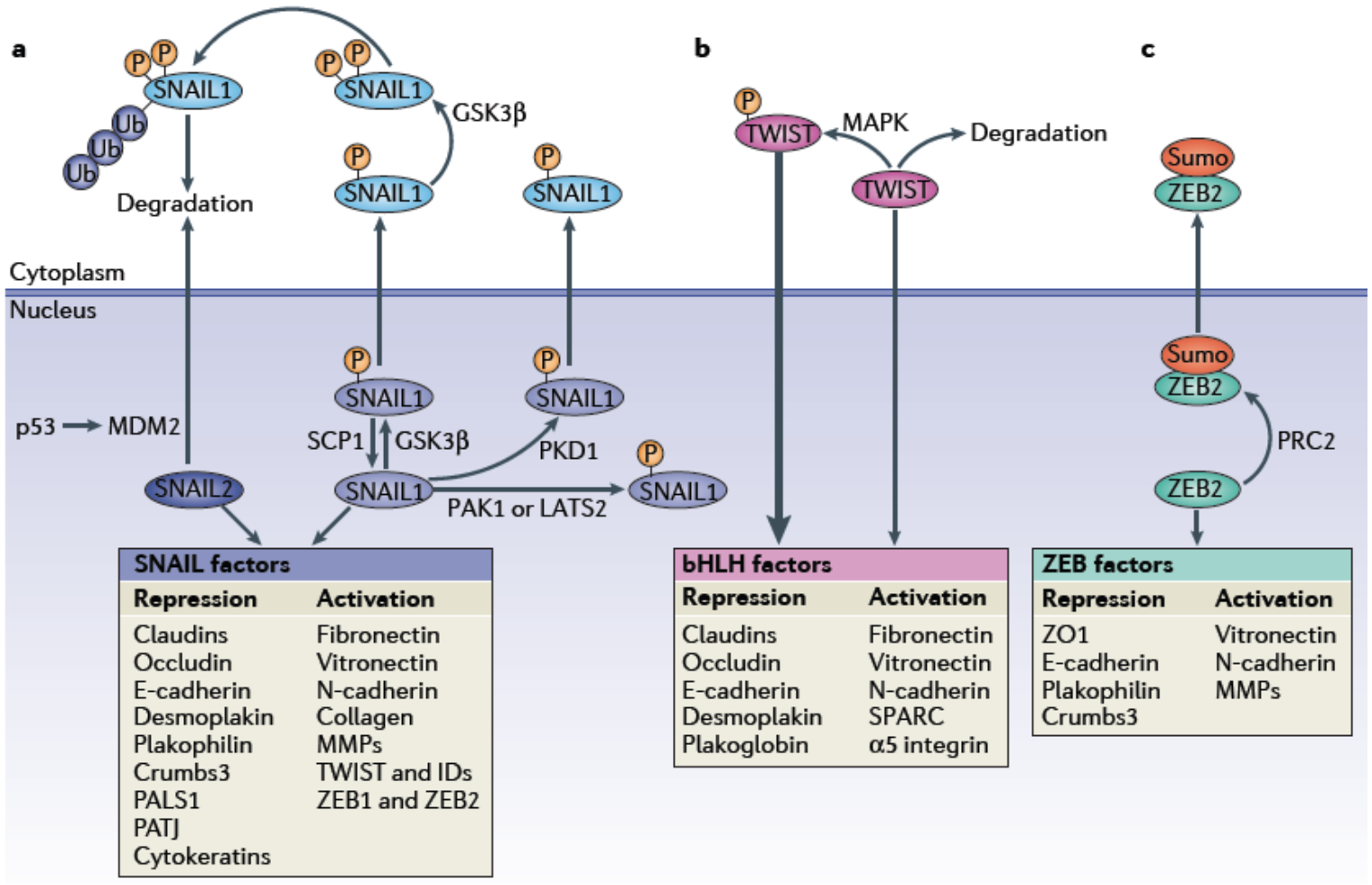
Apical junction disassembly

Lower cell-cell adhesion

Basal lamina degradation

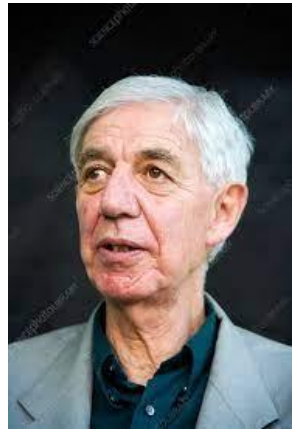
Protrusions
Integrin activation
Cell migration

Classical view of EMT: genetic program

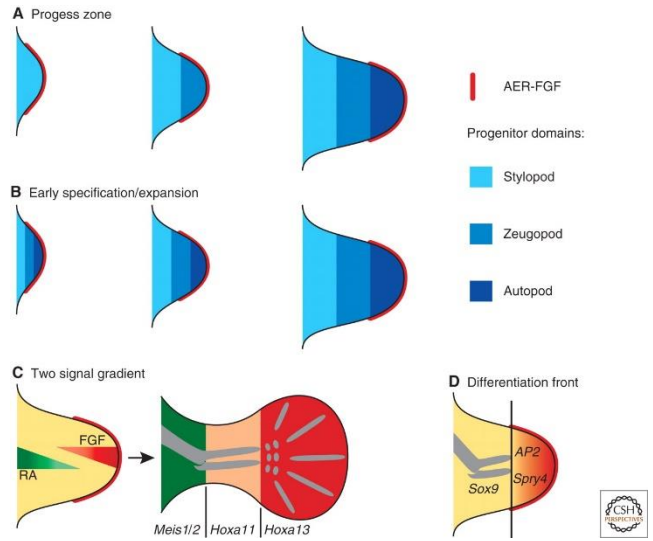


Gastrulation (and EMT)

It is not birth, marriage or death, but gastrulation which is the most important time in your life…

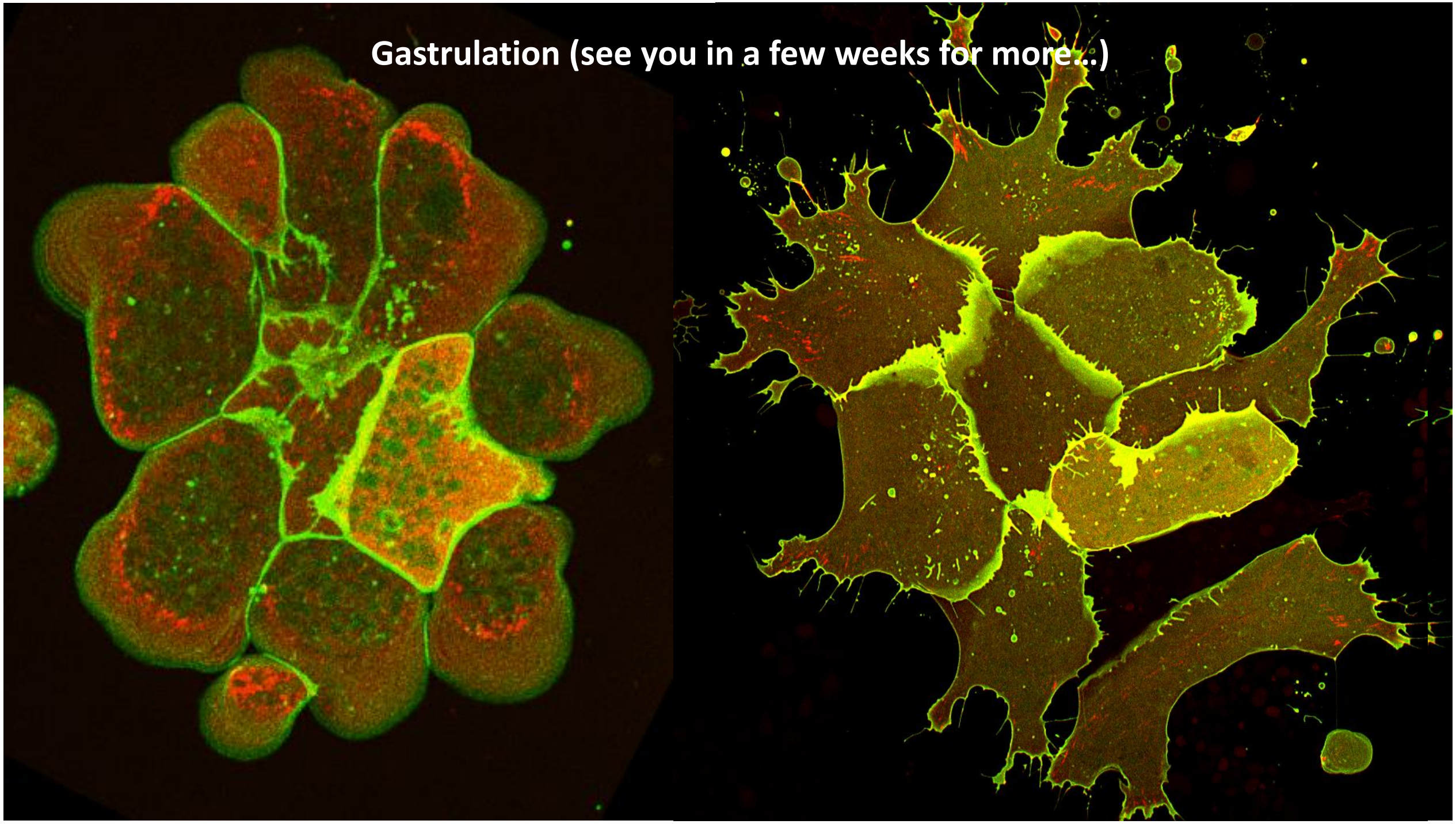


Lewis Wolpert, 1929-2021

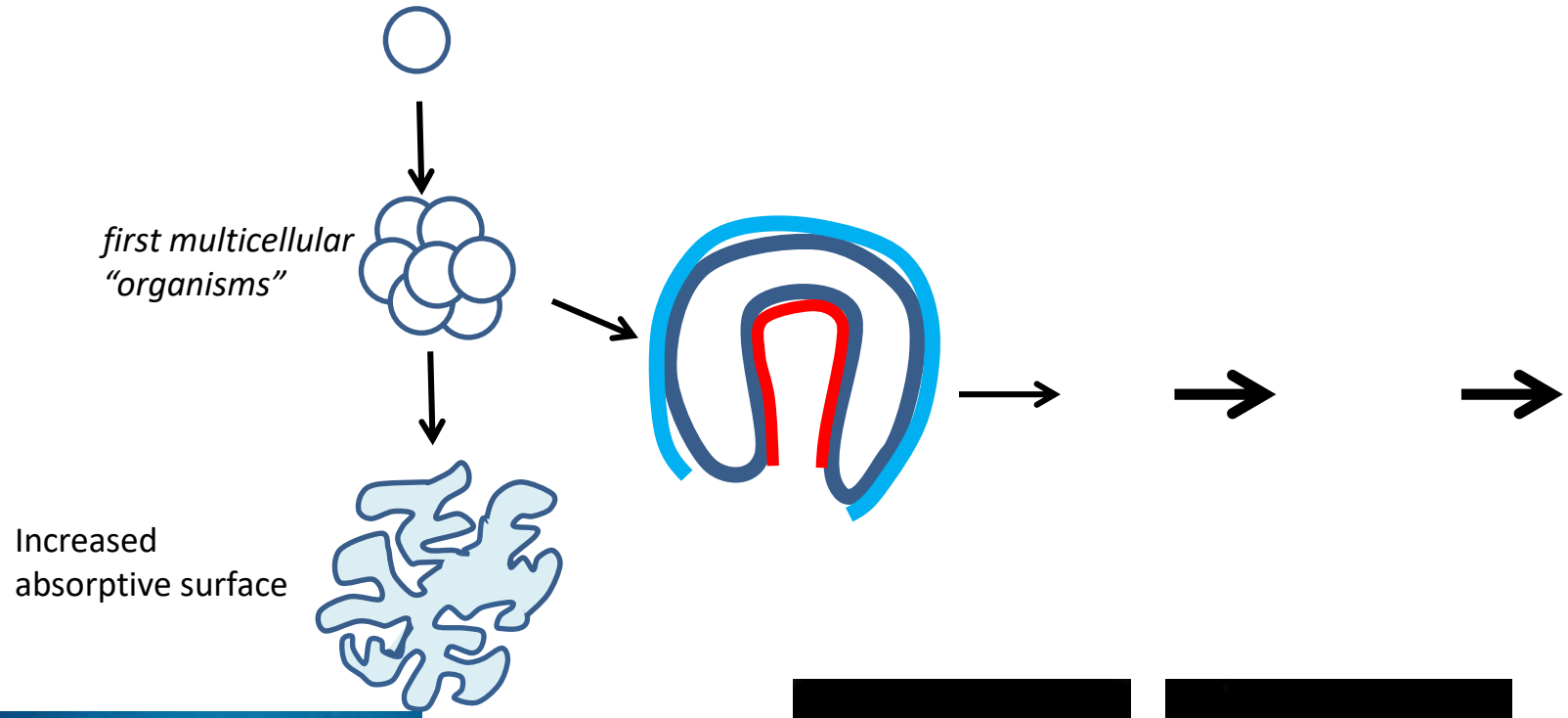


Jean-Denis Bénazet, and Rolf Zeller Cold Spring Harb Perspect Biol 2009;1:a001339

Gastrulation (see you in a few weeks for more…)



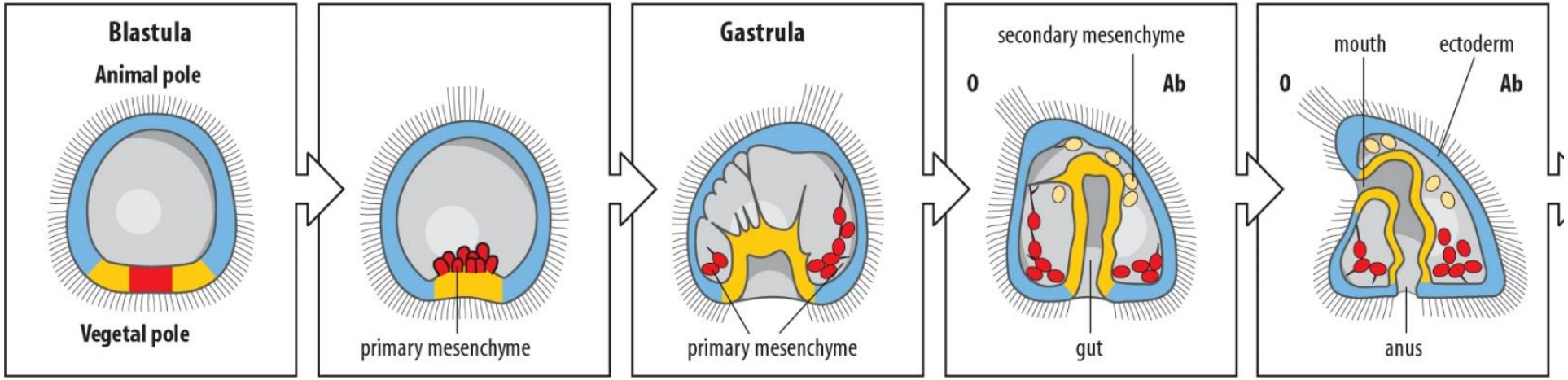
First steps in metazoan morphogenesis



sponges

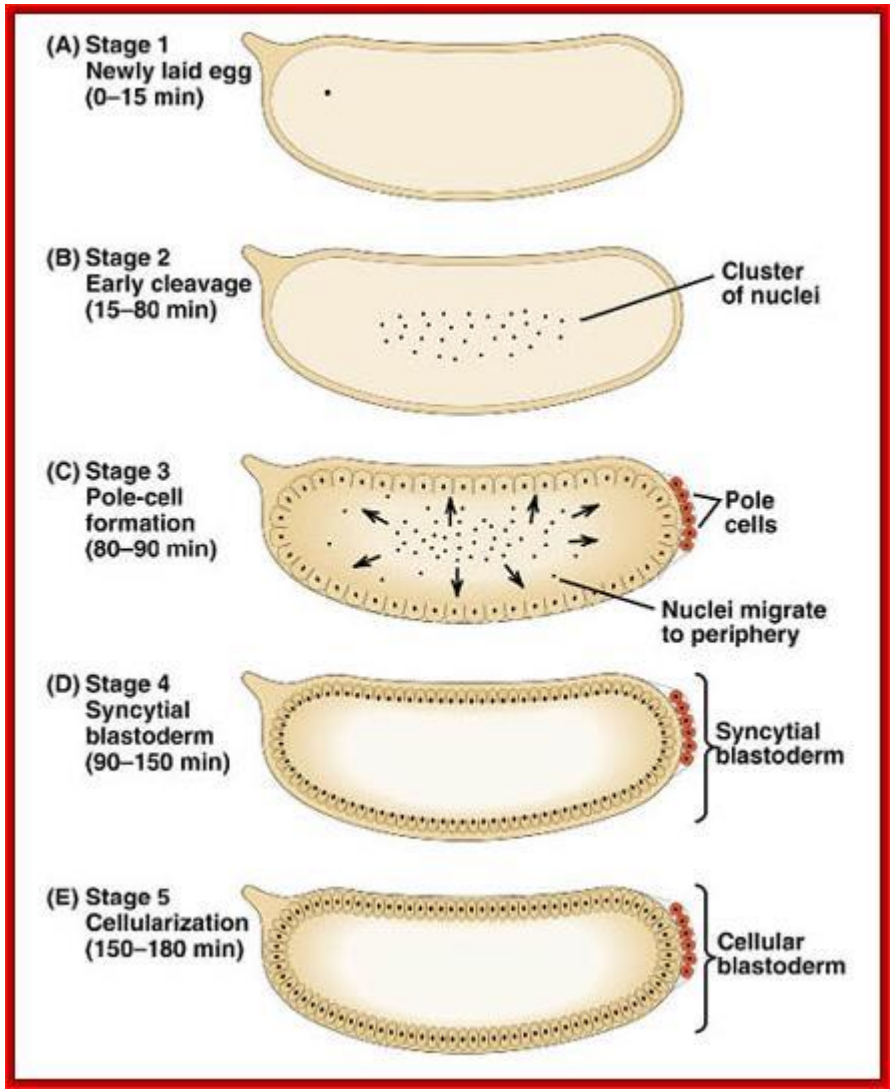
cnidaria

Sea urchin gastrulation

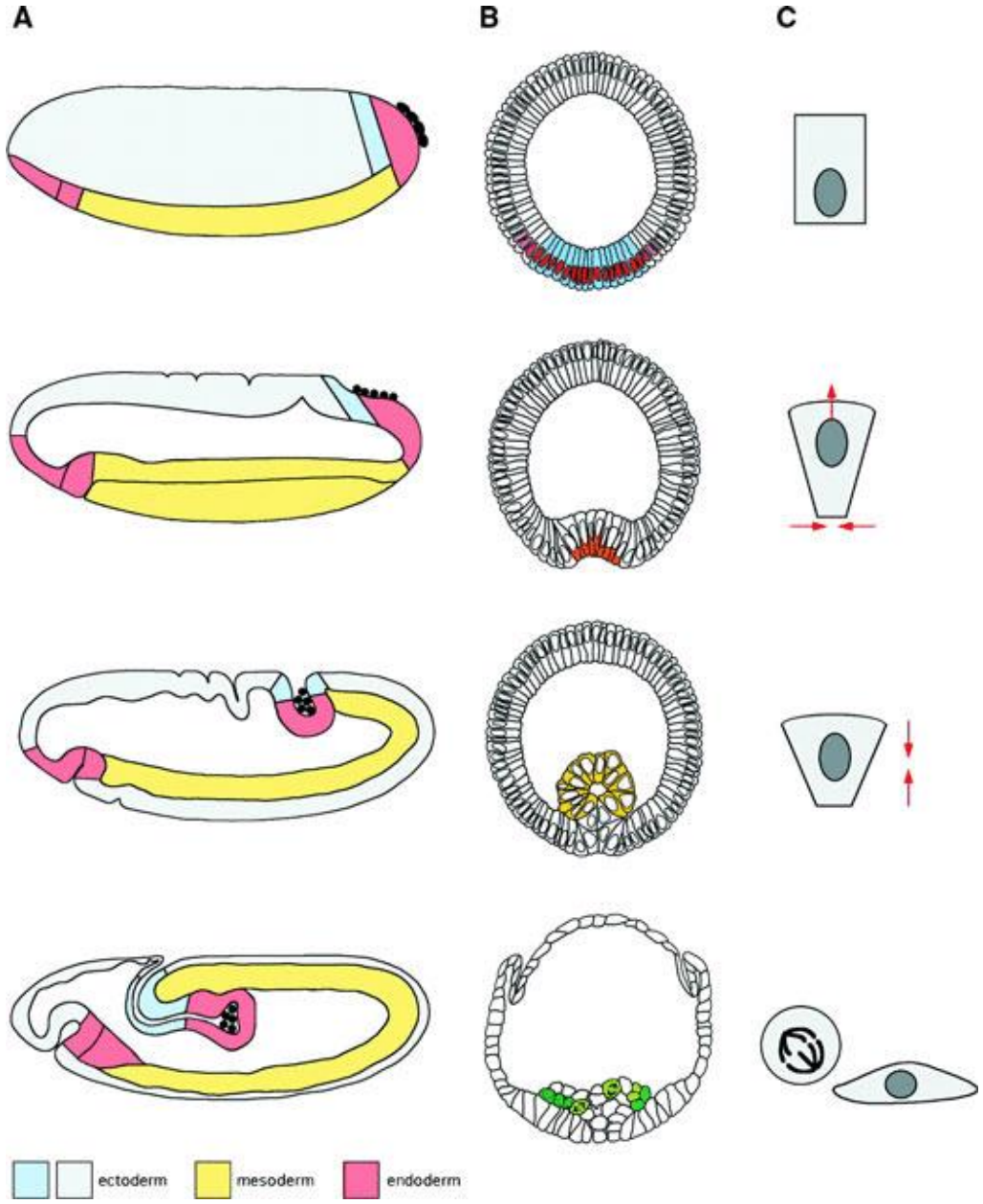


Gastrulation in sea urchin: primary mesenchyme ingression

Drosophila


(A) Stage 1
Newly laid egg
(0–15 min)
(B) Stage 2
Early cleavage
(15–80 min)
Cluster
of nuclei
(C) Stage 3
Pole-cell
formation
(80–90 min)
Pole
cells
Nuclei migrate
to periphery
(D) Stage 4
Syncytial
blastoderm
(90–150 min)
Syncytial
blastoderm
(E) Stage 5
Cellularization
(150–180 min)
Cellular
blastoderm

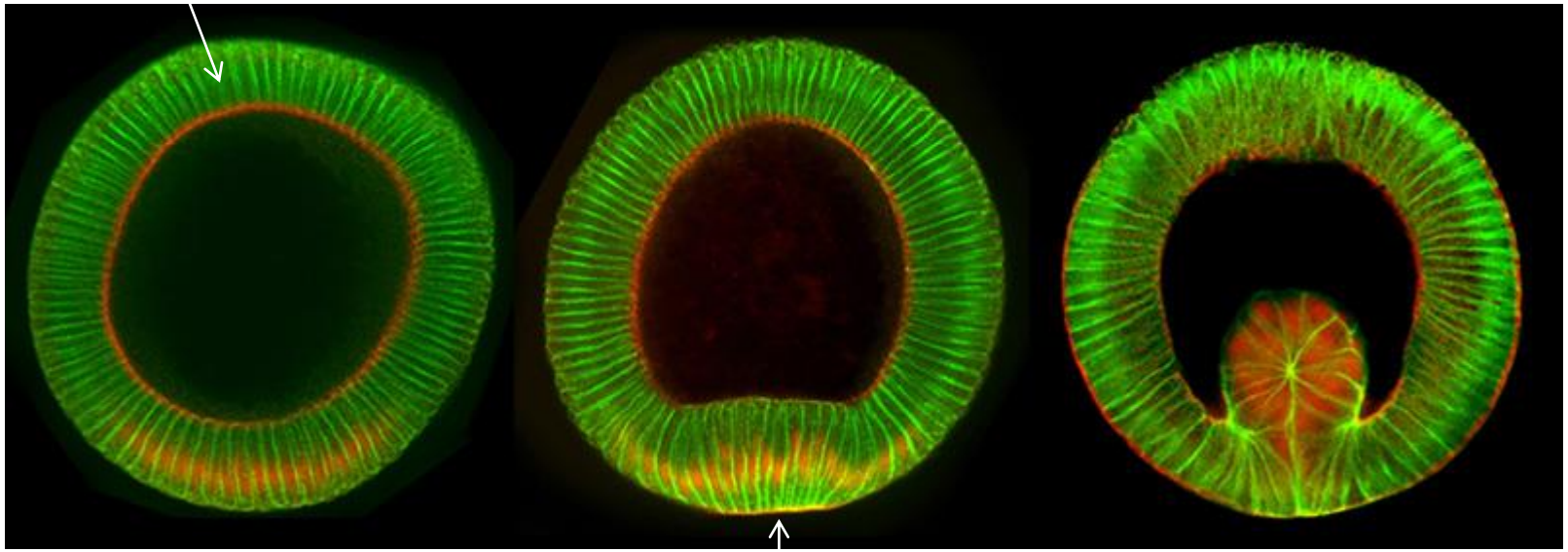
Drosophila gastrulation



Drosophila gastrulation

Blastoderm

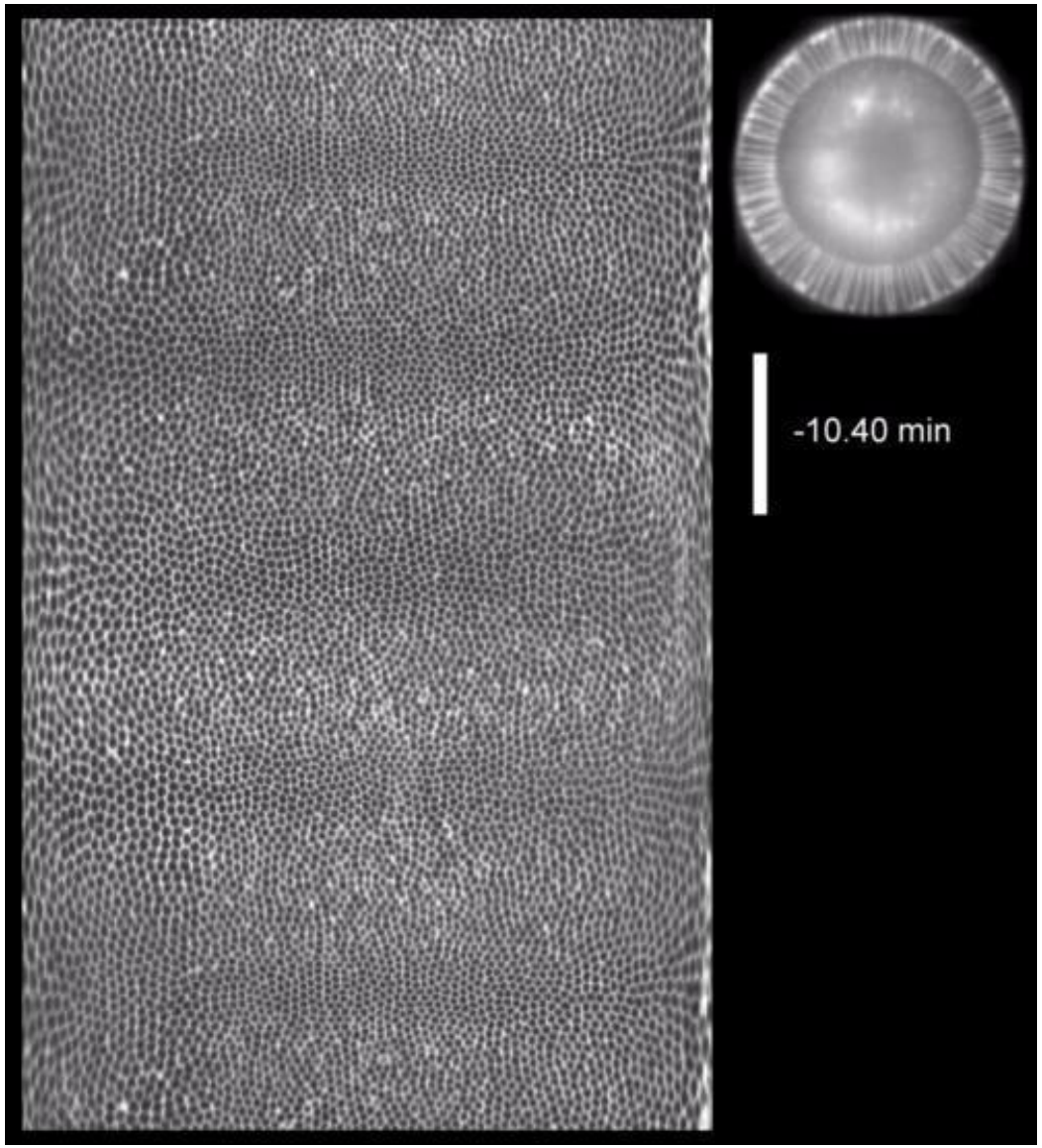
Dorsal



Ventral fullow

Initial phase
= invagination

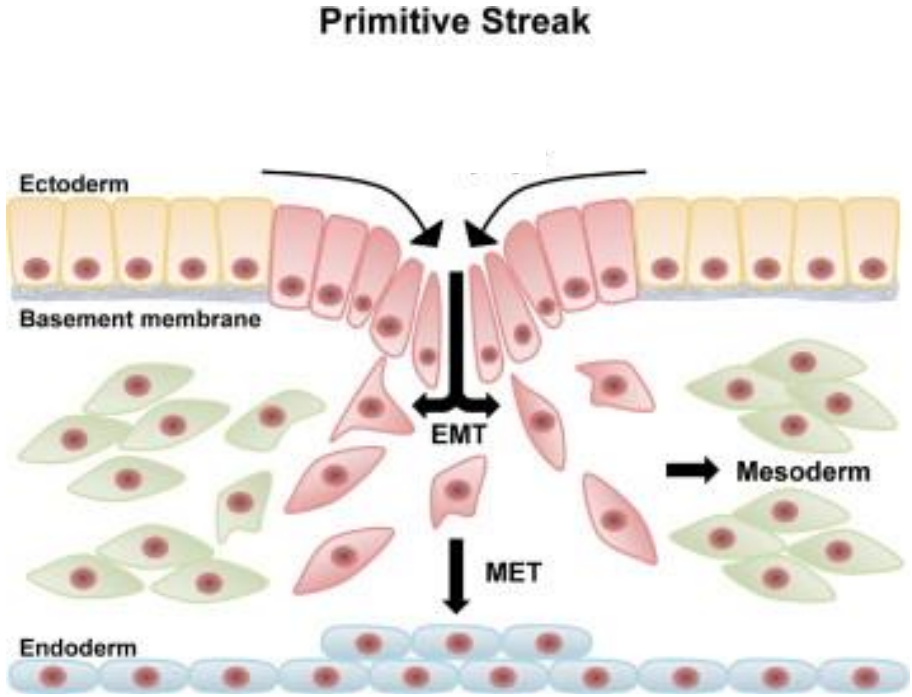
Drosophila gastrulation



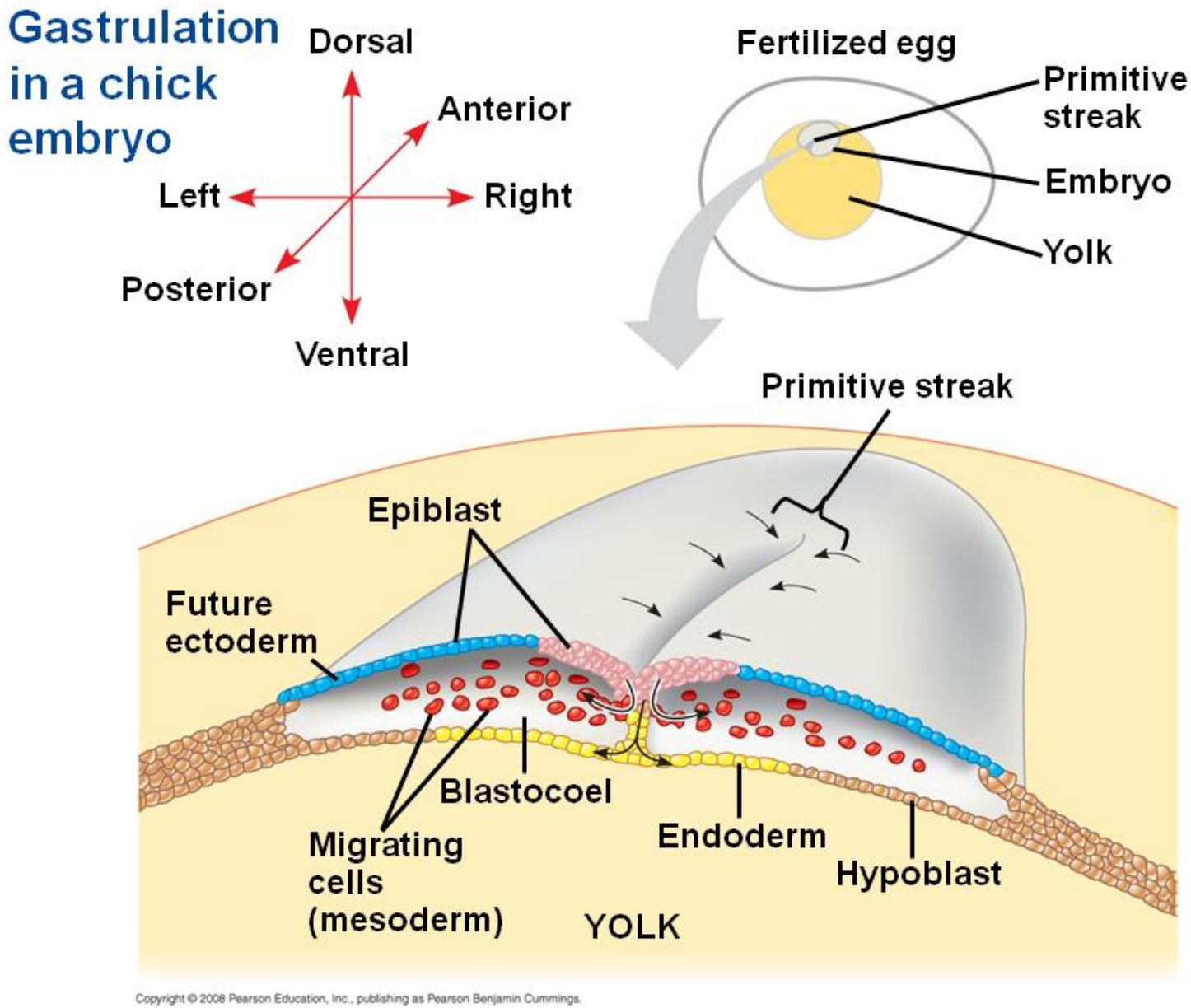
Cross-section
Note that internalized mesoderm is blurry

Superficial view (mesoderm dispappears as in invaginates)

Other gastrulation modes
Ingression (birds, mammals)



Gastrulation in amniotes: Ingression



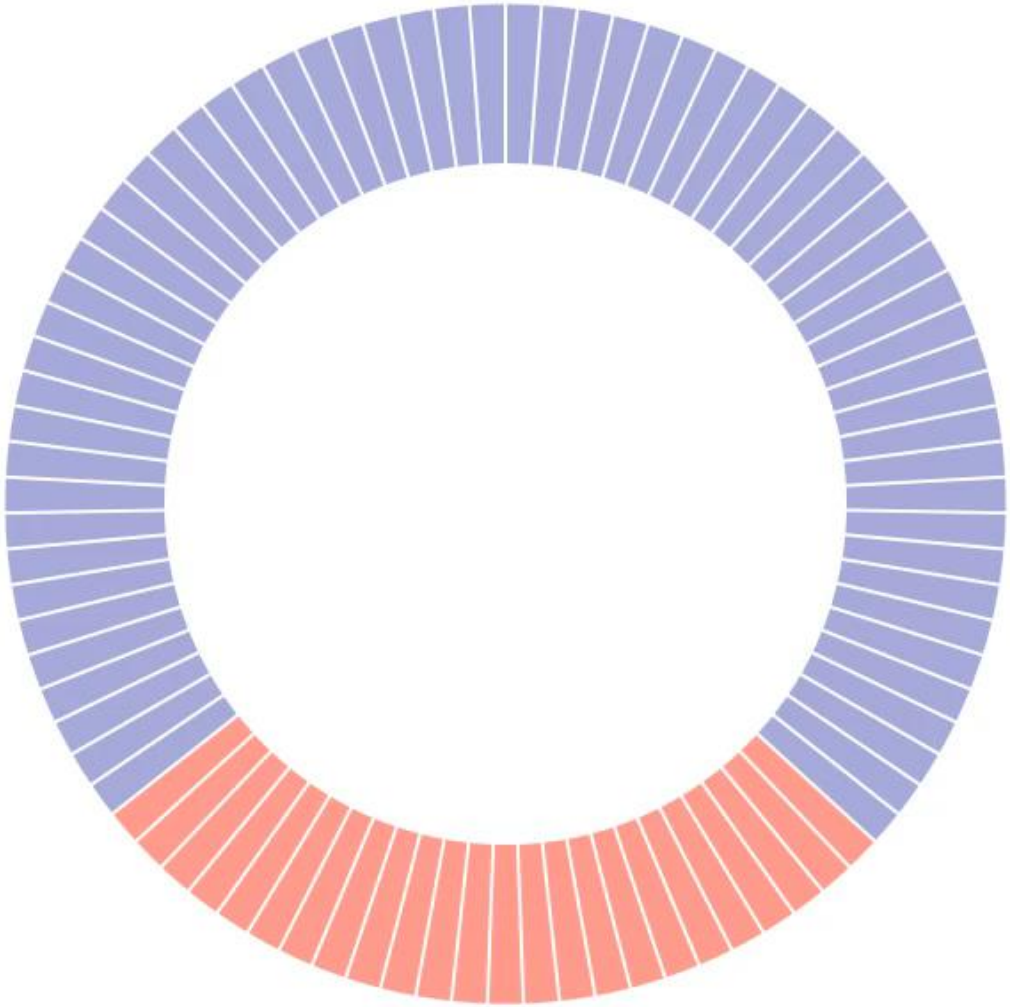
Gastrulation can use partial aspects of EMT

Examples:

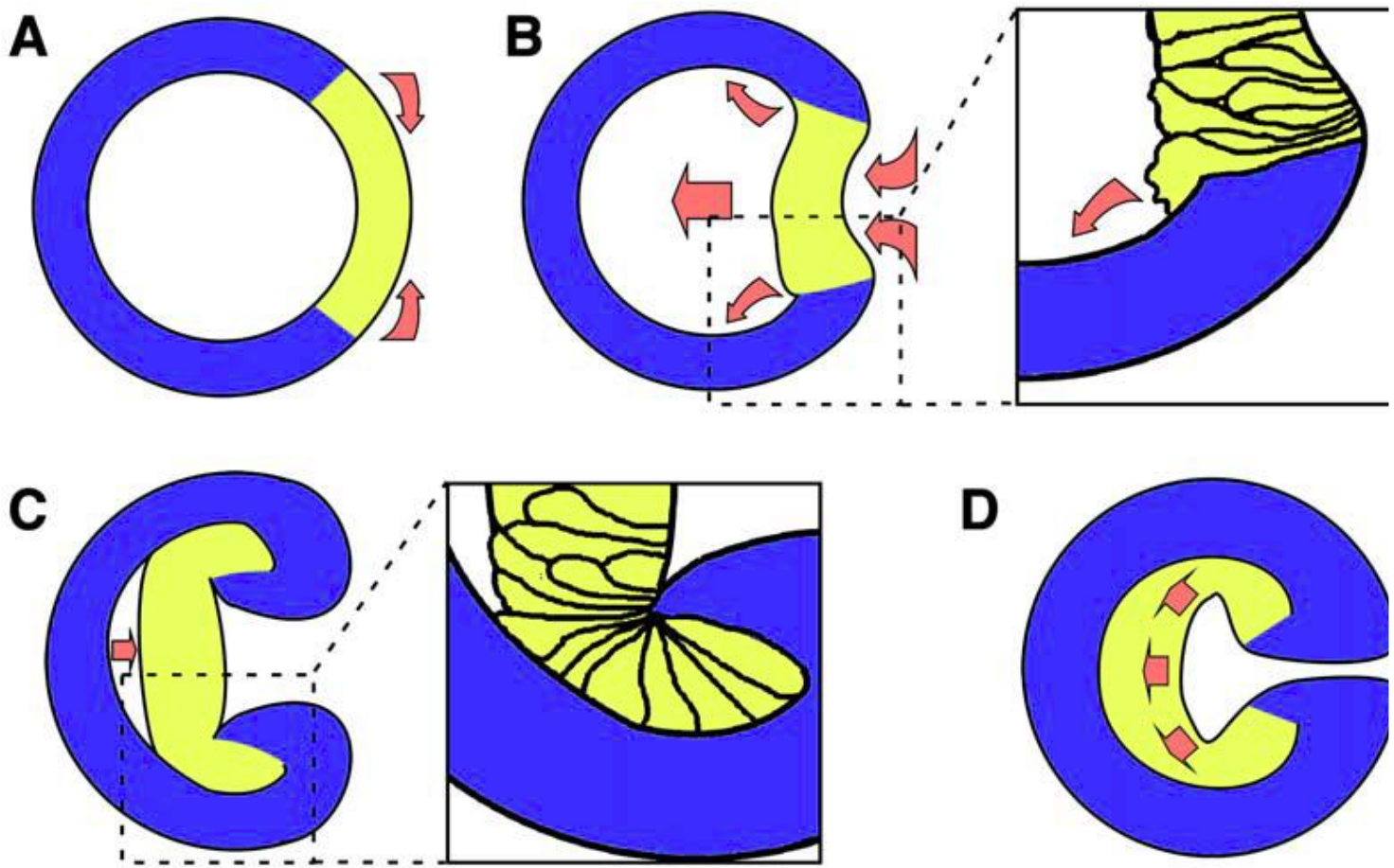
Cnidarians (See anemones, jellyfish, coral)

Amphibians (Xenopus)

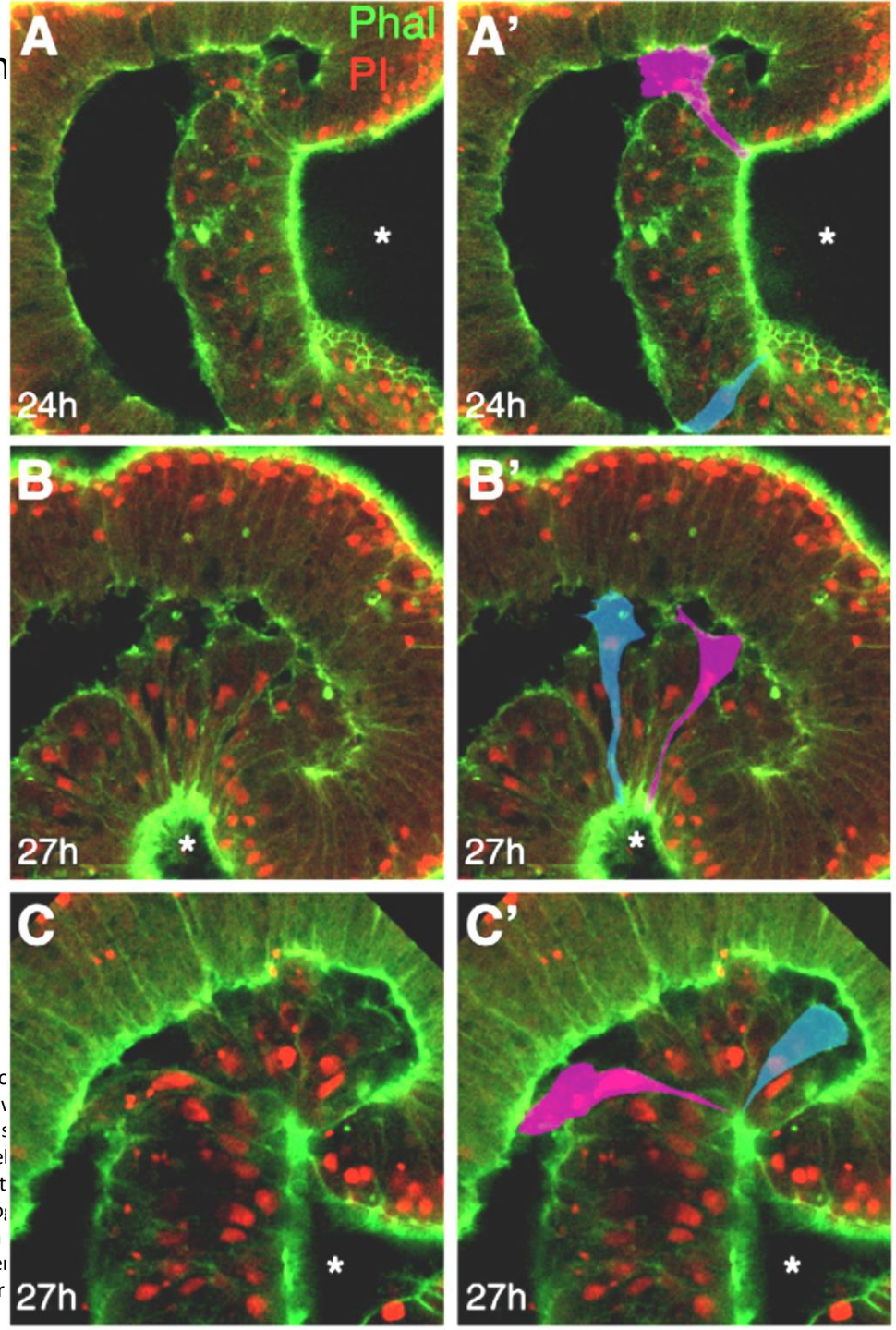
Changes in cell shape: Gastrulation by invagination: Simulation of endoderm invagination in cnidarians



Invagination in cnidarians: apical constriction, elongation, basal expansion



Invagination al expansion

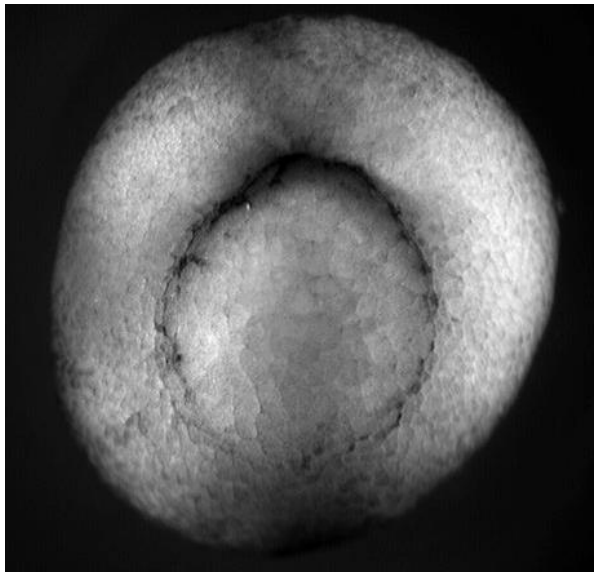


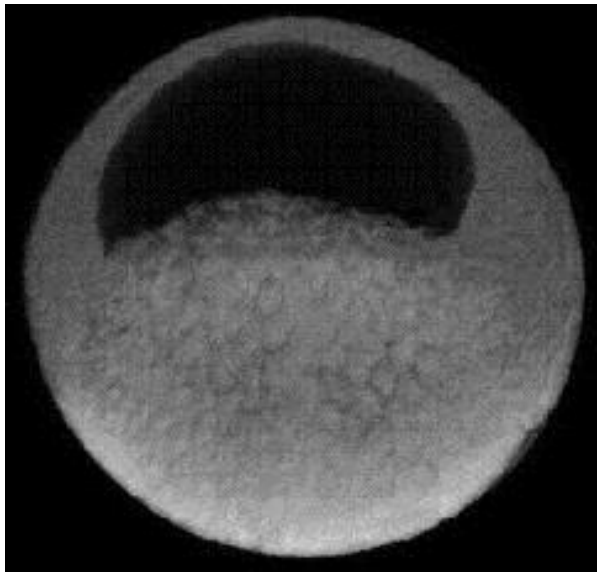
ıtal Biology 305 (2007) 483–497
ı in the cnidarian Nematostella
:curs via invagination not ingression
ɡie a, Marymegan Daly b, Mark Q.

Fig. 3. Gastrulation in Nematostella c
(green) and PI (red). The images shov
blastopore lip cells in each image fals
mass and migrate into the blastocoel
and remain a monolayer even after t
assume a more squamous morpholo
injected during cleavage stages with
the projections back to the archente
from n=50 embryos examined. Aster

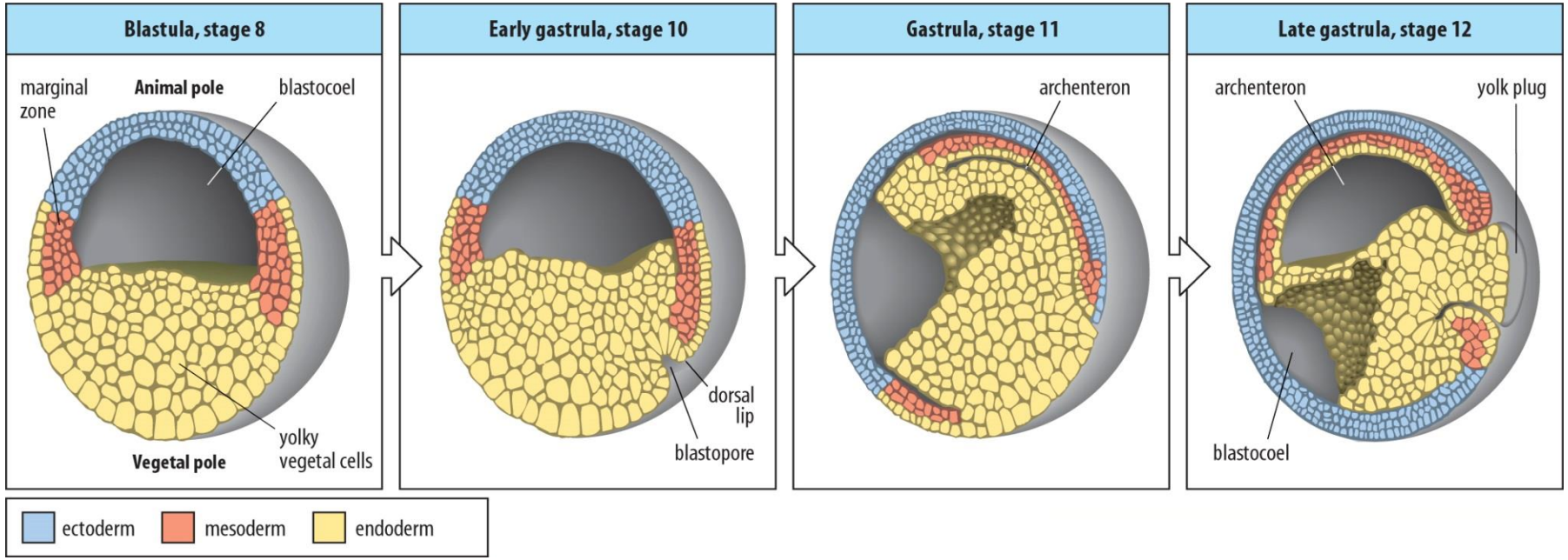
stained with phalloidin
:ctively, with two
ls detach from the endodermal
:reme fashion in panels B′, C′),
:trulation, the endodermal cells
h one blastomere was
bottle cells can be seen. Note
; are representative examples

Gastrulation in Xenopus laevis



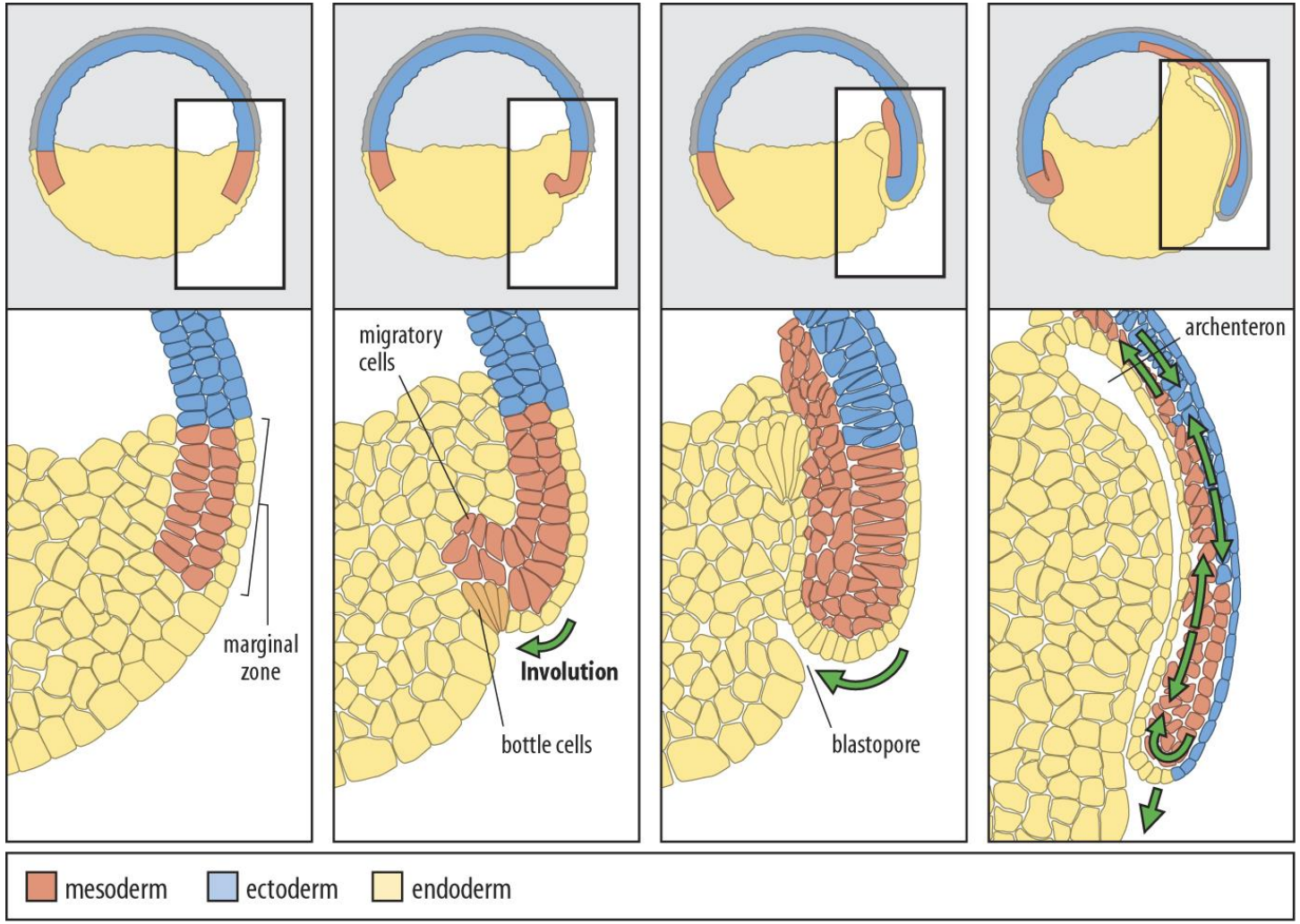


Xenopus gastrulation



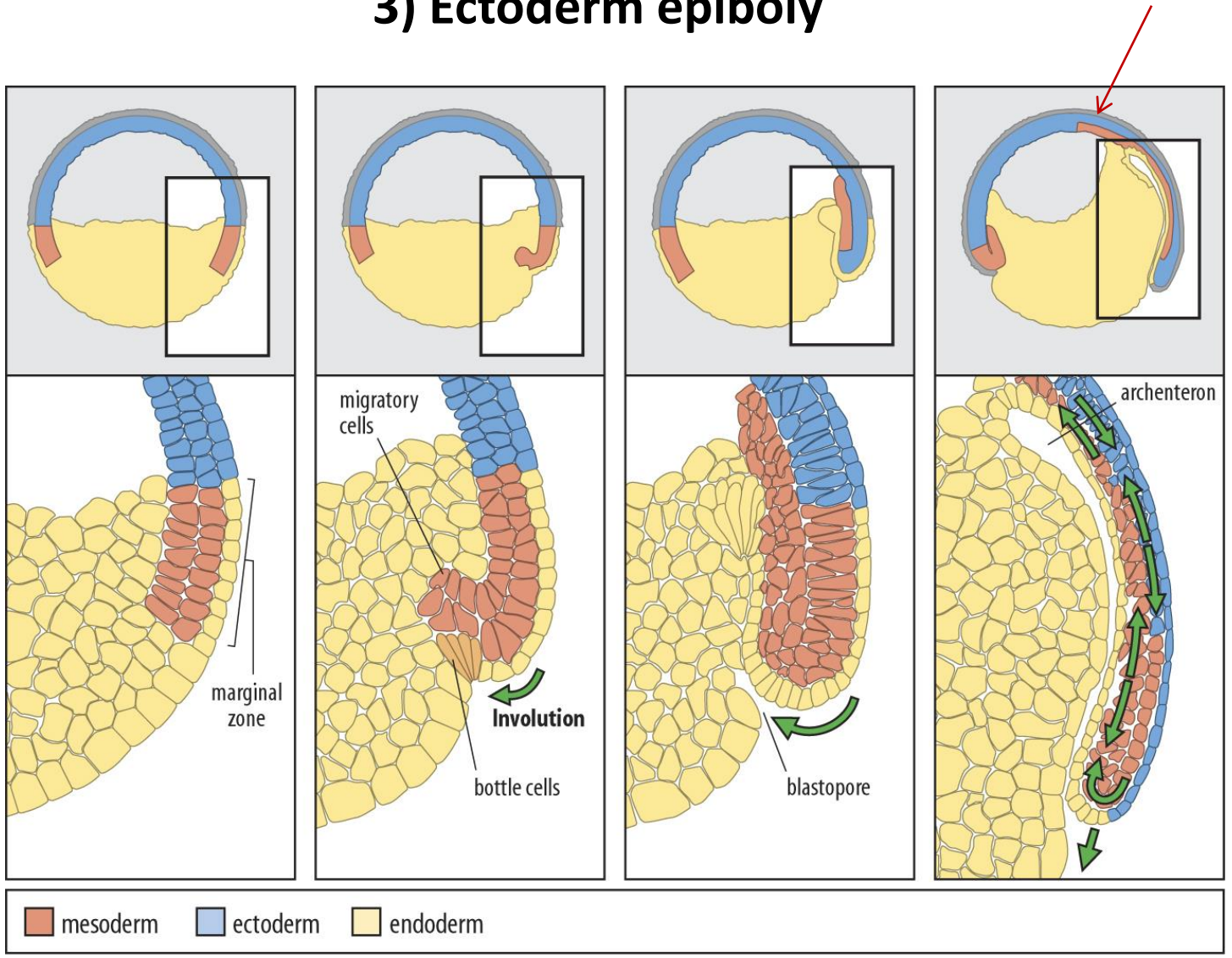
Xenopus gastrulation

2) Involution



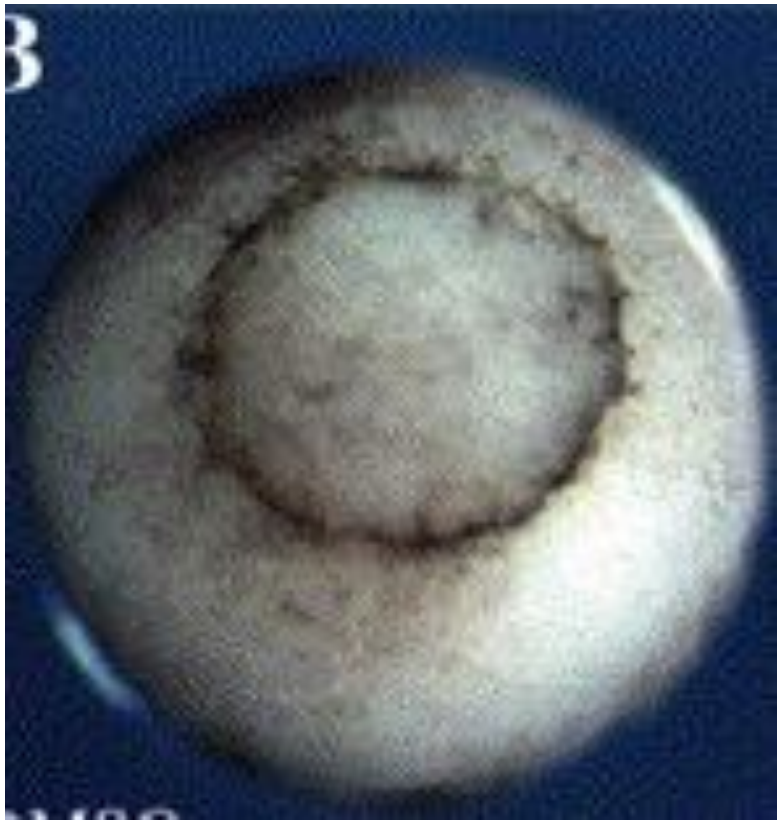
Xenopus gastrulation

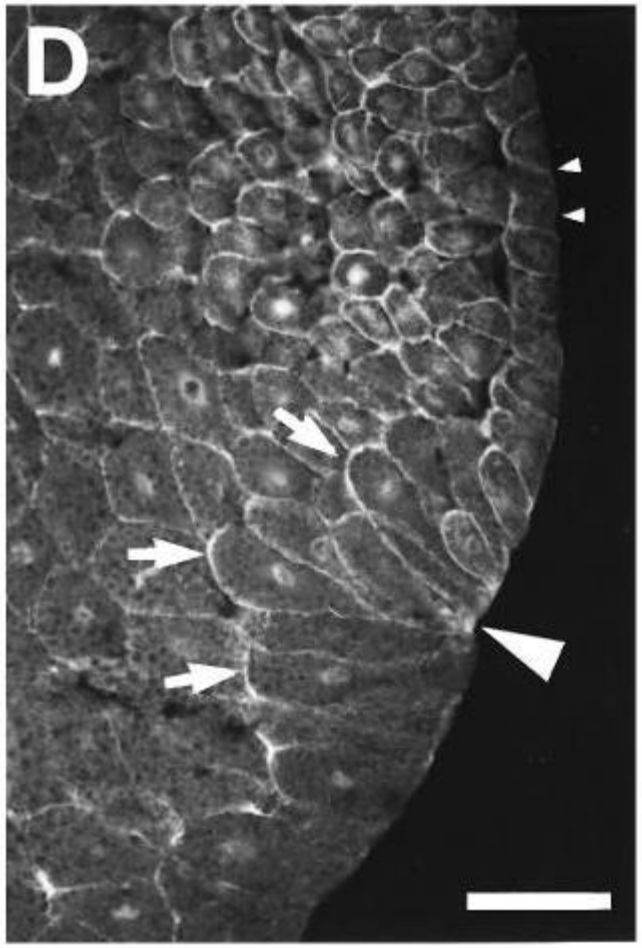
3) Ectoderm epiboly



Xenopus gastrulation

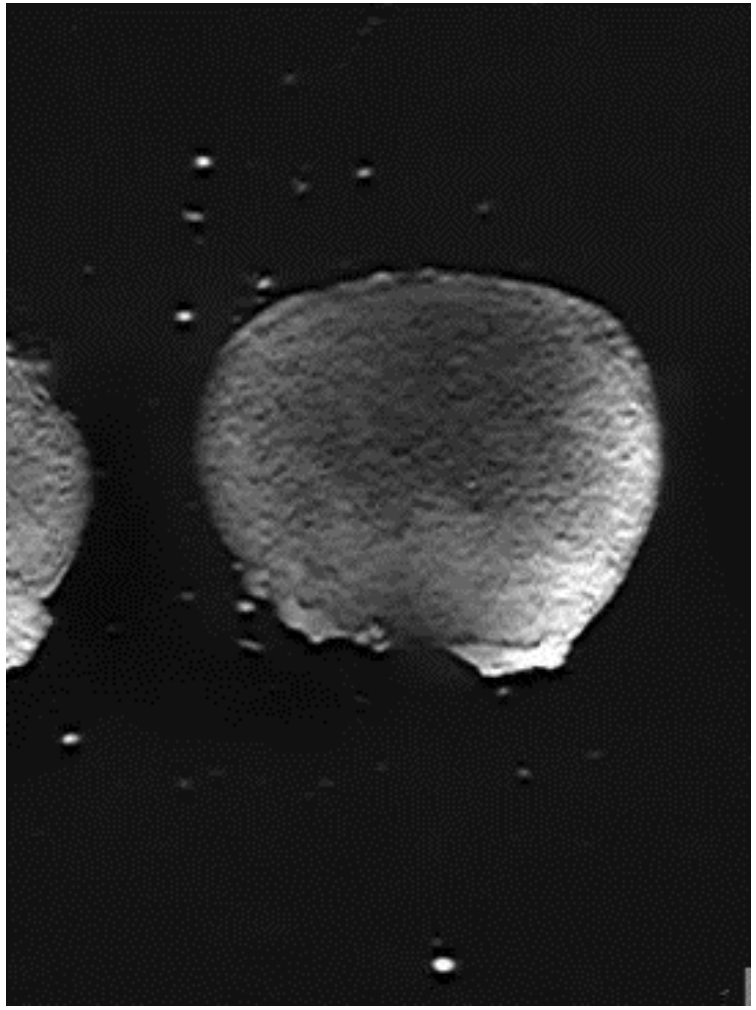
Invagination (“bottle cells”)





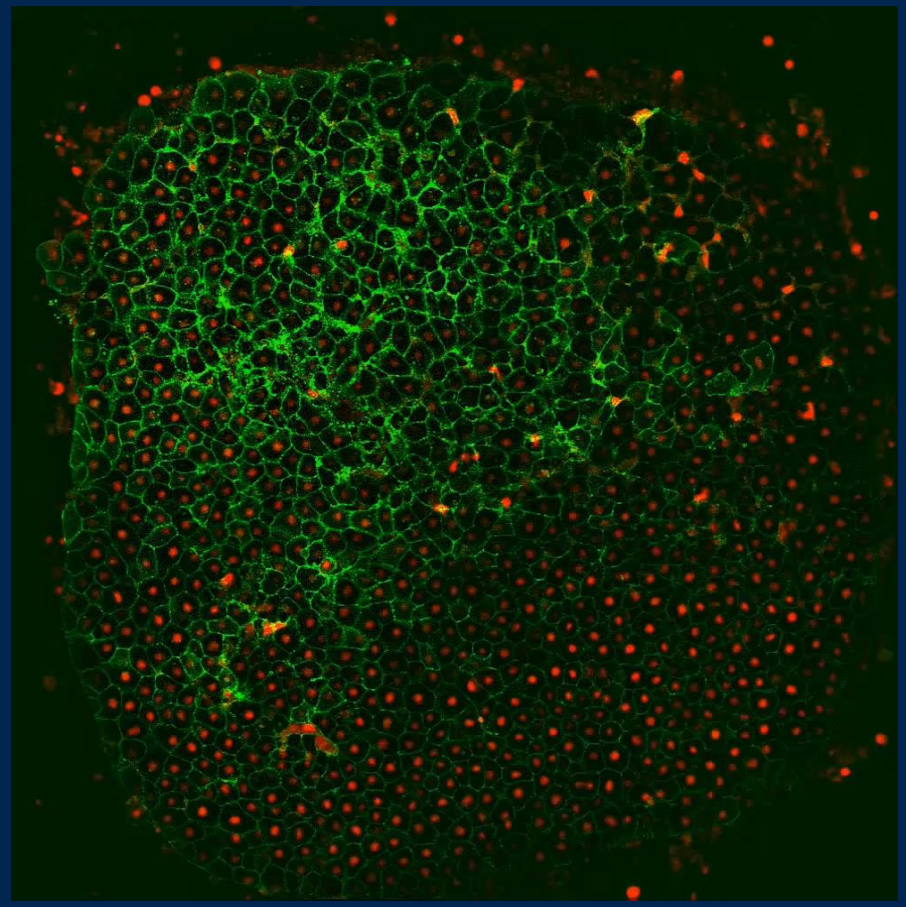
Xenopus gastrulation

Involution = collective migration of a coherent tissue



Mesoderm tissue explant

Mesoderm



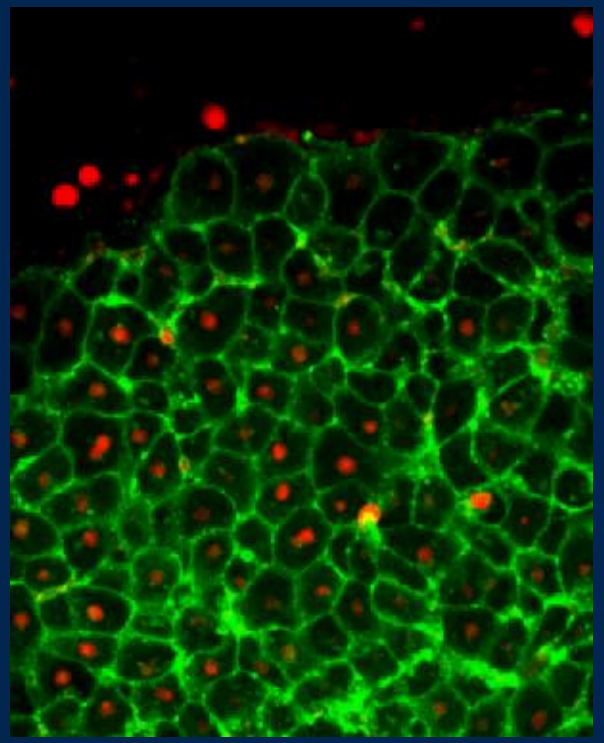
Ectoderm

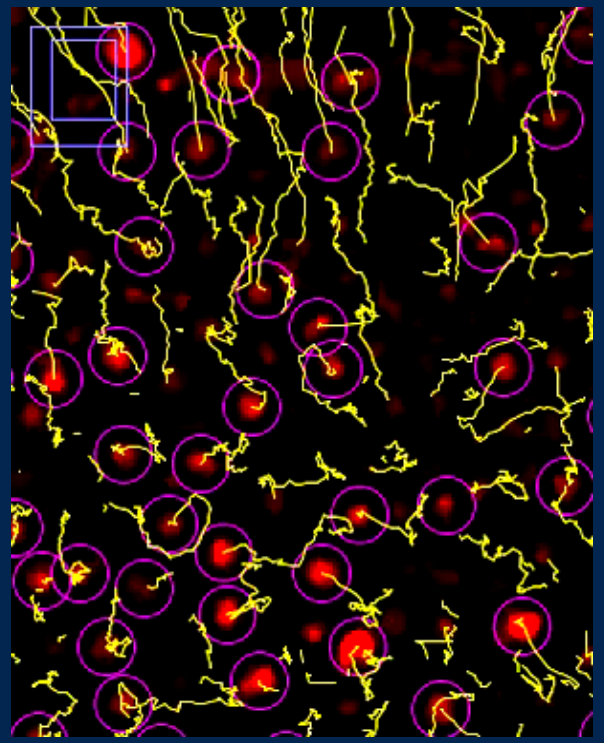
Membrane GFP

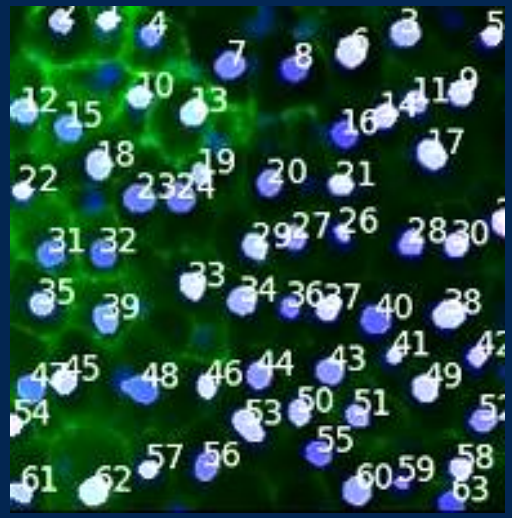
Nuclei

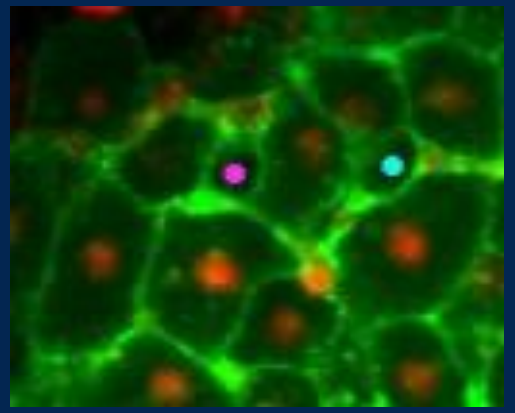
David Rozema and Francois Fagotto

Dissection of cell motility inside embryonic tissues



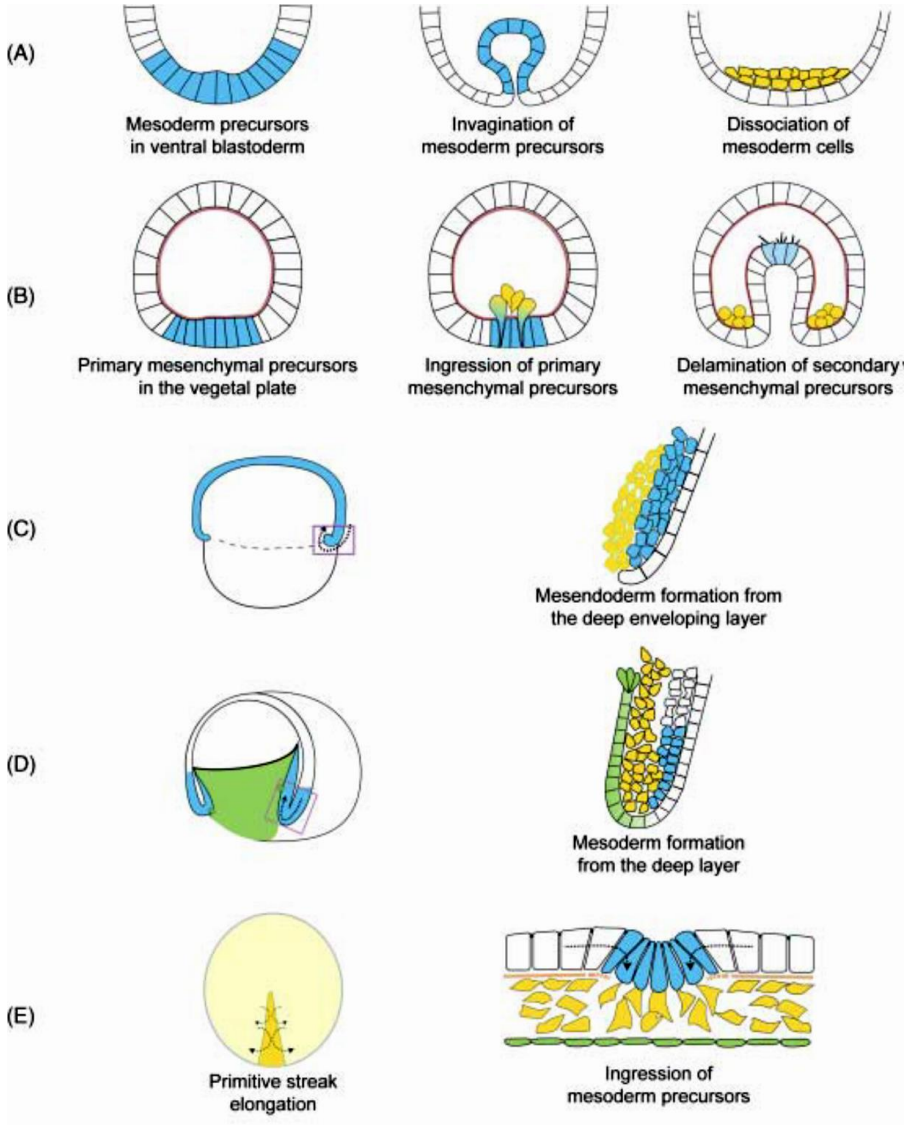




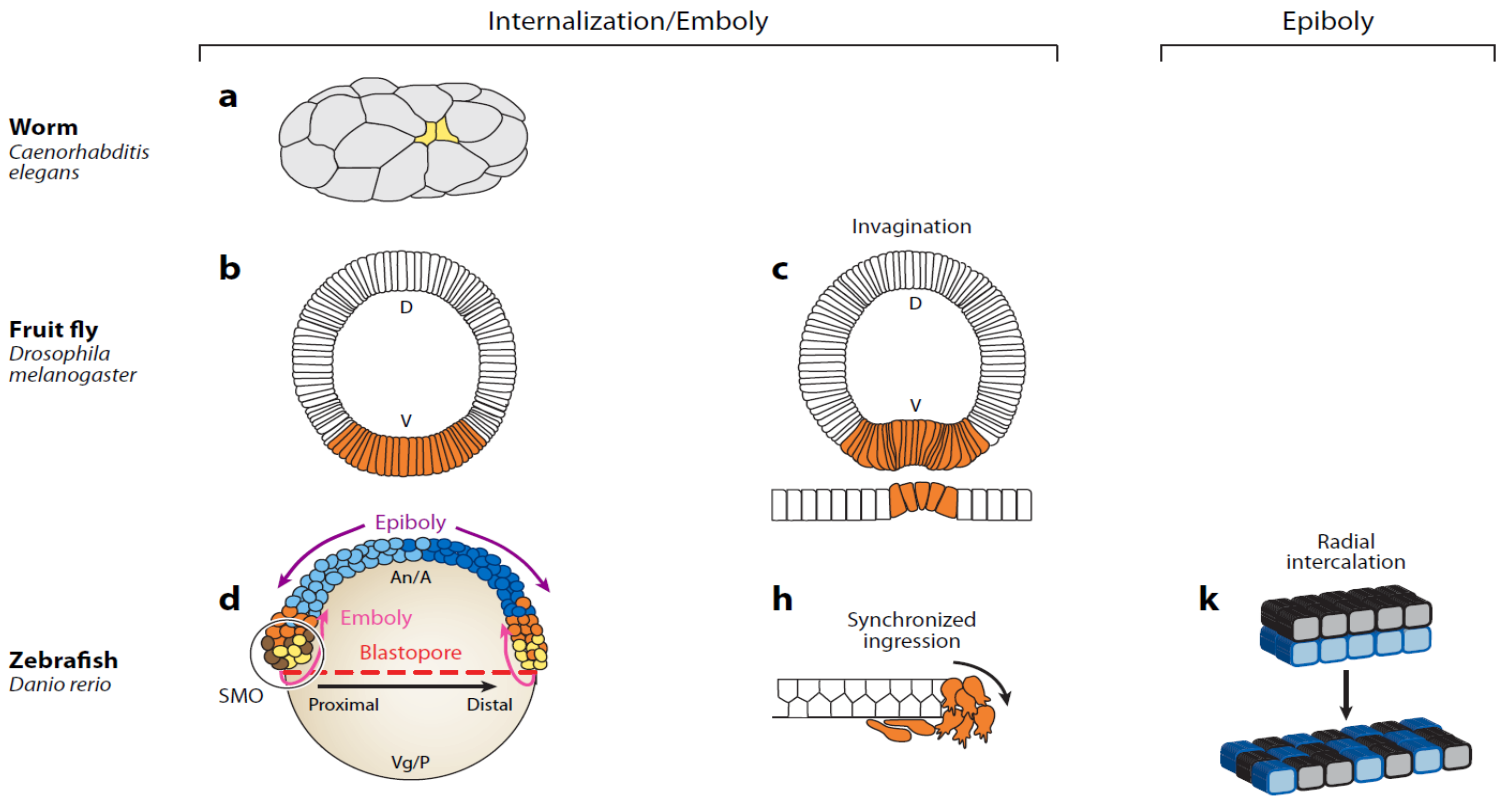


David Rozema and Francois Fagotto

Various modes of gastrulation

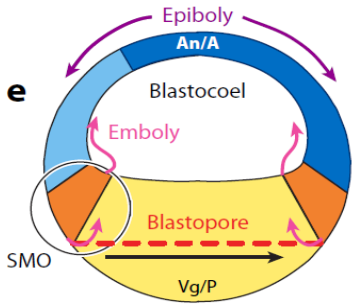


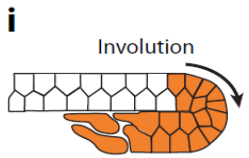
Various modes of gastrulation

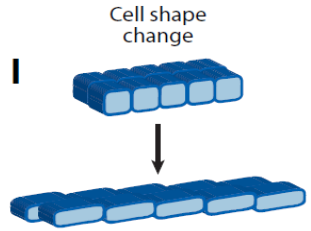


Various modes of gastrulation

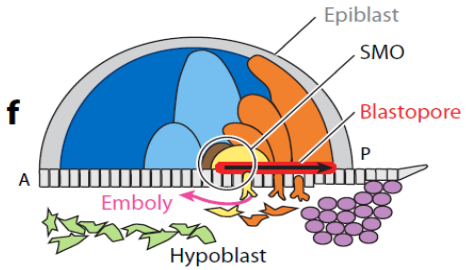
Frog
Xenopus laevis

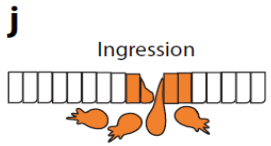


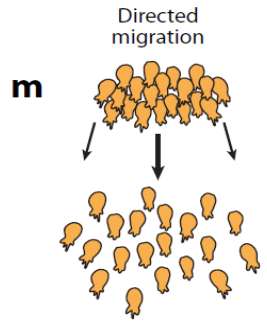




Chicken
Gallus gallus





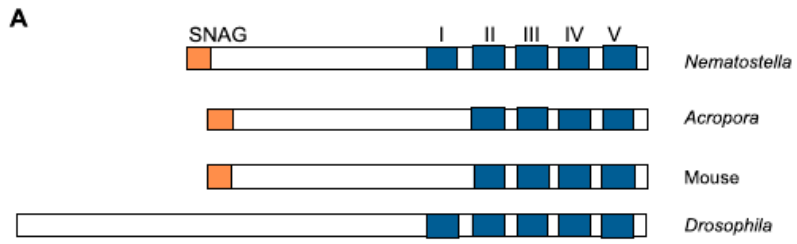


Conserved regulators of EMT in development

Transcription factors:
Snail
Twist

Mesoderm:
T/Brachyury
Goosecoid

Snail sequence alignment



B

```
                                  I                                                  II
NvSnailA       : CHQCNKGYSTPLGLAKHQQFHCNT----HHKKSLTCKHCDKLYVSLGALKMHIRTH
NvsnailB       : CPNCMKGFNALATLMRHQYFYCPPT---QHKRPLHCKYCEKLYDSLGALKMHIRTH
Acropora       : LNRAKKPQKRERNASTSDVSQRKNK---RTRKELACKHCDKNYLSLGALKMHIRTH
Podocoryne     : IDKSKE----QINVPKKSKVPRKGK---NSR-HYSCKYCDKDYMSLGALKMHIRTH
Patella        : CDSCKKSYSTFSGLSKHKQFHCAS----QIKKEPNCKYCDKTYVSLGALKMHIRTH
Dm_worniu      : CQDCGKSYSTYSGLSKHQQFHCPSAEGNQVKKVPSCKNCDKTYVSLGALKMHIRTH
Branchiostoma  : CPQCAKSYSTYSGLTKHKQFHCVT----QSKKAPNCKYCDKVYVSLGALKMHIRTH
Chicken_Slug   : CNLCNKTYSTFSGLAKHKQLHCDA----QSRKSPSCKYCDKEYVSLGALKMHIRTH
Homo_snail     : CFHCHKPYHTLAGLARHQQLHCHLQ---VGR-VPTCKYCDKEYTSLGALKMHIRTH
Mouse_scratch  : CGECGKTYATSSNLSRHKQTHRSLD----SQLARRSPTCKVVVSMPAMAYHLLLH

                                 III                                  IV
NvSnailA       : TLPCKCSTCGKAFSRPWLLQCHIRTHTGEKPYQCTNCKRAFADRSNLRAHMQTH
NvsnailB       : TLPCKCKICGKAFSRPWLLQCHVRTHTGEKPYKCTQCQRAFADRSNLRAHLQTH
Acropora       : TLPCKCTICGKAFSRPWLLQGHIRTHTGEKPYQCPKCQRAFADRSNLRAHLQTH
Podocoryne     : TLPCQCKICGKSFSRPWLLQCHIRTHTGERPFVCSYCGRAFADRSNLRAHMQTH
Patella        : TLPCKCKLCGKAFSRPWLLQGHIRTHTGEKPFSCQHCGRAFADRSNLRAHLQTH
Dm_worniu      : TLPCKCPICGKAFSRPWLLQGHIRTHTGEKPFSCQHCNRAFADRSNLRAHMQTH
Branchiostoma  : TLPCKCKICGKAFSRPWLLQGHVRTHTGEKPFACPHCSRAFADRSNLRAHLQTH
Chicken_Slug   : TLPCVCKICGKAFSRPWLLQGHIRTHTGEKPFSCPHCNRAFADRSNLRAHLQTH
Homo_snail     : TLPCTCKICGKAFSRPWLLQGHVRTHTGEKPYACSHCSRAFADRSNLRAHLQTH
Mouse_scratch  : DLRHKCGVCGKAFSRPWLLQGHMRSHTGEKPFGCAHCGKAFADRSNLRAHMQTH

                                  V
NvSnailA       : AVVKKYSCSRCKKSFSRMSLLVEHEDSGC
NvsnailB       : SDVKKYSCKQCSKSFSRMSLLLKHEGS-C
Acropora       : SSVKKYSCSQCSRSFSRMSLLVKH-QYSC
Podocoryne     : VDVKKYECRKCMKSFSRMSLLTKHEEFDC
Patella        : SDVKKYSCRSCSKTFSRMSLLLKHEDGCC
Dm_worniu      : SDVKKYSCPTCTKSFSRMSLLAKHLQSGC
Branchiostoma  : SDIKKYSCKNCSKTFSRMSLLTKHEEAGC
Chicken_Slug   : SDVKKYQCKNCSKTFSRMSLLEKHEESGC
Homo_snail     : SDAKKYRCRRCTKTFSRMSLLARHEESGC
Mouse_scratch  : SAFKHFQCKRCKKSFALKSYLNKHYESAC
```

C

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NvSnailA       : MPRSFLVKK
NvSnailB       : MPRSFLVKT
Acropora       : MPRSFLVKK
Podocoryne     : MPRSFLVKK
Dm_escargot    : MPRSFLVKK
Xenopus_snal   : MPRSFLVKK
zebrafish_sna: MPRSFLVKK
Homo_Scratch   : MPRSFLVKK
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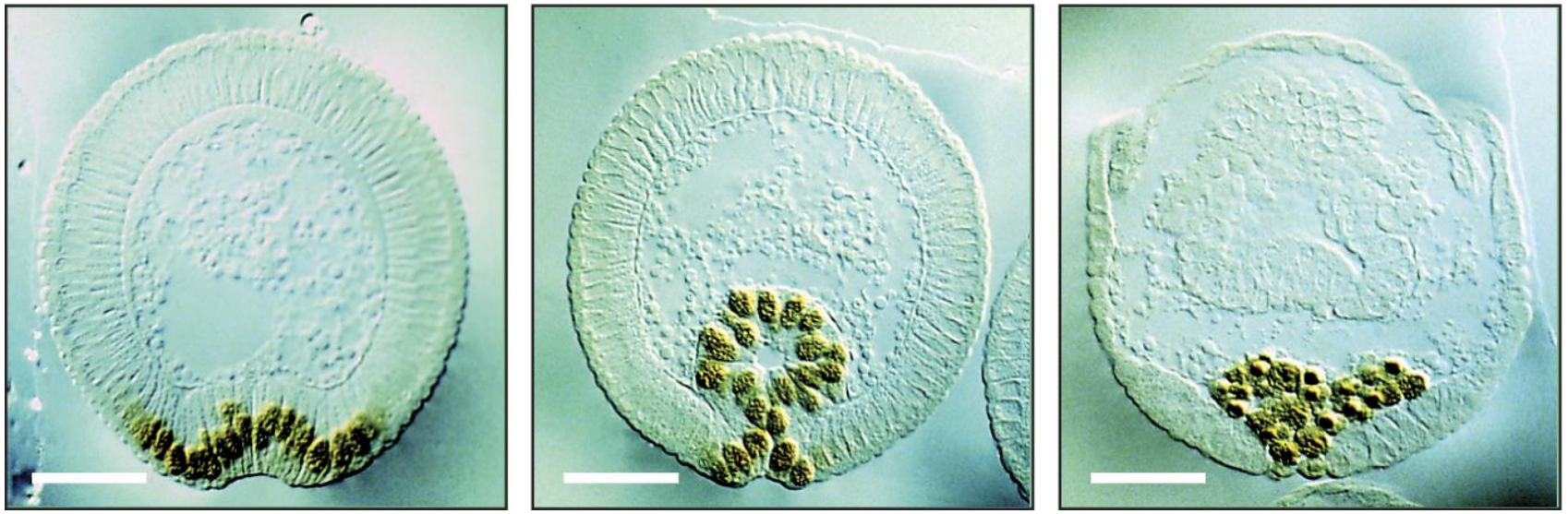
Regulation of morphogenesis:
Patterning and control of cell behavior

Example: Gastrulation

Snail marks prospective migratory cells



Drosophila

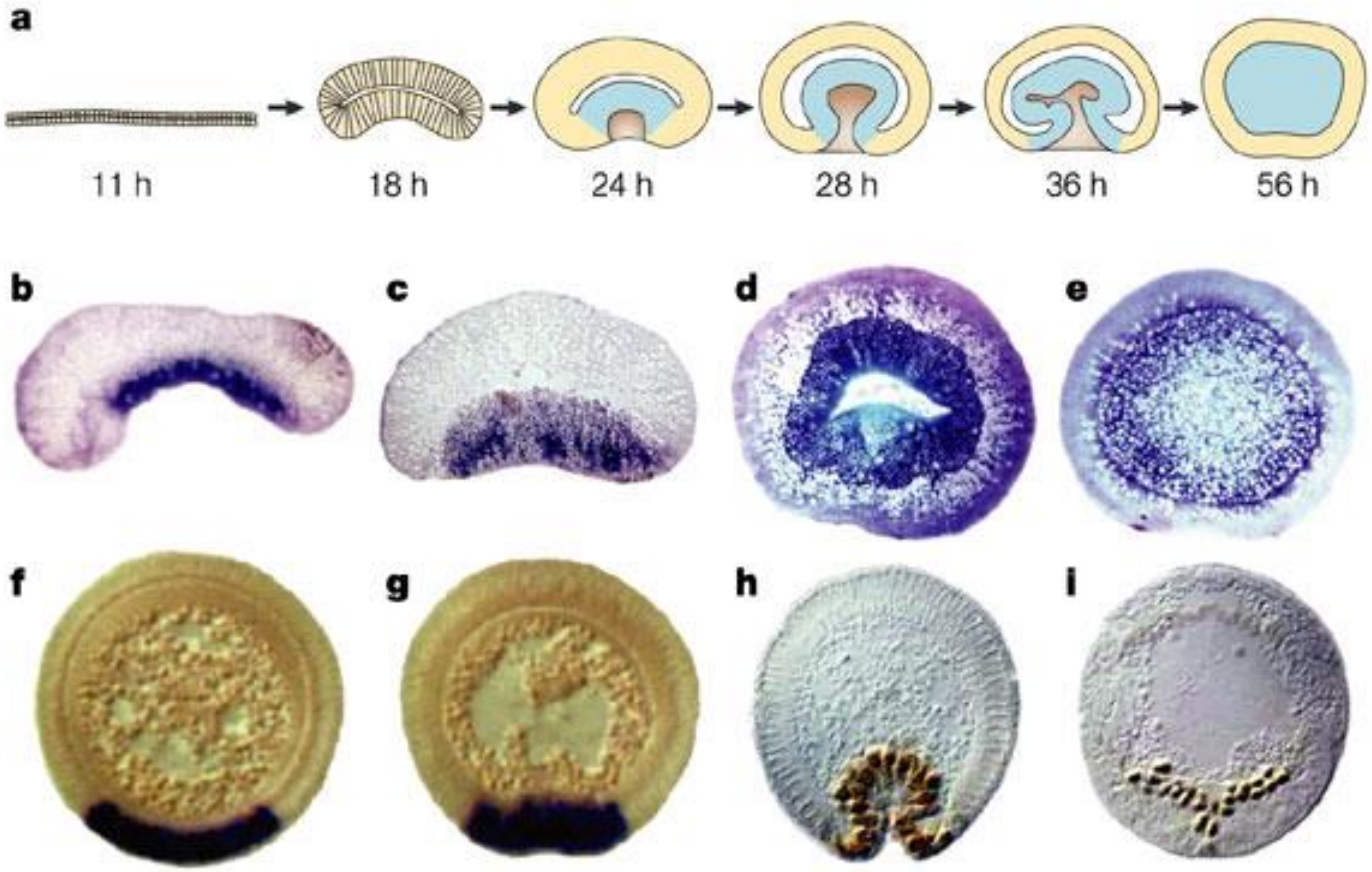
Regulation of morphogenesis:
Patterning and control of cell behavior

Example: Gastrulation

Snail

Cnidaria
(Nematostella)

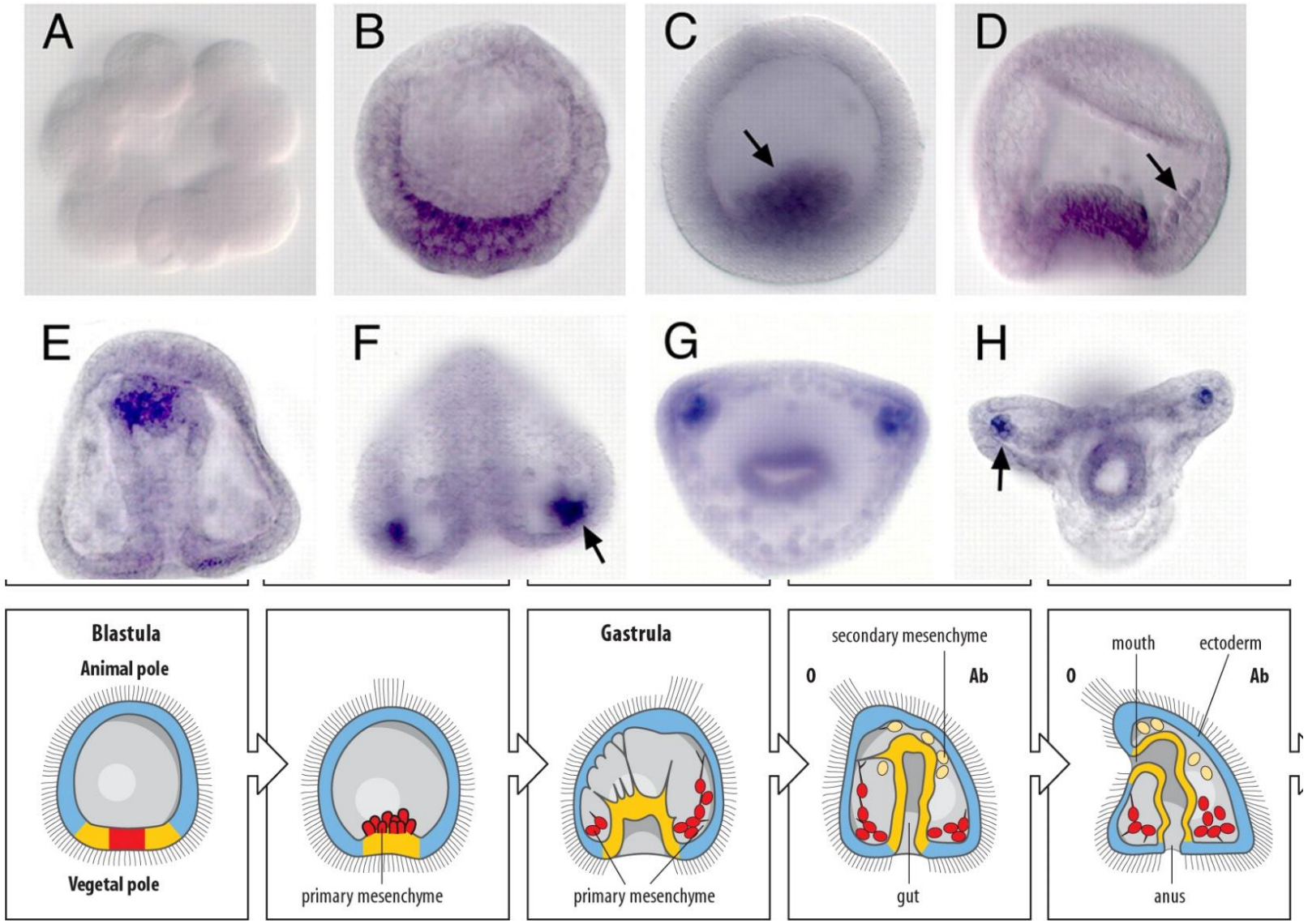
Drosophila



Nature Reviews Genetics
A simple plan — cnidaria
Eldon E. Ball, David C. H

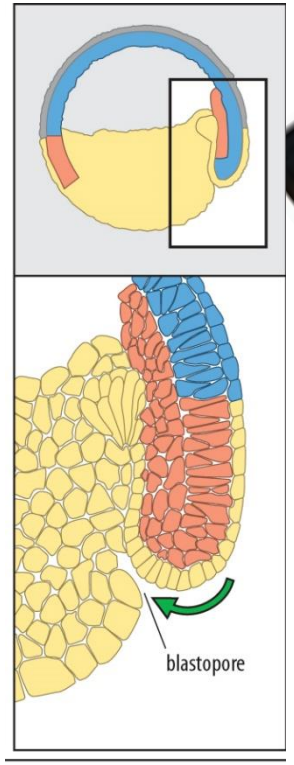
Nature Reviews | Genetics

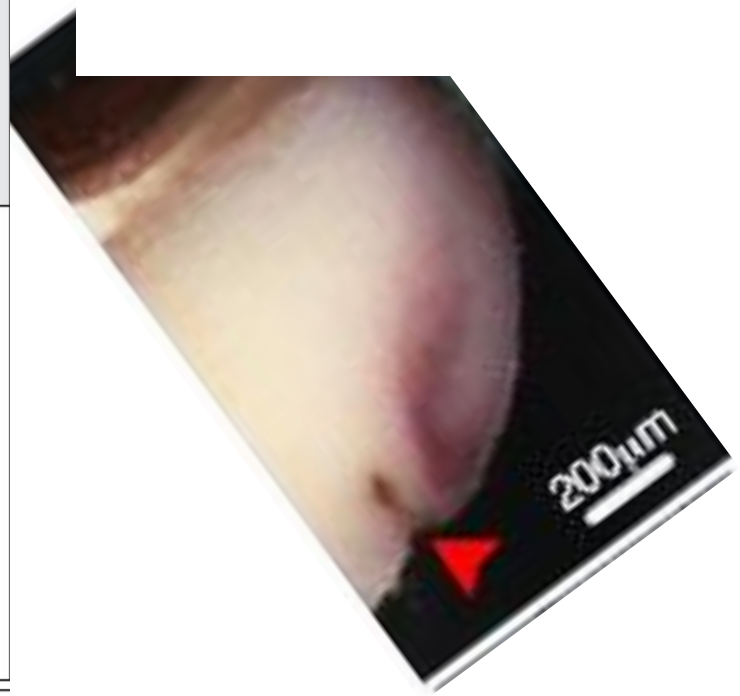
Dynamic pattern of Lvsnail mRNA expression during sea urchin development.



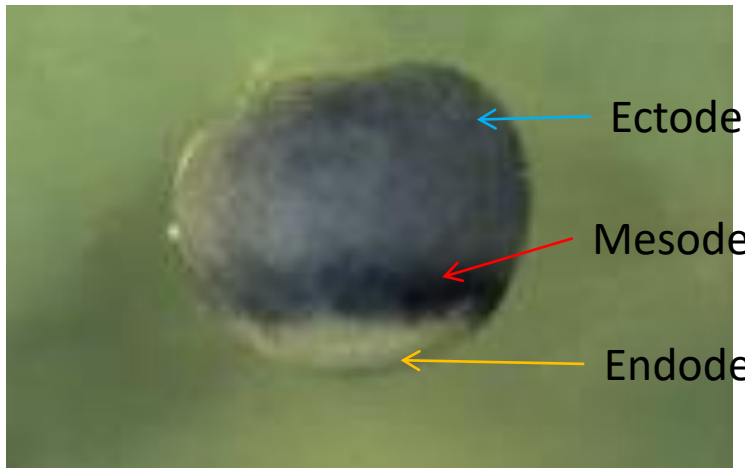
Shu-Yu Wu, and David R. McClay Development 2007;134:1061-1070

Snail expression in Xenopus gastrula





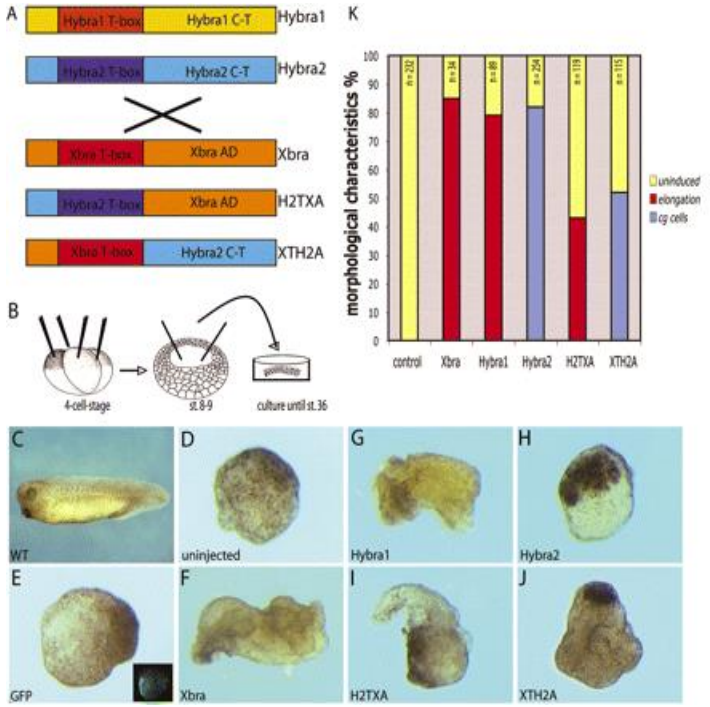
View from bottom



Side view

Regulation of morphogenesis:
Patterning and control of cell behavior

Example: Gastrulation Conserved “modules”



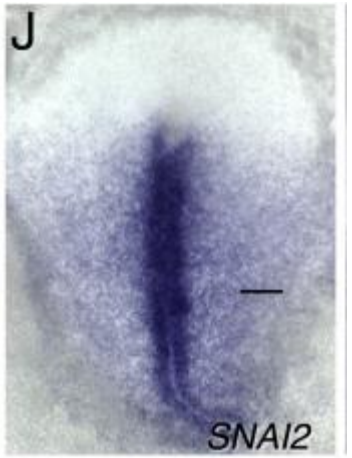
Divergent functions of two ancient *Hydra Brachyury* paralogues suggest specific roles for their C-terminal domains in tissue fate induction

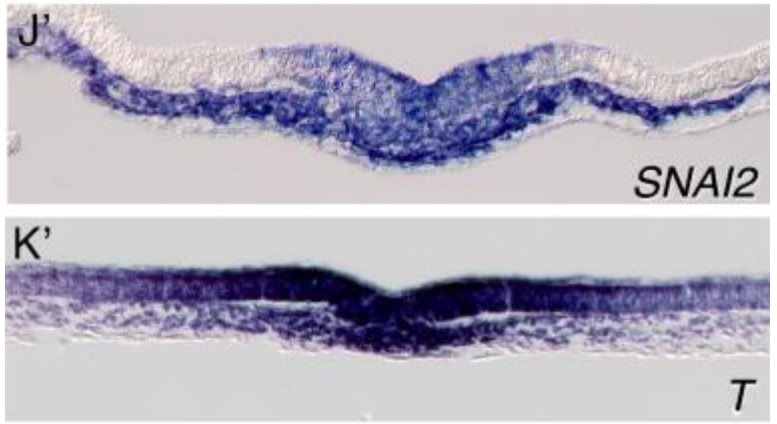
Holger Bielen, Sabine Oberleitner, Sylvain Marcellini, Lydia Gee, Patrick Lemaire, Hans R. Bode, Ralph Rupp,Ulrich Technau

Development 2007 134: 4187-4197; doi: 10.1242/dev.010173

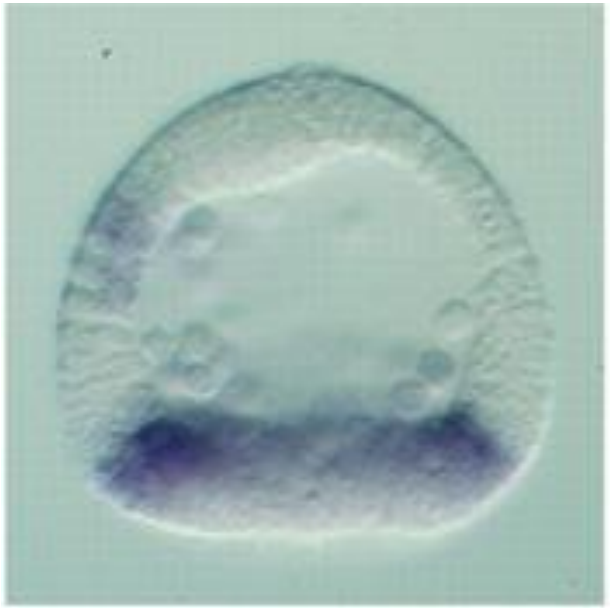
Snail and T/Brachyury expression in the chicken gastrula

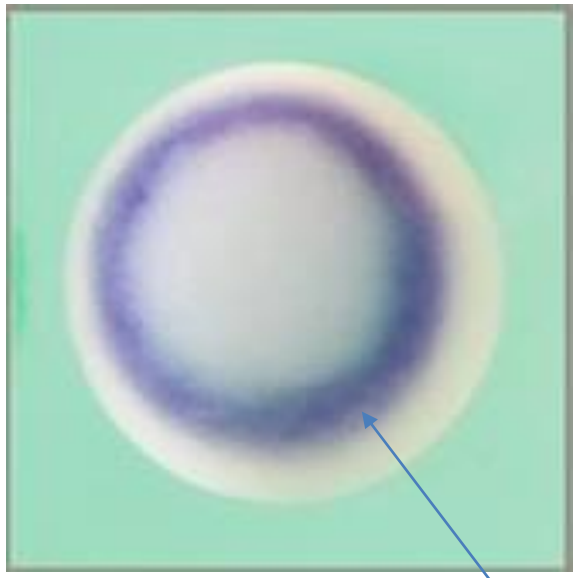
Primitive streak





Brachyury expression in sea urchin and Xenopus

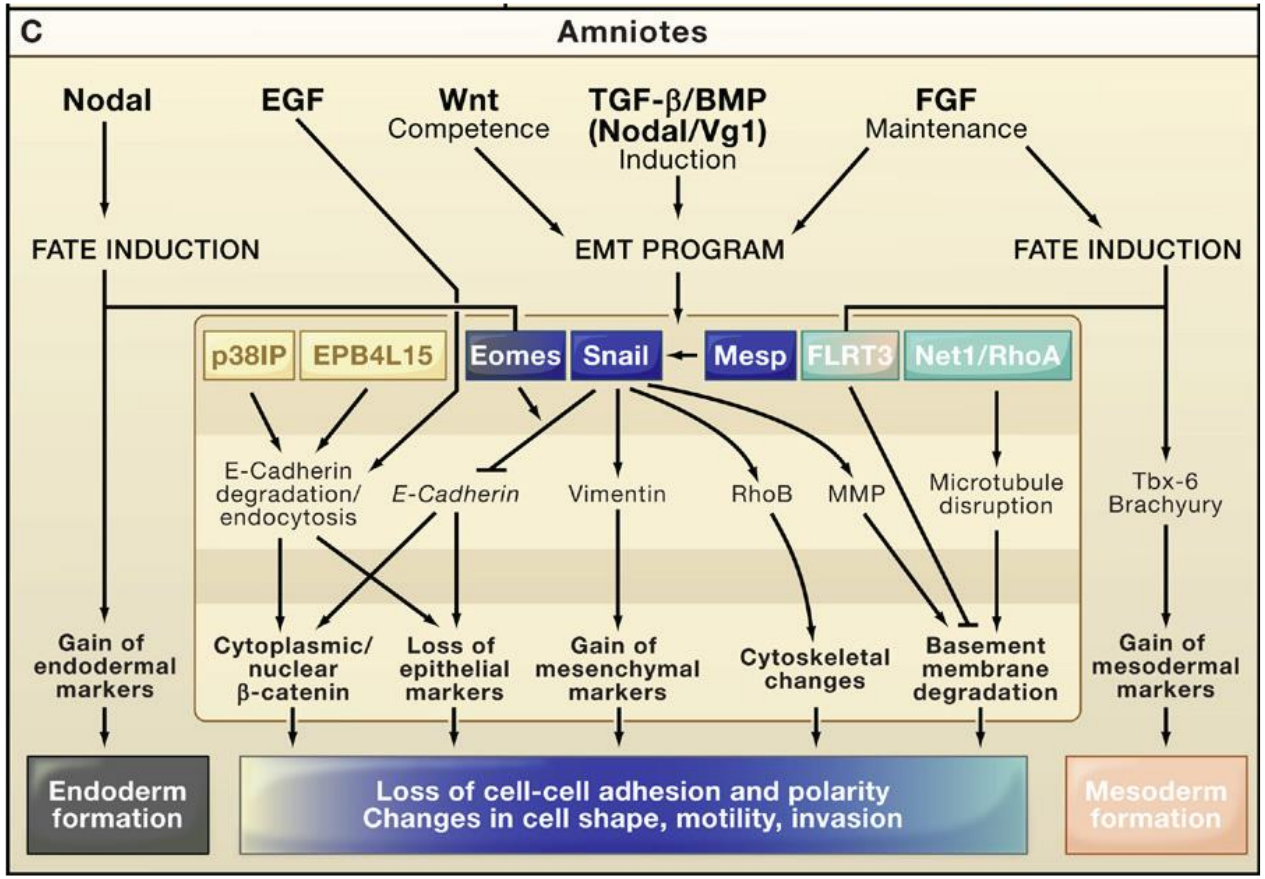




Blastopore lip, prospective mesoderm

Genetic program for EMT during Gastrulation in Amniotes

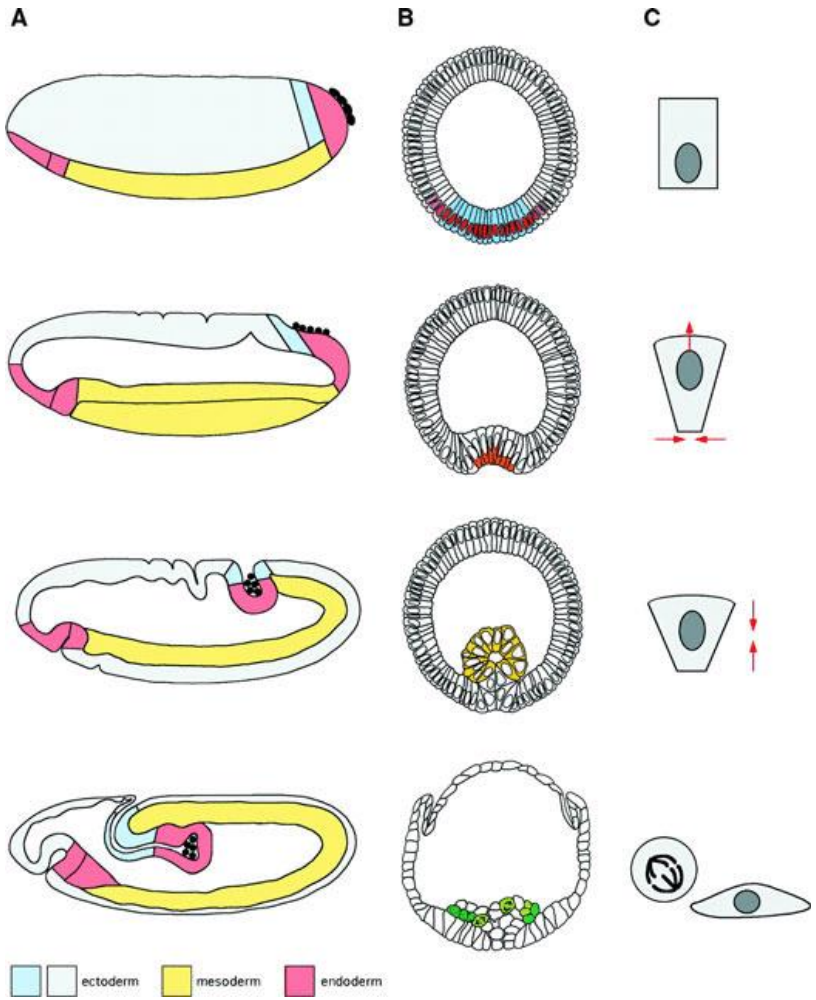
Figure 2. Genetic Pathways Governing Gastrulation
(A) The gene regulatory network governing EMT during gastrulation in the sea urchin embryo. A specification step involving Wnt8 signaling leads to HesC repression, switching on the EMT regulatory program, and inducing the ingression of the primary mesenchymal cells (PMCs). Alx1, aristaless-like 1.
(B) Mesoderm invagination in Drosophila. Twist and Snail pathways cooperate to modulate cell adhesion and cytoskeletal changes to undergo gastrulation movements and mesoderm spreading. The arrows indicate the flow of the pathway, not direct transcriptional regulation. Abl, Abelson kinase; Htl, Heartless (Drosophila FGF receptor); Dof, downstream of FGFR; Fog/Cta, folded in gastrulation/ concertina.
(C) Genetic pathways controlling gastrulation in amniotes. Convergence of signaling pathways at the posterior part of the embryo leads to primitive streak formation and initiation of the EMT as well as the mesodermal fate program. Snail genes are key regulators of the EMT program during gastrulation in amniotes as they control cellcell adhesion, cell shape, and motility. Additional mechanisms such as endocytosis, lysosomal targeting, and degradation of the E-cadherin protein together with the control of basement membrane integrity explain the rapid and drastic changes occurring in ingressing cells during gastrulation. The induction of endodermal and mesodermal fates is mainly governed by the FGF and Nodal pathways through specific regulators and the contribution of some of the genes involved in the EMT program. EPB4L5, FERM and actin-binding domains-containing band 4.1 superfamily member; FLRT3, Fibronectin-leucine-rich-transmembrane protein-3; Net-1, neuroepithelial transforming factor 1; MMP, metalloproteinases; p38IK, p38 interacting kinase.



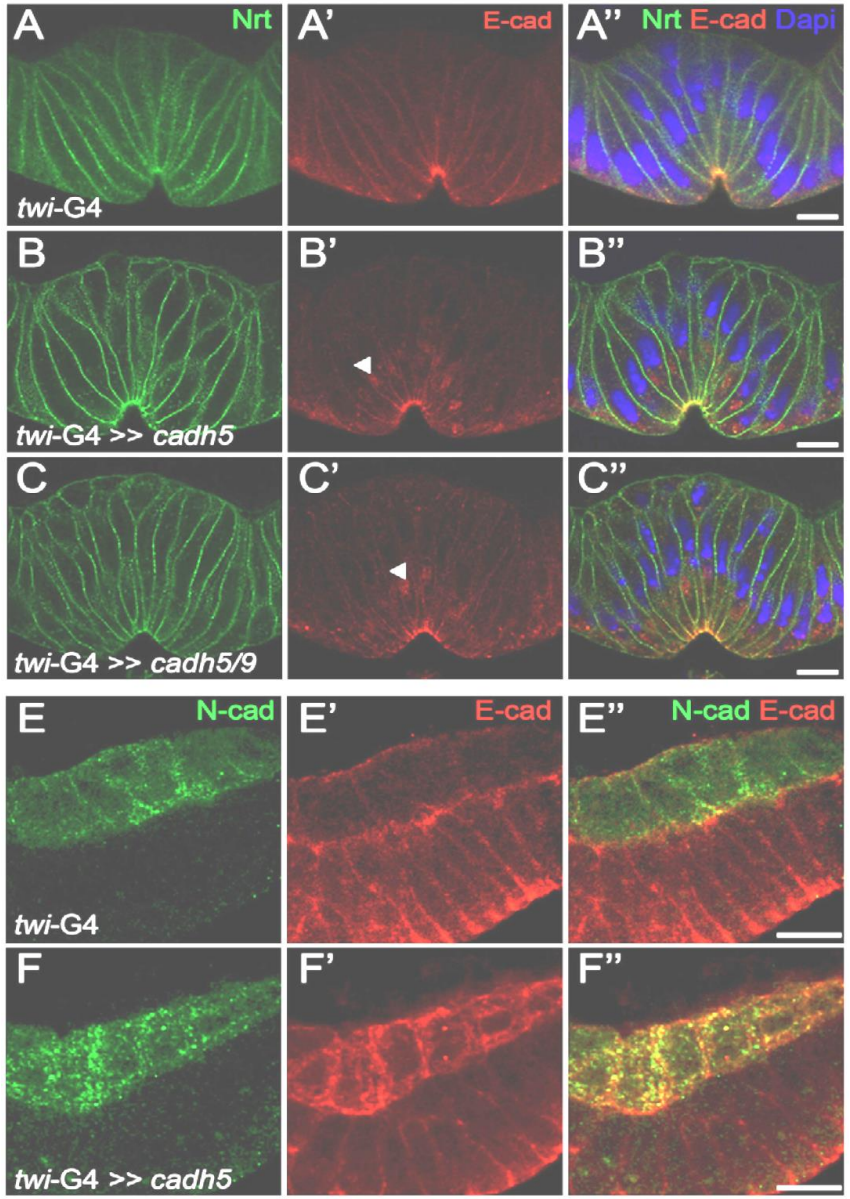
E-cadherin downregulation is not required for gastrulation

Zebrafish: Only E-cadherin
Xenopus: Only C-cadherin (~E-cadherin)
Drosophila: Switch E- to N-cadherin, but…..

Drosophila gastrulation

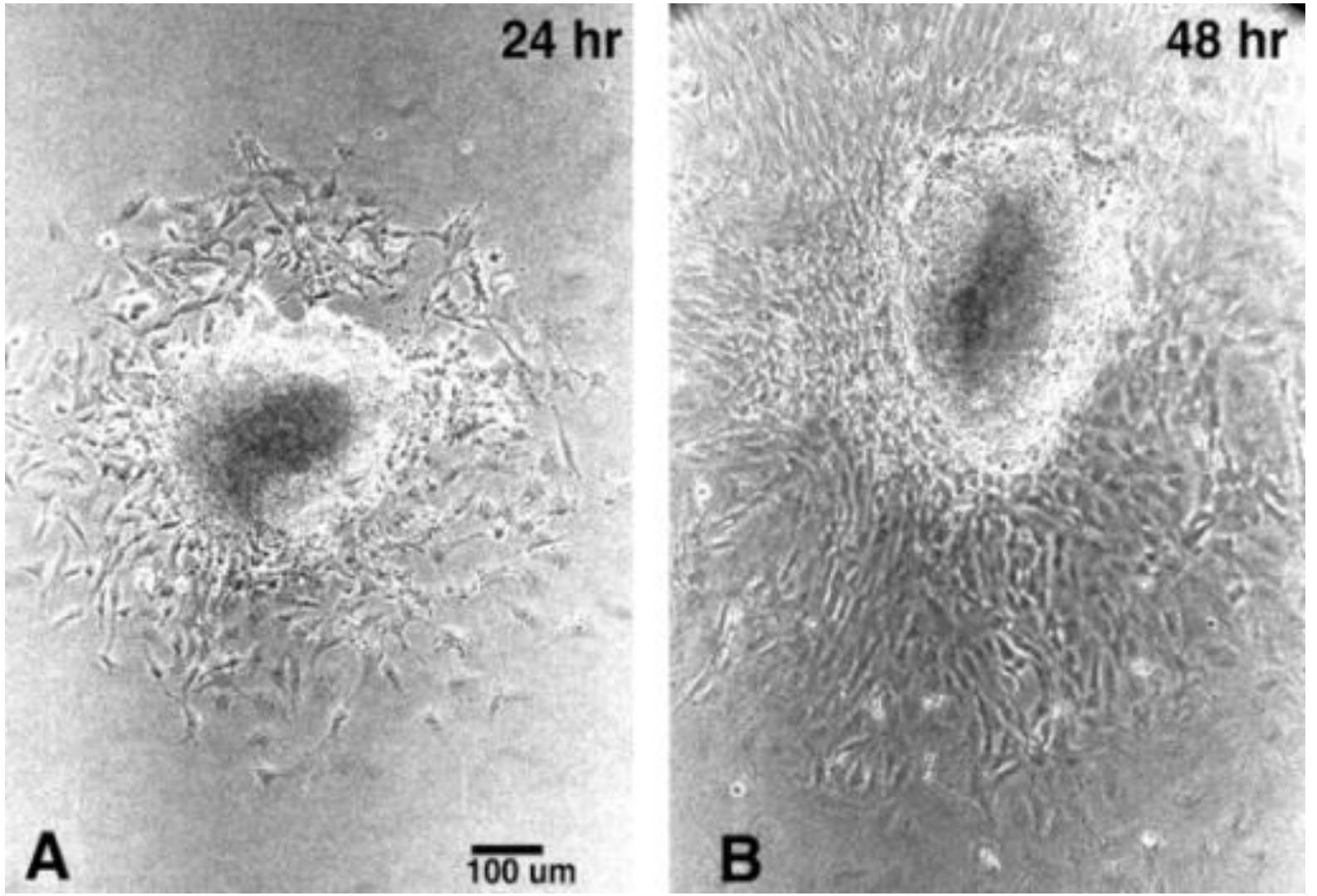


Mis-expression of E-cadherin in the embryonic mesoderm of Drosophila

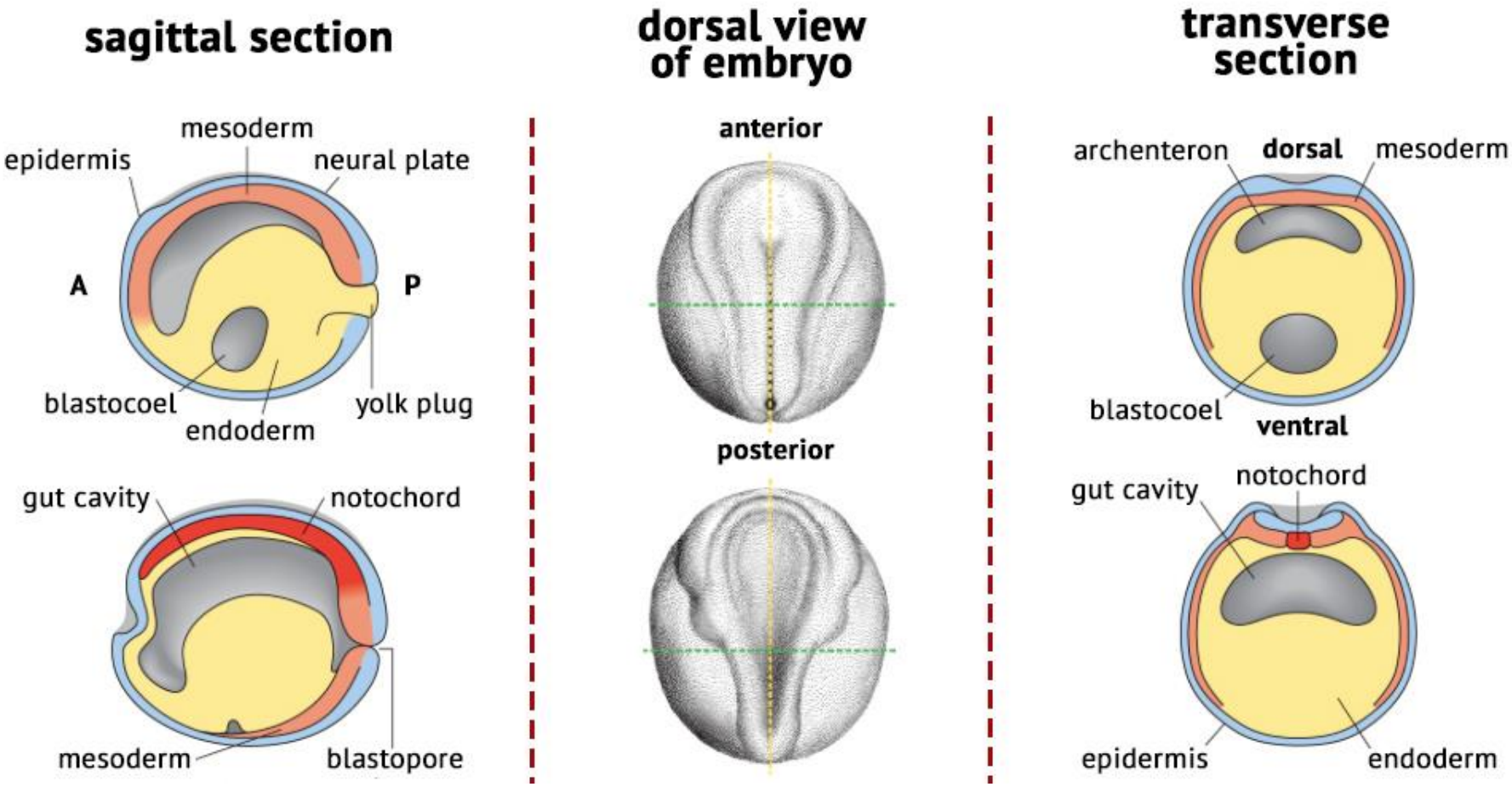


Cadherin switching during the formation and differentiation of the Drosophila mesoderm – implications for epithelial-to mesenchymal transitions
Gritt Schafer1, Maithreyi Narasimha, Elisabeth Vogelsang and Maria Leptin
Journal of Cell Science (2014) 127, 1511–1522

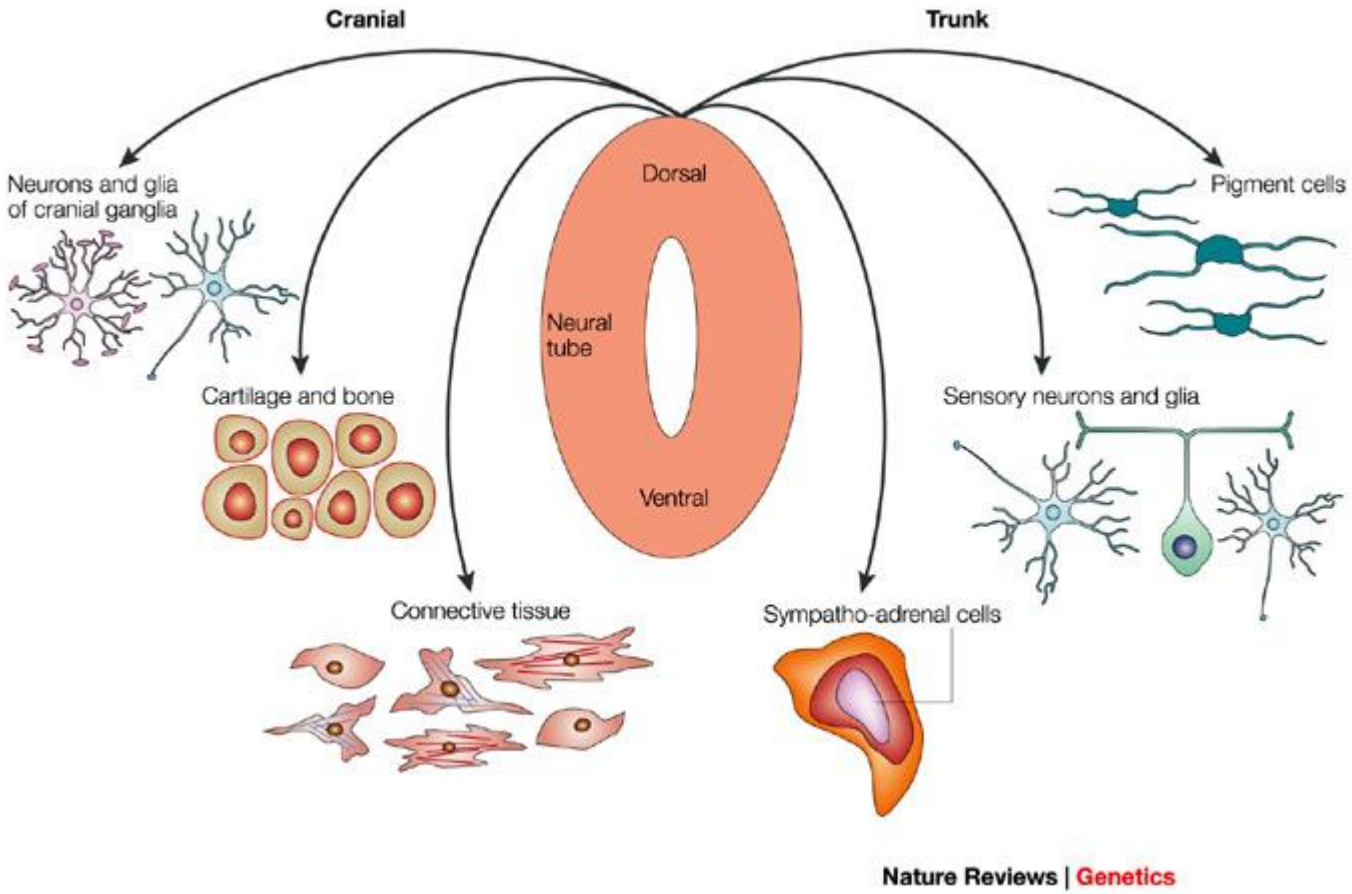
Neural crest cells



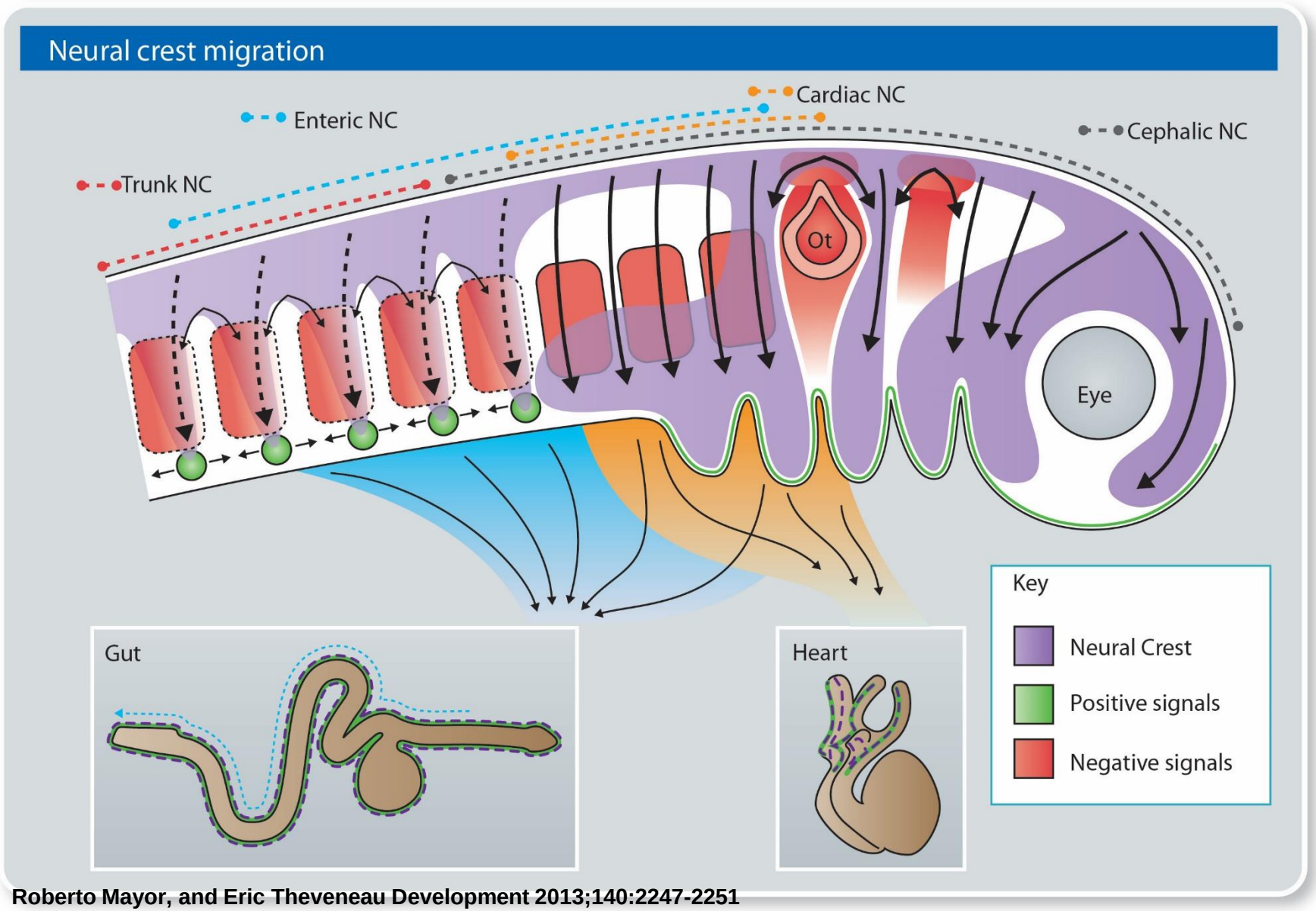
Neural crest cells



Neural crest cells

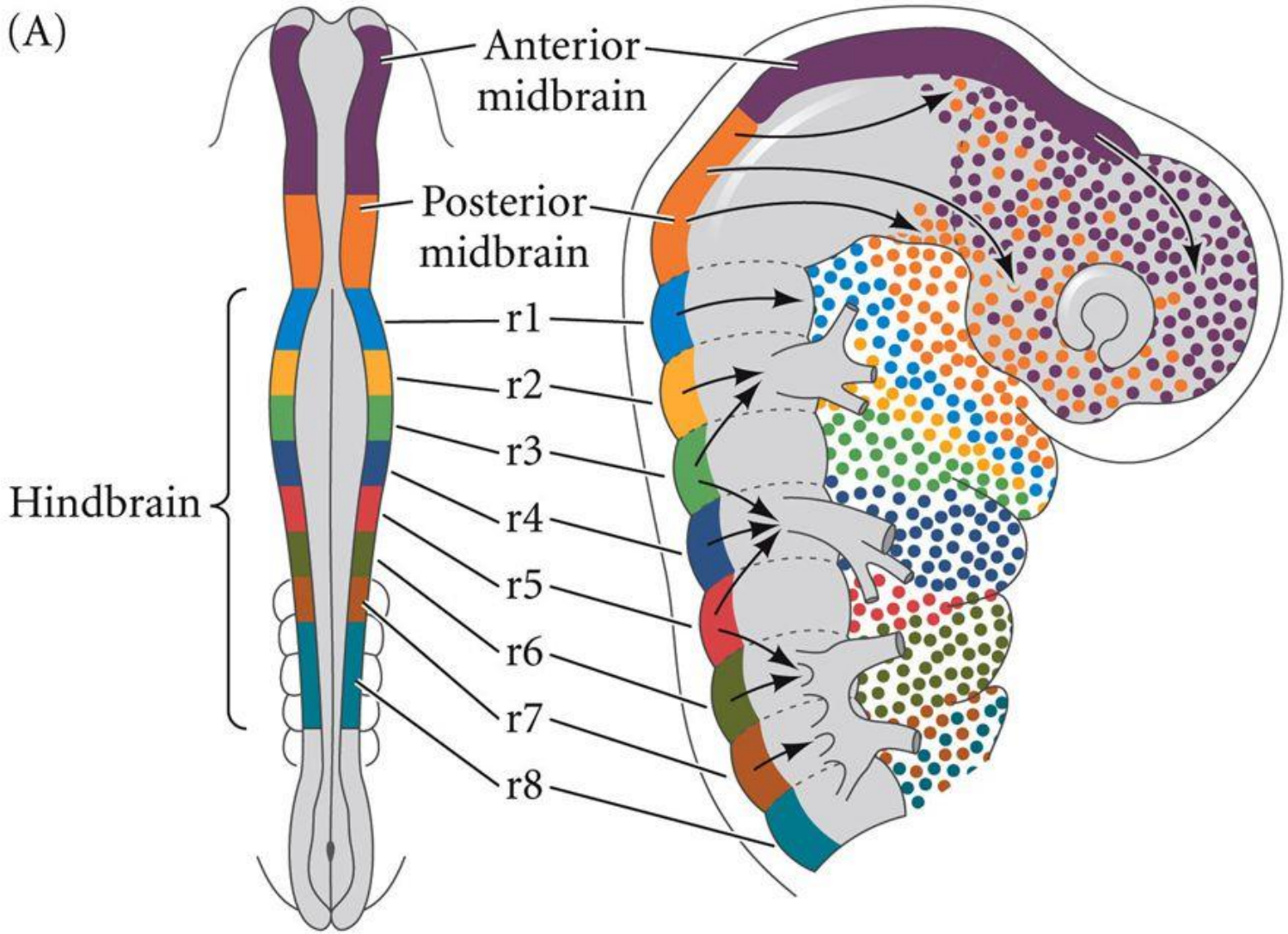


Neural crest cells



Roberto Mayor, and Eric Theveneau Development 2013;140:2247-2251

Figure 10.10 Cranial neural crest cell migration in the mammalian head (Part 1)



DEVELOPMENTAL BIOLOGY, **9e, Figure 10.10 (Part 1)**

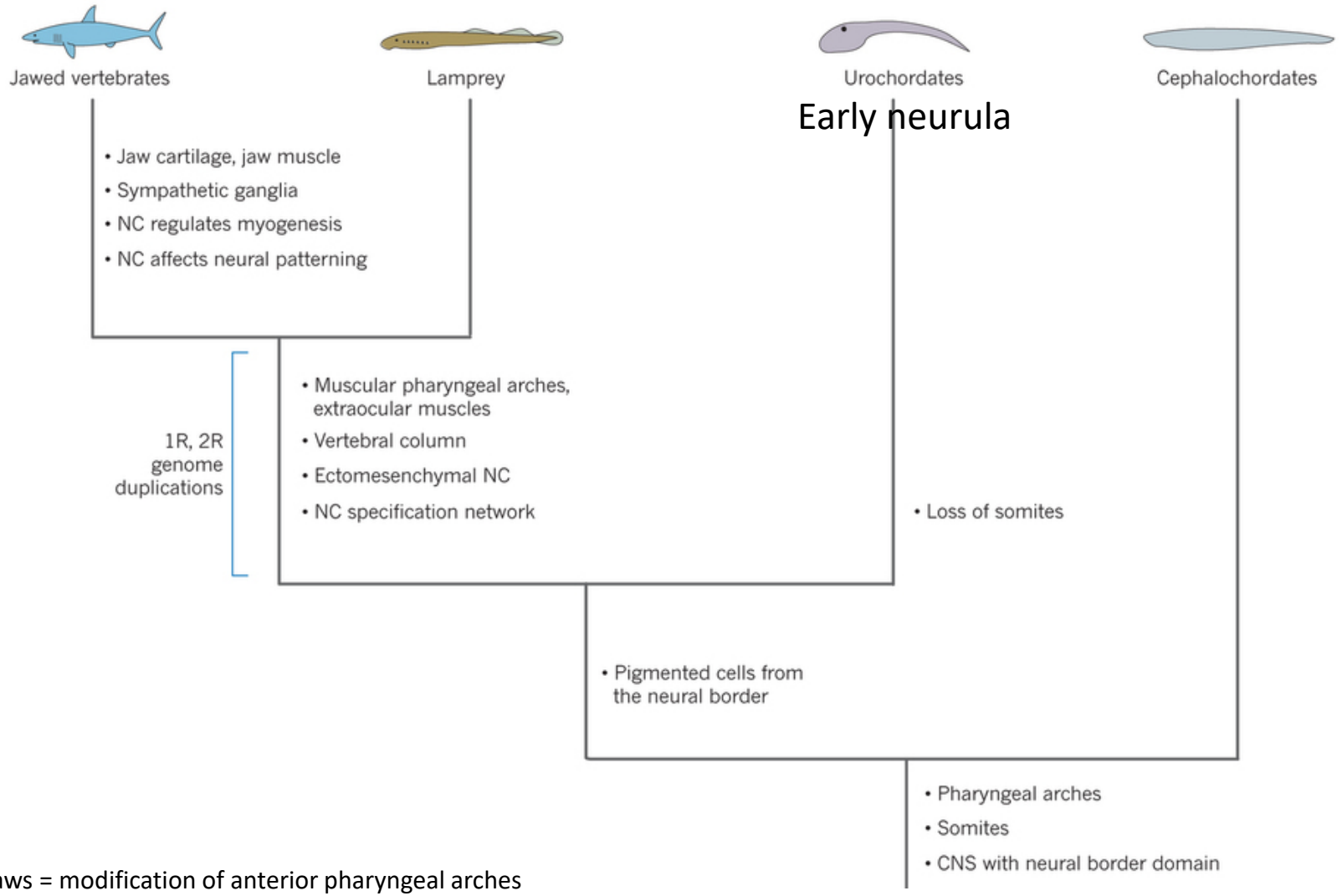
Figure 1 | **Skeletal fate of cranial neural crest cells in vertebrates.** The embryo figure shows colonization of the head and pharyngeal arches by diencephalic,
anterior and posterior mesencephalic, and rhombencephalic neural crest cells (NCCs), as indicated by the colour code. The diagram is representative of chick, mouse,
and human embryos, although the NCC migratory pathways might differ slightly in different species. The skull drawings show comparative contributions of NCC
populations to cranial skeletal elements of humans, mice and birds. Drawings are based on NCC fate-mapping studies and on extrapolation of avian and mouse data
to known homologues in the human[7,9–13,63,156,157]. Some bones, including the squamosal (SQ), alisphenoid (AS), and pterygoid (PT), are shown with mixed contribution
from different NCC populations. Note that in mammals the frontal (FR) and parietal (PA) bones have been reported to be of neural crest and mesodermal origin,
respectively[13]. In birds, the frontal and parietal bones have been reported to be either entirely derived from NCCs[12], as shown in the figure, or derived from a dual neural
crest/mesodermal origin[7,10]. AN, angular bone; AR, articular bone; BA, basihyal; BA1–BA3, pharyngeal arches 1–3; CB, ceratobranchial; CO, columella; DE, dentary
bone; di, diencephalon; EB, epibranchial; EN, entoglossum; FNP, frontonasal process; HY, hyoid bone; IN, incus; IS, interorbital septum; JU, jugal bone; MA, malleus;
mes, mesencephalon; MX, maxillary bone; NA, nasal bone; NC, nasal capsule; PL, palatine bone; PM, premaxillary bone; QU, quadrate; RP, retroarticular process;
R1–R7, rhombomeres 1–7; SO, scleral ossicles; ST, stapes; ZY, zygomatic bone.

Cranial neural crest and the building of the vertebrate head

•Fabio Santagati &
•Filippo M. Rijli

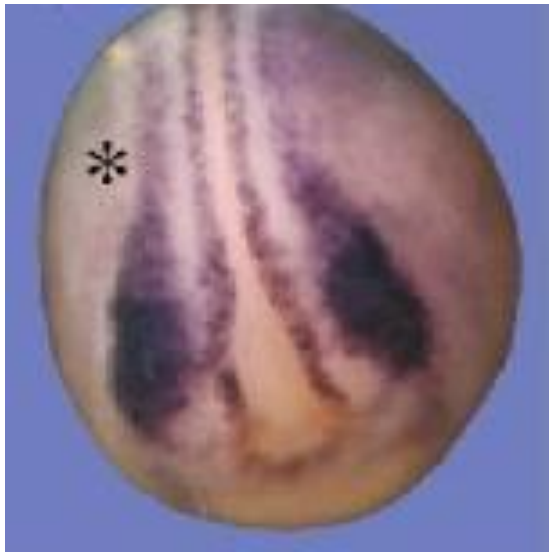
Nature Reviews Neuroscience **volume 4**, pages 806–818 (2003)

Origin of neural crest cells

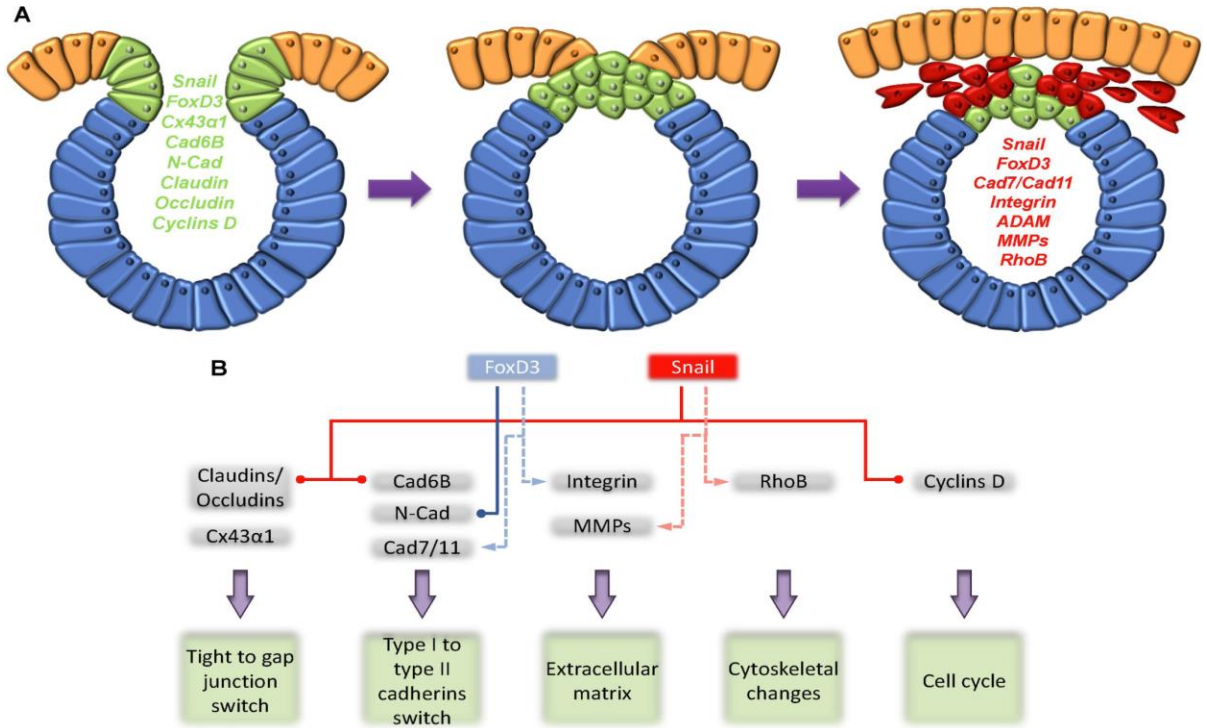


Jaws = modification of anterior pharyngeal arches

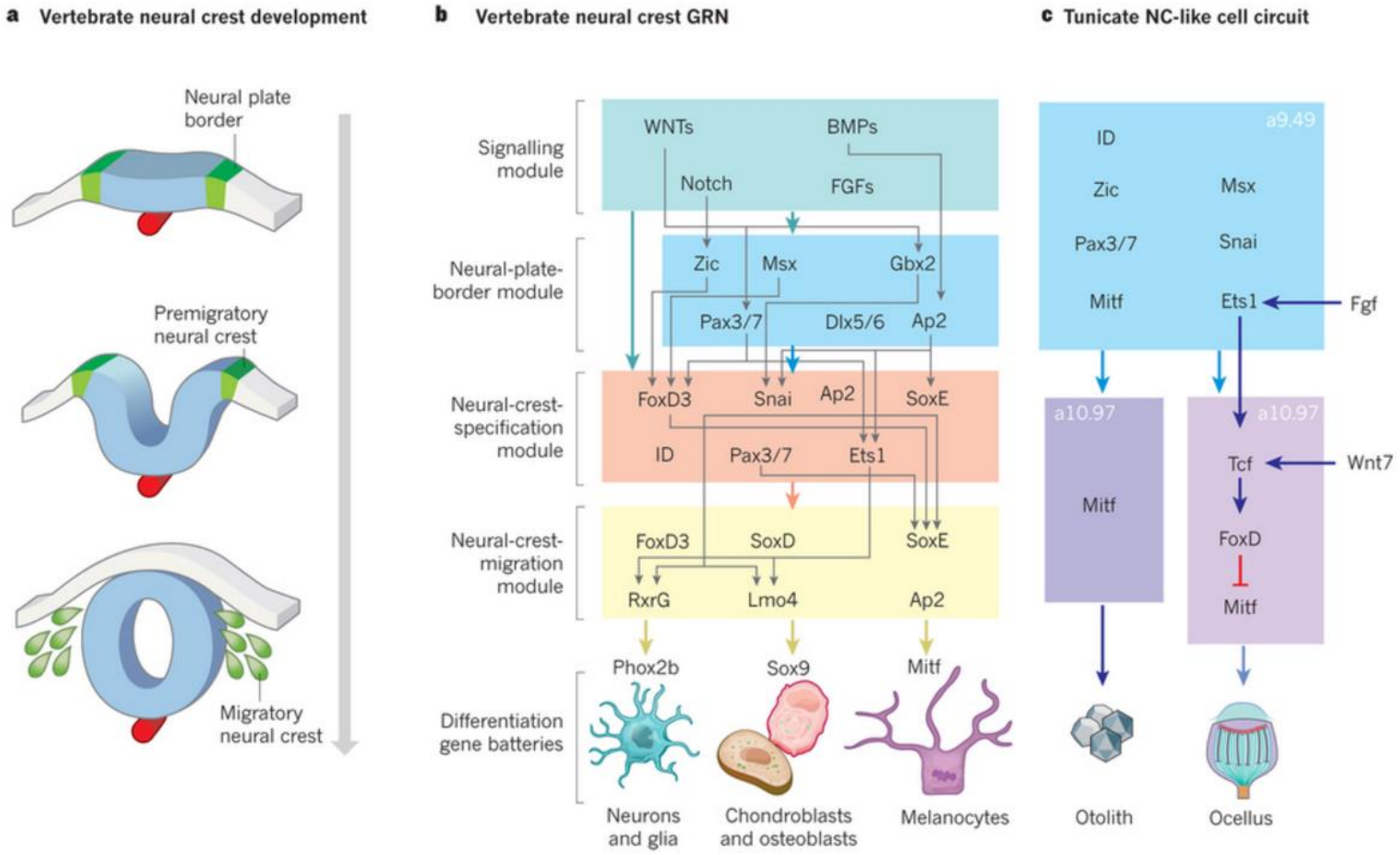
Snail expression in the Xenopus neurula



Neural crest cells

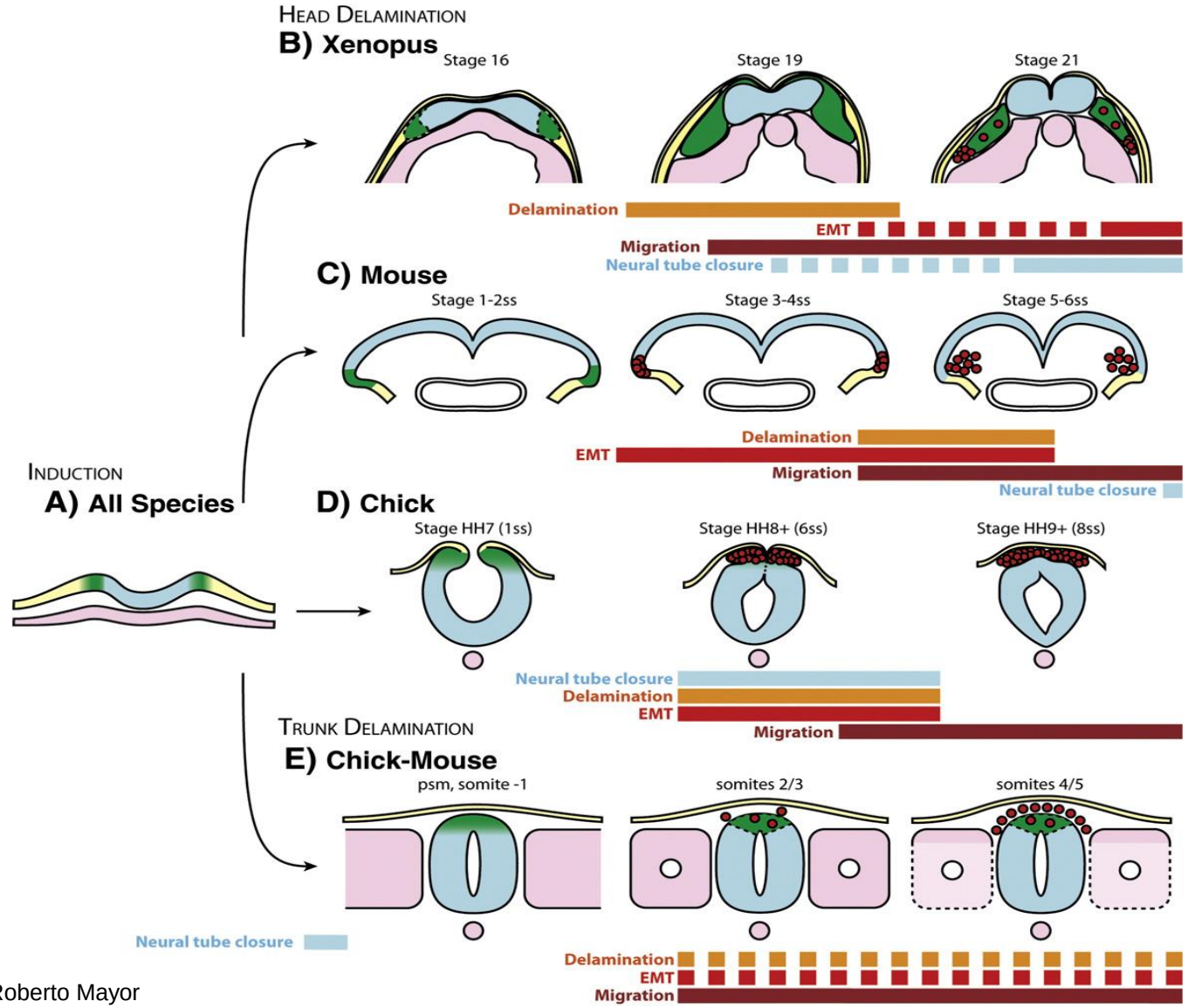


Neural crest cells



Evolution of vertebrates as viewed from the crest
Stephen A. Green1, Marcos Simoes-Costa1 & Marianne E. Bronner

EMT in neural crest cells: Differential temporal sequences

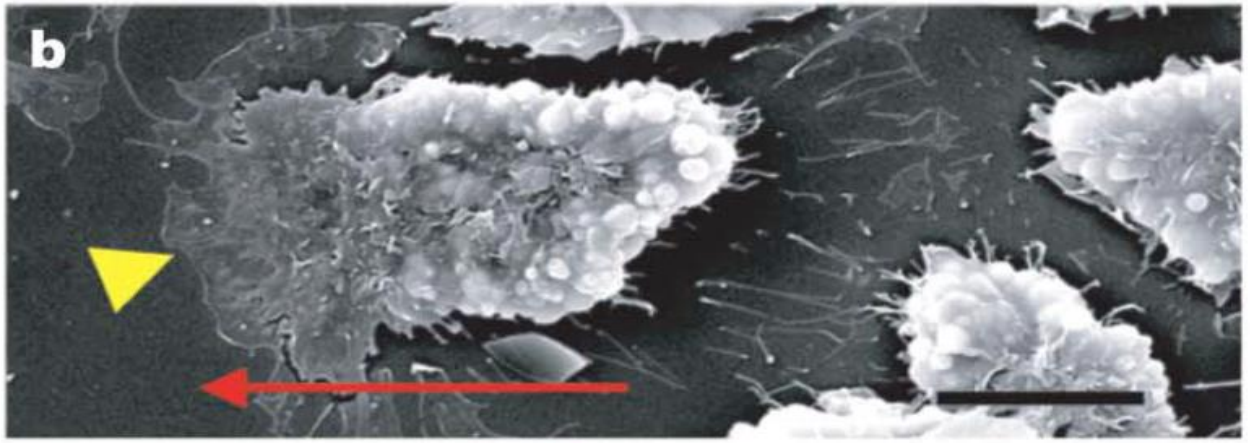


Eric Theveneau, Roberto Mayor

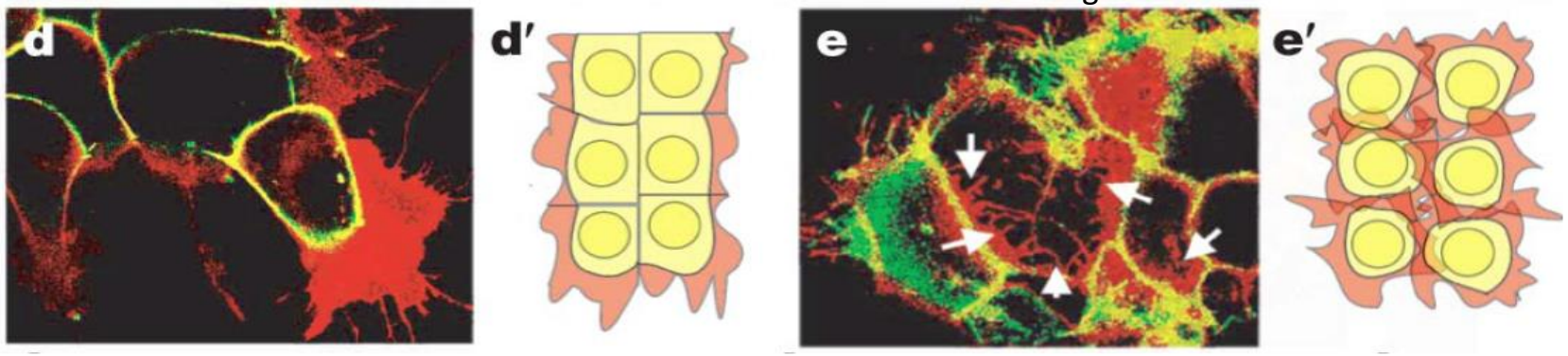
Neural crest delamination and migration: From epithelium-to-mesenchyme transition to collective cell migration

Developmental Biology, Volume 366, Issue 1, 2012, 34–54

Contact inhibition of locomotion in neural crest cells



Dom neg Dsh – PCP inhibition



Contact inhibition of locomotion *in vivo* controls neural crest directional migration

Carlos Carmona-Fontaine[1], Helen K. Matthews[1], Sei Kuriyama[1], Mauricio Moreno[1], Graham A. Dunn[2], Maddy Parsons[2], Claudio D. Stern[1] & Roberto Mayor[1]

NATURE | Vol 456 | 18/25 December 2008

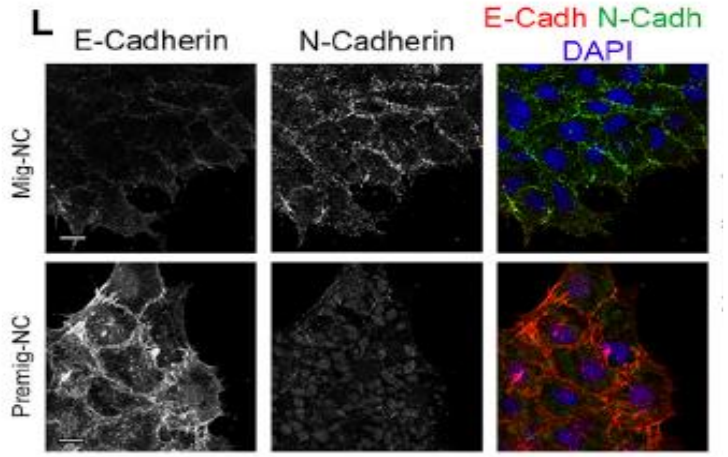
Role of E- to N-cadherin switch in neural crest cells

Cadherin Switch during EMT in Neural Crest Cells Leads to Contact Inhibition of Locomotion via Repolarization of Forces

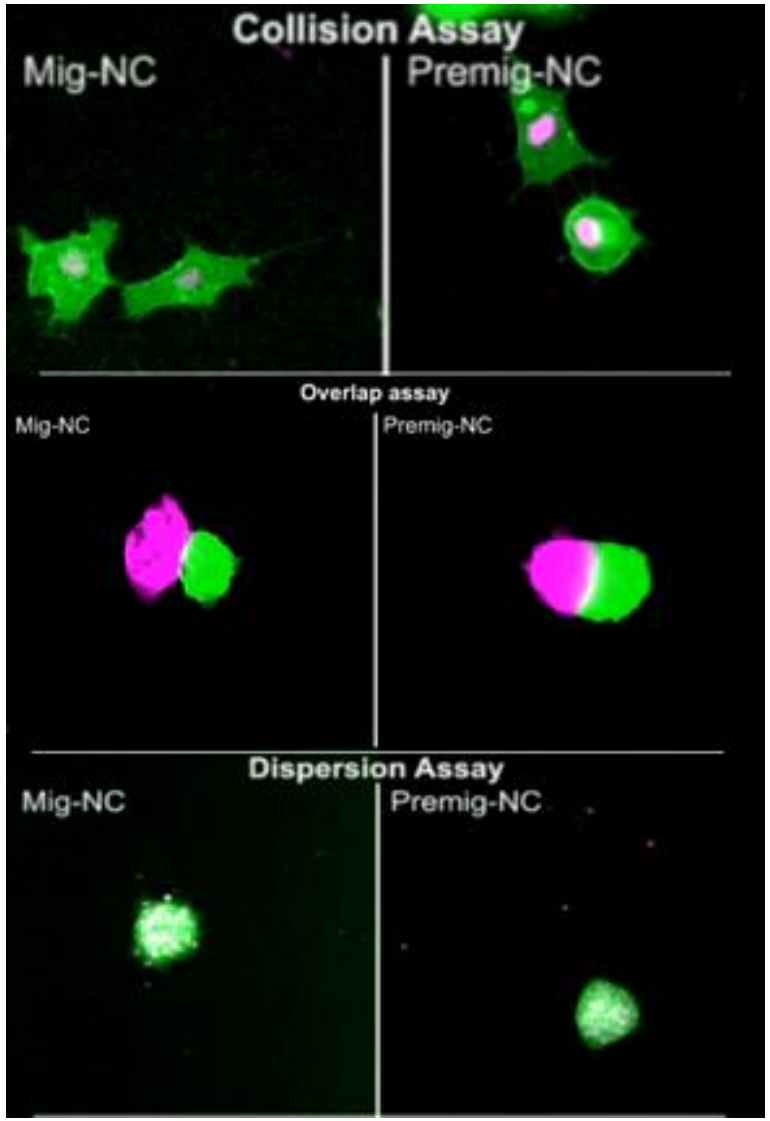
Elena Scarpa,[1] András Szabó,[1] Anne Bibonne,[2] Eric Theveneau,[1,2] Maddy Parsons,[3] and Roberto Mayor[1,*]
[1]Cell and Developmental Biology Department, University College London, Gower Street, London WC1E 6BT, UK
[2]Centre de Biologie du Développement–UMR5547, Centre National de la Recherche Scientifique and Université Paul Sabatier, Toulouse 31400, France
[3]Randall Division of Cell and Molecular Biophysics, Kings College London, London SE11UL, UK
*Correspondence: r.mayor@ucl.ac.uk
http://dx.doi.org/10.1016/j.devcel.2015.06.012

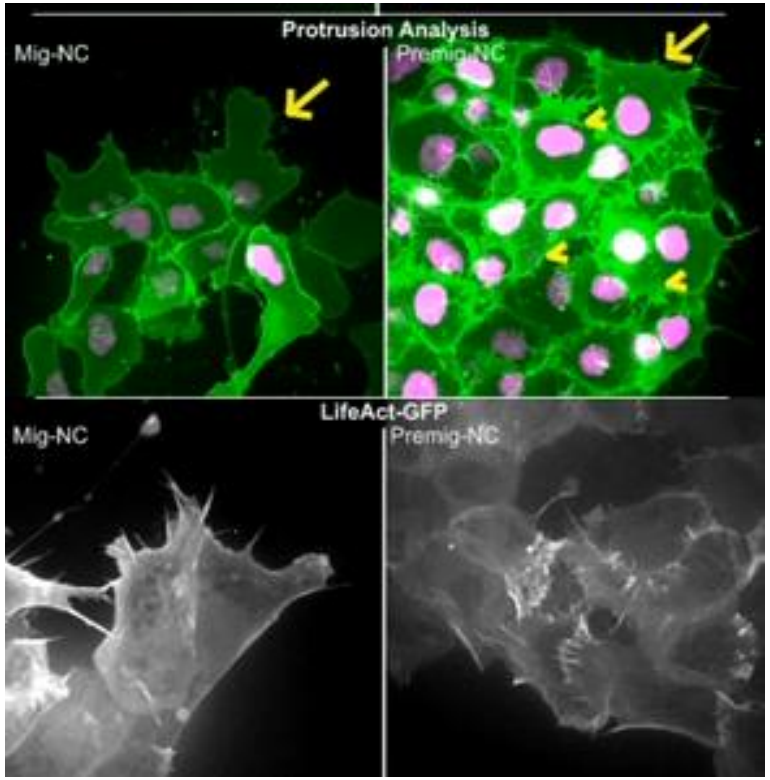
Pre-migratory

Migratory



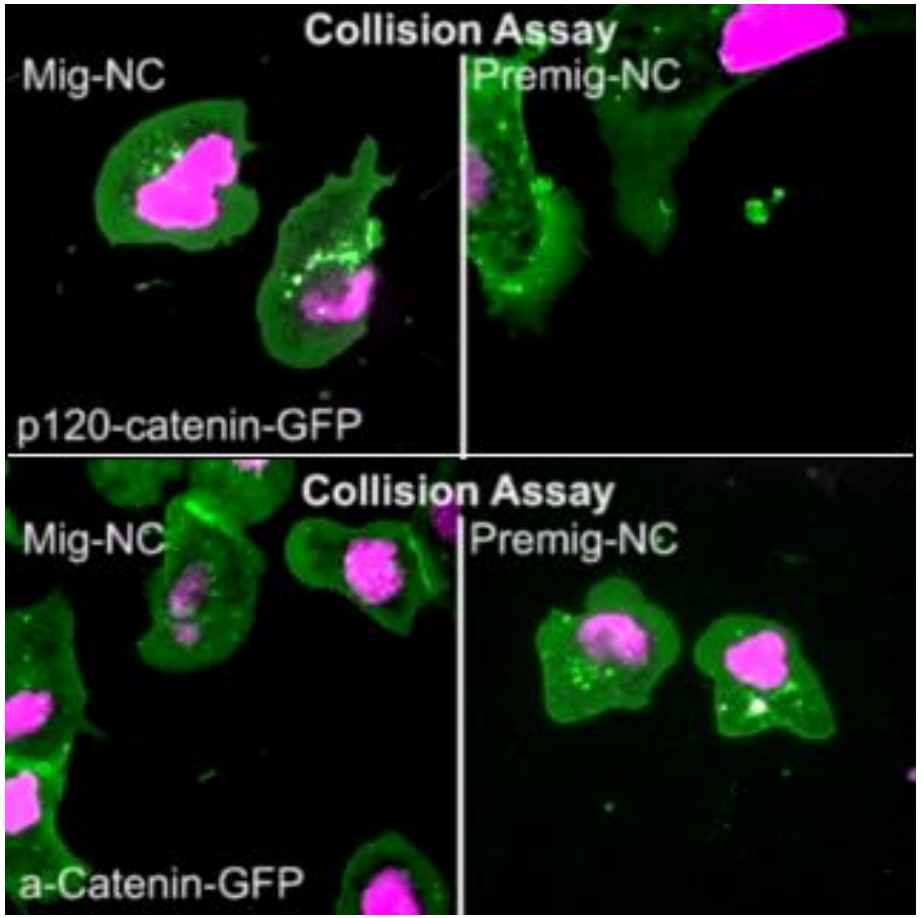
Contact Inhibition of Locomotion (CIL) Is a Developmentally Regulated Property of NC Cells





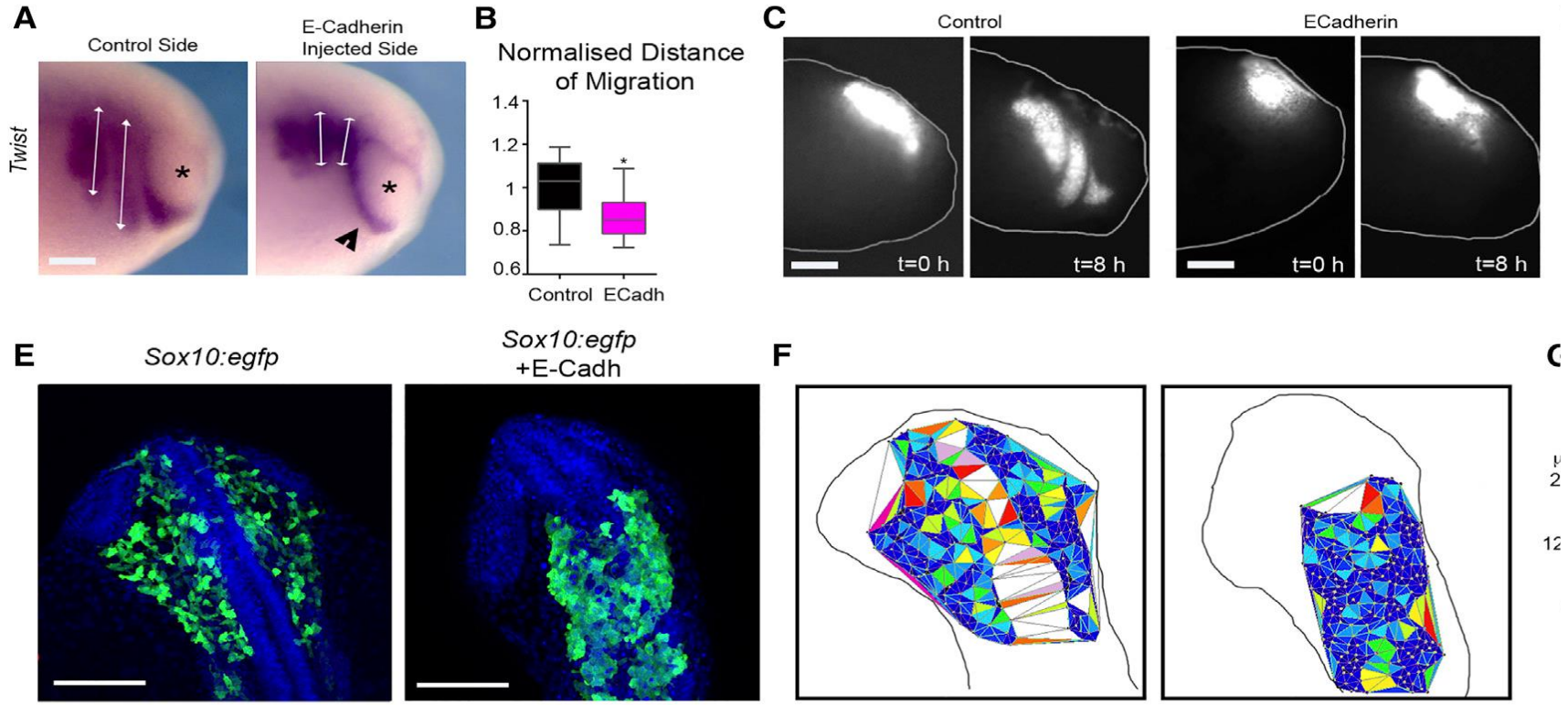
Scarpa et al., 2015, Developmental Cell 34, 421–434

Different Dynamics of Junction Disassembly in Migratory and Premigratory NC Cells



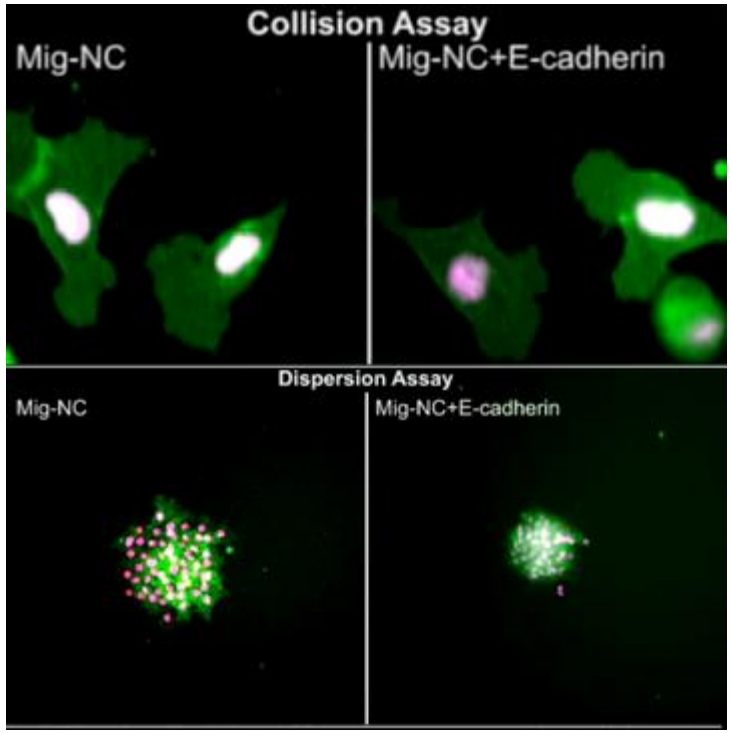
Scarpa et al., 2015, Developmental Cell 34, 421–434

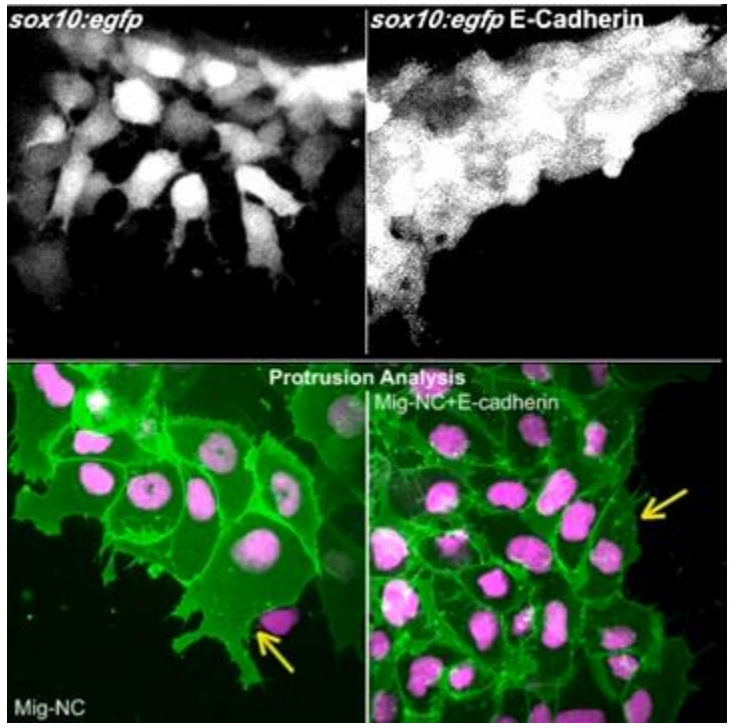
E-Cadherin Suppresses CIL In Vivo



Scarpa et al., 2015, Developmental Cell 34, 421–434

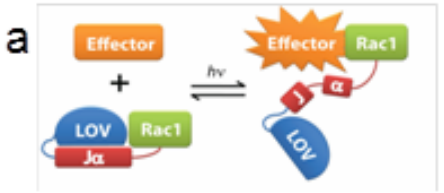
E-Cadherin Suppresses CIL In Vitro

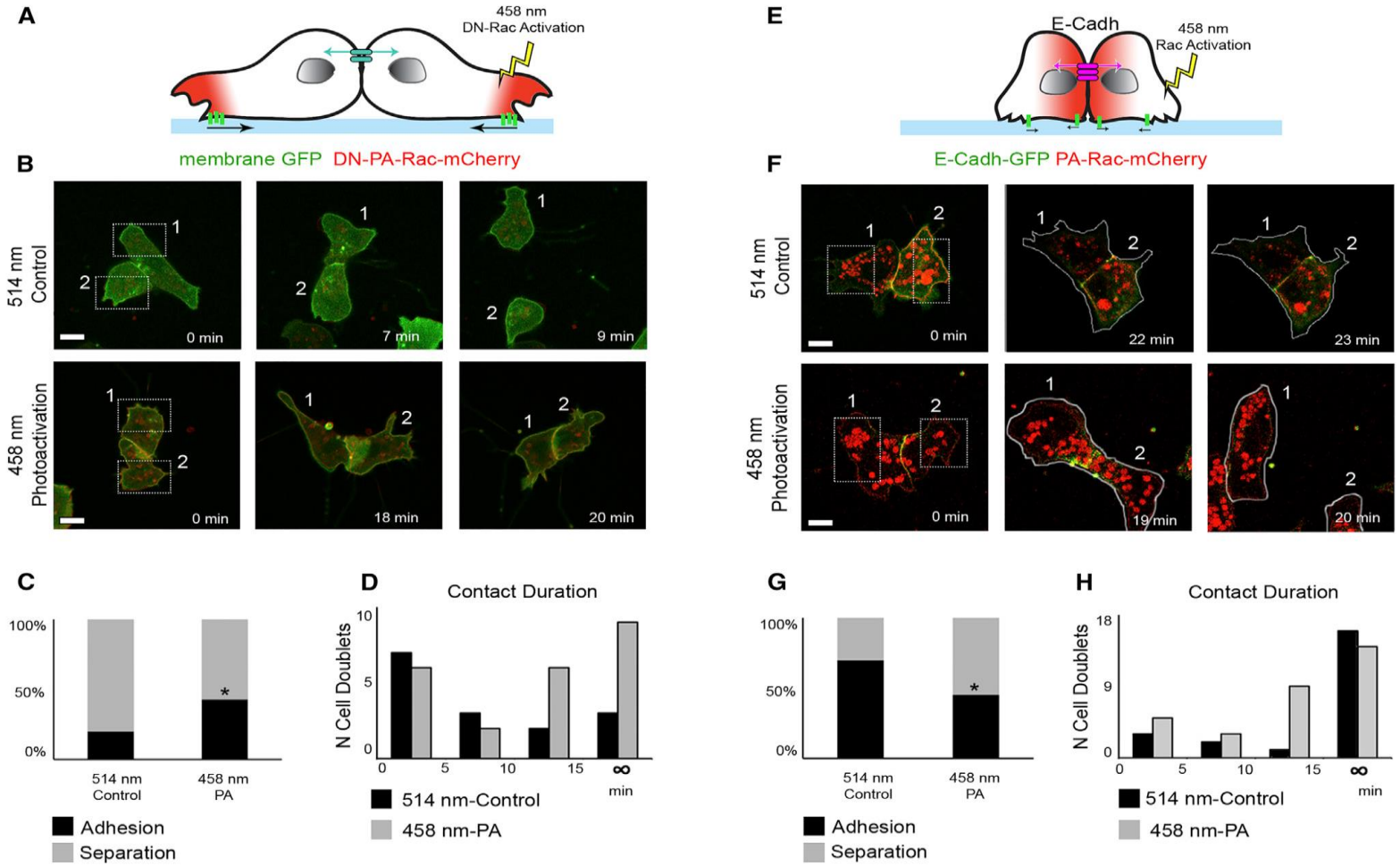




Scarpa et al., 2015, Developmental Cell 34, 421–434

E-Cadherin Suppresses CIL In Vitro





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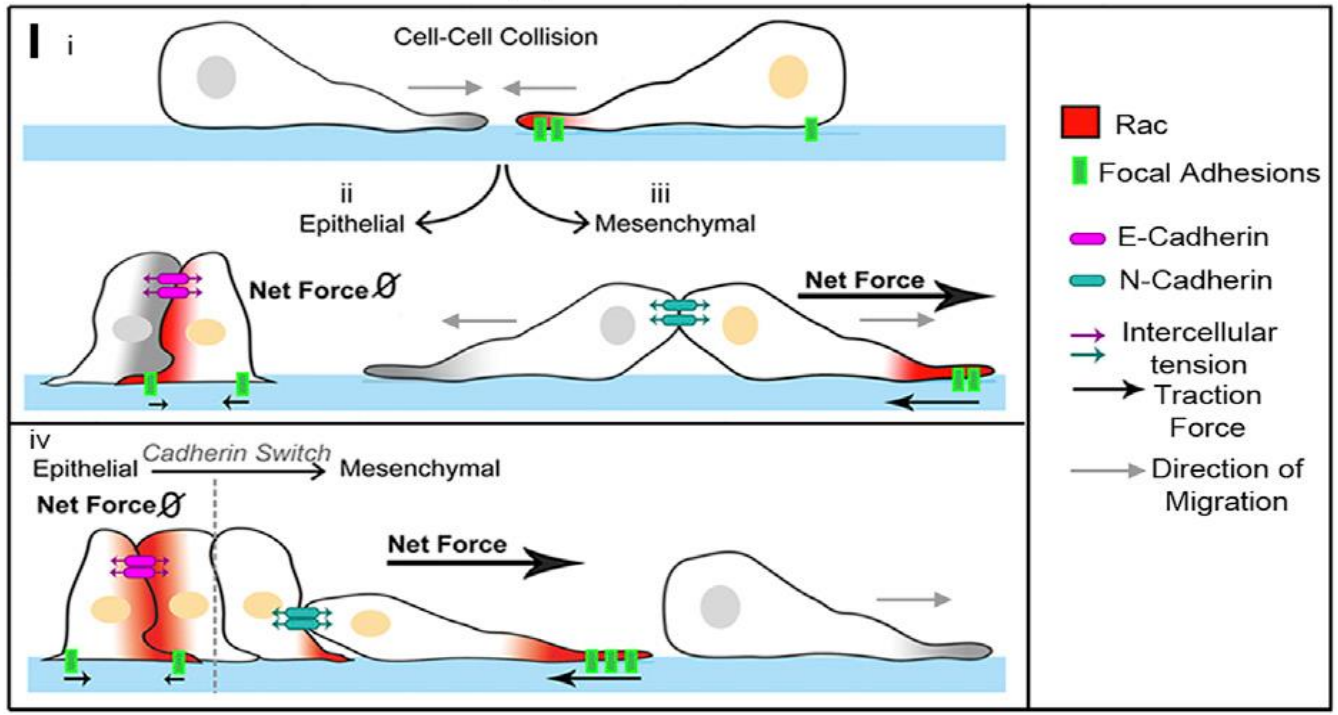

Scarpa et al., 2015, Developmental Cell 34, 421–434

Collective cell migration of neural crest cells

In vivo collective cell migration requires an LPAR2-dependent increase in tissue fluidity

Lysophosphatidic acid receptor

Sei Kuriyama,[1,2] Eric Theveneau,[1] Alexandre Benedetto,[3] Maddy Parsons,[4] Masamitsu Tanaka,[2] Guillaume Charras,[1,3] Alexandre Kabla,[5] and Roberto Mayor[1]

[1]Cell and Developmental Biology Department, University College London, London WC1E 6BT, England, UK
[2]Department of Molecular Medicine and Biochemistry, Akita University Graduate School of Medicine and Faculty of Medicine, Akita City, Akita 010-8543, Japan
[3]London Centre for Nanotechnology, University College London, London WC1H 0AH, England, UK
[4]Randall Division of Cell and Molecular Biophysics, Kings College London, London SE11UL, England, UK
[5]Engineering Department, Mechanics and Materials Division, Cambridge University, Cambridge CB2 1PZ, England, UK

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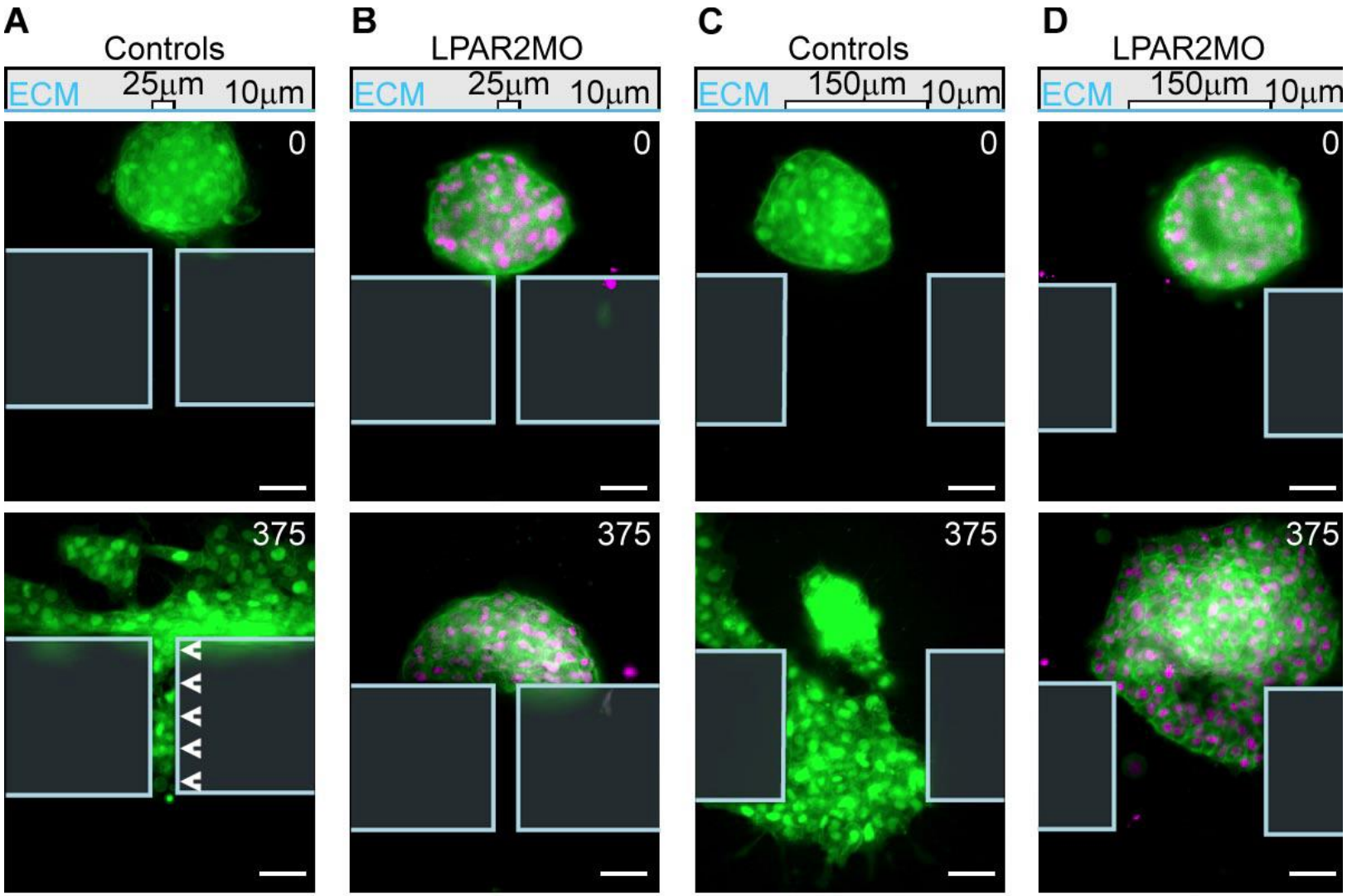
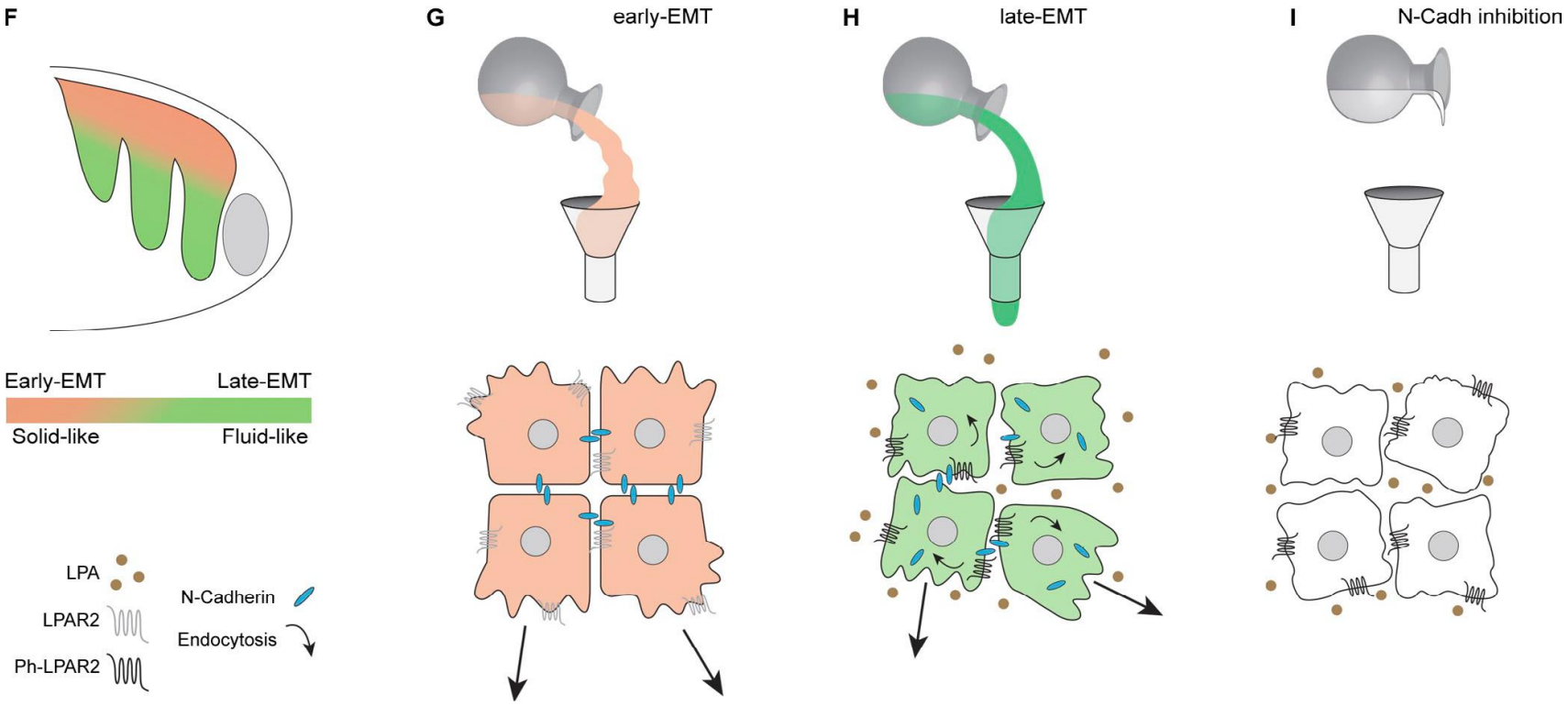
J. Cell Biol. Vol. 206 No. 1 113–127
www.jcb.org/cgi/doi/10.1083/jcb.201402093

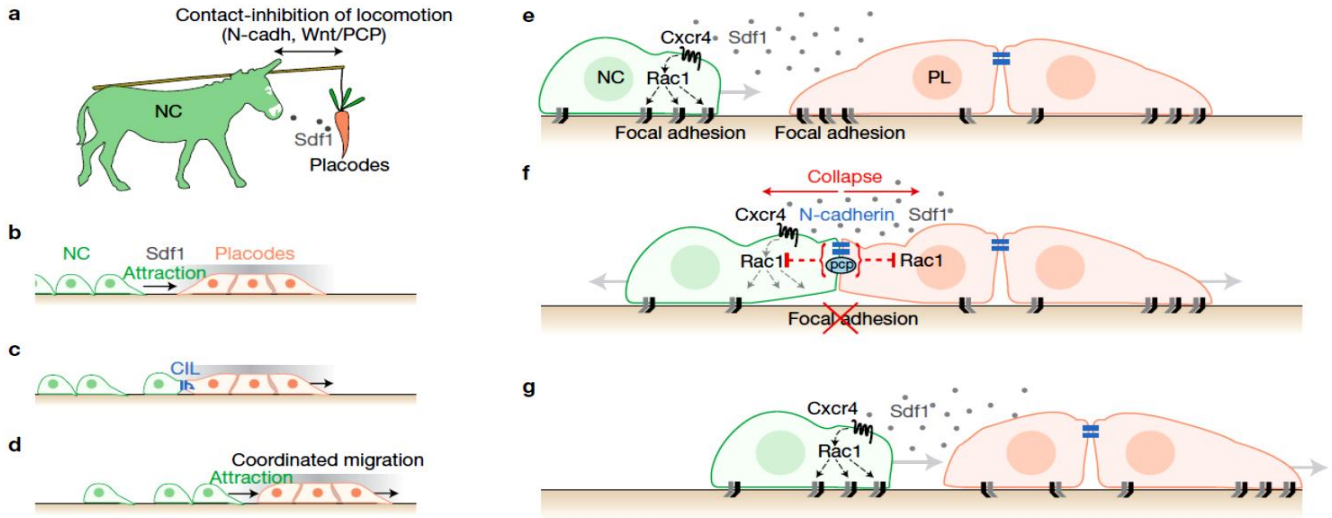
Collective cell migration of neural crest cells



Collective cell migration of neural crest cells



Directional collective migration: Chemotaxis and CIL ("Chase and run")



Chase-and-run between adjacent cell populations promotes directional collective migration

Eric Theveneau[1], Benjamin Steventon[1,2,4], Elena Scarpa[1], Simon Garcia[1,3], Xavier Trepat[3], Andrea Streit[2] and Roberto Mayor[1,5]

NATURE CELL BIOLOGY VOLUME 15 | NUMBER 7 | JULY 2013

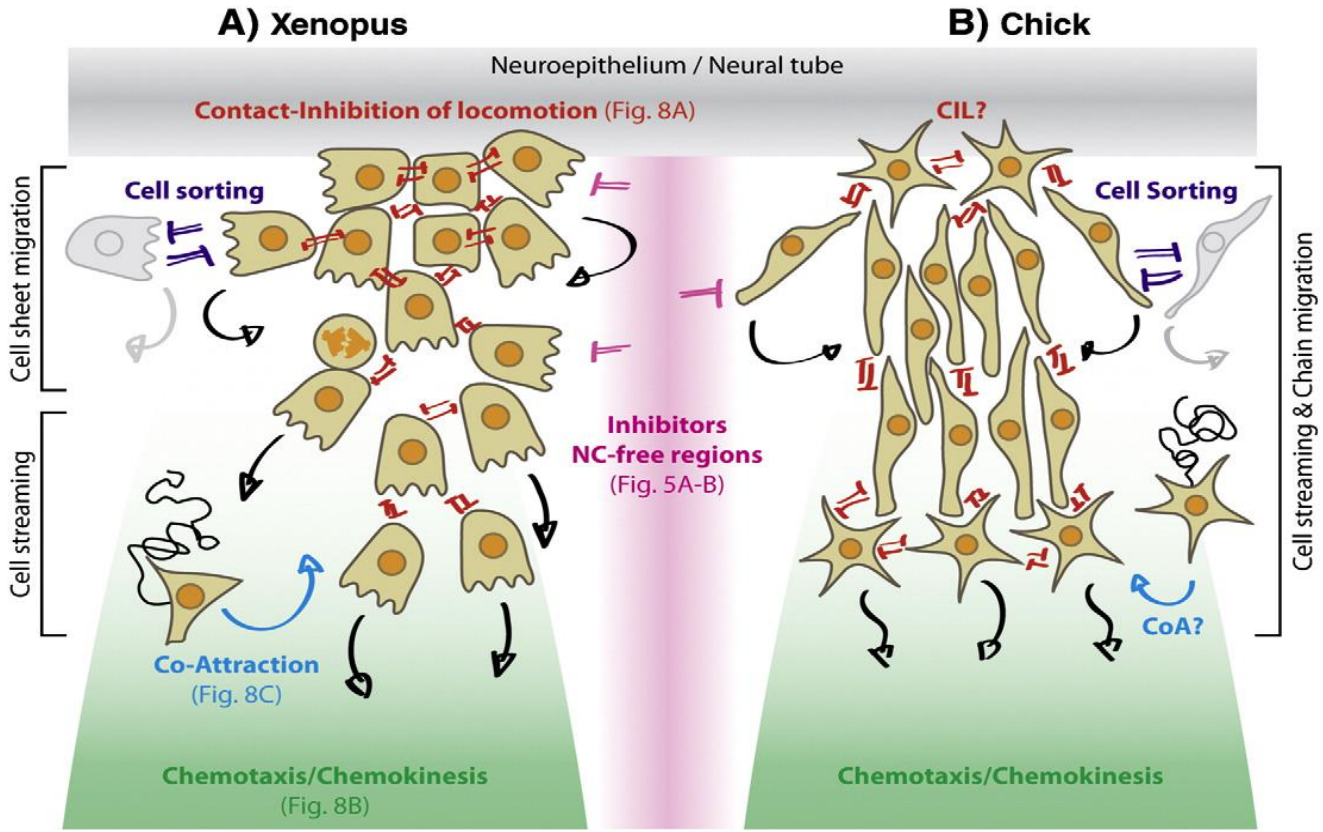


Fig. 7. Cell–cell interactions and external signals regulating collective cell migration of cephalic NC cells. (A) Xenopus cephalic NC cells start migrating as a cell sheet. Cells located at the border of the population exhibit a clear cell polarity with cell protrusions oriented towards the outside. On the contrary, cells inside the population that are completely surrounded by other NC cells show no obvious polarity and display only cryptic protrusions. As migration proceeds the population becomes more mesenchymal and migration turns into a cell streaming. Cell–cell contacts in groups or between single cells trigger Contact-Inhibition of Locomotion (CIL, red inhibitory arrows) which leads to the collapse of cell protrusions. CIL, through its effect on cell polarity, is essential for coordinated migration and sensing of external cues. Cells that lose contacts with other cells have poor chemotactic response (tortuous path) but are actively attracted back towards other NC cells by co-attraction (blue arrows).Modified after Theveneau et al. (2010) and Carmona-Fontaine et al. (2011). Seemain text for details. (B) Chick cephalicNC cells undergo cell streaming and chain migration. Collisions between cells lead to the collapse of cell protrusions reminiscent of CIL (red inhibitory arrows) and a gathering behavior reminiscent of CoA (blue arrows). Modified after Teddy and Kulesa (2004). In both Xenopus and chick isolated cells migrate less efficiently than cells in groups or chains (shown as tumultuous paths). NC cells at the border of a stream may encounter NC cells from an adjacent stream (gray cells) but differential expressions of ephrin/Eph molecules prevent mixing. In addition, inhibitors (ephrins/Eph, class3-semaphorins) present in the surrounding tissues (shades of pink) induce the collapse of cell protrusions and restrict NC migration to specific routes. Finally, chemotactic and chemokinetic factors promoting motility and targeting NC cells to specific locations are shown as shades of green.

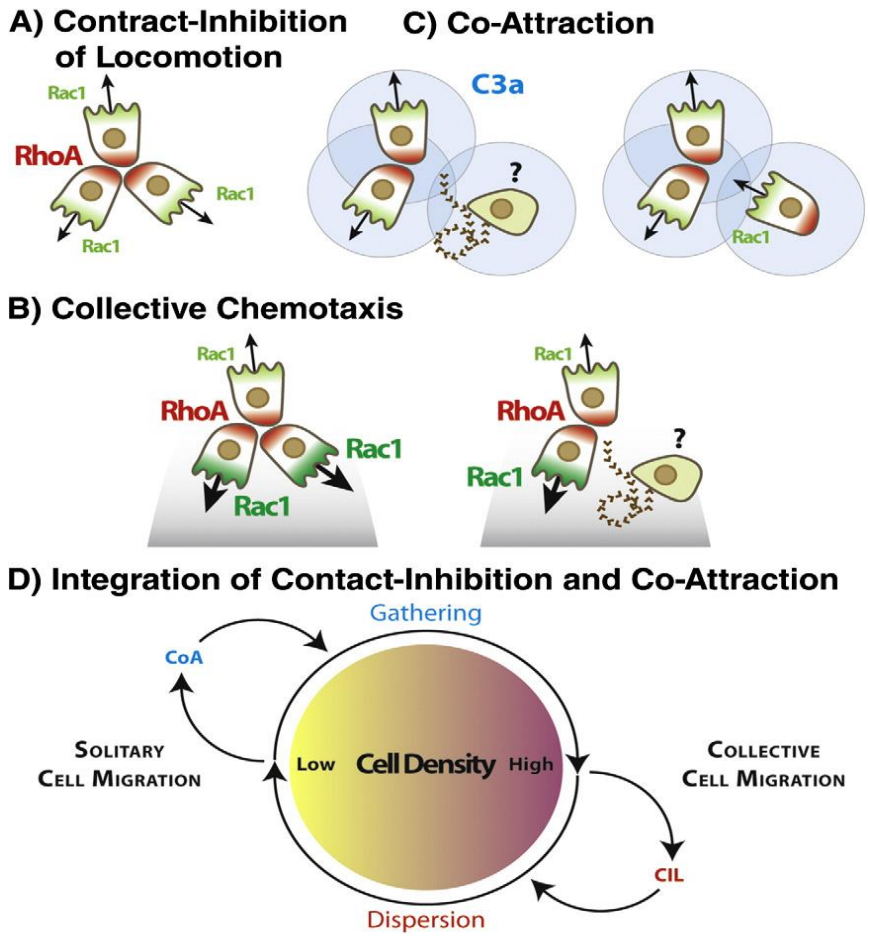


Fig. 8. Contact-Inhibition, chemotaxis and Co-Attraction cooperate to promote collective migration in Xenopus cephalic NC cells. (A) NC cells are polarized due to cell–cell interactions mediating Contact-Inhibition of Locomotion (CIL). They show high RhoA activity at the contact and high Rac1 at the free edge. (B) External attractant further stabilizes well-oriented protrusions (increased Rac1 activity) creating a directionality bias towards region of high concentration of attractant. Cells that detach from the cluster transiently lose polarity (brown cell) and are unable to read external attractant. (C) Each NC cell is secreting C3a (blue circles) which acts as a local attractant promoting co-attraction (CoA) and gathering of NC cells. (D) CoA compensate for cell dispersion induced by CIL but also positively feedbacks into CIL by promoting cell collisions while cells are gathering back together. Altogether CIL and CoA help NC cells to undergo collective cell migration while retaining mesenchymal properties.

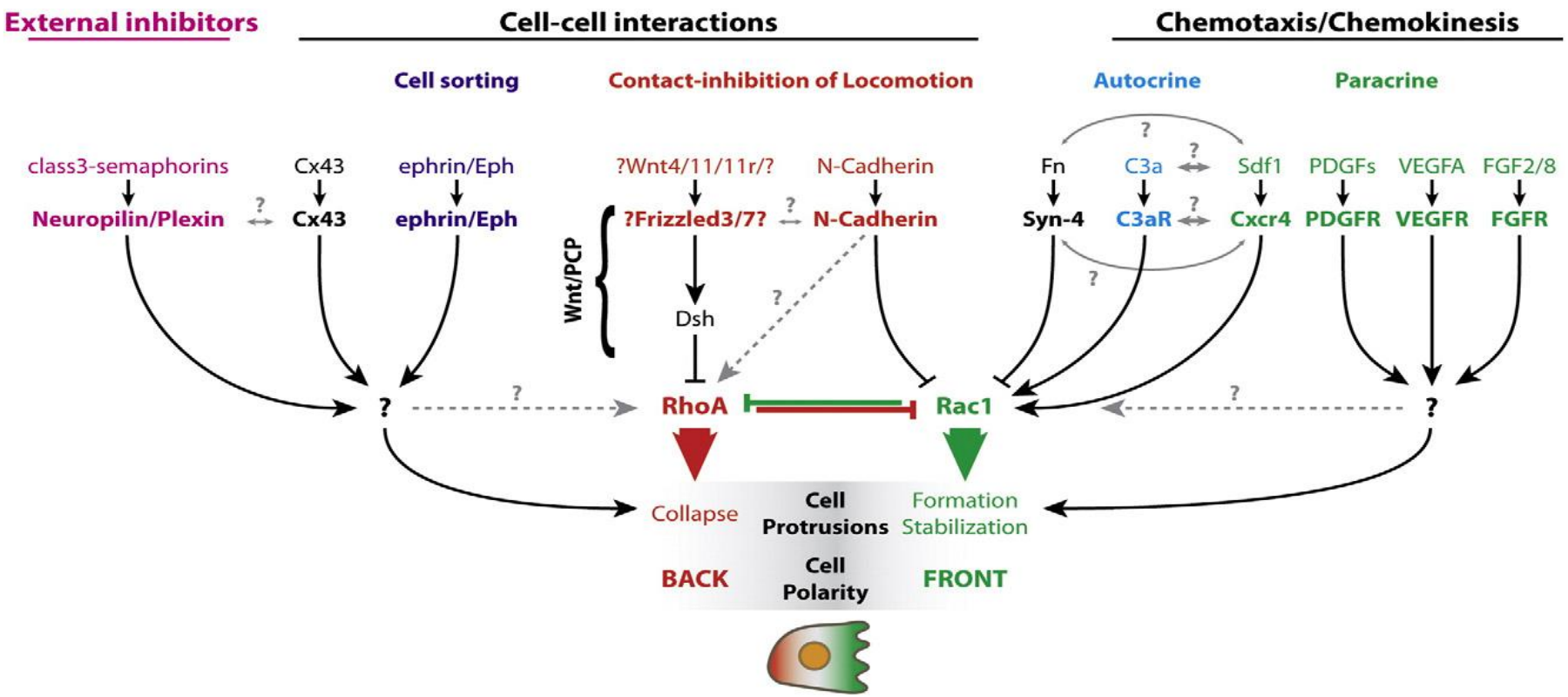
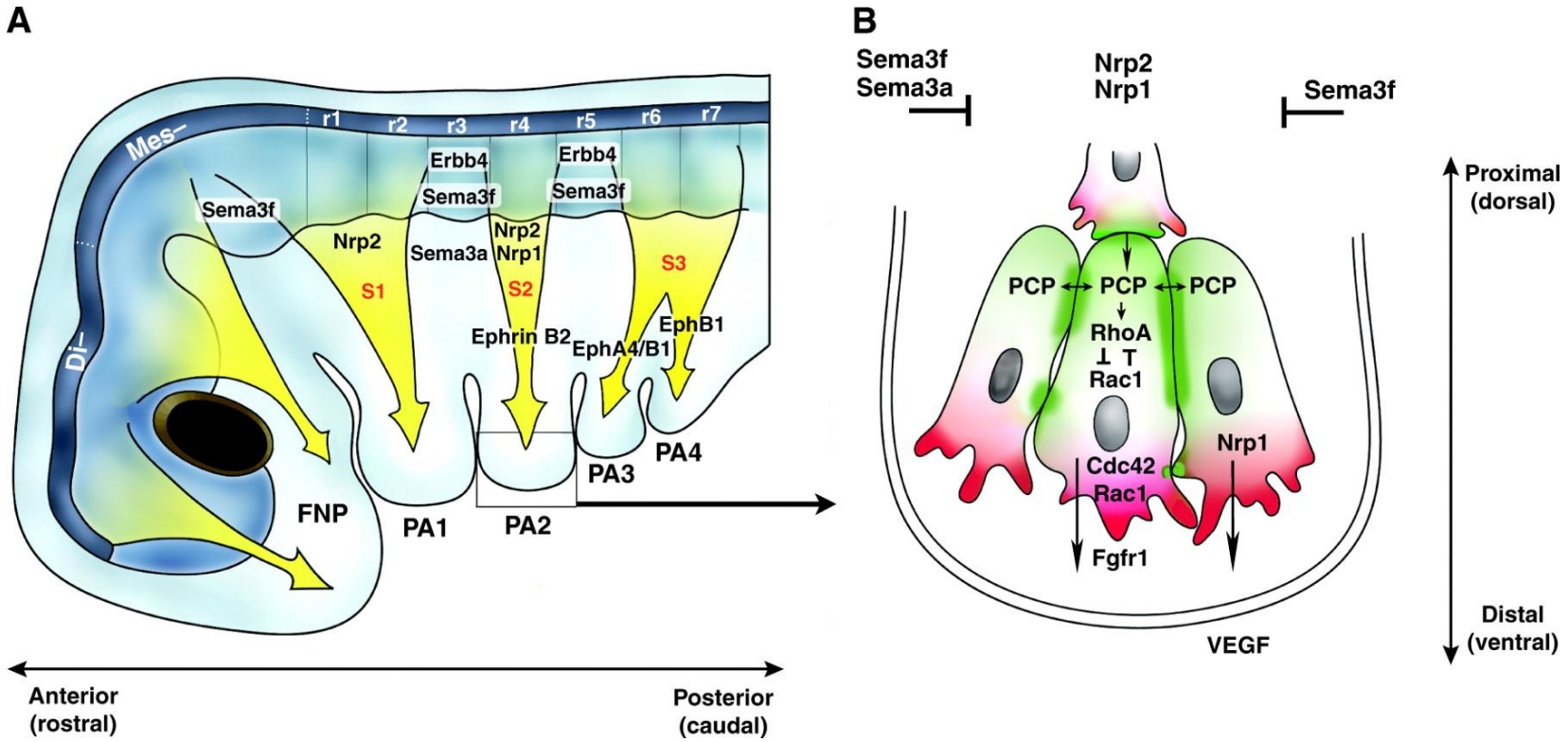


Fig. 9. Signal integration. Summary of the different classes of signaling pathways involved in regulating cephalic NC cell motility and polarity. External inhibitors produced by surrounding tissues are here represented by semaphorins. Cell–cell interactions include: ephrin/Eph signaling among NC cells and between NC cells and their surrounding tissues; but also GAP junctions (Cx43) and CIL (Wnt/PCP, Cadherins) among NC cells. Semaphorin and ephrin signaling promote the collapse of cell protrusions, possibly through RhoA activation. Connexin-43 (Cx43)-based GAP junctions are required for NC cells to polarize upon cell contacts and to interpret semaphorin signaling. How this effect is mediated remains unknown. CIL relies on PCP signaling and N-Cadherin-based cell–cell contacts. CIL promotes RhoA activity and blocks Rac1. Syndecan-4 inhibits Rac1. Paracrine chemokinetic/chemotactic factors include Sdf1, VEGFA, FGF2/8 and PDGFs. Sdf1/Cxcr4 signaling activates Rac1. Downstream effectors of PDGF, VEGF and FGF pathways responsible for their positive effect on NC cell migration are unknown but likely to eventually regulate the small Rho GTPases. Autocrine signals are represented by complement factor C3a and its cognate receptor C3aR. C3a/C3aR signaling activates Rac1. Many crosstalks are likely to take place between pathways as several common effectors can be found. Neuropilin-1 can act as co-receptor for Plexins, VEGFR and PDGFR. Syndecan-4 (Syn-4) binds to Sdf1 and Fibronectin (Fn) and can act as a co-receptor for Cxcr4. C3a and Sdf1 can bind to each other while CXCR4 and C3aR can interact. Please note that data from Xenopus, chick, mouse and fish embryos are mixed in this figure. See main text for details and references.

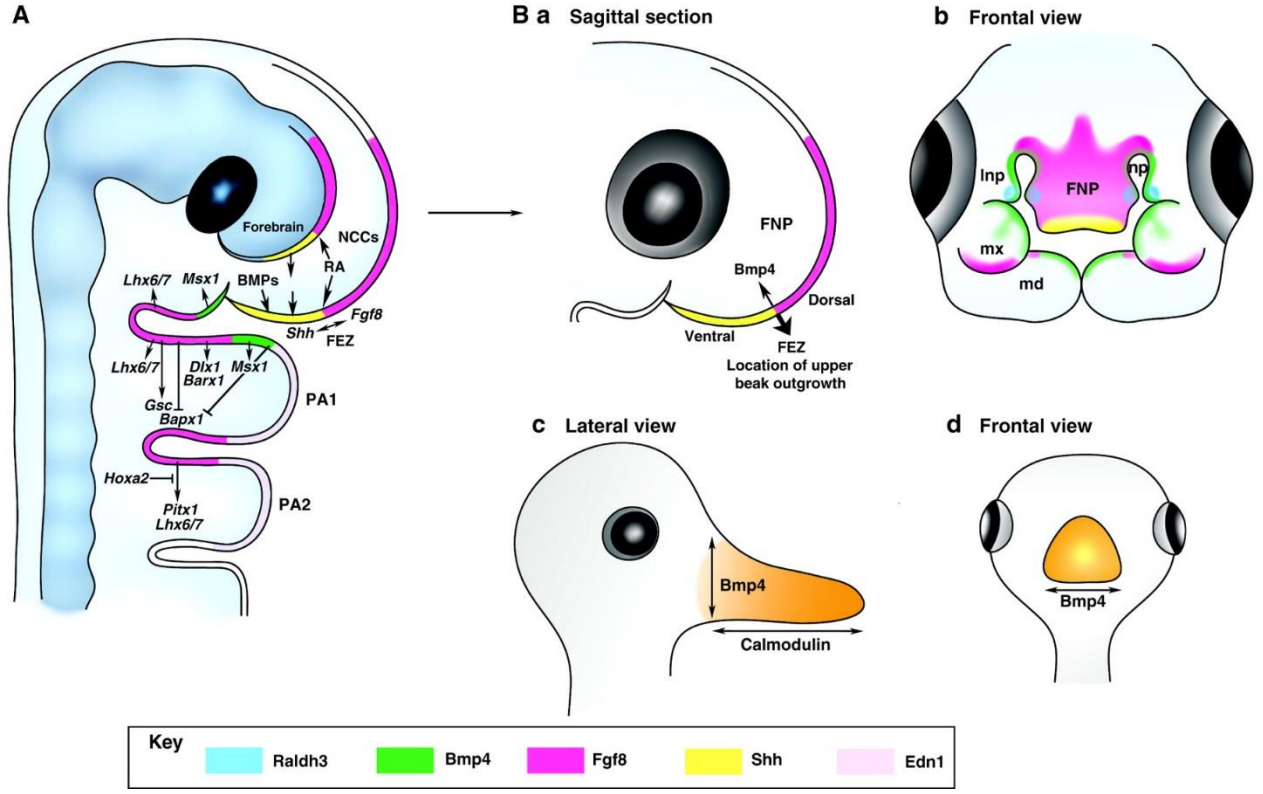
Segmental and directional migration of cranial neural crest cells.



Maryline Minoux, and Filippo M. Rijli Development
2010;137:2605-2621

Environmental signals and patterning of craniofacial and pharyngeal structures.

Make me a duck, please!



Maryline Minoux, and Filippo M. Rijli Development 2010;137:2605-2621

Development
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The neural crest

Roberto Mayor and Eric Theveneau

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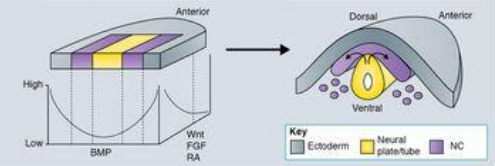
The neural crest (NC) is a multipotent cell population that migrates extensively during embryogenesis and differentiates into a wide variety of cell types. In particular, the NC forms most of the peripheral nervous system and pigment cells and makes oustanding contributions to the head and neck.

NC formation

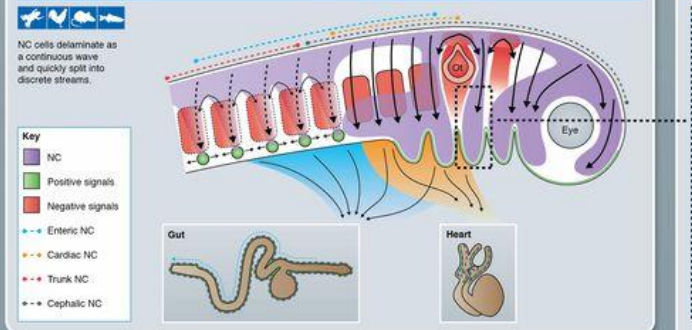
NC cells are induced at the neural plate border by intermediate levels of BMP signalling and high levels of Wnt, FGF and RA signalling.

These signals induce several transcription factors whose co-expression defines the NC territory and controls delamination.



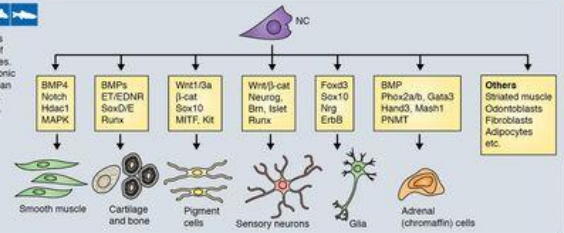
NC migration

NC cells delaminate as a continuous wave and quickly split into discrete streams.



NC differentiation

NC differentiates into a plethora of different cell types. No other embryonic cell population can generate such a diversity of cells.



Mechanisms of NC migration

NC migration can be subdivided in a series of different biological processes

Epithelial-mesenchymal transition (EMT)

Snail2, Foxd3, Sox9/10
Ets1*, LSox5*, p53* (loss)

Prospective NC cells

* Expressed in cephalic NC only

Migratory NC cells

Before migration, NC cells undergo EMT. There is a global change of cell adhesion properties and motility which helps trigger the onset of migration.

Key
E-cad
N-cad
Type II cad

Contact-Inhibition of locomotion

Owing to contact-inhibition locomotion (CIL), NC cells are polarised by contact with one another. This leads to cell dispersion.

Key
RhoA N-cad
Rac1 Wnt/PCP

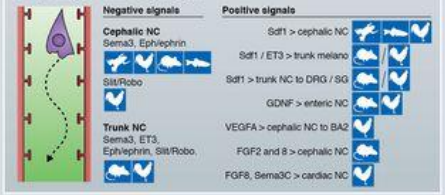
Co-attraction (or mutual cell attraction)

NC cells attract each other by co-expressing an attractant (C3a) and its receptor (C3aR). This paracrine chemotaxis helps to maintain a cluster configuration during collective migration.

Key C3aR C3a

NC guidance

Negative signals are located at the border of each NC stream. Positive signals are located along the NC pathways or within the target regions



Negative signals

Cephalic NC
Sema3, Eph/ephrin
Slit/Robo

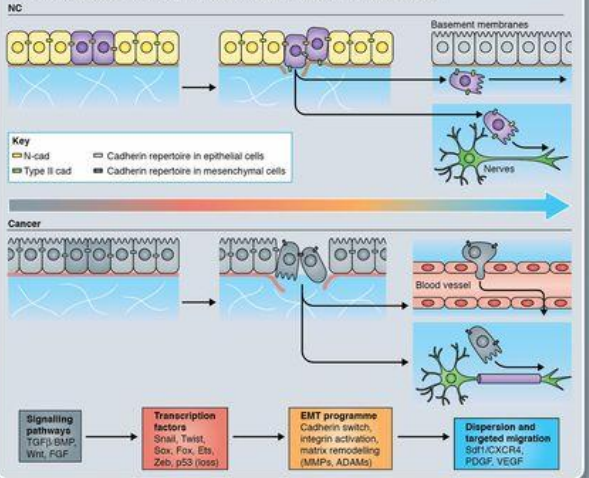
Trunk NC
Sema3, ET3, Eph/ephrin, Slit/Robo.

Positive signals

Sdf1 > cephalic NC
Sdf1 / ET3 > trunk melano
Sdf1 > trunk NC to DRG / SG
GDNF > enteric NC
VEGFA > cephalic NC to BA2
FGF2 and 8 > cephalic NC
FGF8, Sema3C > cardiac NC

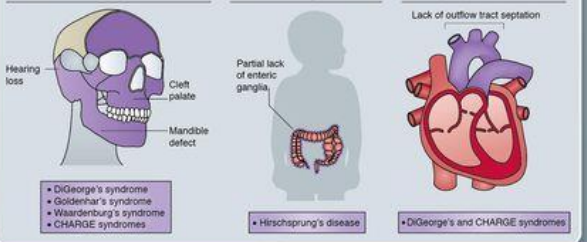
NC migration versus cancer metastasis

NC has been proven as a good system to understand cancer progression. Many of the key factors that promote cancer cell migration have been initially studied in NC migration. It is likely that cancer cells hijacked the NC migratory program.



Neurocristopathies

Syndromes and congenital defects due to improper NC development (i.e. incomplete migration or reduced survival) are called neurocristopathies. Some of the main affections are presented below with examples of the diseases in which they occur. Other symptoms such as mental retardation and pigmentation defects are also frequent in neurocristopathies.



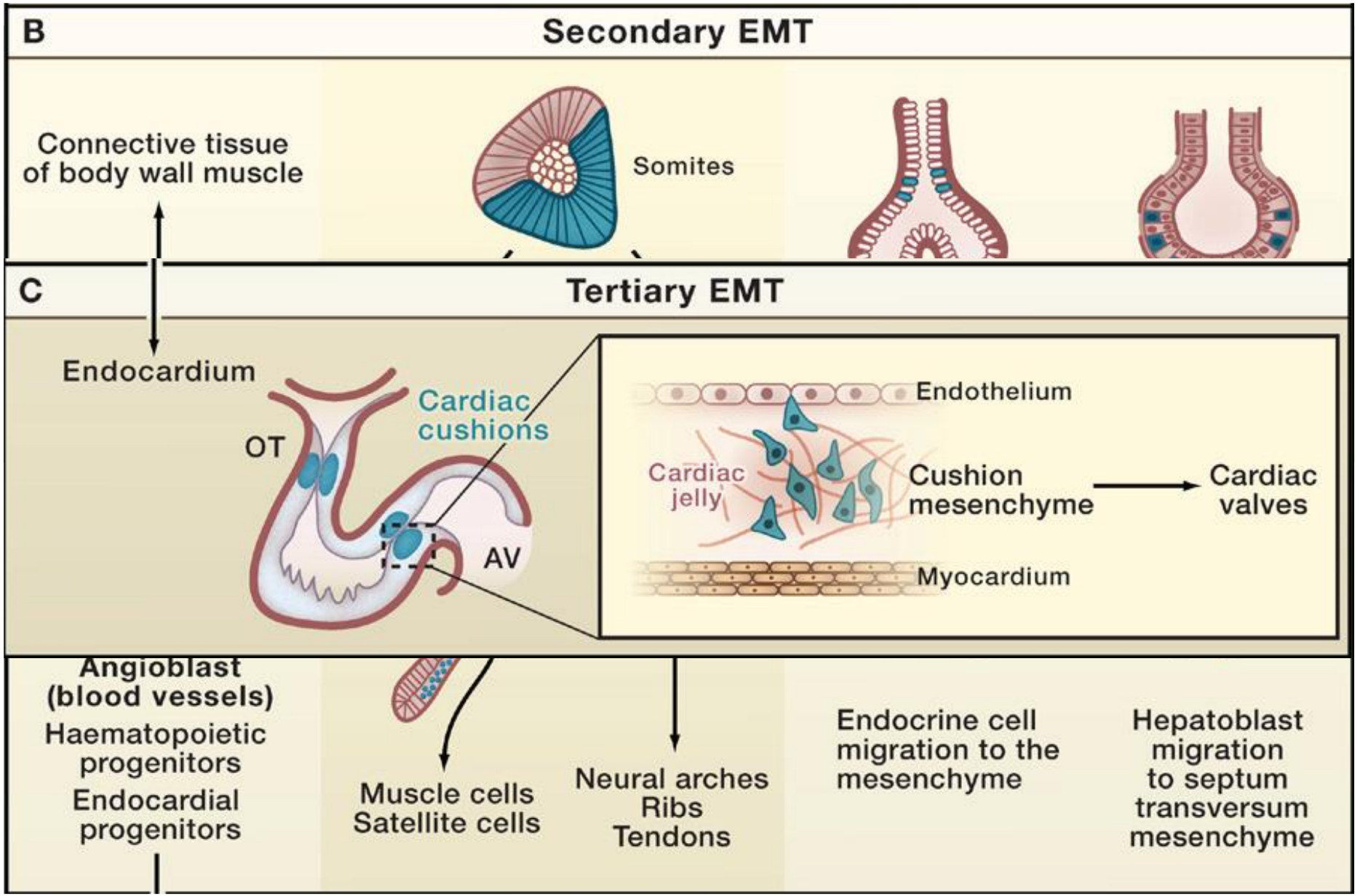
Abbreviations: ADAM, a disintegrin and metalloproteinase; β-cat, beta-catenin; BMP, bone morphogenetic protein; Brn, subgroup of the POU (Pit-Oct-Unc) family of transcription factors; C3a, complement factor 3a; C3aR, complement factor 3a receptor; Cxcr4, CXC chemokine receptor 4; DRG, dorsal root ganglia; EDNR, endothelin receptor; ErbB, erythroblastic leukaemia viral oncogene-like family of receptor tyrosine kinases (also known as the Her family); ET, endothelin; ETs, E26 family of transcription factors; FGF, fibroblast growth factor; Fox, Forkhead box family of transcription factors; Gata, GATA-binding family of transcription factors; GDNF, glial cell-derived neurotrophic factor; Hand, heart and neural crest derivatives expressed protein family of transcription factors; Hdac, histone deacetylases; Kit, tyrosine protein kinase Kit; MAPK, mitogen-activated protein kinase; Mash, mammalian achaete-scute homologue family of transcription factors; melano, melanocytes; MITF, microphthalmia-associated transcription factor; MMP, matrix metalloproteinase; Neurog, neurogenin; Ngn, neurogulin; Ot, otic vesicle; PCP, planar cell polarity pathway; Phox, paired-like homeobox family of transcription factors; PDGF, platelet-derived growth factor; PNMT, phenylethanolamine N-methyltransferase; RA, retinoic acid; Robo, Roundabout family of transmembrane receptors; Runx, Runt-related family of transcription factors; Sdf1, stromal cell-derived factor 1 (Cxcl12); Sema, semaphorin; SG, sympathetic ganglia; Sox, Sry-related HMG-box family of transcription factors; VEGF, vascular endothelium growth factor; Wnt, member of Wingless-int family; Zeb, zinc-finger E-box-binding homeobox family of transcription factors.

Animals in which the experiments were carried out

Frog embryo (*Xenopus laevis*) · Chicken (*Gallus gallus*) or quail (*Coturnix japonica*) embryos · Mouse embryo (*Mus musculus*) · Zebrafish embryo (*Danio rerio*)

Roberto Mayor, and Eric Theveneau Development 2013;140:2247-2251

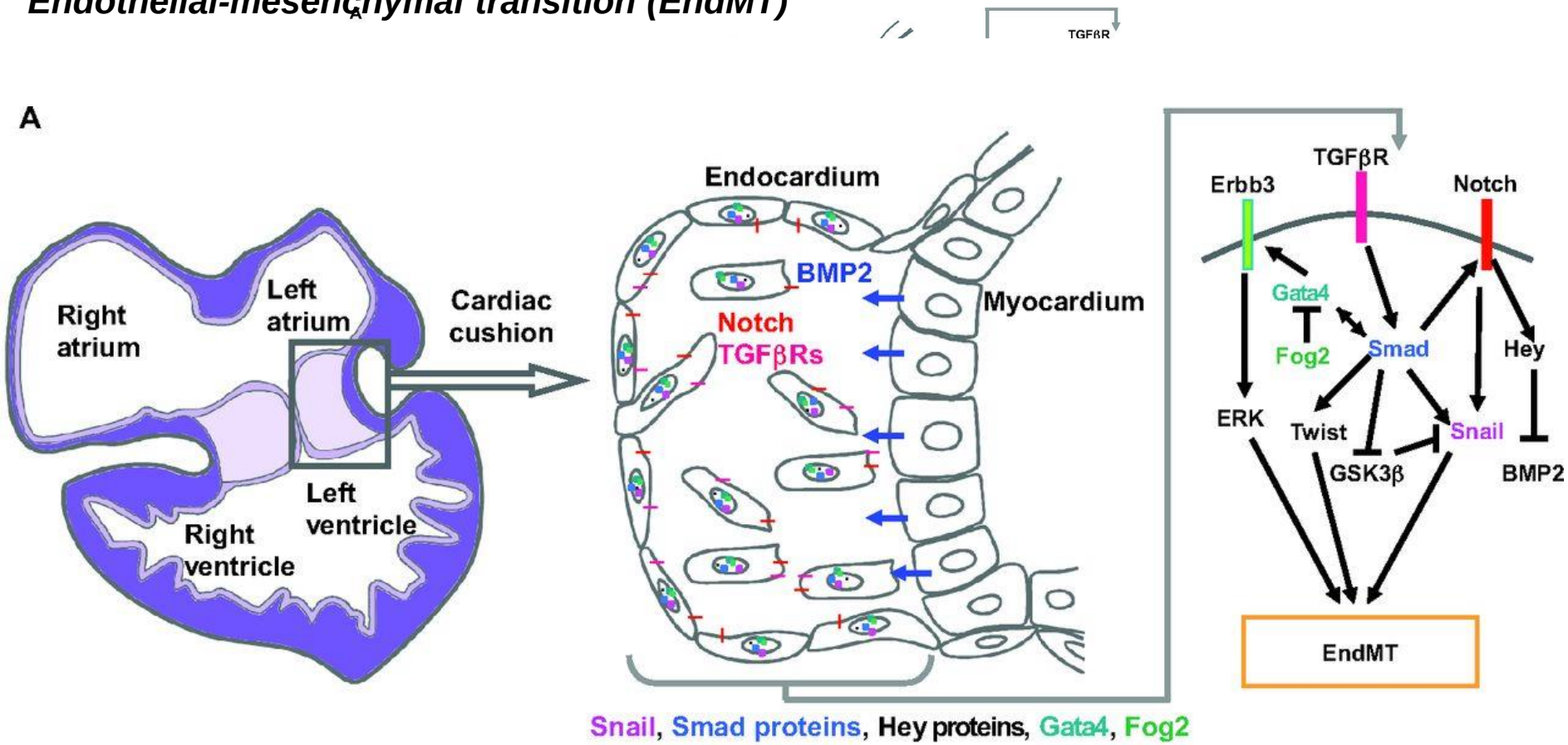
Successive EMT during Embryonic Development



Epithelial-mesenchymal transition and mesenchymal-epithelial transition during heart formation

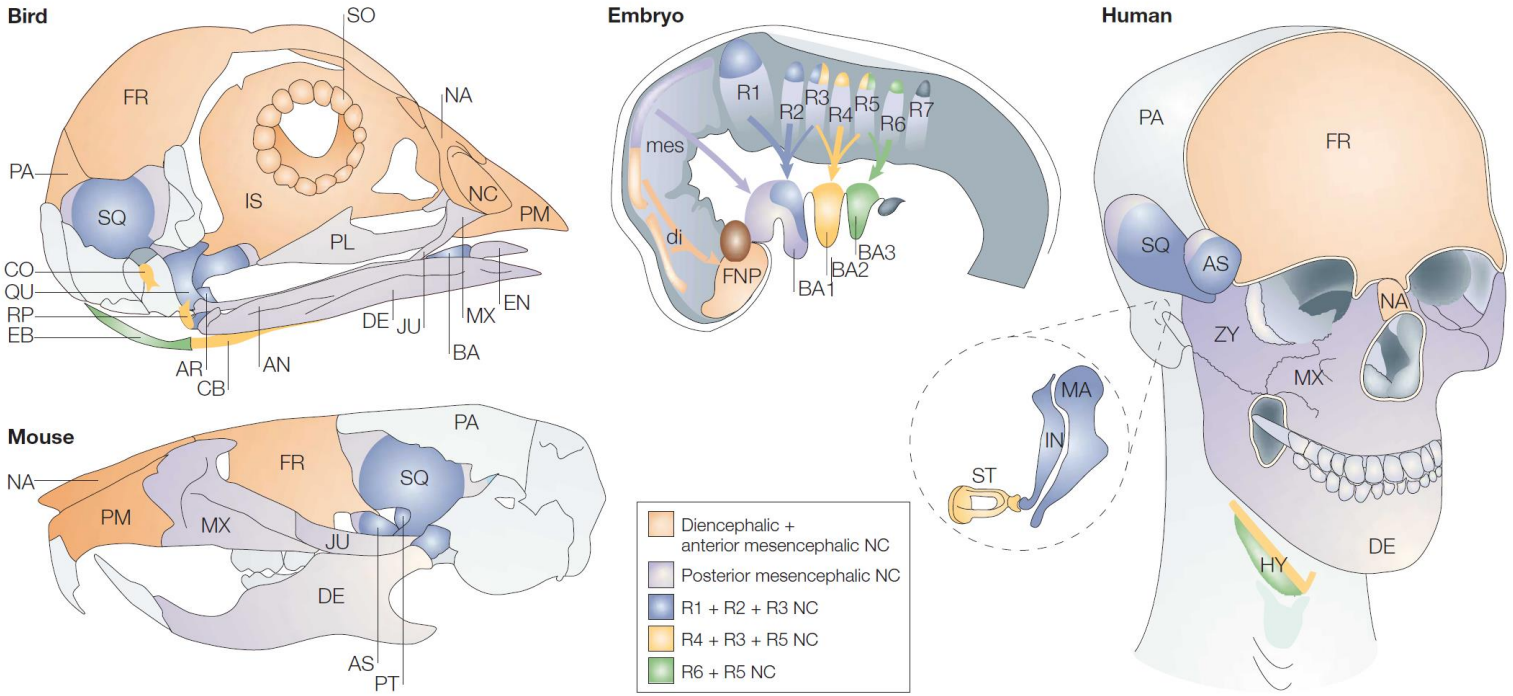
(chick and mouse embryos).

Endothelial-mesenchymal transition (EndMT)



Jormay Lim, and Jean Paul Thiery Development 2012;139:3471-3486

Cell migration makes our look!



Quand j'aurai du vent dans mon crâne
Quand j'aurai du vert sur mes os(ses)
P'tête qu'on croira que je ricane
Mais ça s'ra une impression fosse…

Boris Vian

Cell migration makes our hearts beat!

Aujourd'hui ça et là, les cœurs battent encore,
Et la règle du jeu de l'amour est la même.
Mais les dieux ne répondent plus de ceux qui s'aiment.
Vénus s'est faite femme, et le grand Pan est mort.

George Brassens

Sempé