The later development in xenopus and zebrafish

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Xenopus: gastrulation~ neurulation

outline

- Ectoderm

  1) neural tube formation and differentiation
  2) neural crest cells
  3) eye development

- Mesoderm

  1) paraxial mesoderm: somite
  2) intermediate mesoderm: kidney
  3) lateral plate mesoderm: heart, blood vessels, blood cells

- Endoderm

  gut

outline

- Ectoderm

  1) neural tube formation and differentiation

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- Mesoderm

  1) paraxial mesoderm: somite

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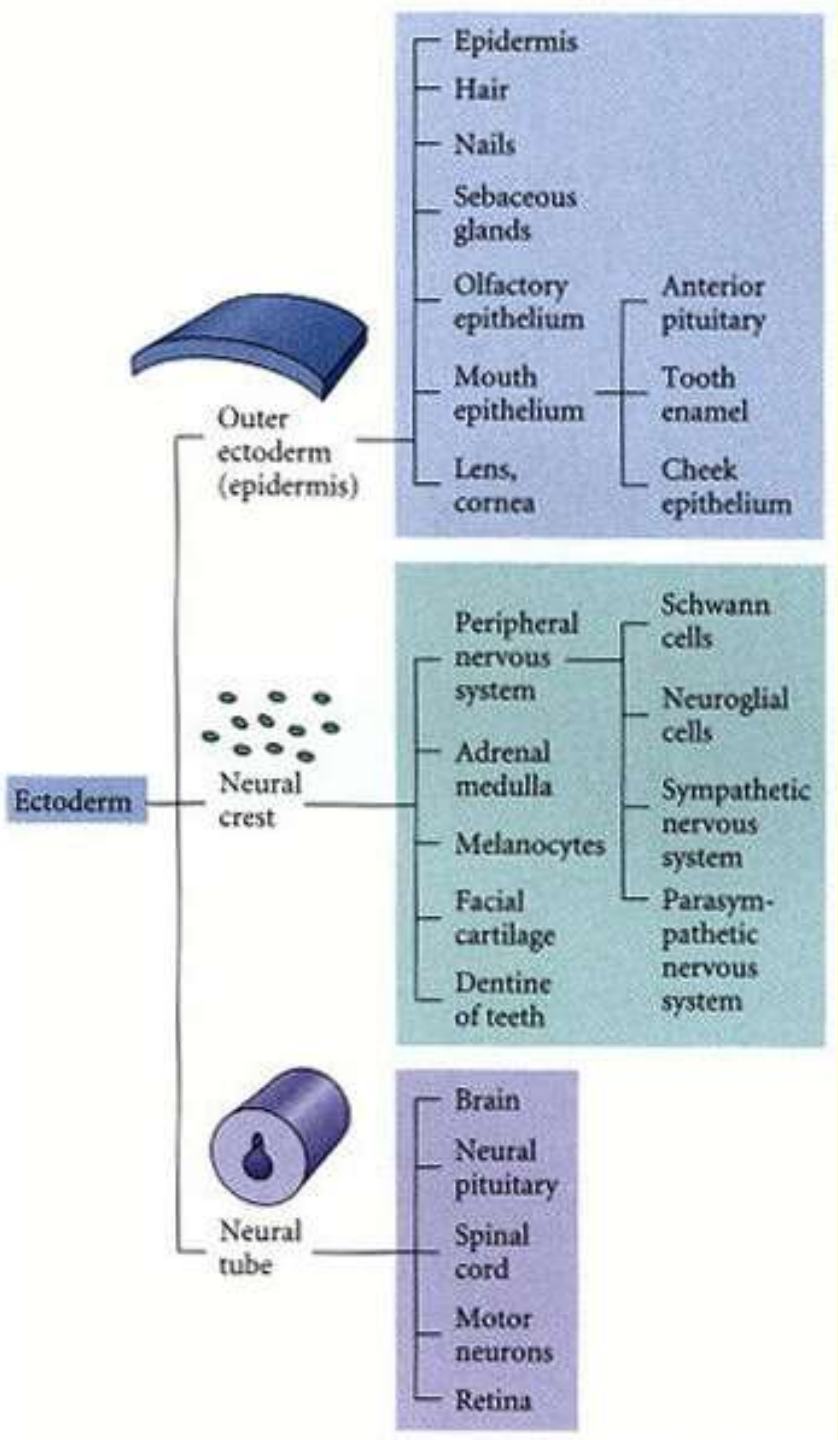
- Endoderm

  gut

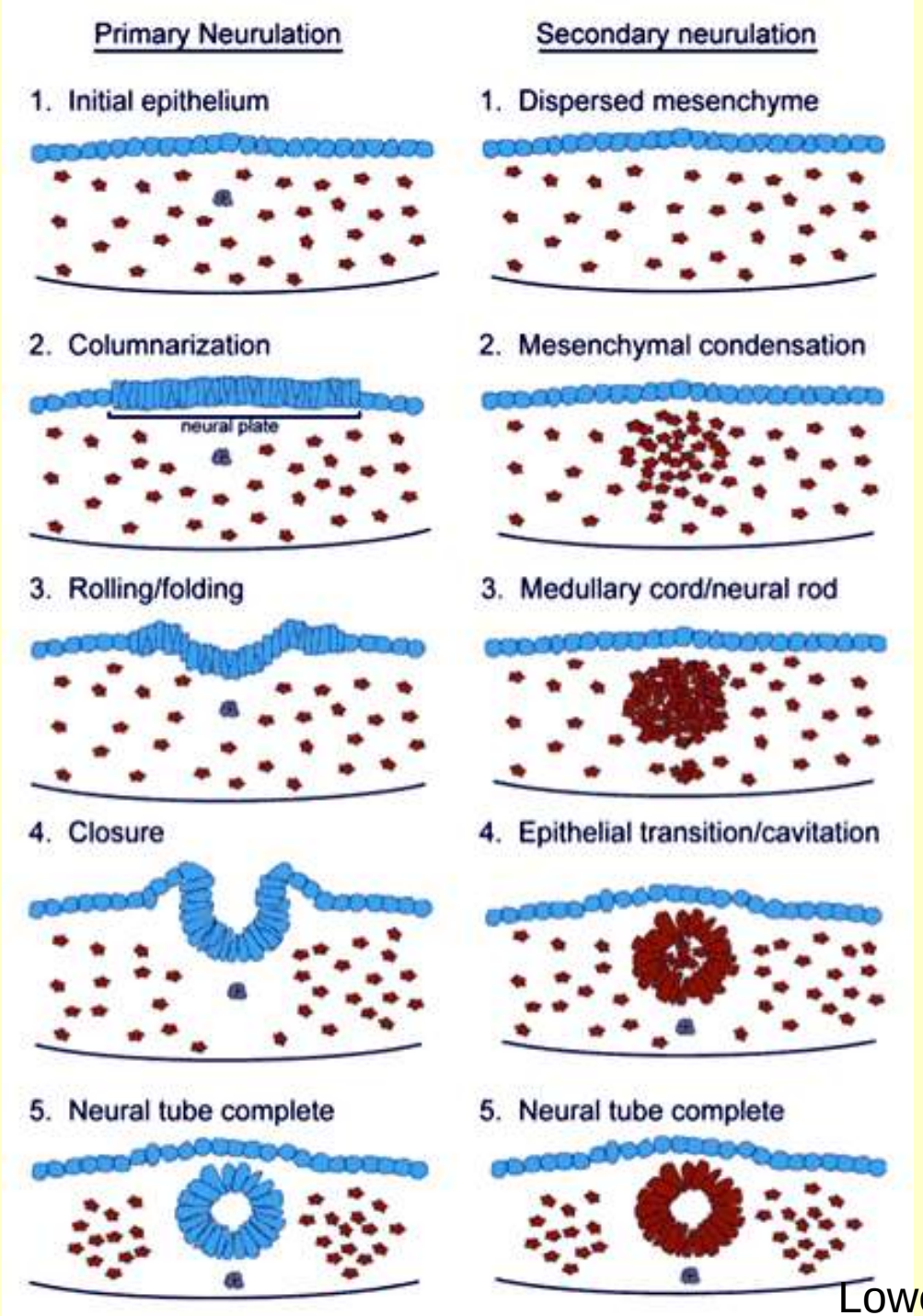
Major derivatives of ectoderm germ layer



Neural tube (神经管) formation

- neural tube (神经管) is the rudiment (原基) of the central nervous system，the formation process of which is called neurulation (神经管形成). There are two major ways of neurulation: primary (初级) neurulation and secondary (次级) neurulation.
- Primary neurulation: neural plate cells →proliferate, invaginate and pinch off →tube (anterior)
- Secondary neurulation: mesenchyme cells→ coalescence (聚集) → cord → hollow → tube (posterior)

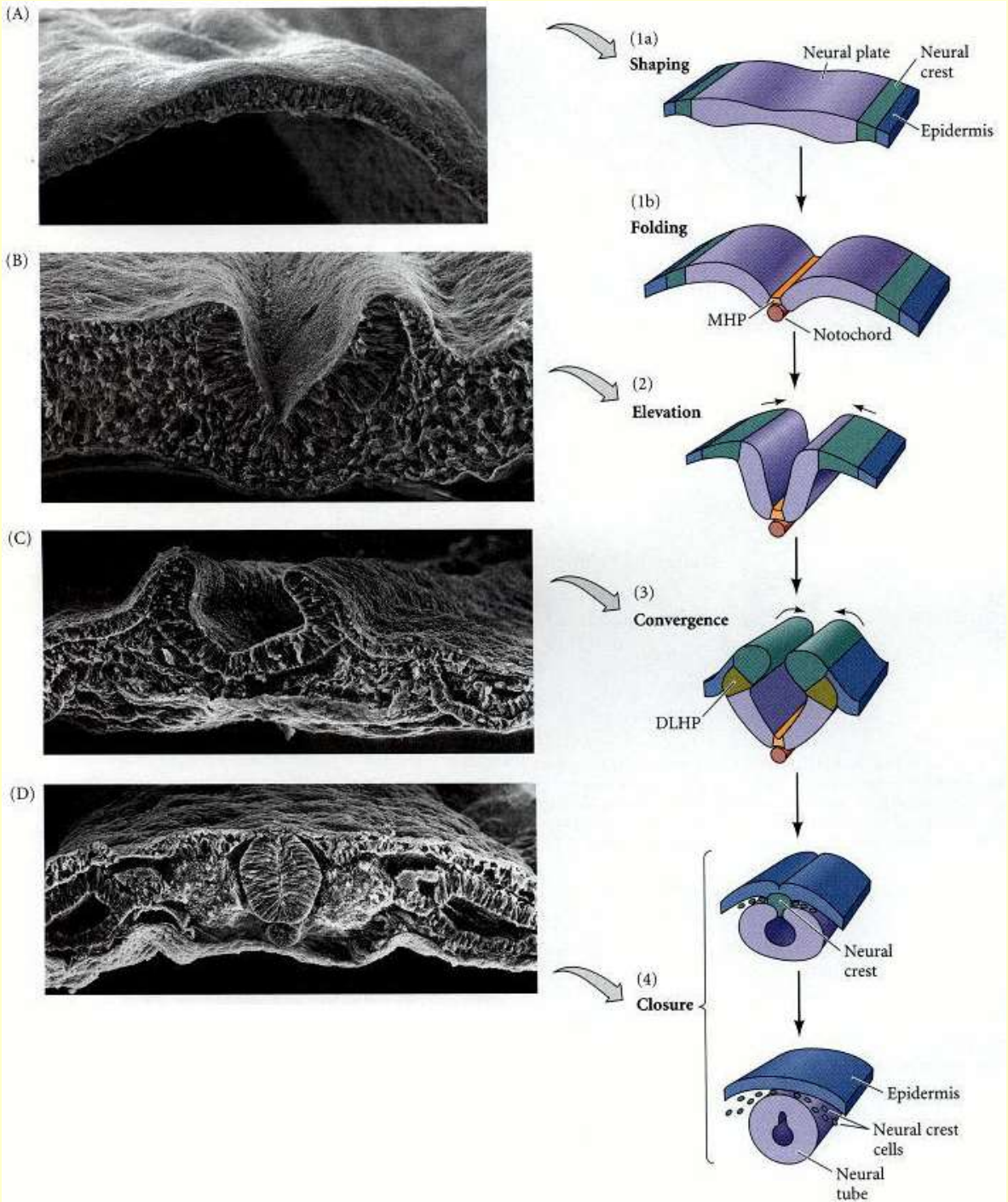
Formation of neural tube: primary neurulation vs secondary neurulation



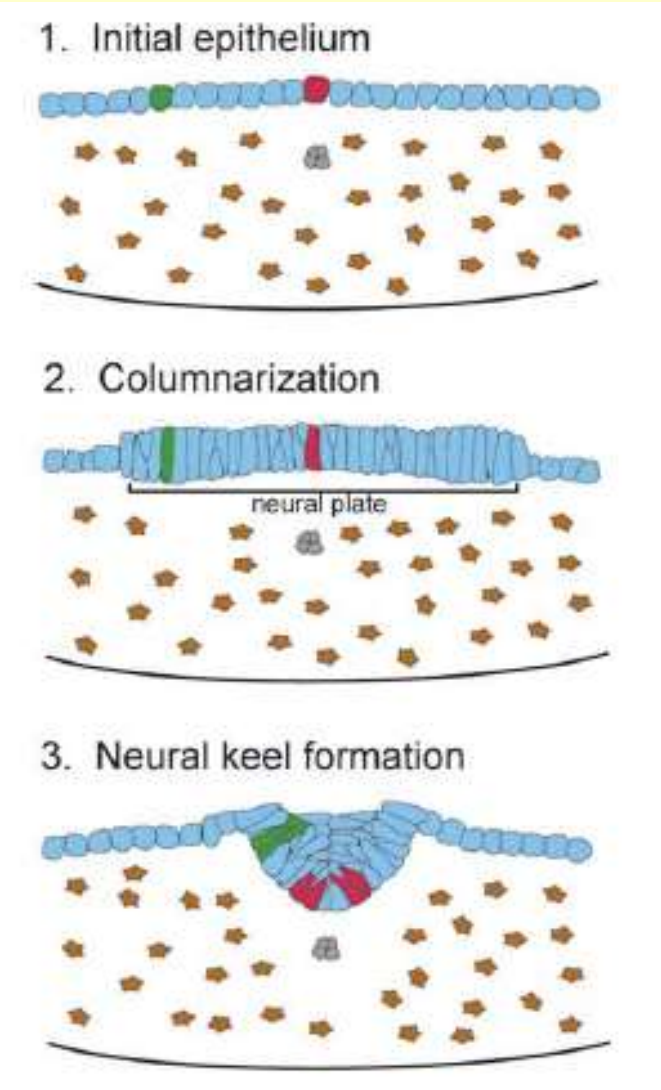
Ectoderm
Mesenchyme

Lowery & sive, 2004

Primary neurulation in chick embryo



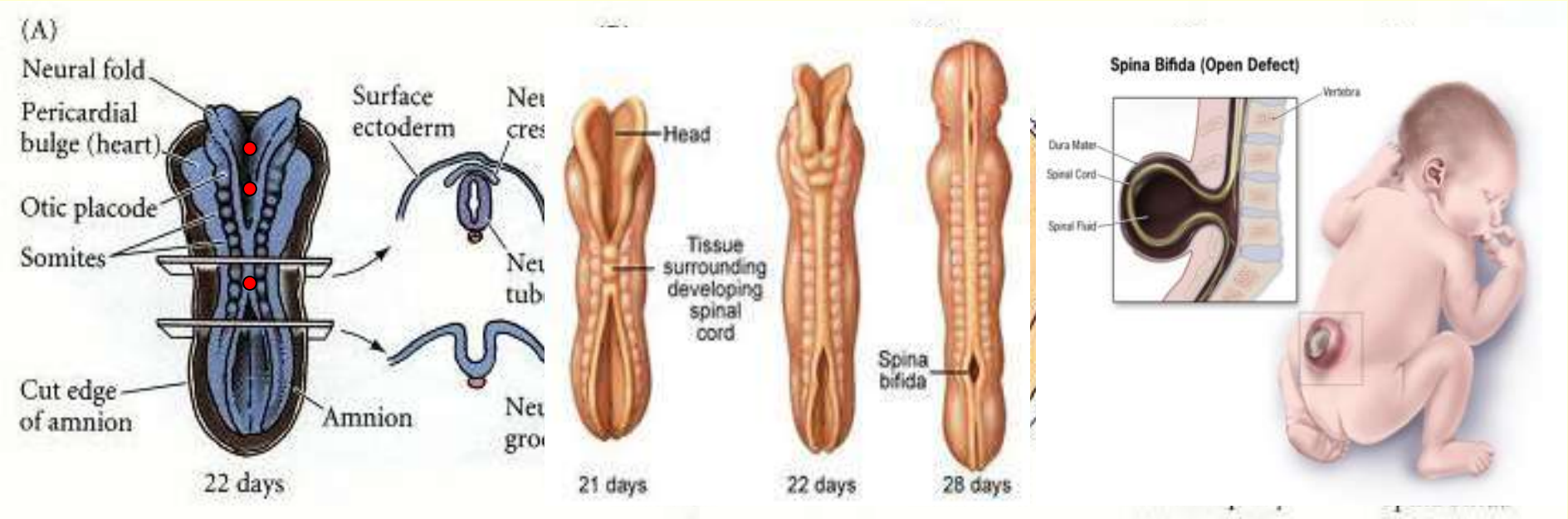
Neural tube formation in zebrafish



斑马鱼中先形成实心的神经杆（neural rod），然后再空心化形成神经管

Lowery & sive, 2004

Neural tube closure defect and human birth defect



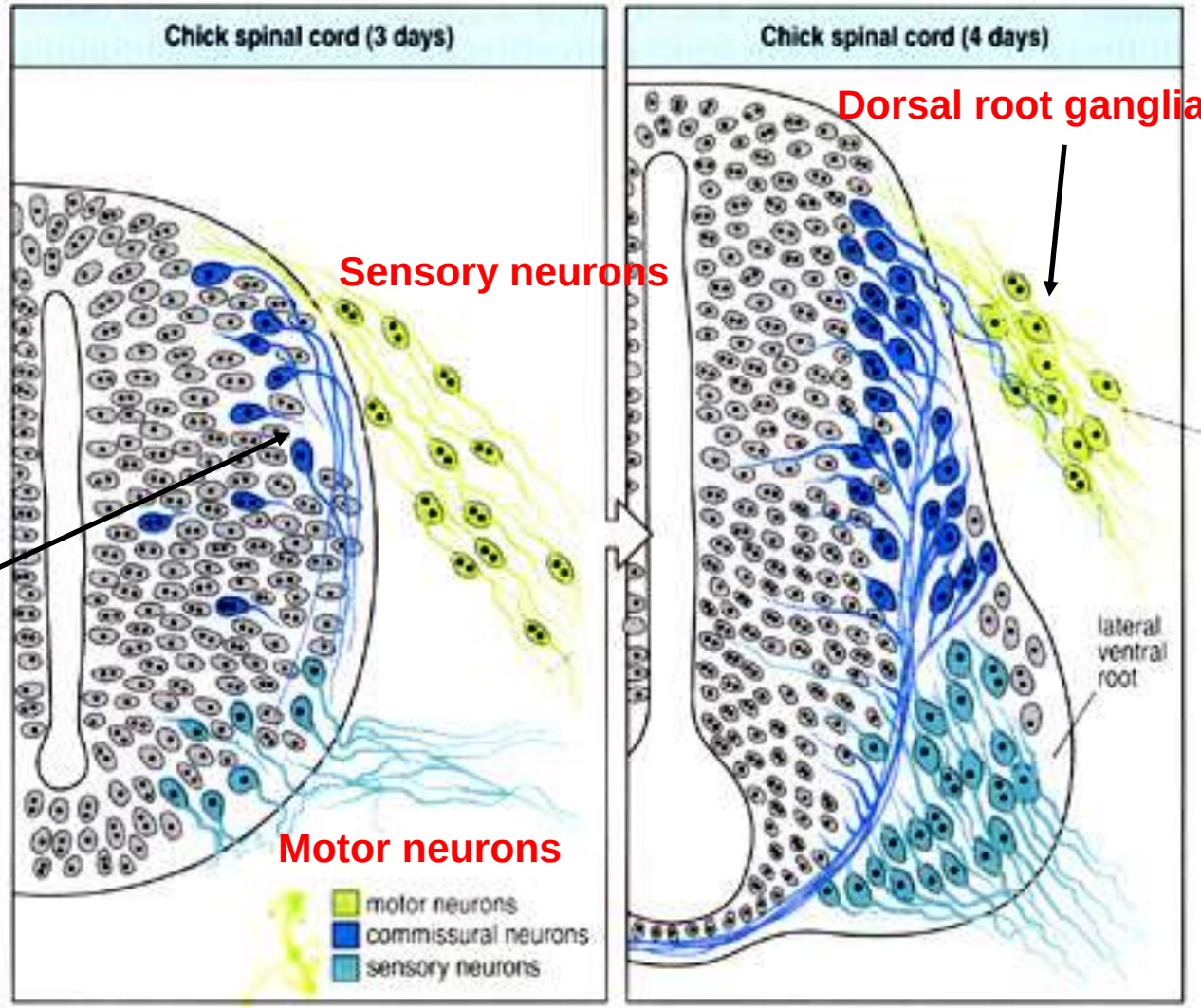
人类的神经管闭合同时开始于大概3个点(如图中红点所示)

如果后部一个点不能正常闭合，则会导致脊柱裂(spina bifida)

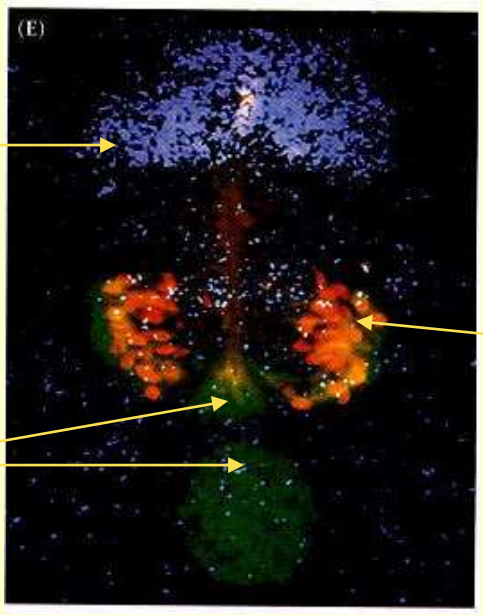
如果前两个点不能开始闭合，则会导致无脑儿(anencephaly)

Chick spinal cord

Fig. 11.12 Formation of sensory and motor neurons in the chick spinal cord. Three days after an egg has been laid, motor neurons are beginning to form within the chick embryo neural tube. One day later, the motor neurons migrate to form the lateral ventral root of the spinal cord. The sensory neurons that migrate from the dorsal part of the spinal cord are derived from neural crest cells and form the segmental dorsal root ganglia (see Section 8-15).



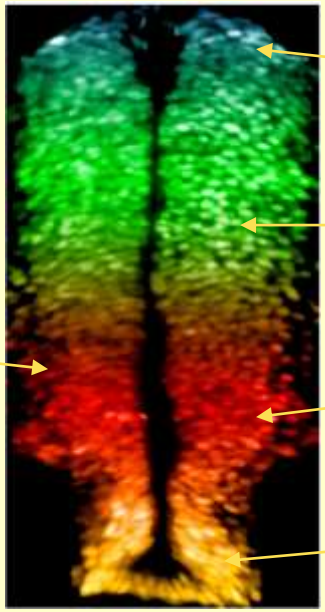
DV patterning of neural tube in chick



dorsalin

Shh

Motor neuron



Pax7 (dorsal)

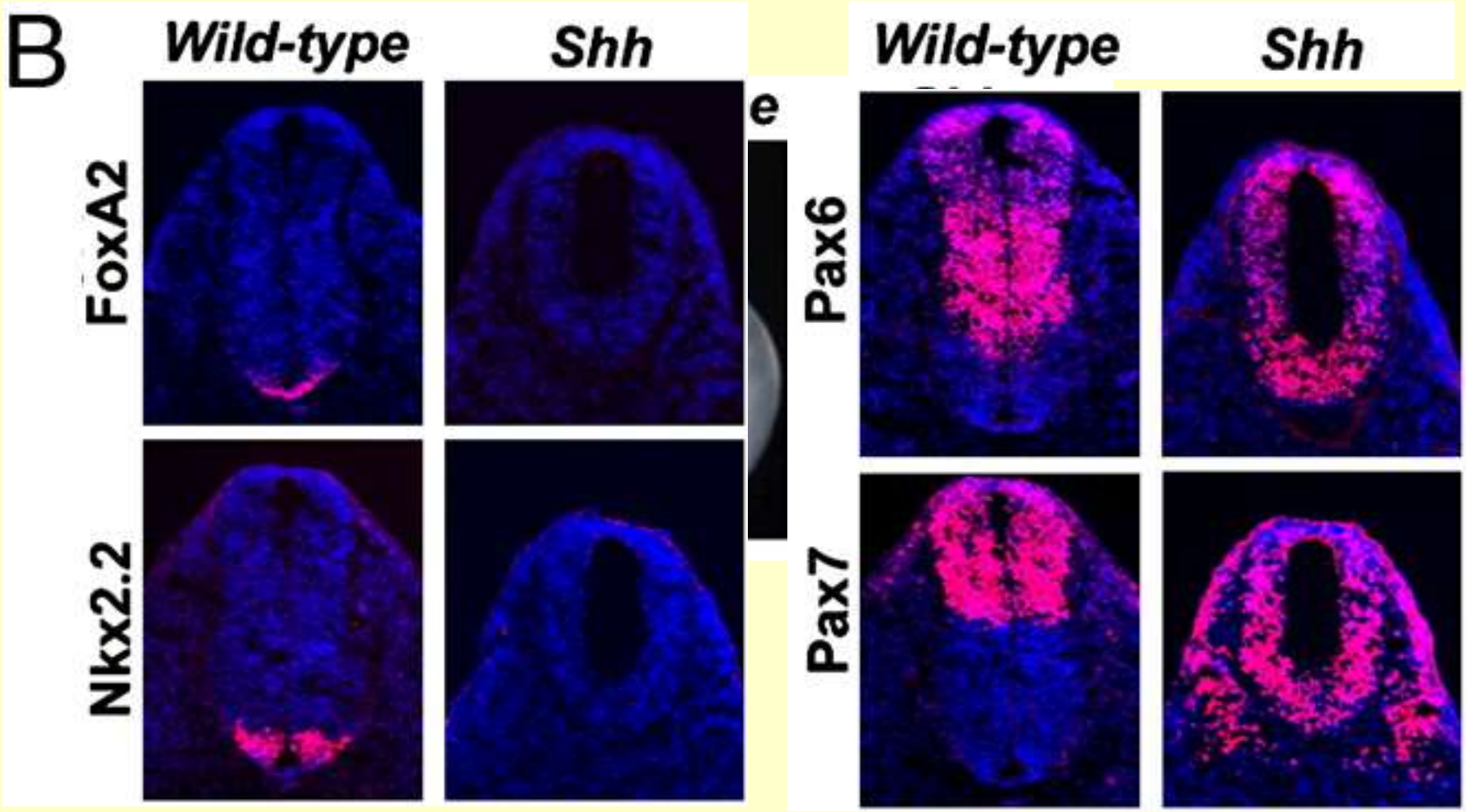
Pax6

Olig2

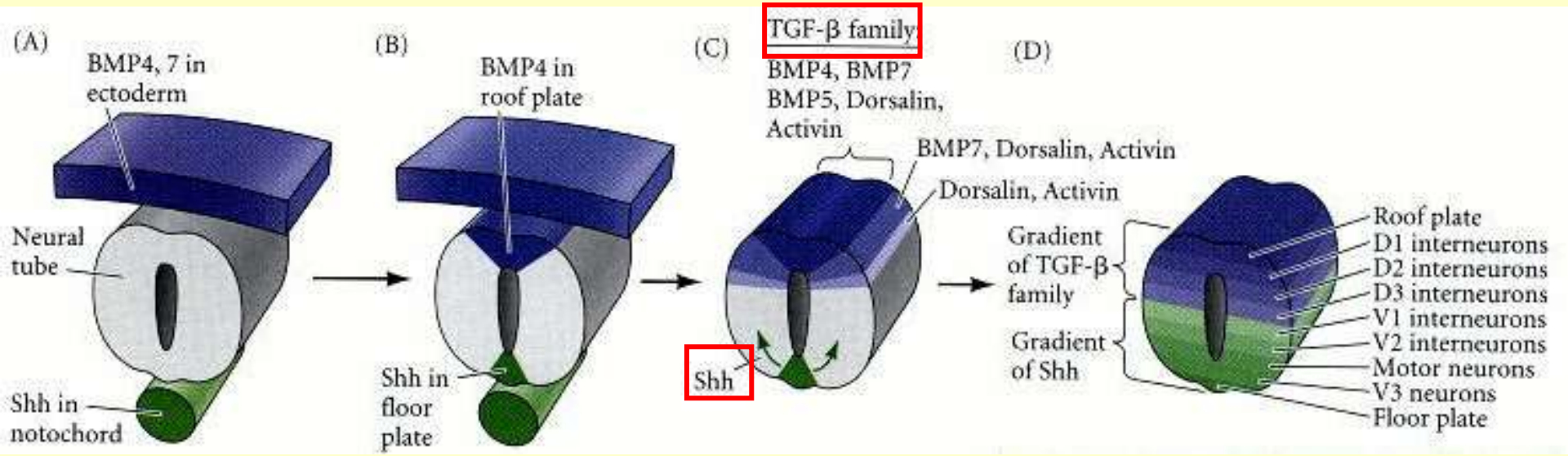
Nkx6.1

How does DV patterning form in neural tube?

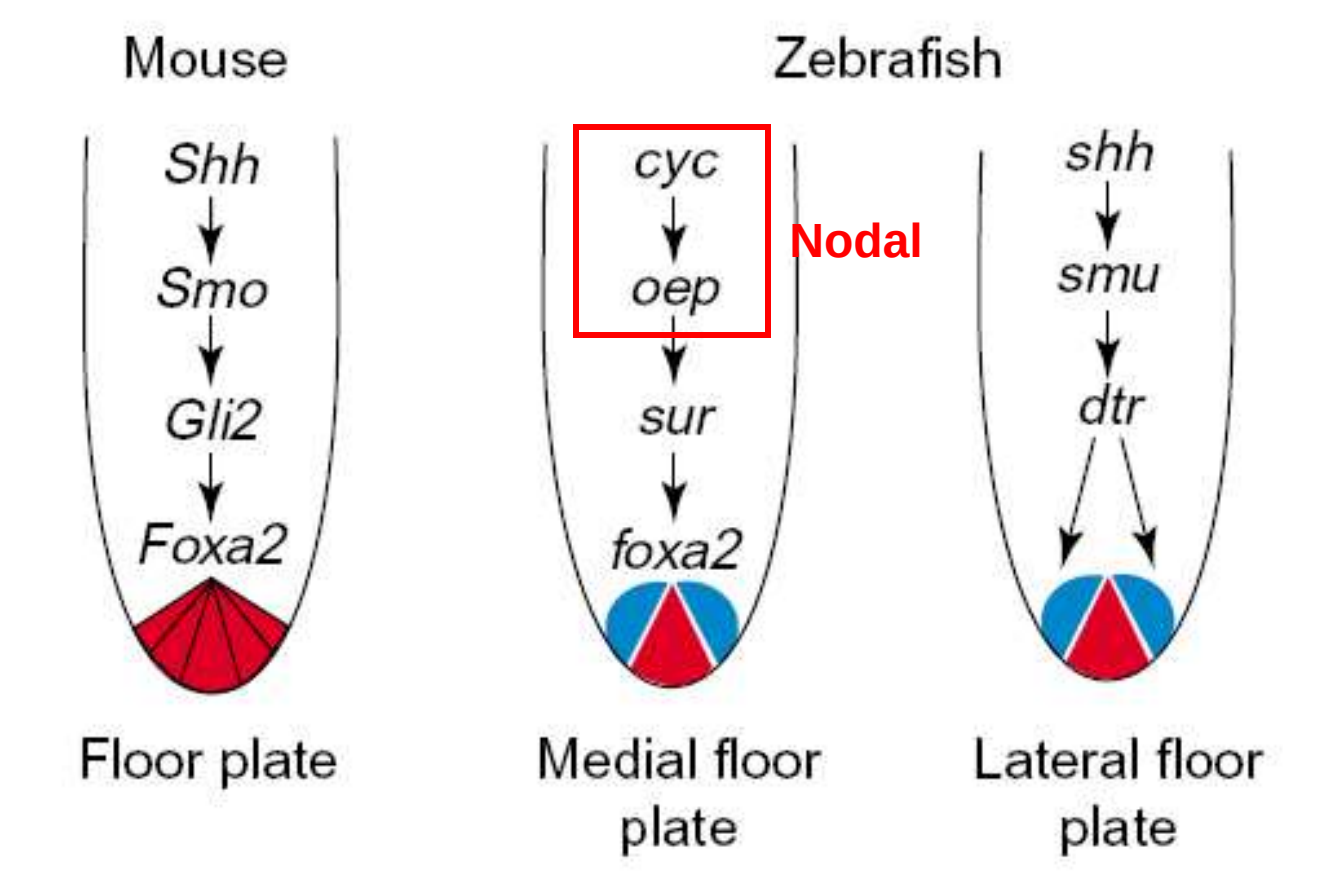
Shh is required for ventral neural cells



DV patterning of neural tube in chick embryos is controled by shh & TGF-β

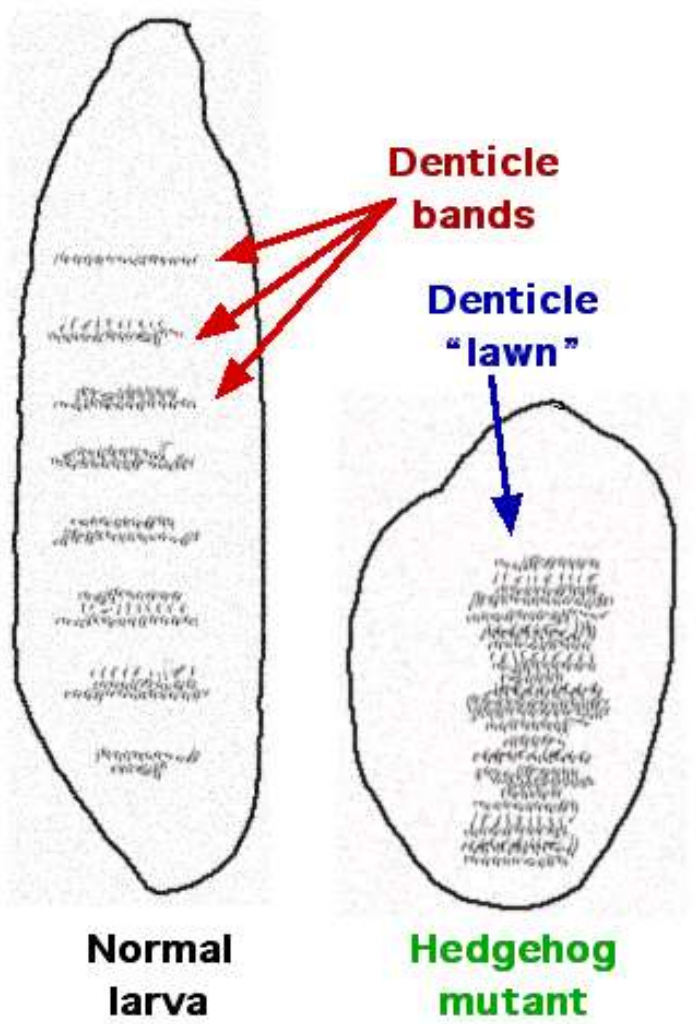


Floor plate patterning in zebrafish is controled by both Nodal and Shh signal



Strahle et al, 2004

Shh



a blue 15-year old anthropomorphic hedgehog
run at supersonic speeds
curl into a ball primarily to attack enemies

Neural tube differenciation: anterior-posterior patterning

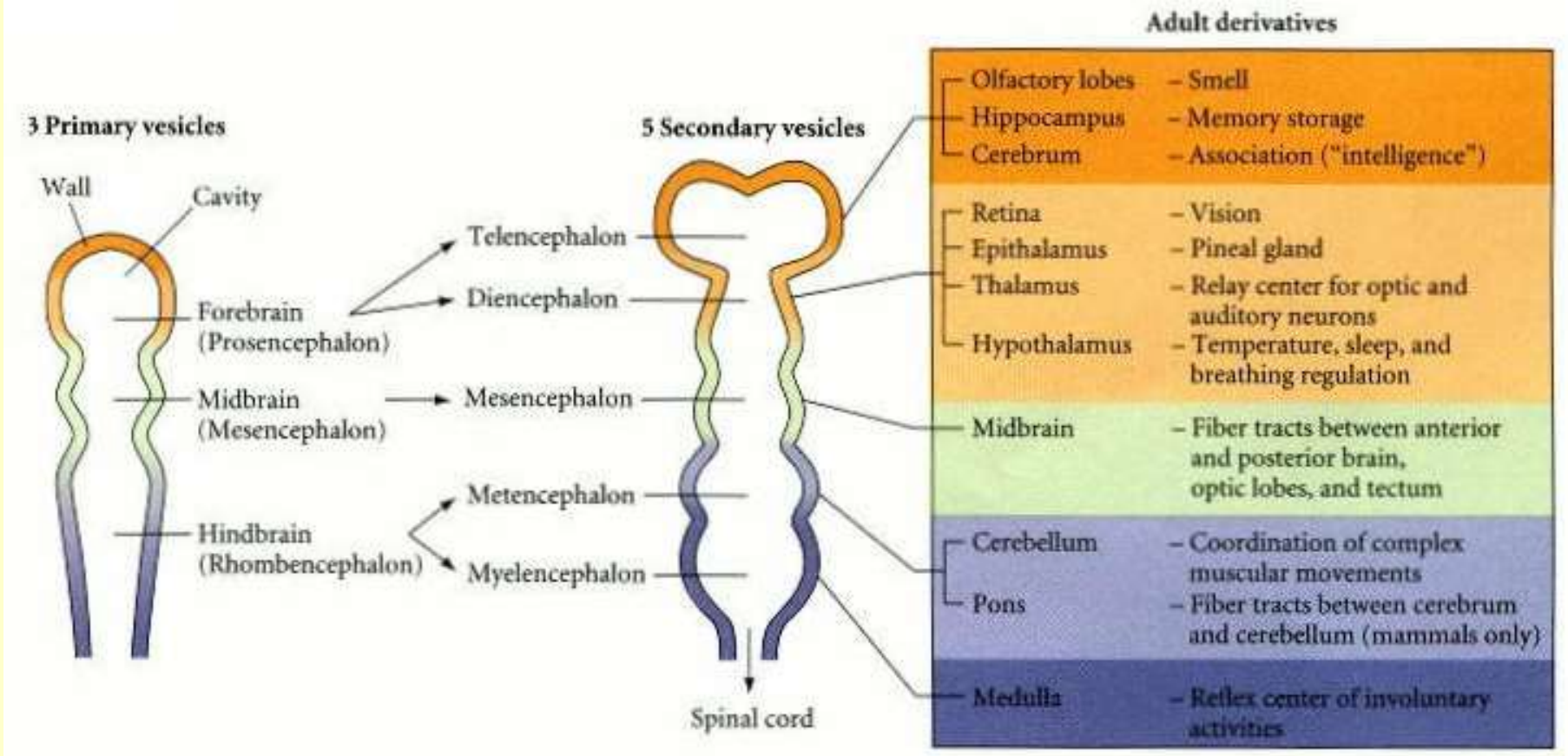
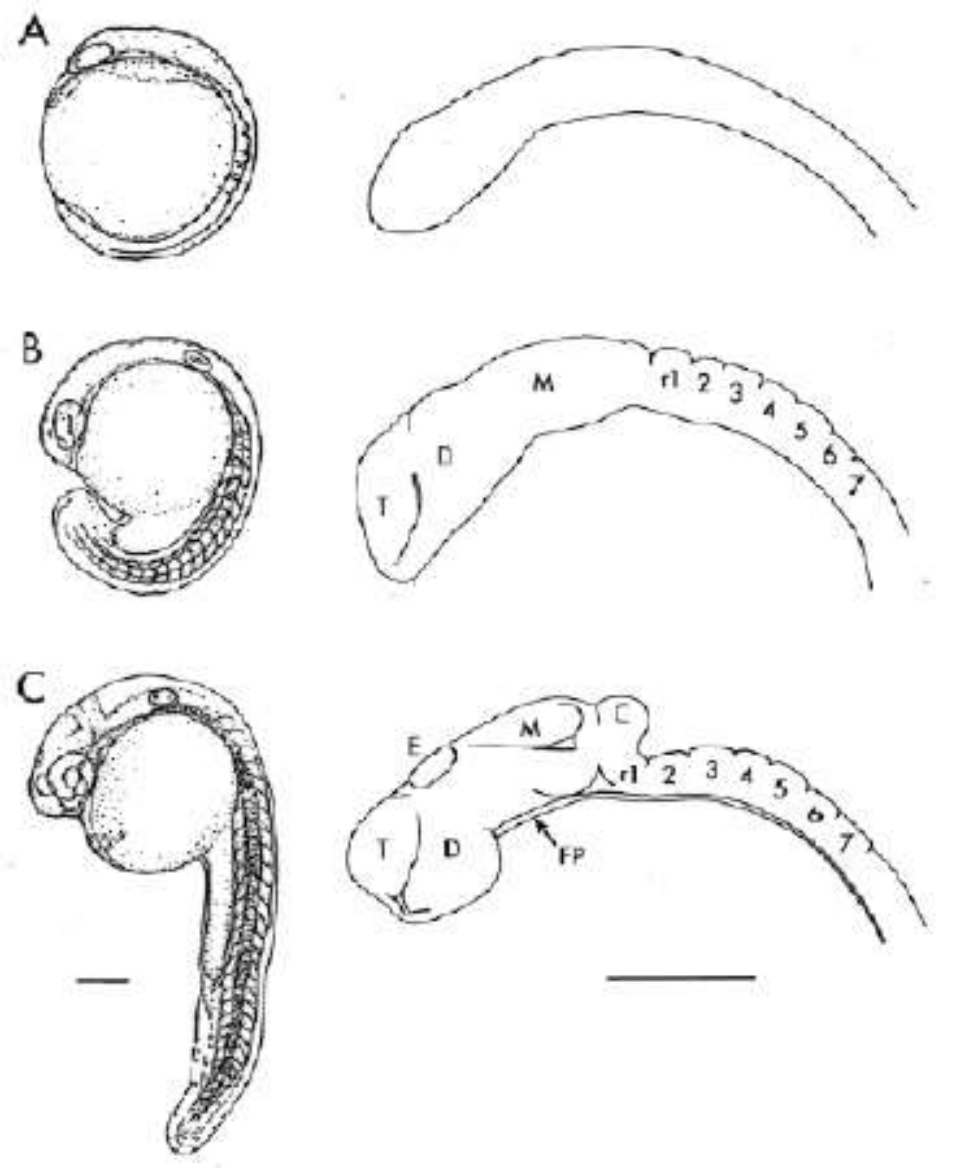


Figure 12.10. Early human brain development. The three primary brain vesicles are subdivided as development continues. At the right is a list of the adult derivatives formed by the walls and cavities of the brain. (After Moore and Persaud 1993.)

Zebrafish brain development



Summary (I)

- Key word:

  primary & secondary neurulation, Shh

- Event and mechanism

  neural tube formation, neural tube patterning

outline

- Ectoderm

  1) neural tube formation and differentiation

  2) neural crest cells

  3) eye development

- Mesoderm

  1) paraxial mesoderm: somite

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- Endoderm

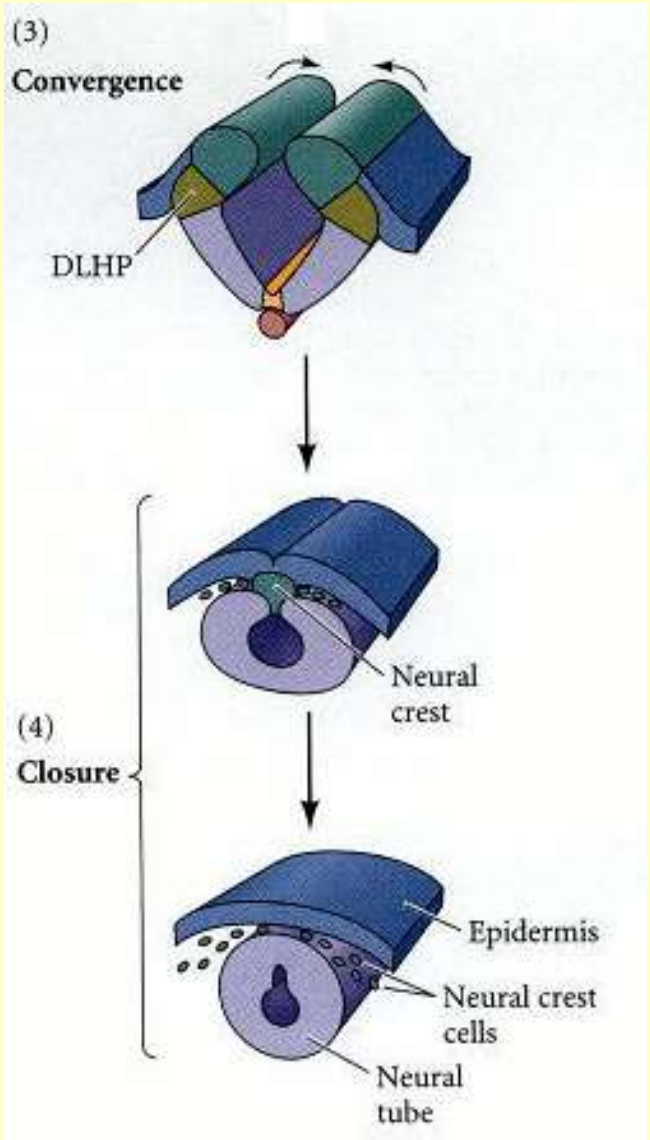
  gut

Neural crest cells (神经嵴细胞)

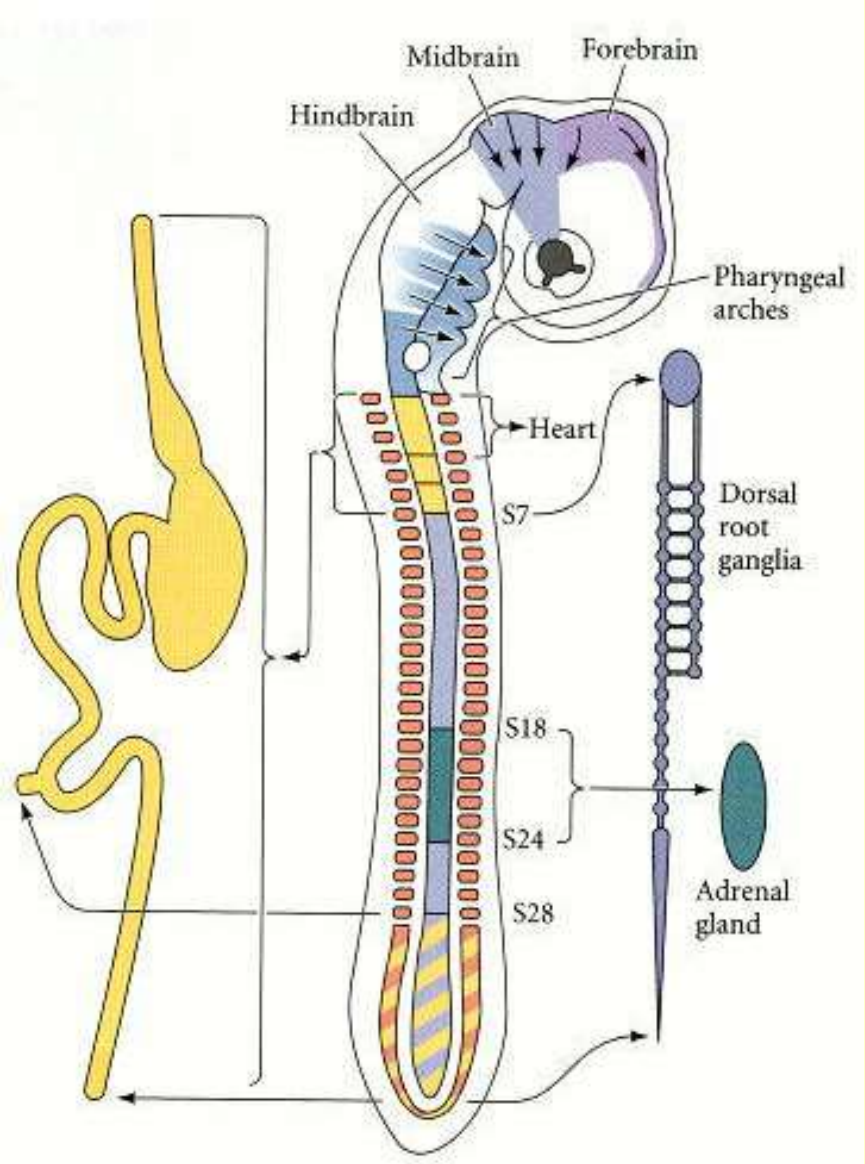
- Specification: at the neural plate-epidermis boundary.

- Feature:
- Migration.
- Multipotency: can differentiate into different type of cells depending on the location.

Neural crest cell formation

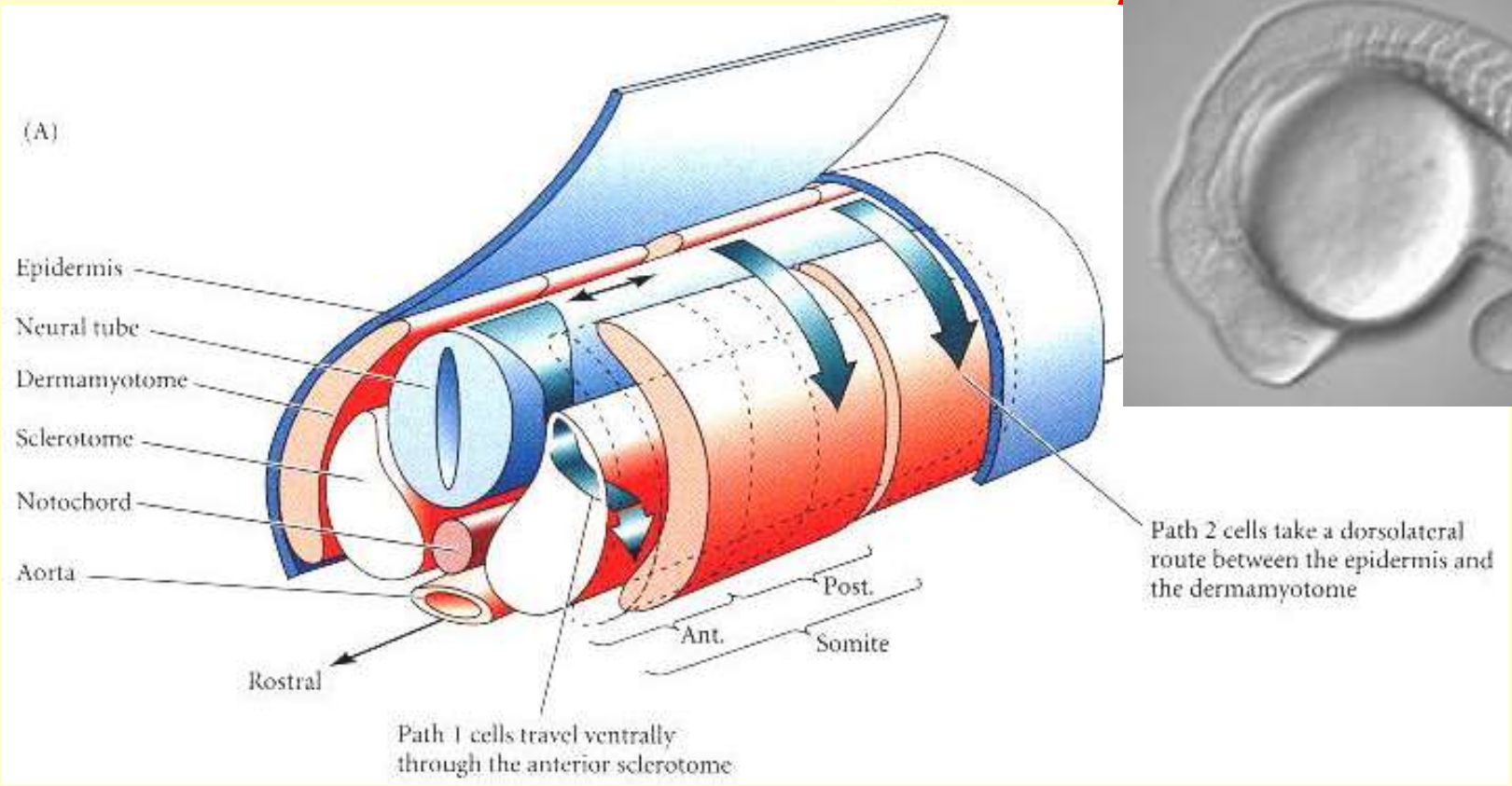


Regions of neural crest



1. cranial（面部）neural crest:→ cranial cartilage (面部软骨), bone, neurons, glia, etc；
2. trunk（躯干）neural crest: → dorsal root ganglia (背部神经节), melanocytes (色素)；
3. vagal (迷走神经) and sacral (骶骨) neural crest: →parasympathetic ganglia (副交感神经) of the gut
4. cardiac（心）neural crest: subregion of the vagal neural crest (交感神经嵴的一部分)，→ melano- cytes, neurons, cartilage, connective tissue (结缔组织)

neural crest cell Migration in trunk of the chick embryo



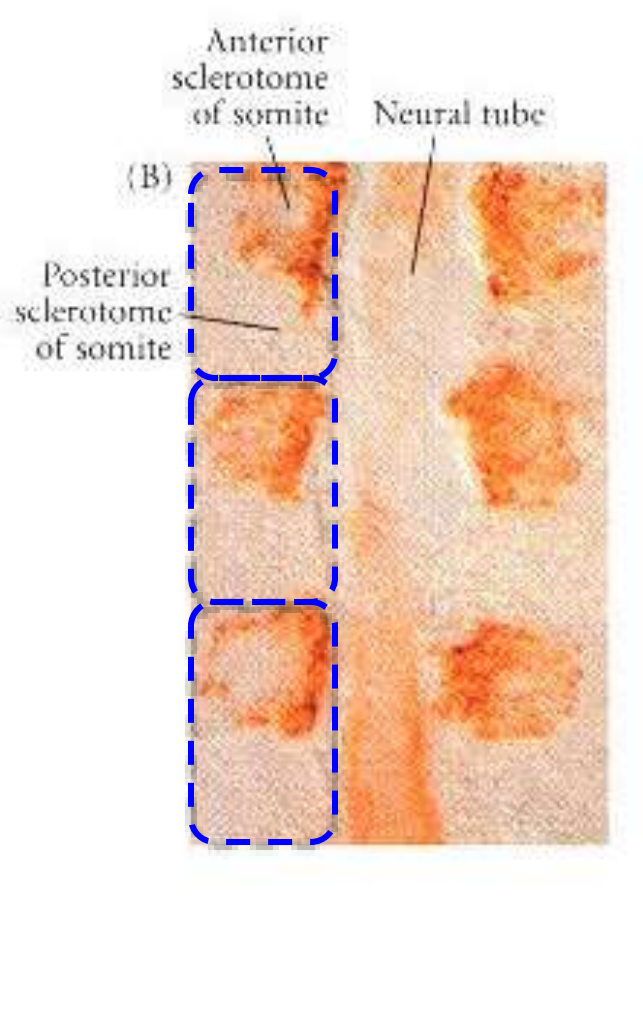
Two major migratory pathways：

The ventral pathway: travel through anterior part of the sclerotome (生骨节).

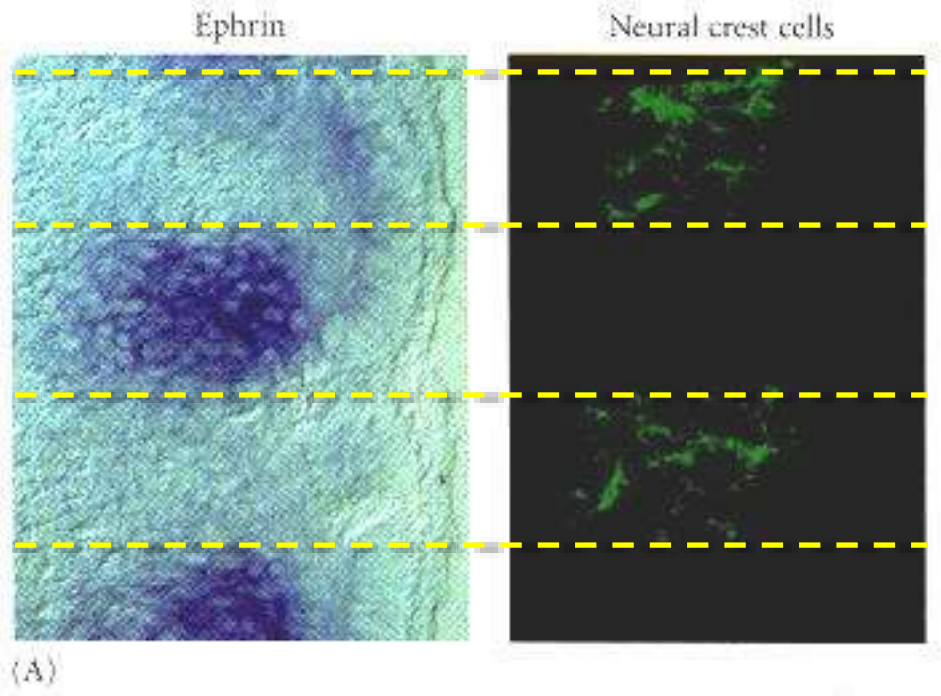
→ sympathetic and parasympathetic ganglia, dorsal root ganglia.

The dorsolateral pathway：travel along the dorsolateral region between epidermis and dermamyotome (生肌节). → melanocytes.

Neural crest cells only migrate through anterior part of the somite



Segmental restriction of neurons by ephrin proteins



Summary (II)

- Key word:
  neural crest cells

- Event and mechanism
  neural crest cells formation, migration

outline

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outline

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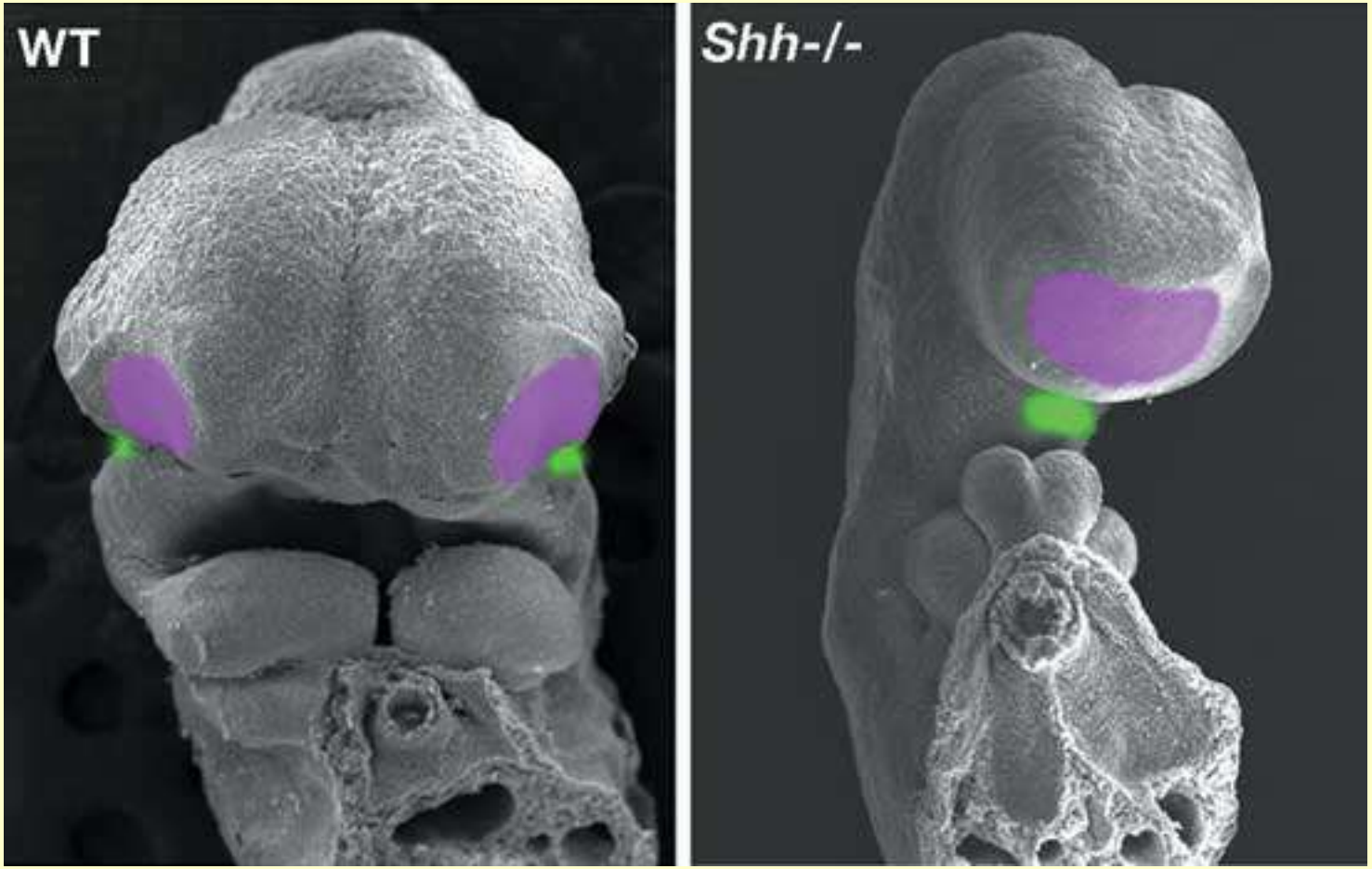
- Endoderm

  gut

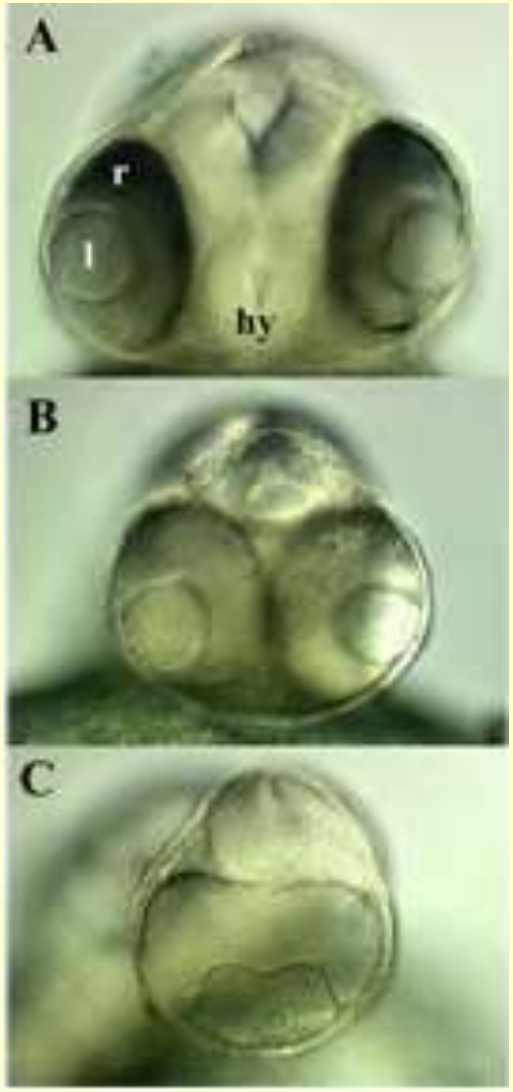
Cyclolamb and cyclopamine

Corn lily (玉米百合)

Mouse cyclopic mutant



Zebrafish cyclopic mutant

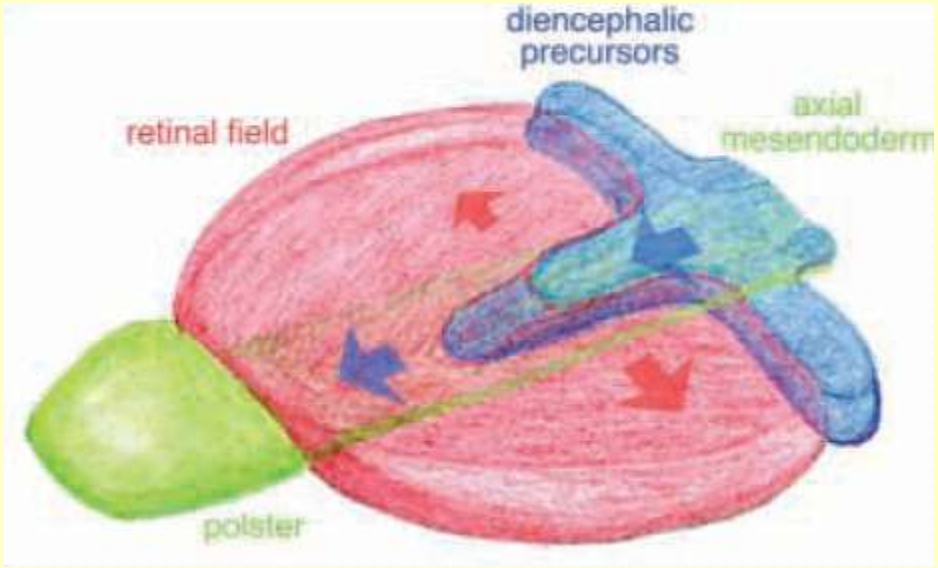


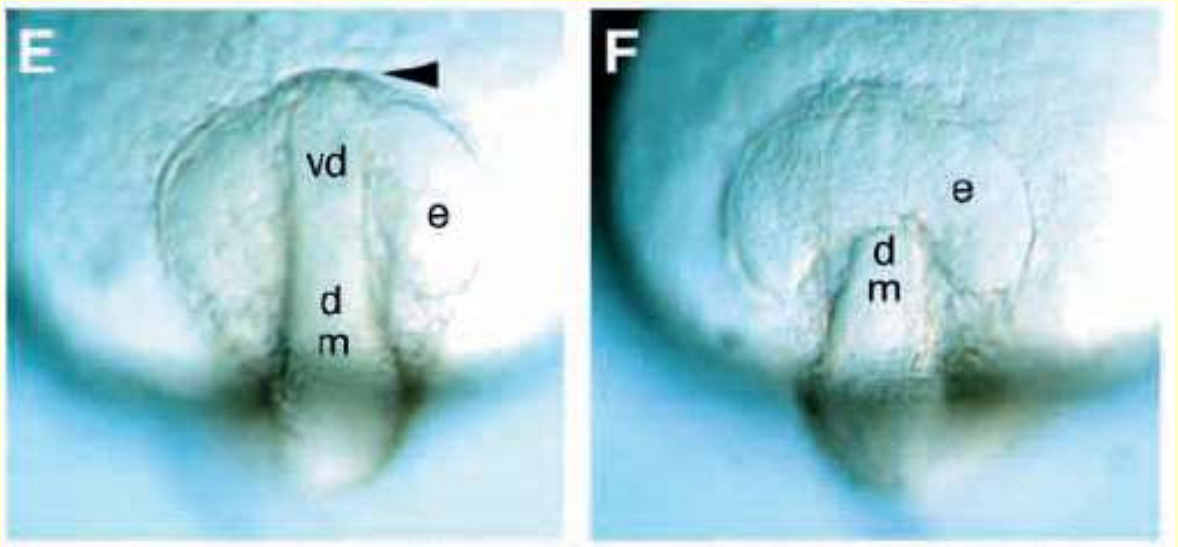
WT

Nodal mutant
(i.e., cyc, sqt, oep)

http://www.ucl.ac.uk/zebrafish-group/research/forebrain.php

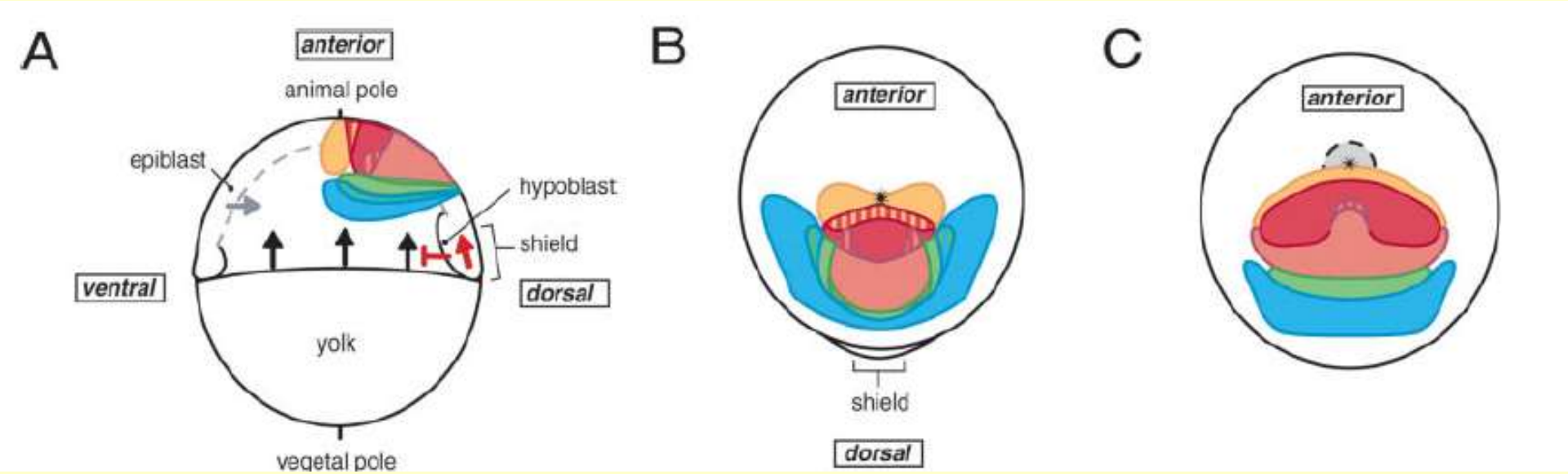
Seperation of the eye field in zebrafish

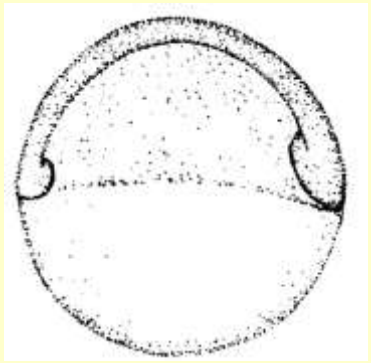


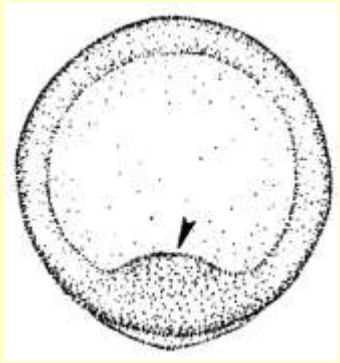


Varga et al, 1999

Seperation of the eye field in zebrafish

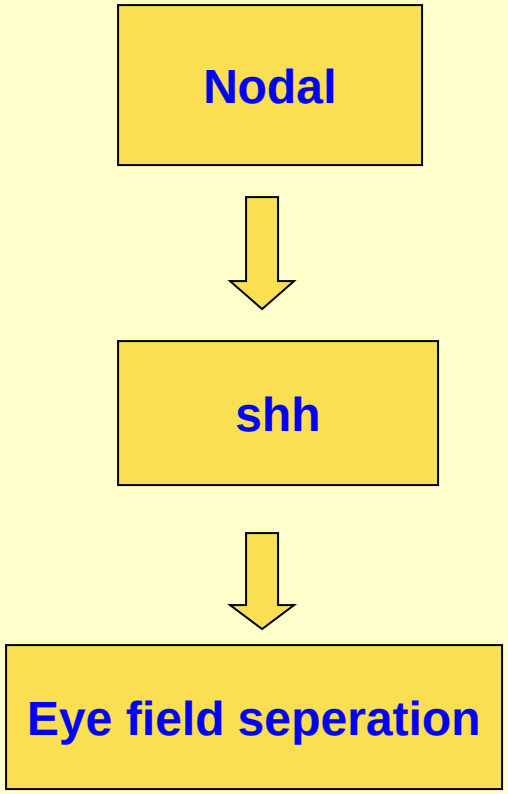




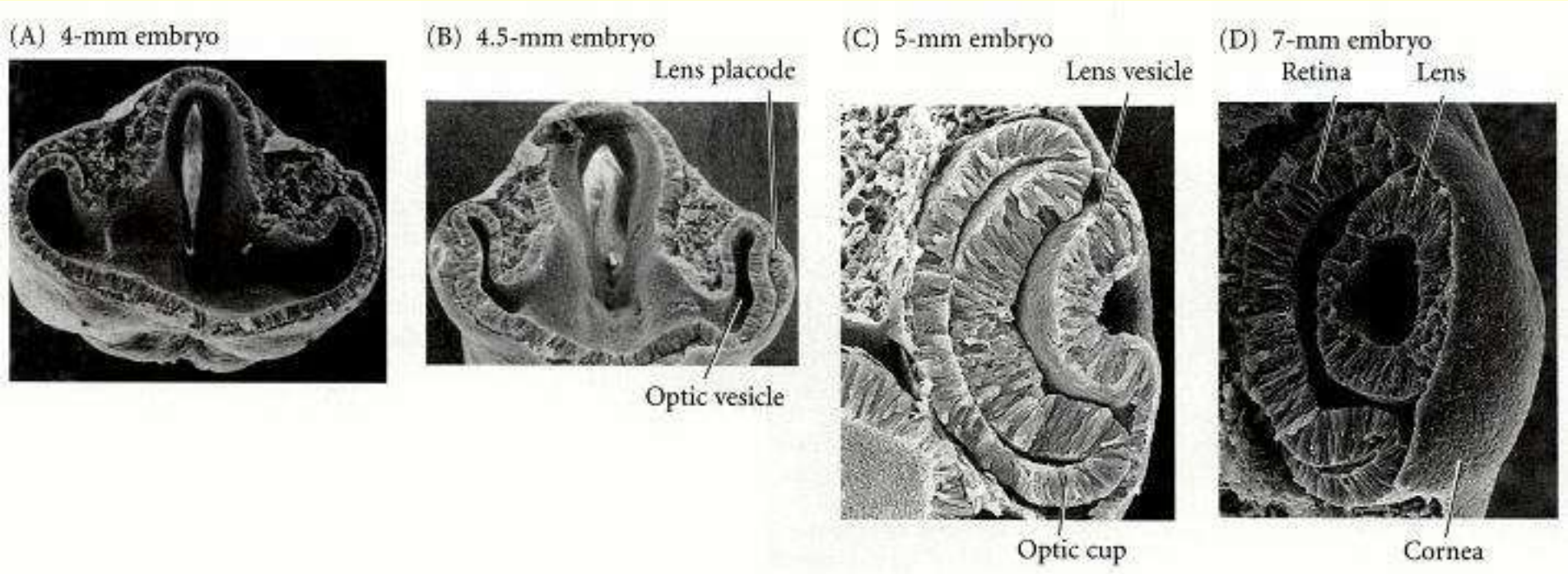


Chuang et al, 2002

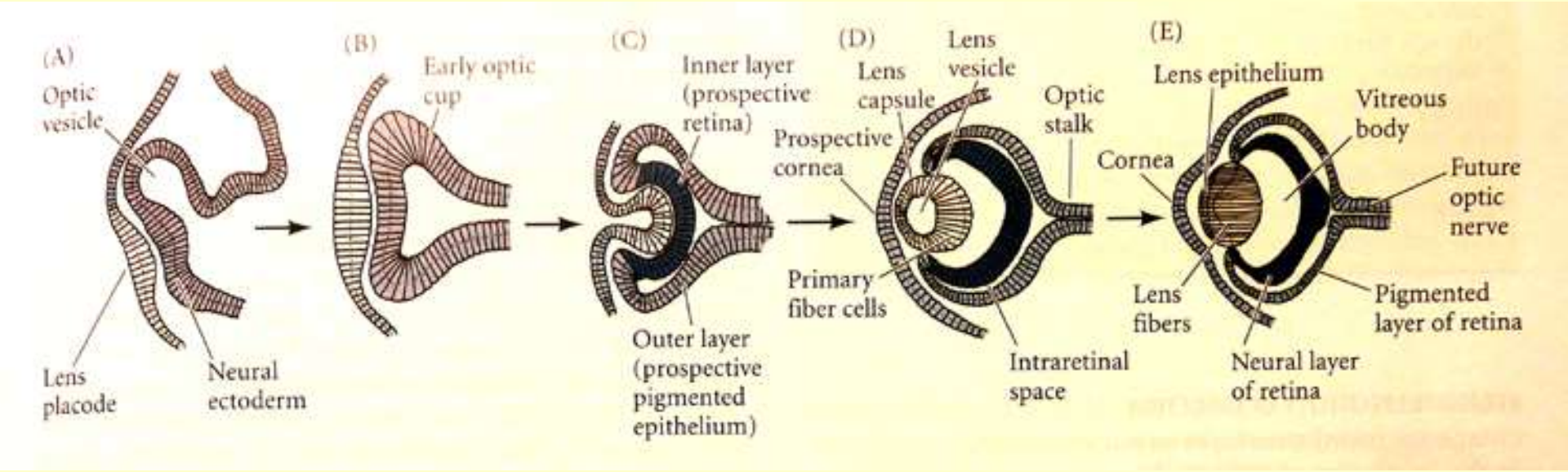
Seperation of eye field requires Shh and Nodal signal



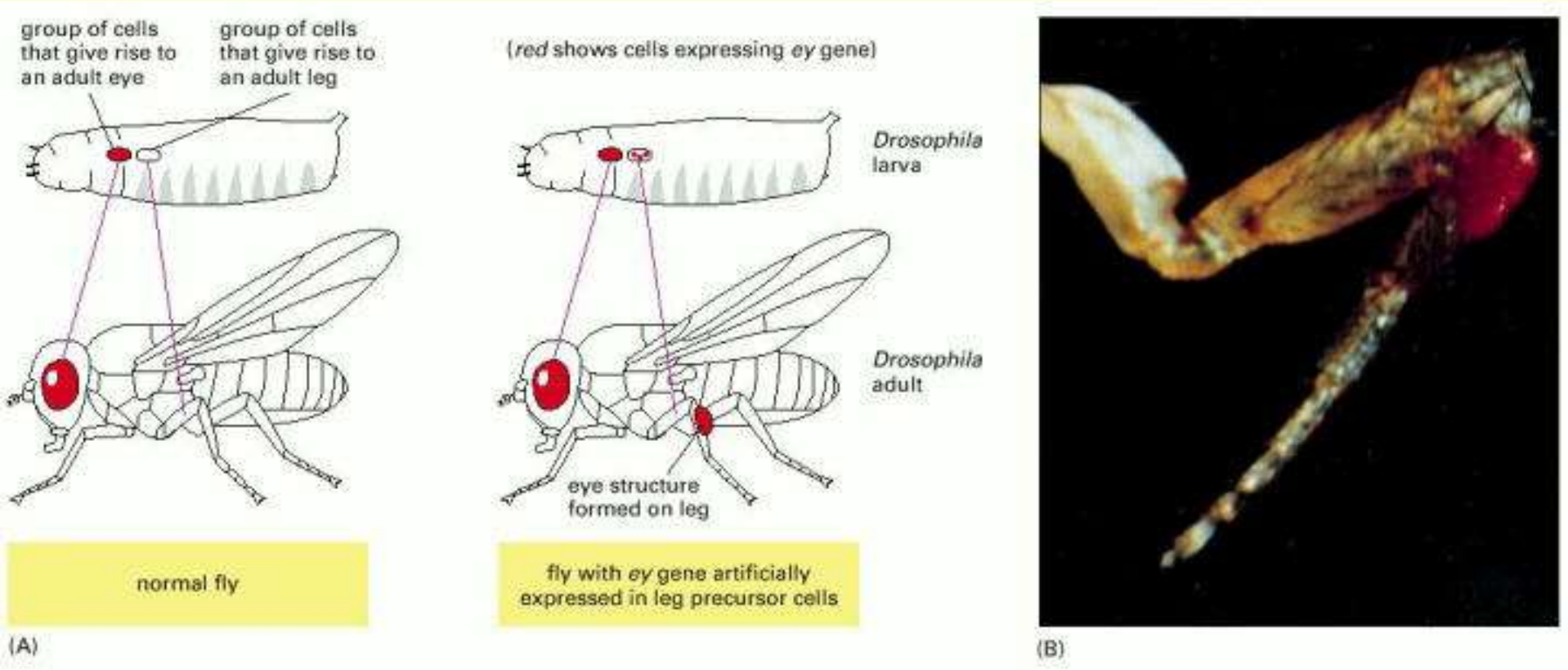
Development of vertebrate eye



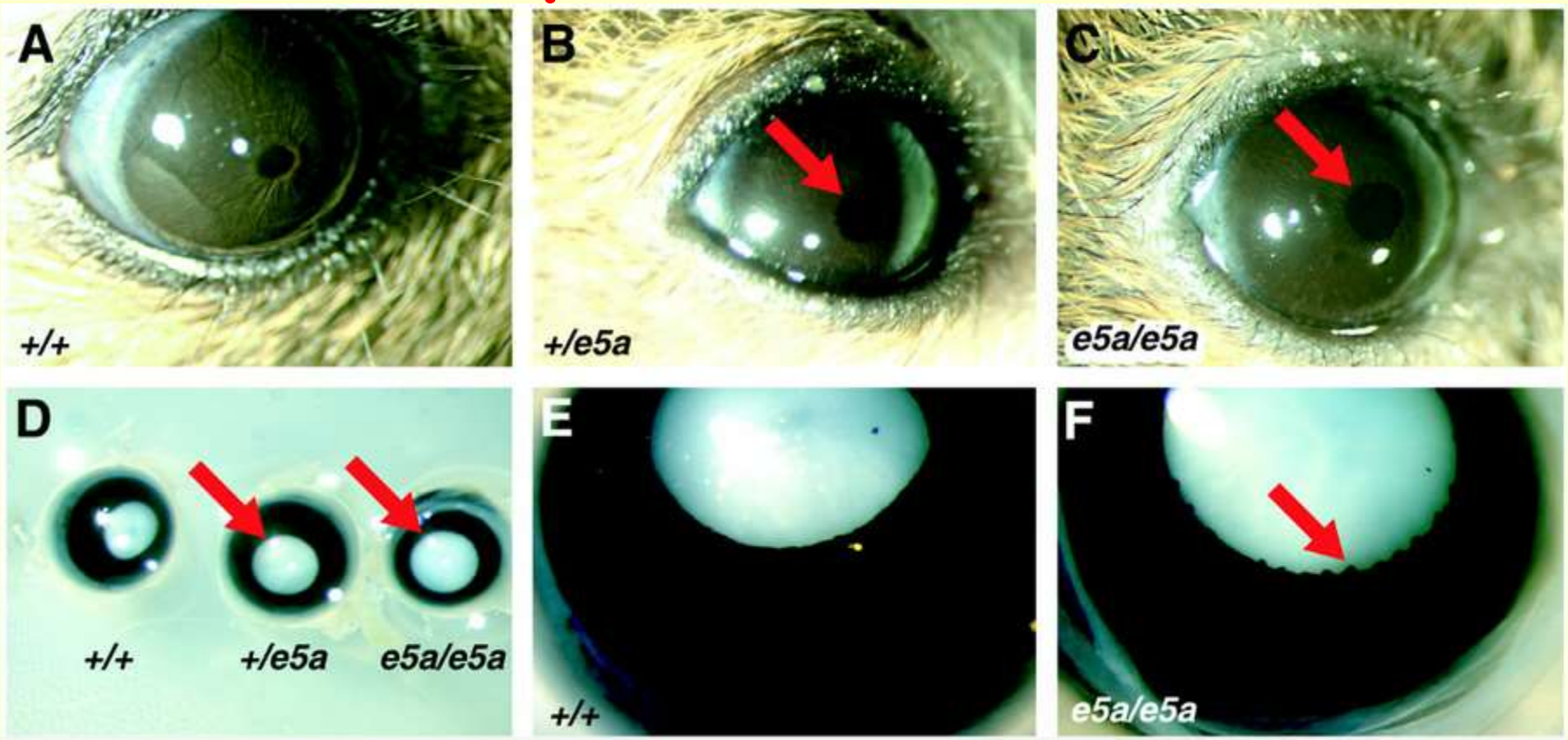
Lens induction



ey/pax6 can ectopically induce eye formation



Pax6 is also important for eye development in mammals



A-C: Eyes of adult wild type (left), $Pax6^{tm1Gfs}/Pax6^{+}$ (center), and $Pax6^{tm1Gfs}/Pax6^{tm1Gfs}$ (right) mice. Arrow indicates hypoplasia of the iris with a larger pupil. D: eyes of adult mice after fixation. Black: iris ; white: lens. Arrow: iris hypoplasia. E & F: a homozygous mouse eye (F) showing an irregular iris (arrow) in the pupil region.

Summary (III)

- Key word:

  eye field, shh, nodal, lens
- Event and mechanism

  eye field seperation, lens induction

outline

- Ectoderm

  1) neural tube formation and differentiation
  2) neural crest cells
  3) eye development

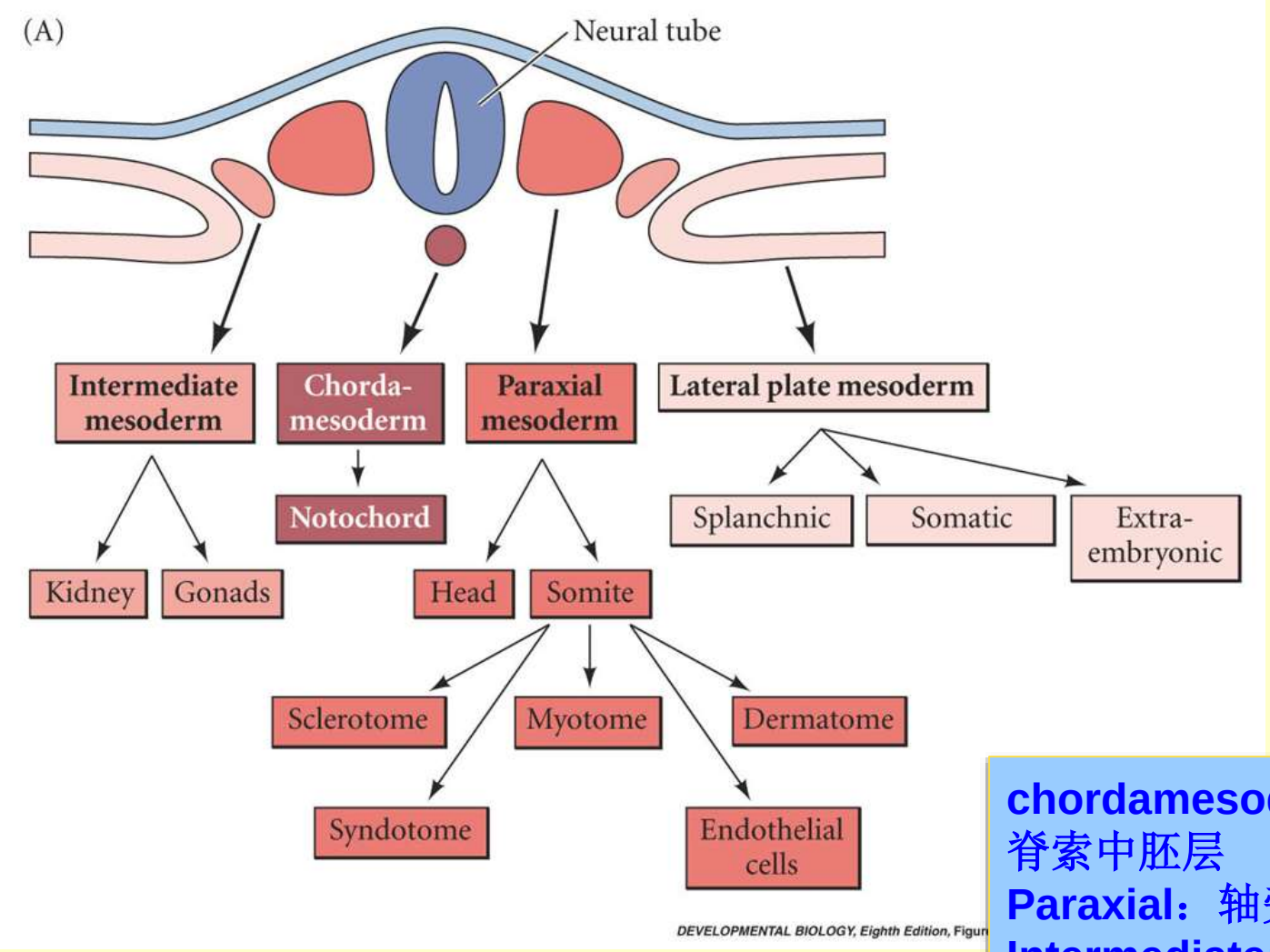
- Mesoderm

  1) paraxial mesoderm （轴旁中胚层）: somite
  2) intermediate （中间）mesoderm : urogenital（泌尿生殖） system
  3) lateral plate （侧板）mesoderm: heart, blood vessels, blood cells

- Endoderm

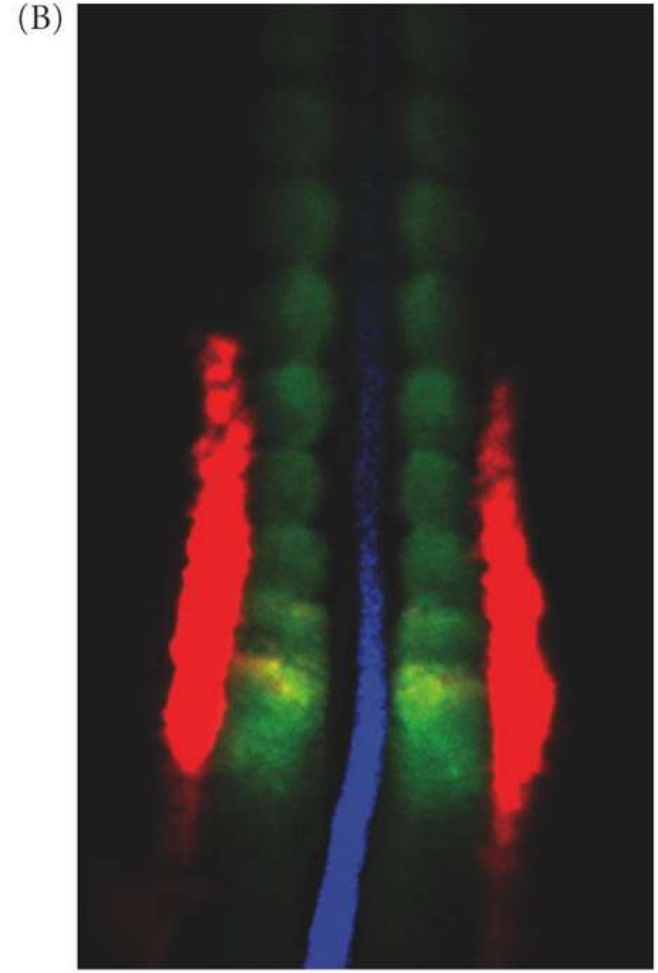
  gut

Mesoderm derivatives (I)



chordamesoderm: 脊索中胚层
Paraxial： 轴旁
Intermediate: 中间
Lateral plate: 侧板

Mesoderm derivatives in chick embryo (II)

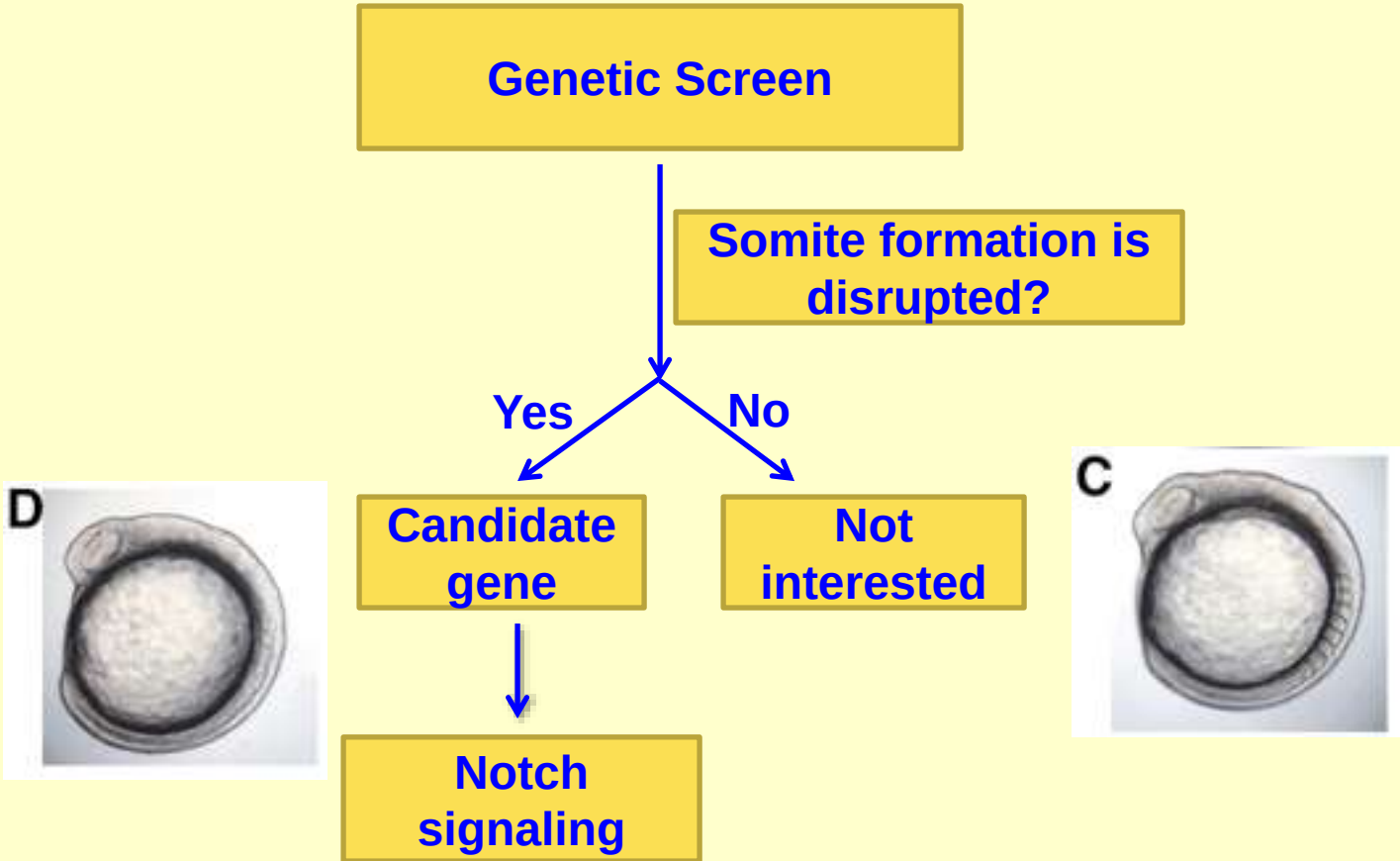


***chordin*: notochord （脊索）**
***paraxis*: somite （体节，轴旁中胚层）**
***pax2*: intermediate mesoderm （中间中胚层）**

Somitogenesis (体节发生) in zebrafish embryo

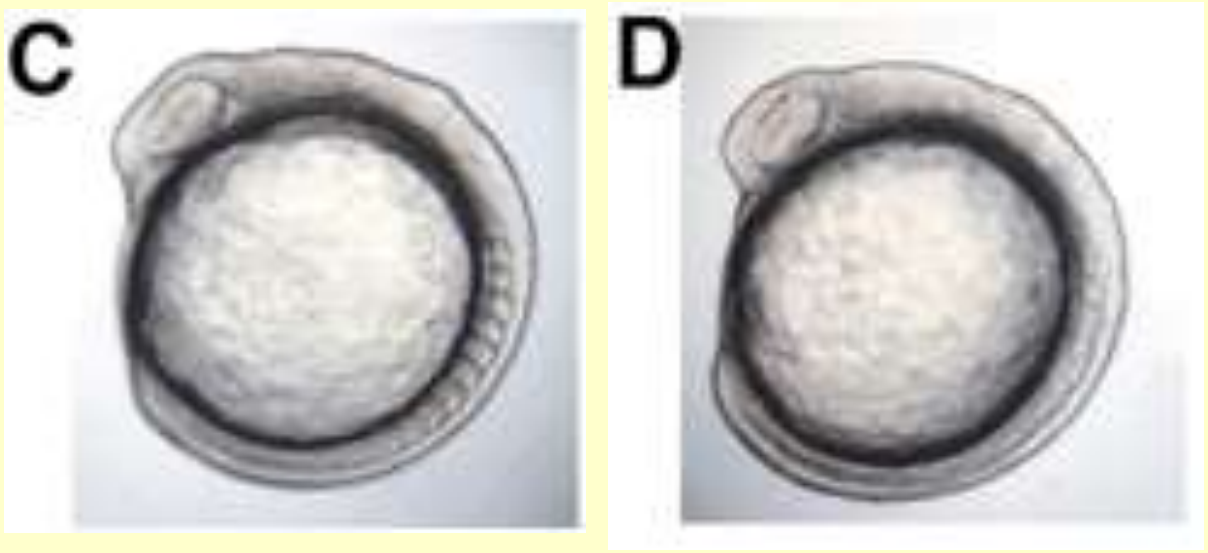
QuickTimePlayer.exe

- What's the mechanism of somitogenesis?

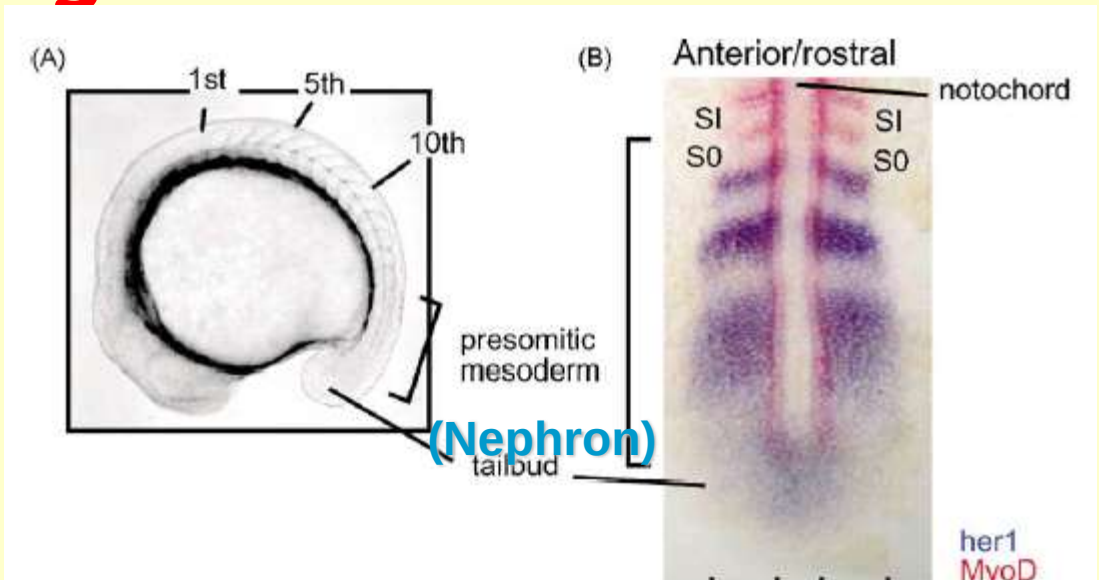


Somitogenesis is disrupted in *her1/her7* double mutant

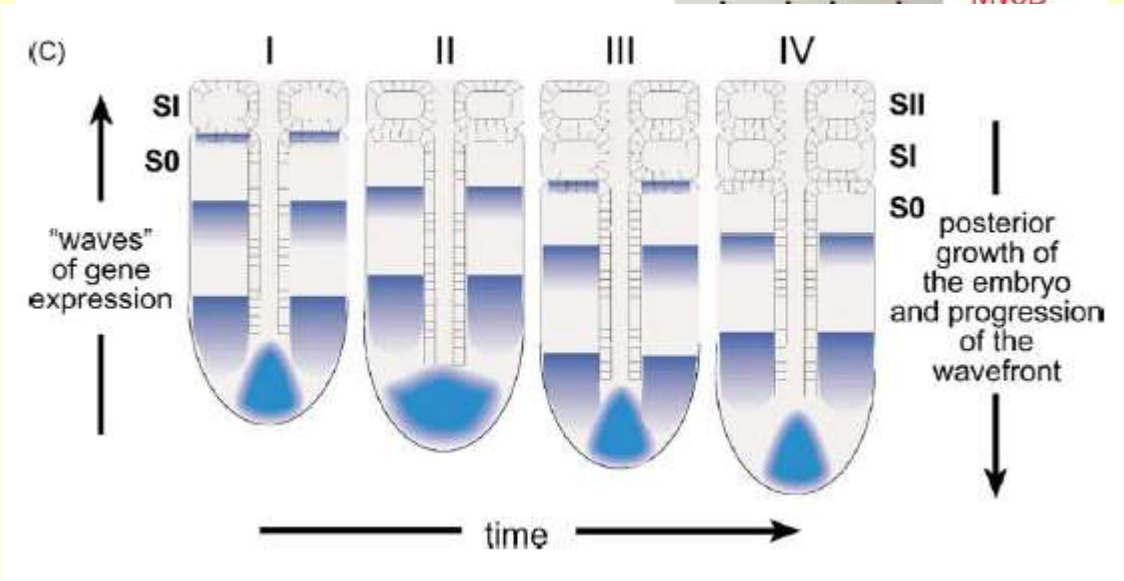
Ctrl	*her1/her7*



"Oscillation"（震荡）pattern of Somitogenesis in zebrafish embryo



(Nephron)



Holley et al, 2002

Notch signaling in wikipedia

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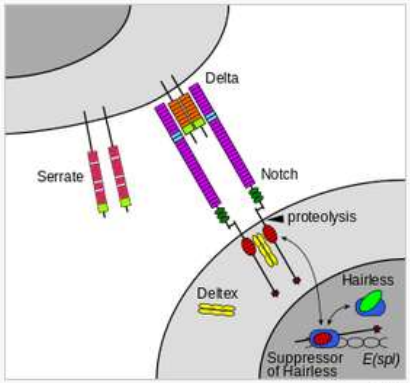
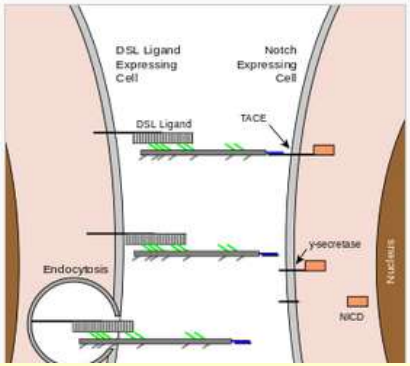


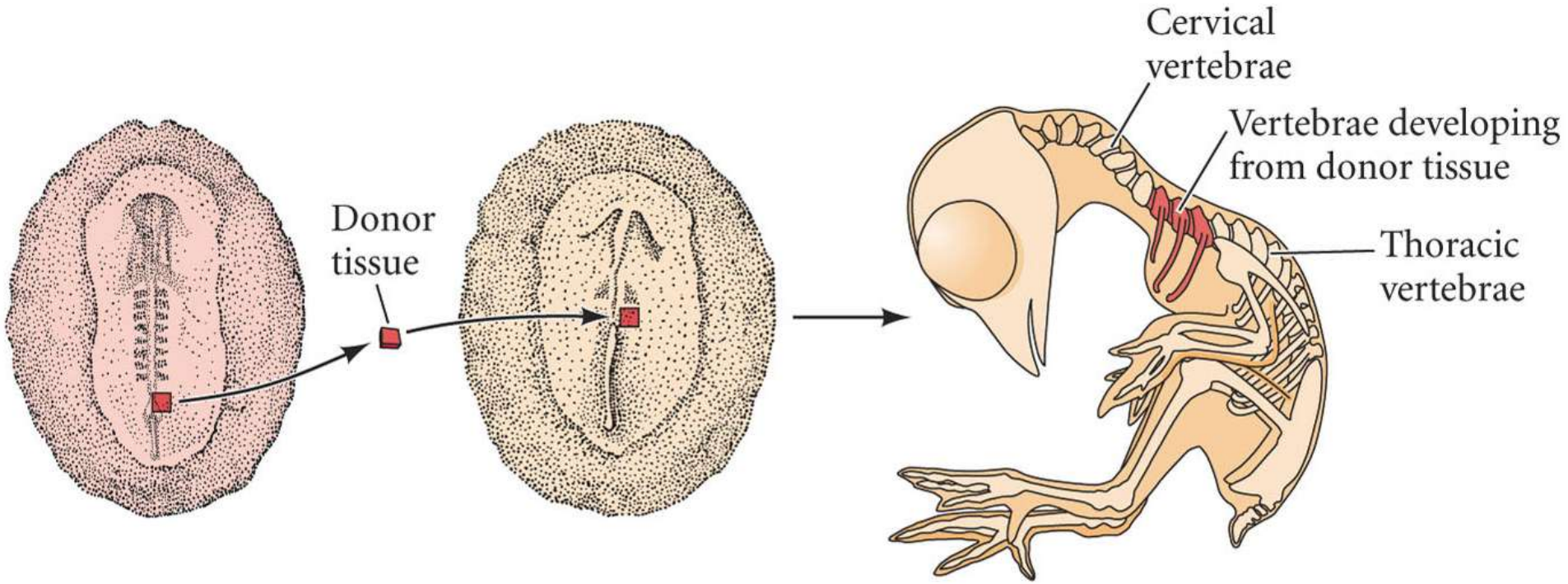
Notch-mediated juxtacrine signal between adjacent cells.



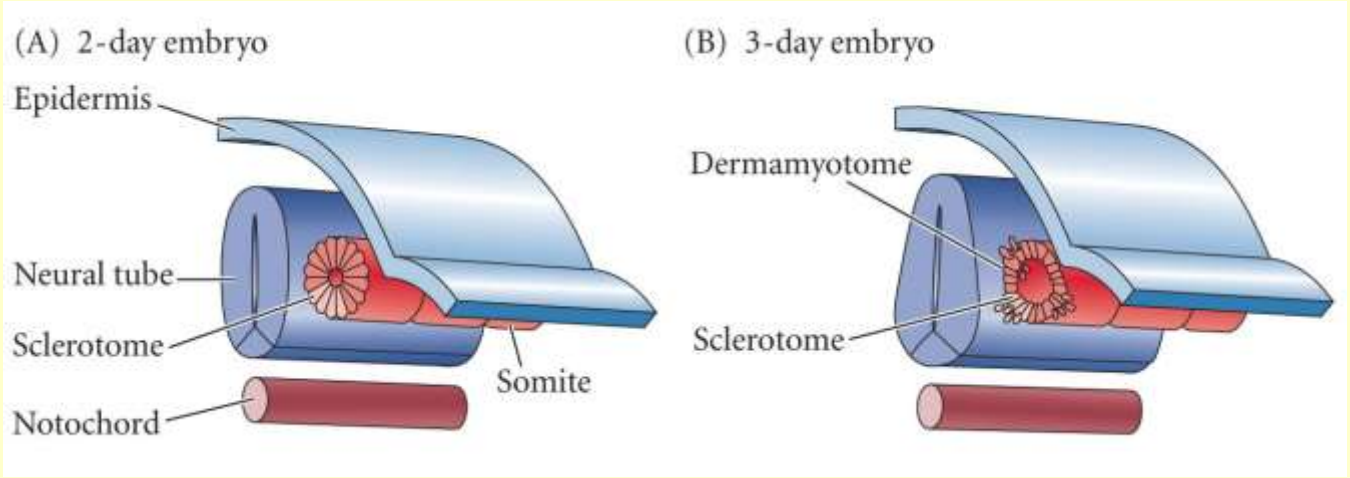
Patterning of somite

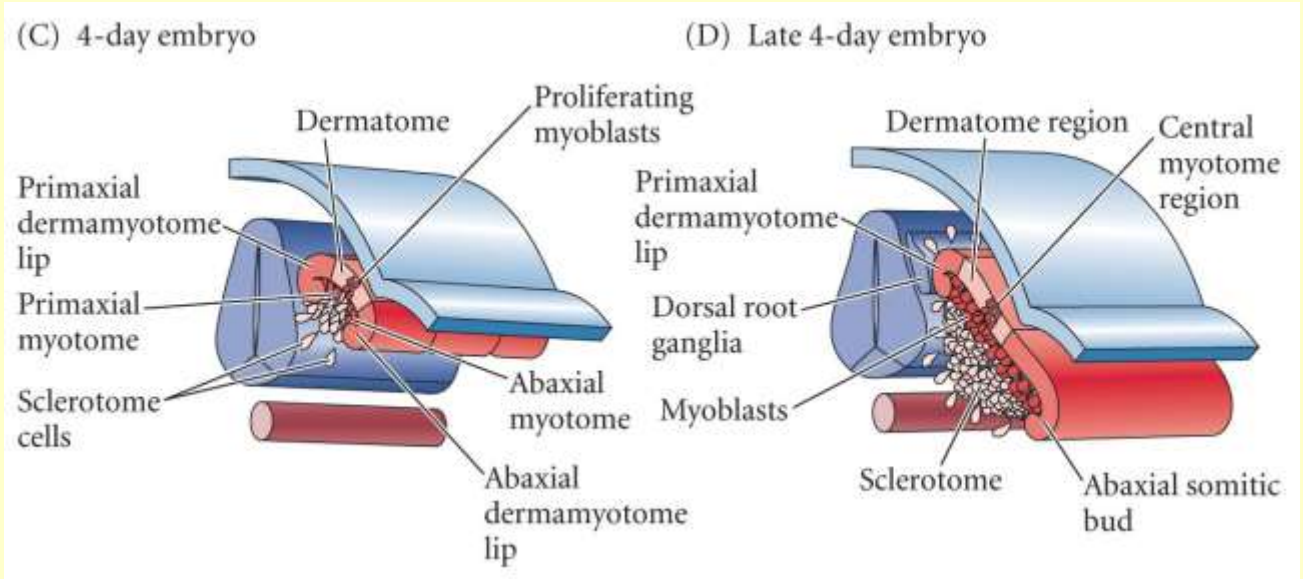
- Anterioposteria (AP, 前后) patterning
- Dorsoventral (DV, 背腹) patterning

AP patterning of somite



DV patterning of somite





Osteogenesis (骨的发生)

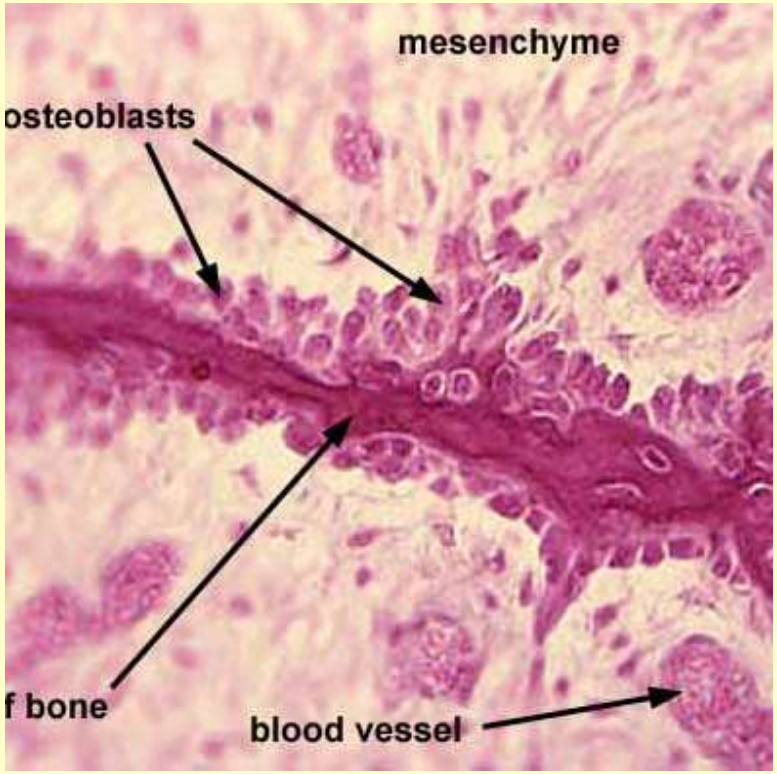
Three cell origins (生骨细胞的来源)：

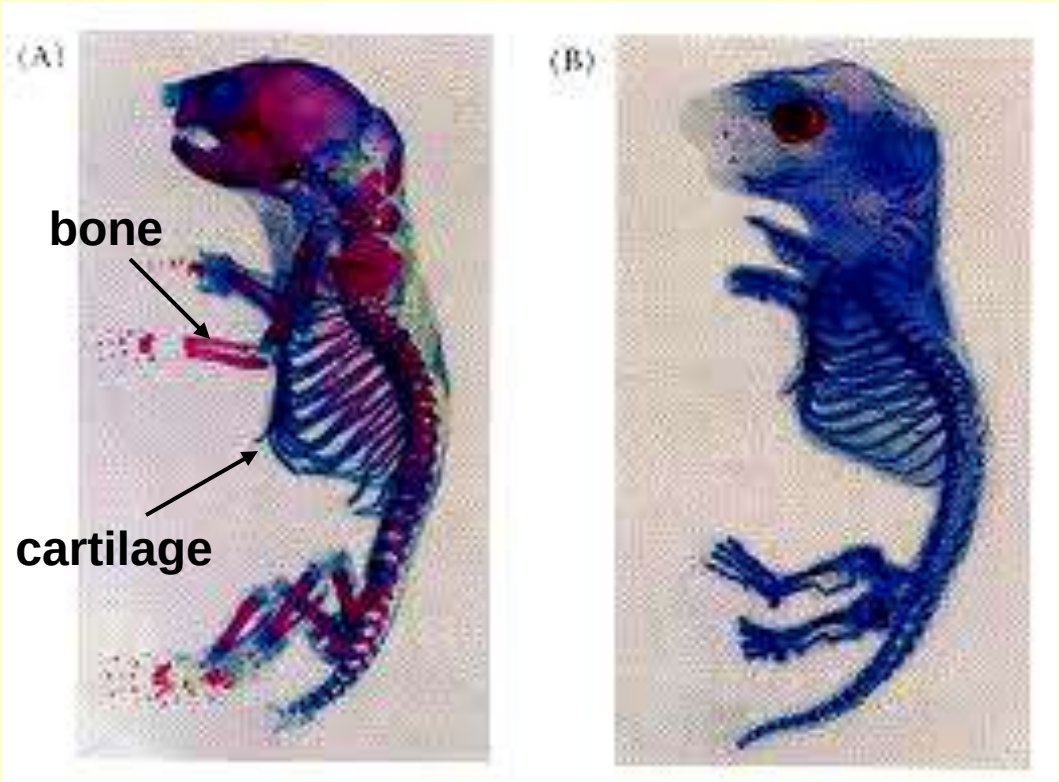
1. Somite (体节)：→ axial skeleton (背部骨骼, 肋骨)
2. Lateral plate (侧板中胚层)：→limb (肢体) skeleton
3. Neural crest cells (神经嵴细胞)：craniofacial bones and cartilage (颅面骨和软骨)

Two major modes of osteogenesis：

1. intramembrane ossification (膜内成骨): mesenchymal cells (间质细胞)→ bone
2. endochondral ossification (软骨内成骨): mesenchymal cells → cartilage (软骨) →bone

Intramembranous (膜内) vs Chondrondral (软骨) Ossification





***Cbfa1*: is required for process of cartilage (软骨) → bone**

BMP promote bone formation

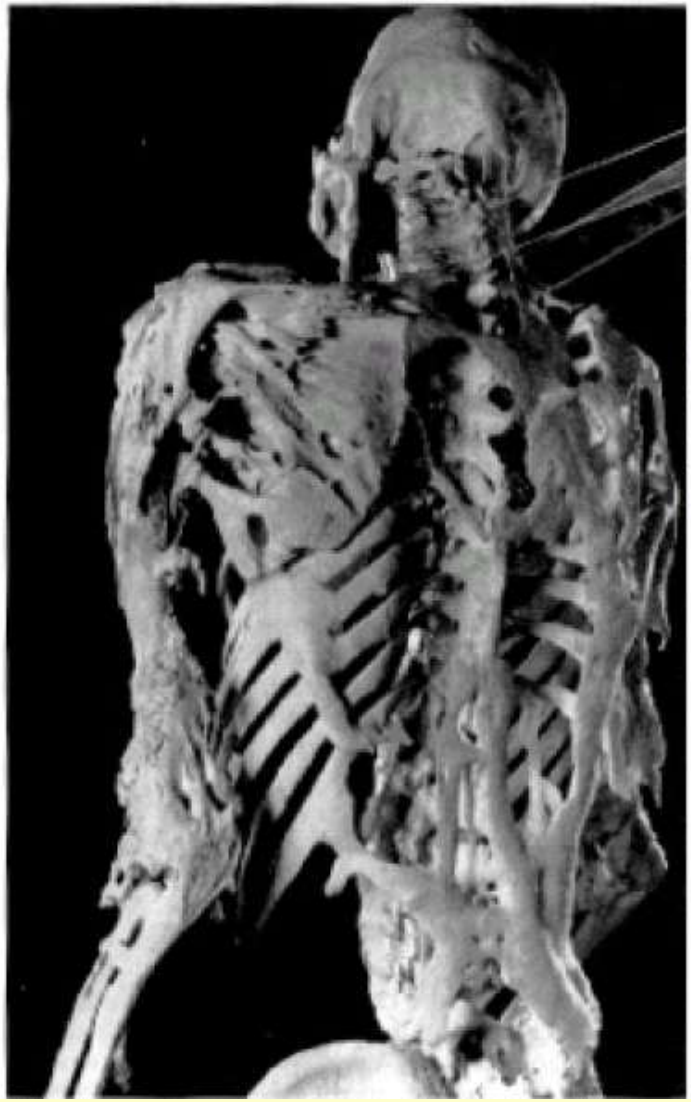


Figure 2. Skeleton of a 40-year-old man who died from pneumonia secondary to fibrodysplasia ossificans progressiva. Plates and ribbonsof ectopic bone can be seen throughout the body. It has been found that overexpression of BMP4 in lymphocytes may be responsible for such diseases.

Bone Morphogenetic Protein (BMP)

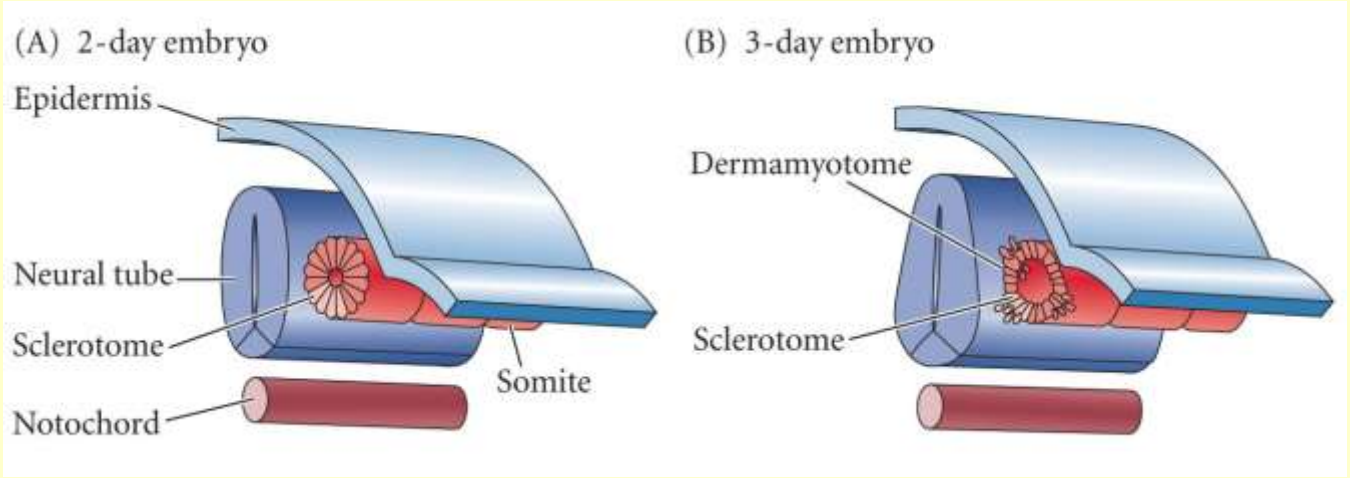
- From the time of Hippocrates (
，古希腊的名医) it has been kn
bone has considerable potentia
regeneration and repair.

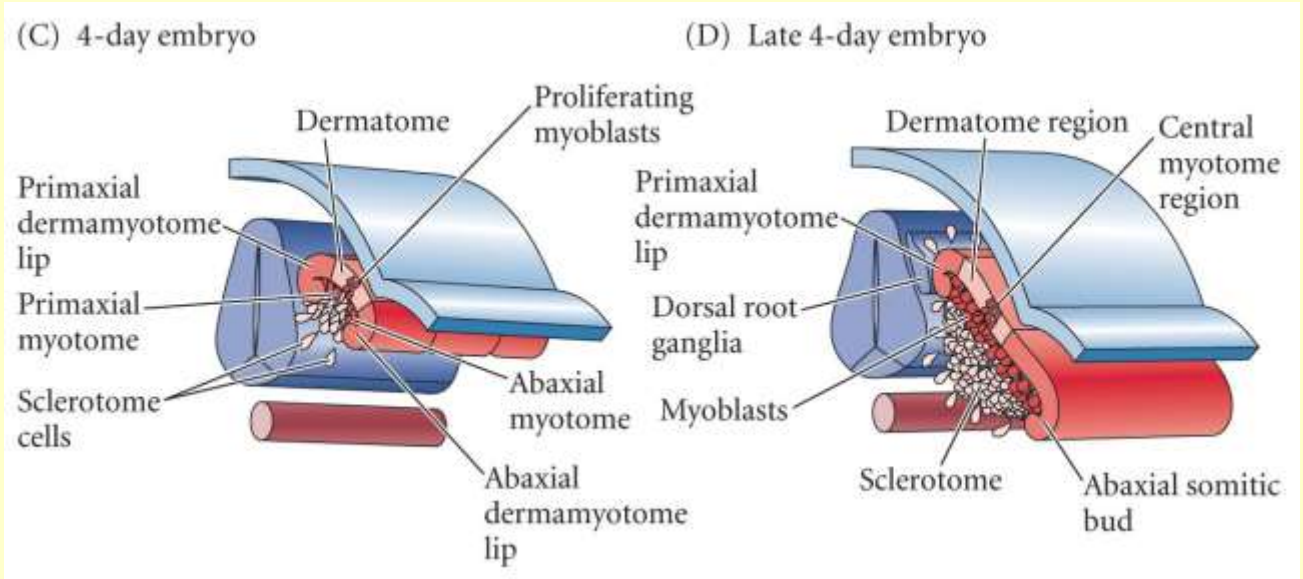
- Senn, a surgeon at Rush Medi
in Chicago, described the utility of bone implants in the treatment of osteomyelitis (骨髓炎骨) and certain bone deformities.

Bone Morphogenetic Protein (BMP)

- Marshall Urist (1914-2001) made the key discovery that demineralized (去除矿物质) segments of bone induced new bone formation when implanted in muscle pouches in rabbits. Marshall Urist proposed the name “Bone Morphogenetic Protein”.

DV patterning of somite





Summary (III)

- Key word:
  paraxial mesoderm, somite, Notch

- Event and mechanism
  somitogenesis, osteogenesis

outline

- Ectoderm

  1) neural tube formation and differentiation
  2) neural crest cells
  3) eye development

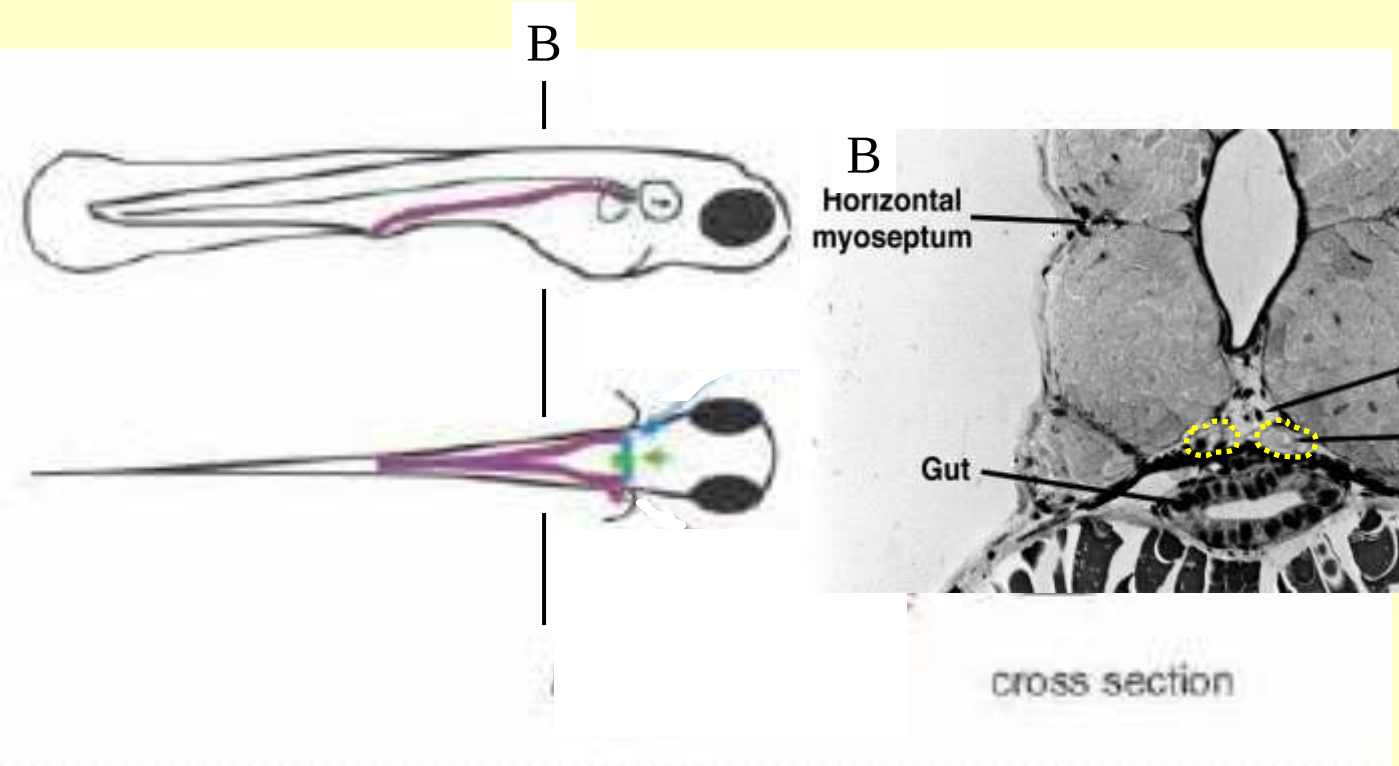
- Mesoderm

  1) paraxial mesoderm: somite
  2) intermediate (中间) mesoderm: urogenital (泌尿生殖) system
  3) lateral plate mesoderm: heart, blood vessels, blood cells

- Endoderm

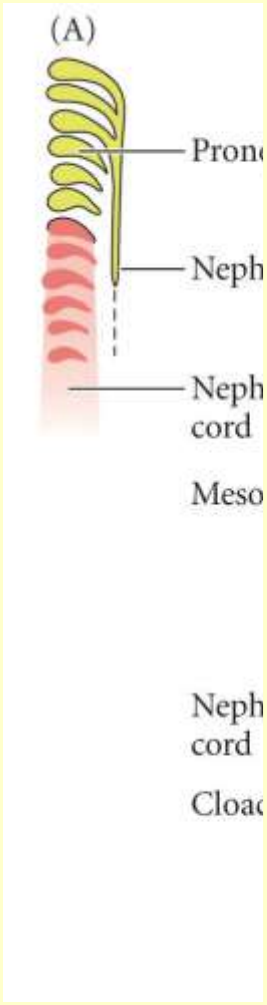
  gut

Pronephros (前肾) in zebrafish



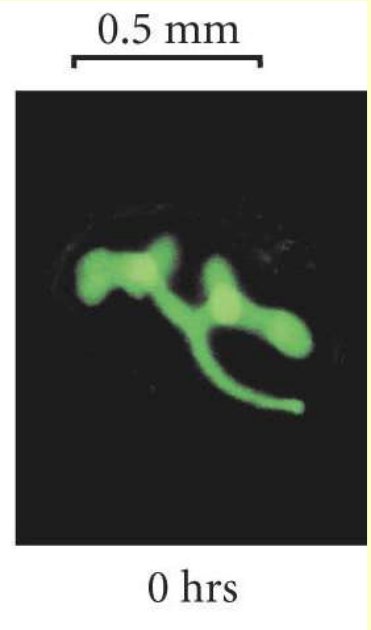
Drummond, 1998
http://zfin.org/zf_info/anatomy/highres/S054.jpeg

General scheme of development in the vertebrate kidney



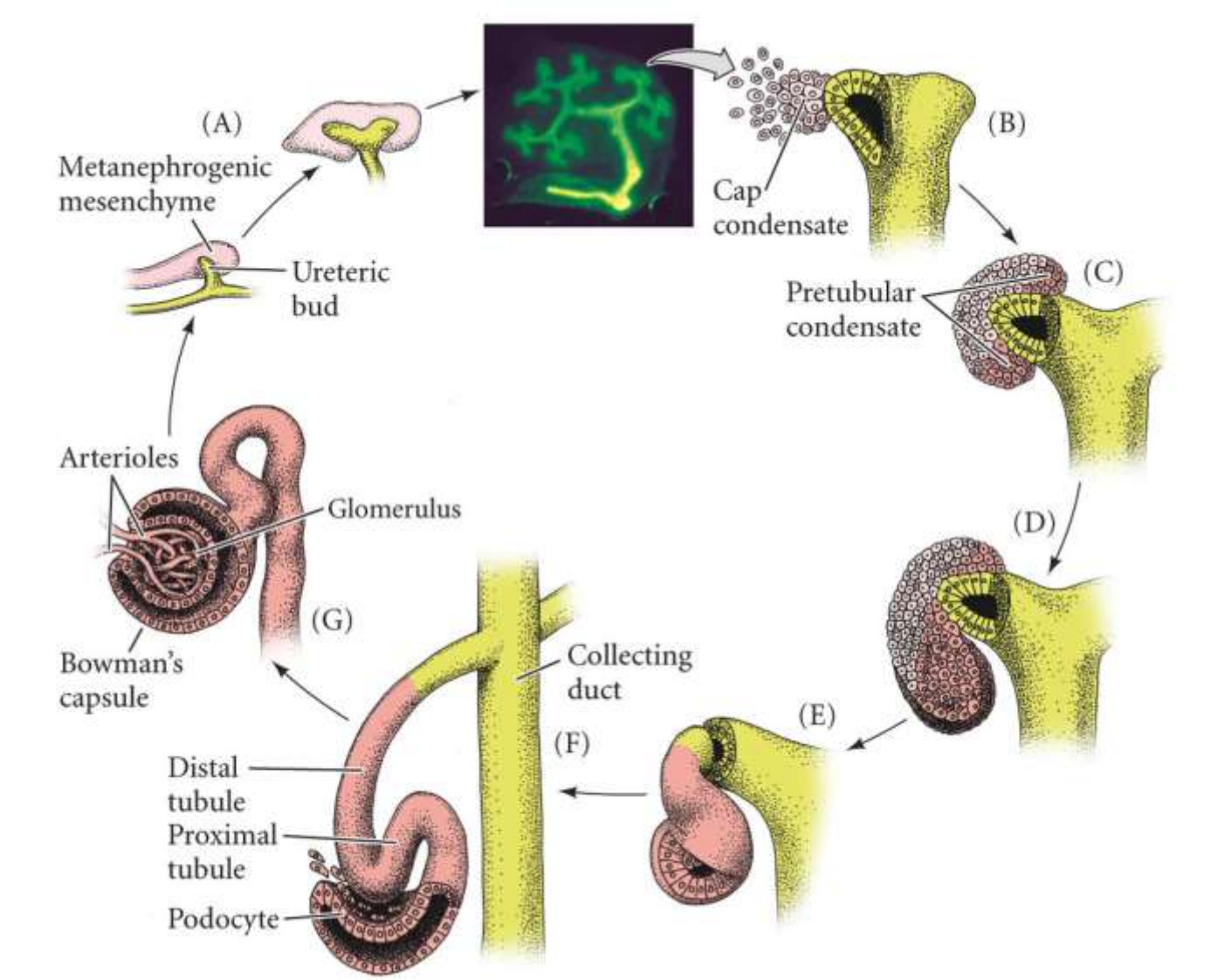
Pronephros: 前肾；mesonephros: 中肾；metanephros: 后肾

Kidney induction in vitro

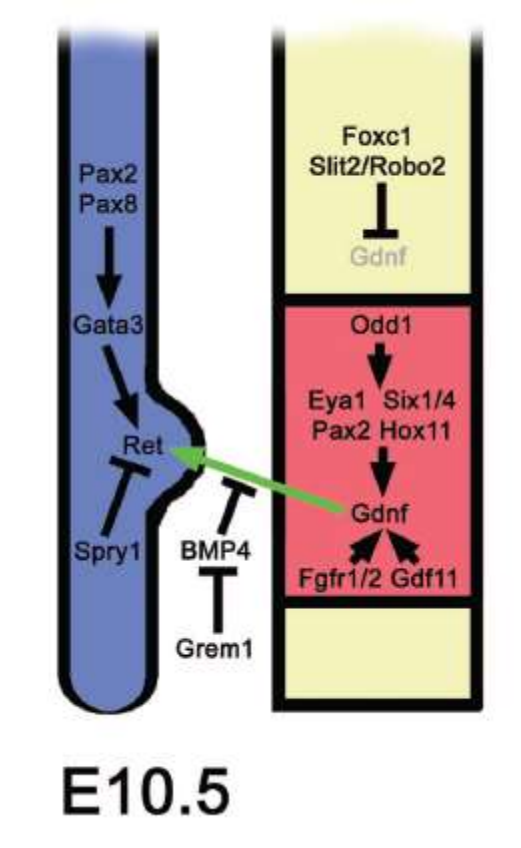


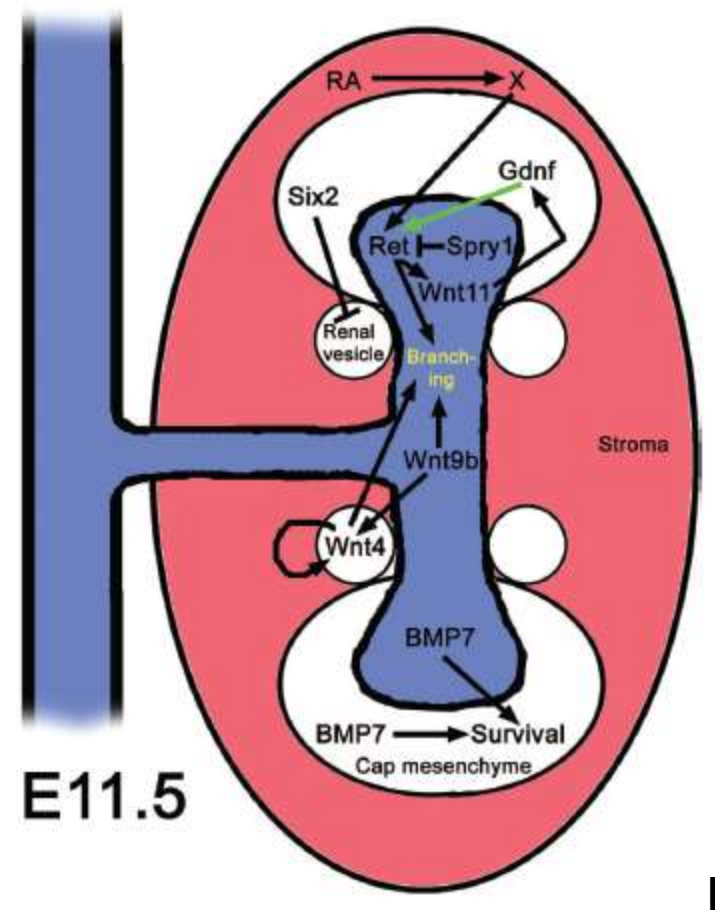
Hoxb7:GFP
Kidney rudiment from 11.5-day mouse embryo

Reciprocal induction in the development of mammalian kidney

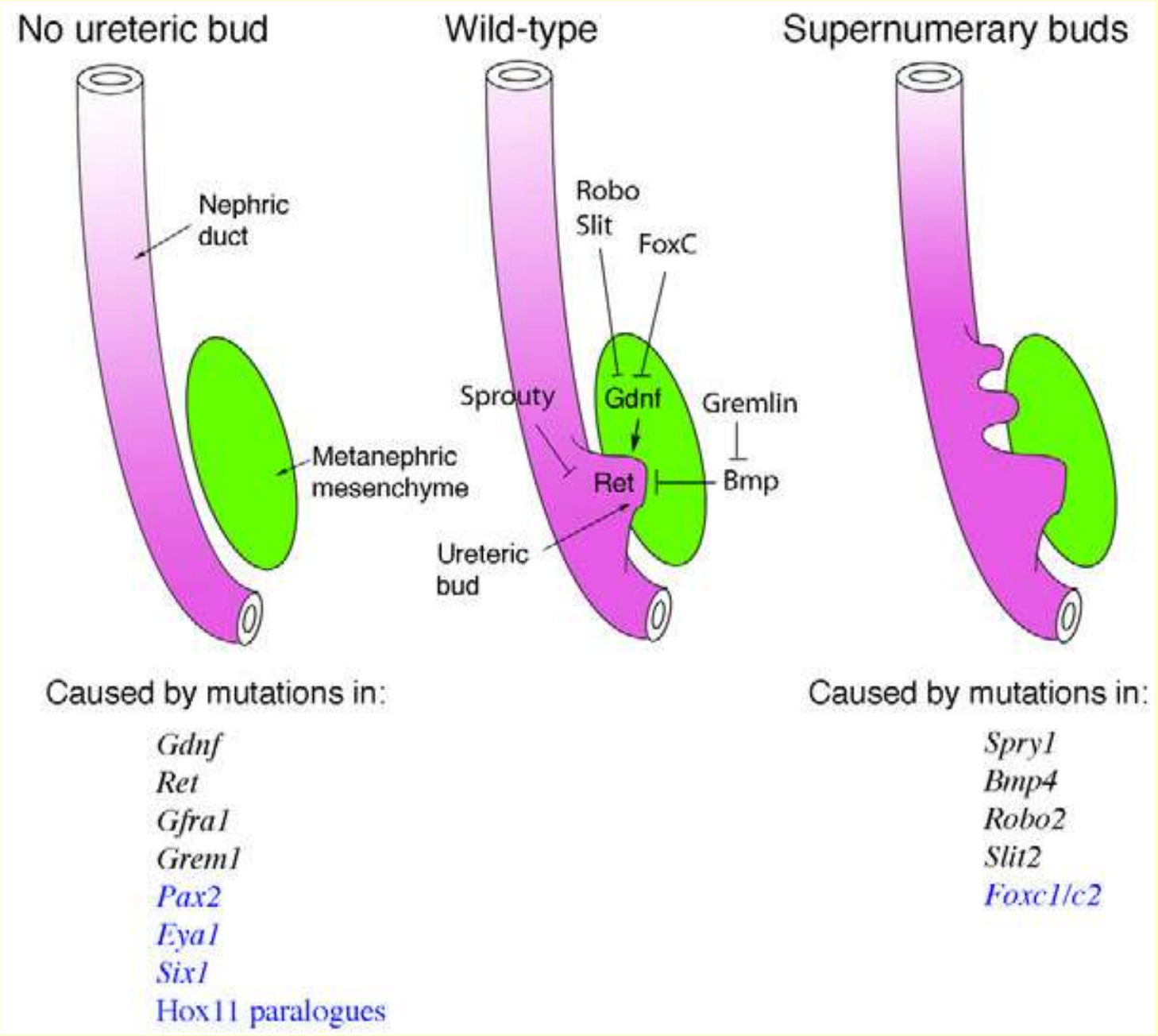


Key molecular pathways involved in early metanephric kidney development





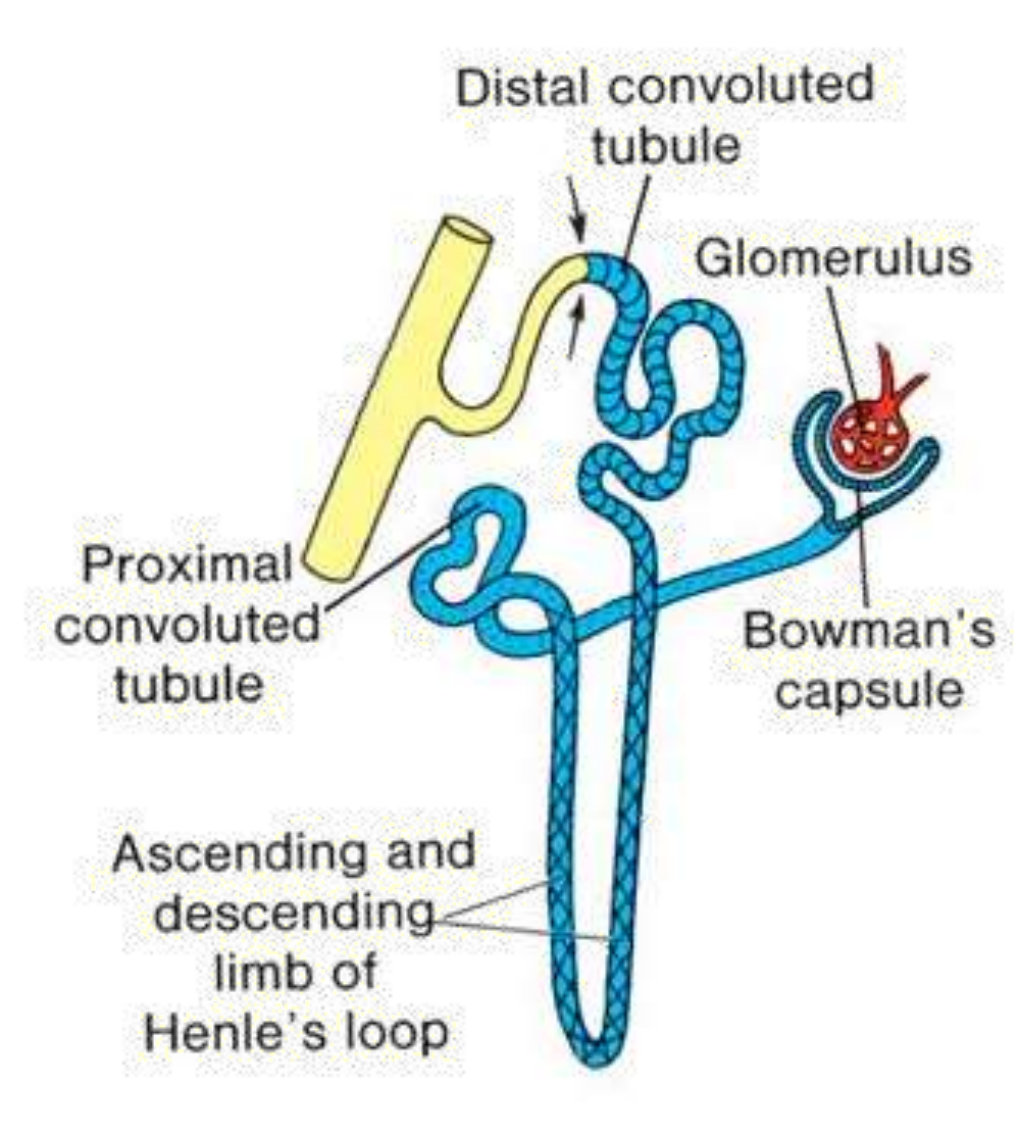
Davidson, 2008, StemBook


No ureteric bud
Wild-type
Supernumerary buds
Nephric duct
Metanephric mesenchyme
Robo
Slit
FoxC
Sprouty
Gdnf
Gremlin
Ret
Bmp
Ureteric bud
Caused by mutations in:
Gdnf
Ret
Gfra1
Grem1
Pax2
Eya1
Six1
Hox11 paralogues
Caused by mutations in:
Spry1
Bmp4
Robo2
Slit2
Foxc1/c2

Development of the Metanephros

Two Systems:

- **Collecting System**
- **Excretory System (Nephron)**



Summary (IV)

- Key word
- Event and mechanism

outline

- Ectoderm

  1) neural tube formation and differentiation
  2) neural crest cells
  3) eye development

- Mesoderm

  1) paraxial mesoderm: somite
  2) intermediate mesoderm: kidney
  3) lateral plate mesoderm: heart, blood vessels, blood cells

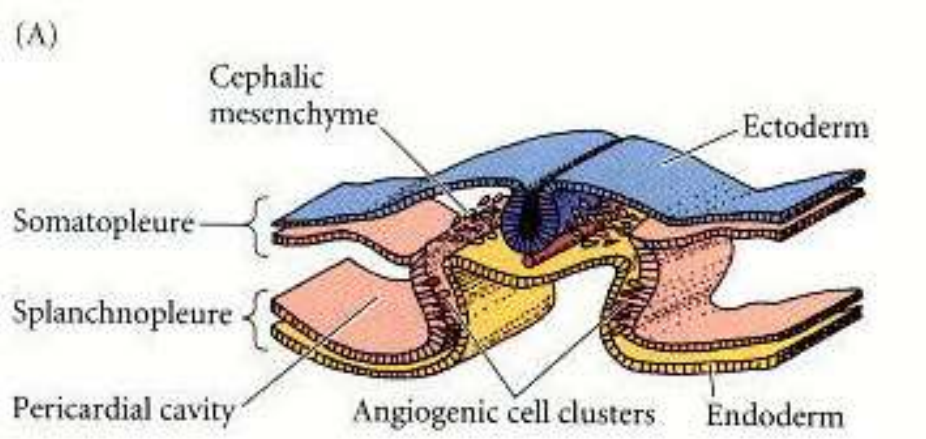
- Endoderm

  gut

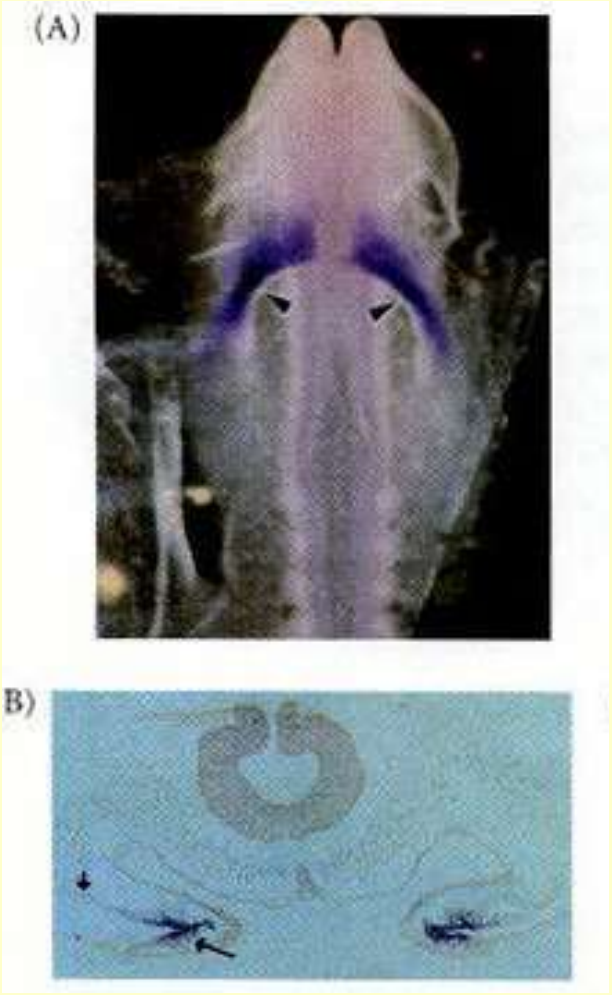
Heart formation

- Specification of heart tissures—heart primordia (心原基的形成)
- Fusion of the heart primordia and initial heartbeats （心原基迁移融合成单一的心管, 心跳启动）
- Looping（环绕）(rightward heart looping) and formation of heart chambers

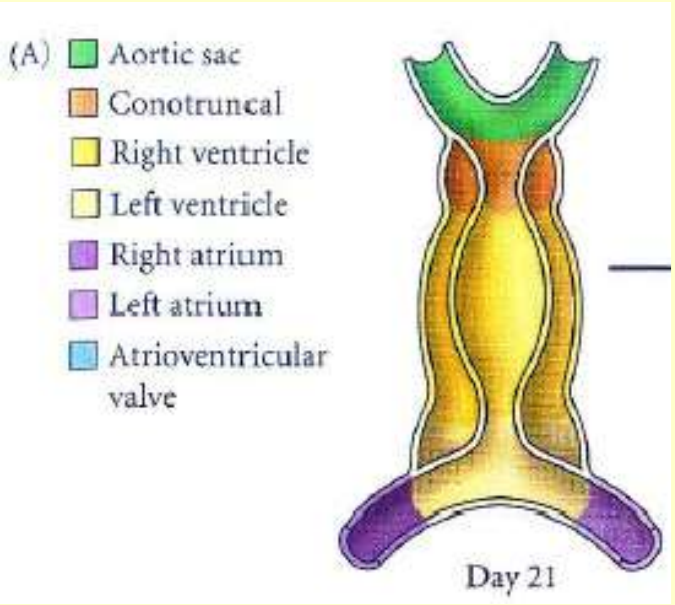
Heart tube formation in chick



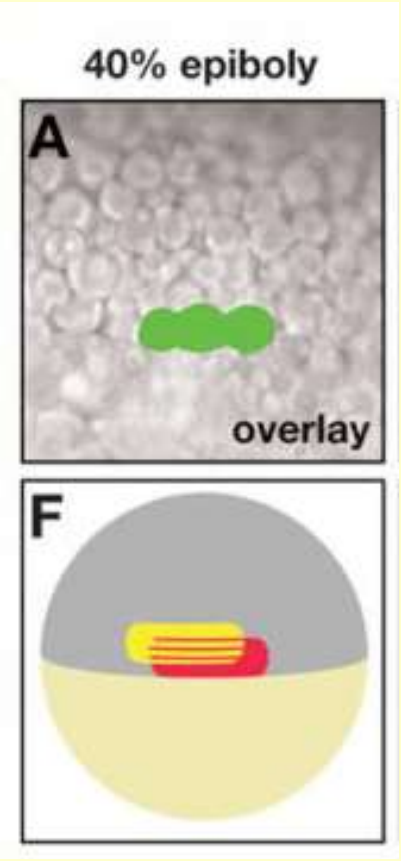
Migration of Heart primordia



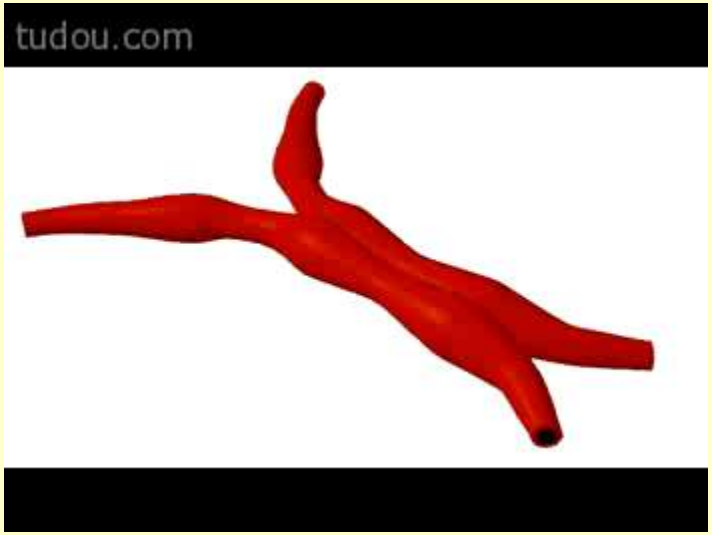
Looping and formation of human heart chambers



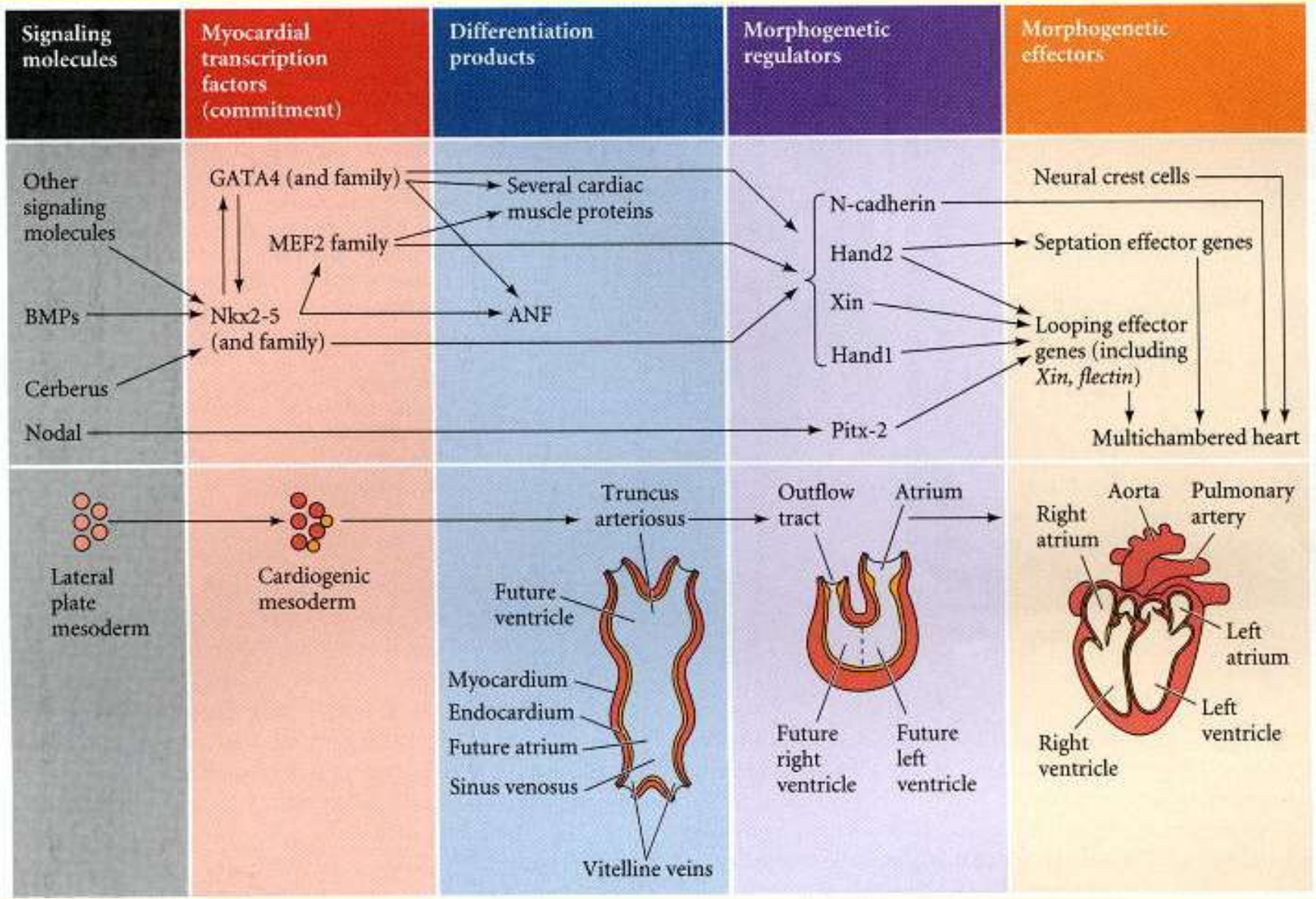
Heart formation in zebrafish



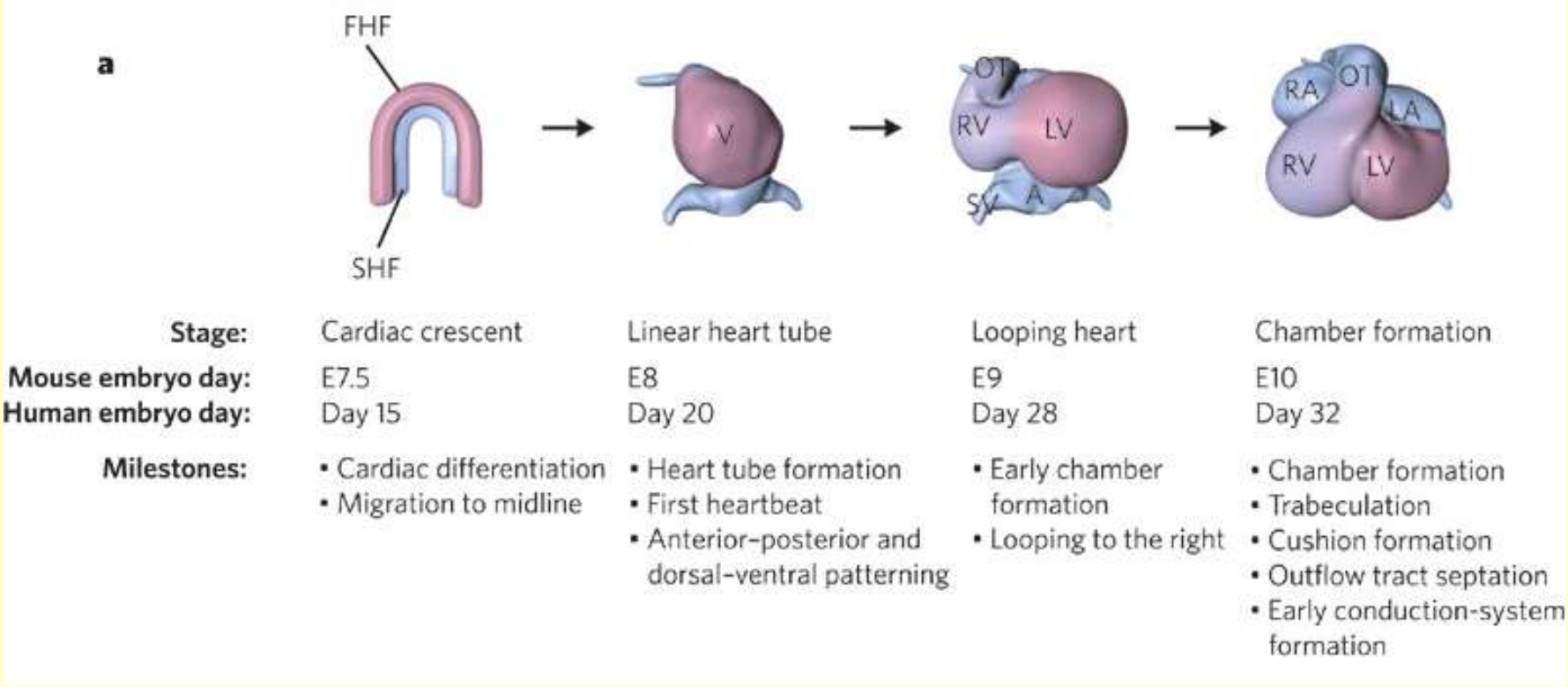
Heart formation in human



Cascade of heart development



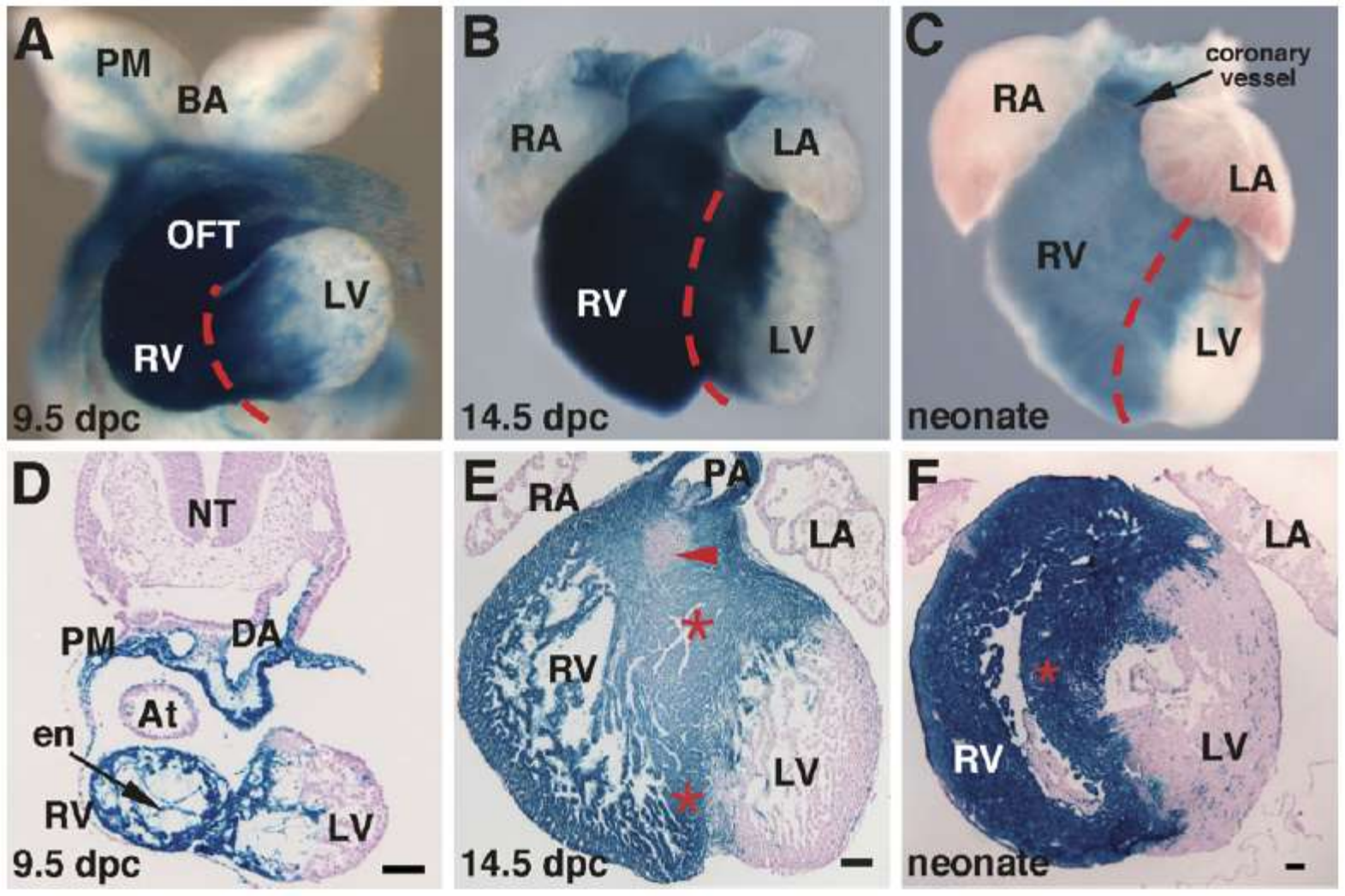
Second Heart Field



Stage:	Cardiac crescent	Linear heart tube	Looping heart	Chamber formation
Mouse embryo day:	E7.5	E8	E9	E10
Human embryo day:	Day 15	Day 20	Day 28	Day 32
Milestones:	• Cardiac differentiation • Migration to midline	• Heart tube formation • First heartbeat • Anterior–posterior and dorsal–ventral patterning	• Early chamber formation • Looping to the right	• Chamber formation • Trabeculation • Cushion formation • Outflow tract septation • Early conduction-system formation

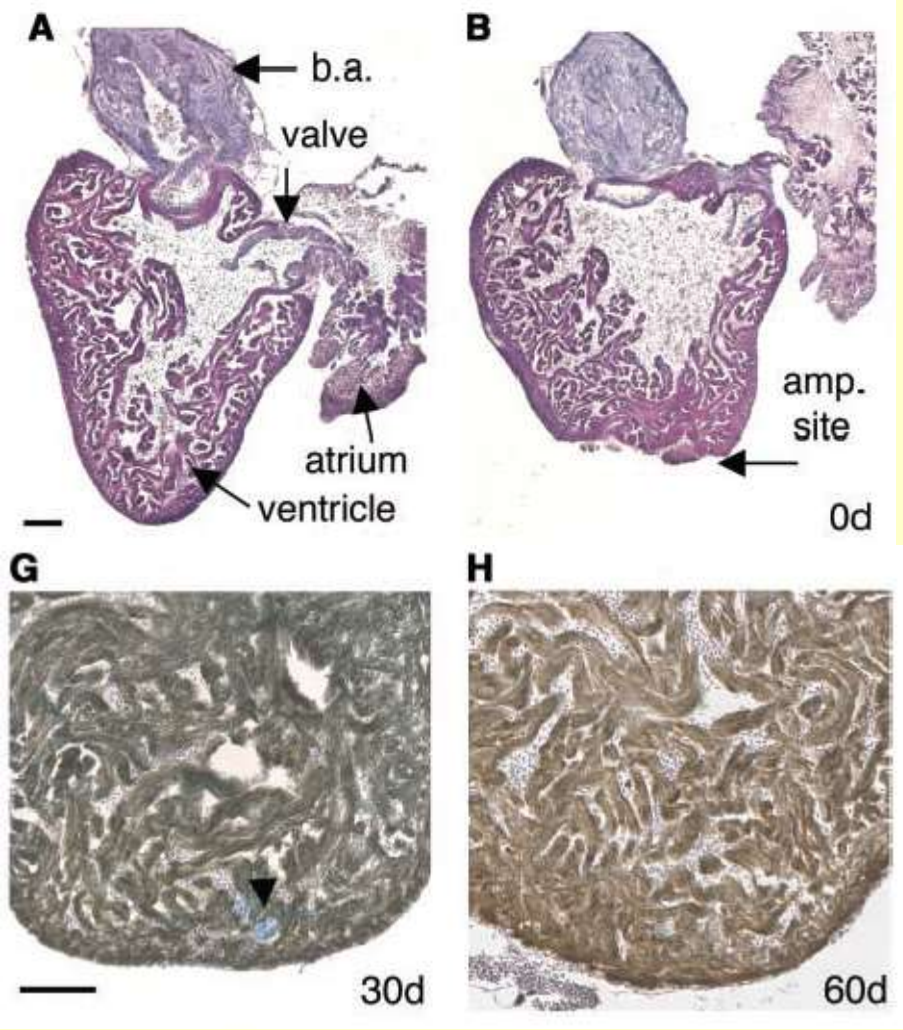
Buck, 2005

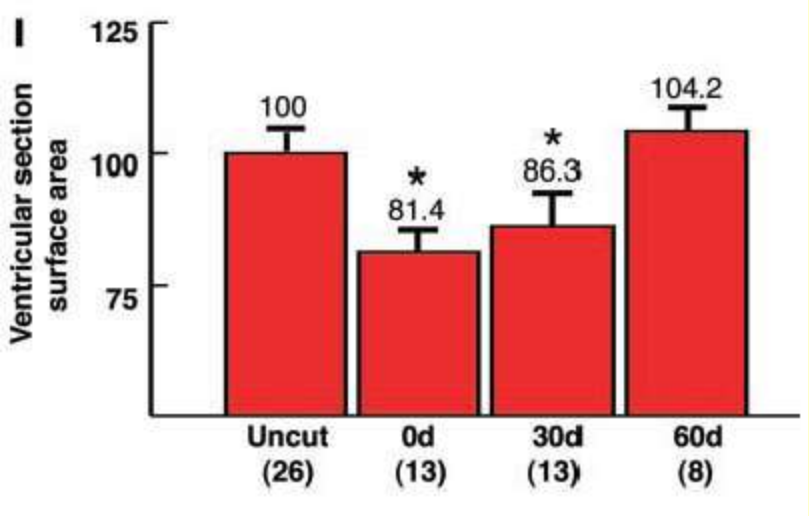
Mef2c-AHF-Cre marks the SHF and its descendants.



Black, 2007

Heart Regeneration





Poss, *et al.*, 2002 Science

Origin of regenerated cardiac cell: progenitor vs dedifferentiation?

Cell

nature Vol 464|25 March 2010|doi:10.1038/nature08899

LETTERS

Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation

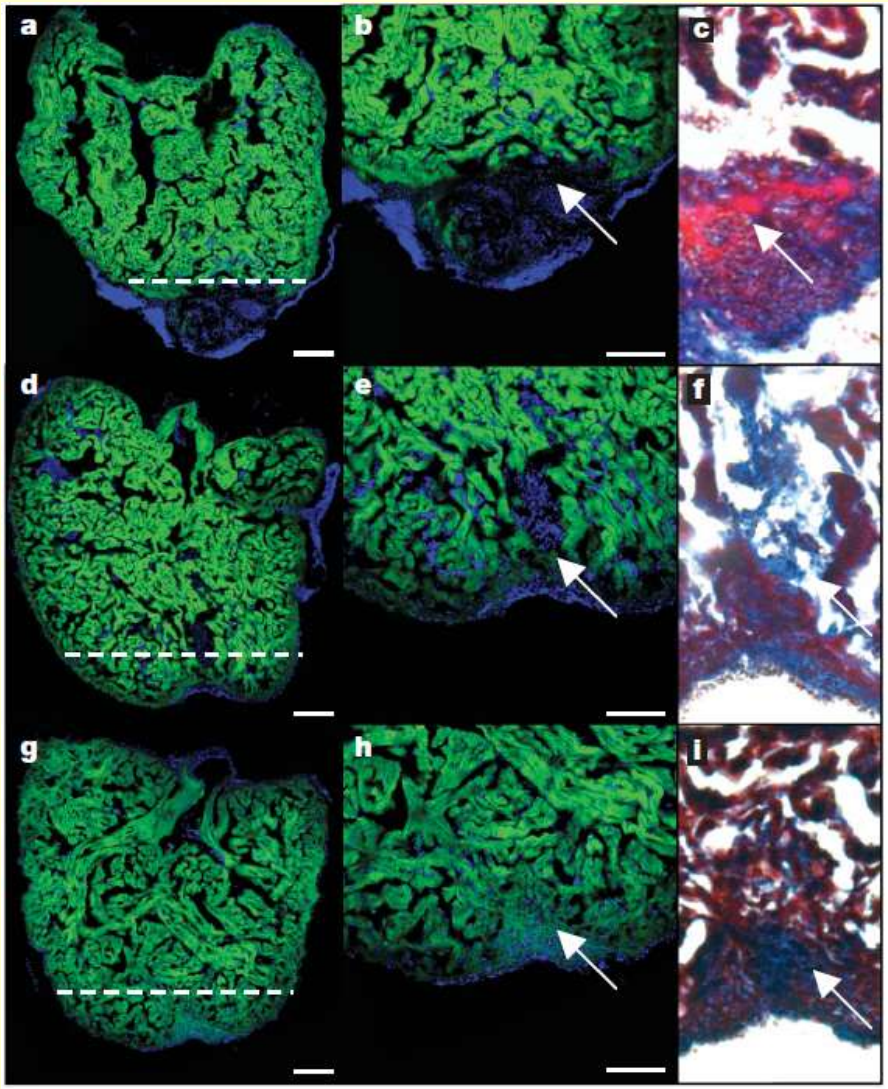
Chris Jopling[1], Eduard Sleep[1,2]†, Marina Raya[1]†, Mercè Martí[1], Angel Raya[1,2,3]† & Juan Carlos Izpisúa Belmonte[1,2,4]

Regenerated cardiomyocytes are derived from differentiated cardiomyocytes

7 dpa

14 dpa

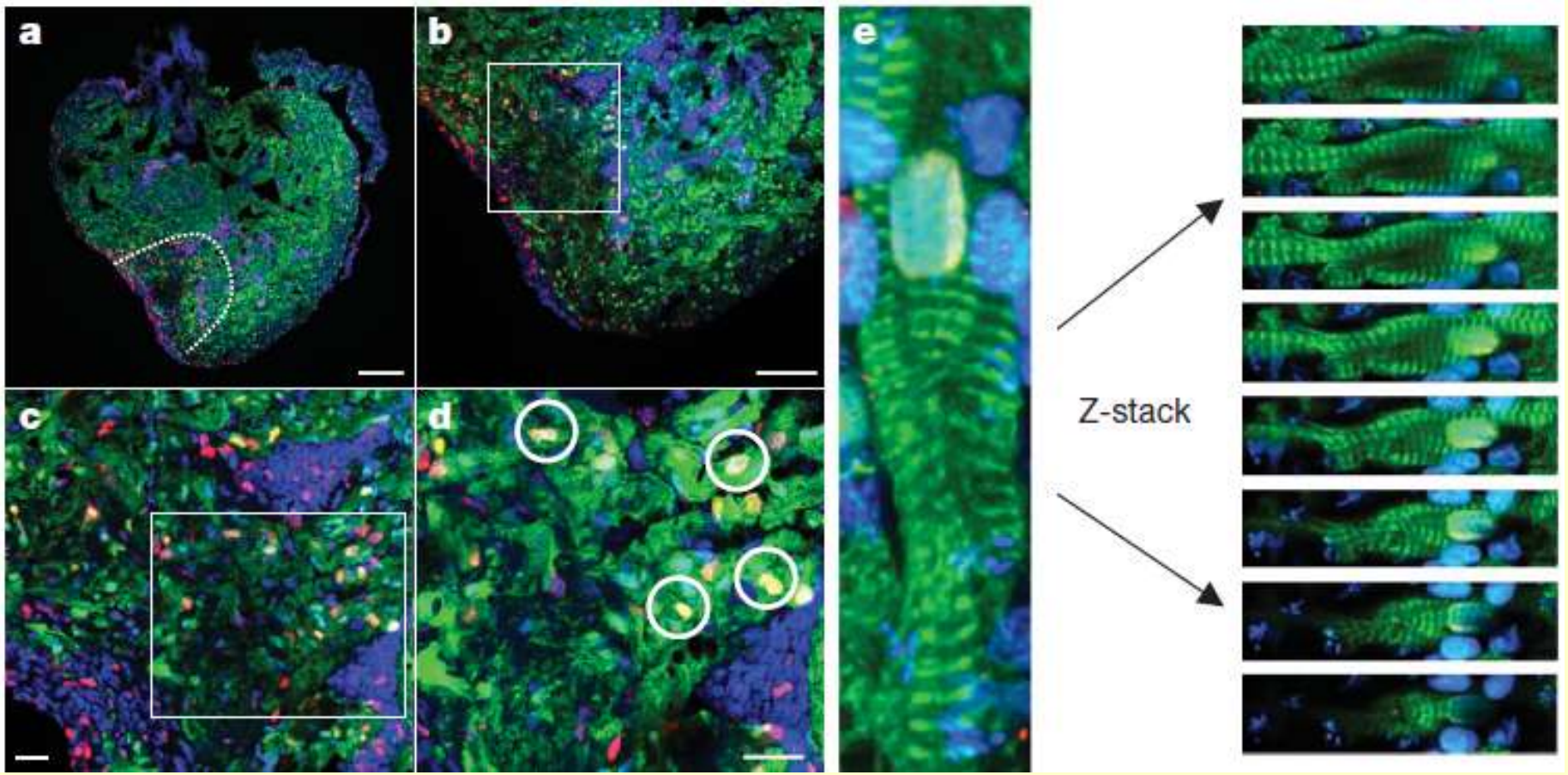
30 dpa



tg-cmlc2a-Cre-Ert2; tg-cmlc2a-LnL–GFP

Jopling, *et al.*, 2010 Nature

Differentiated cardiomyocytes re-enter the cell cycle

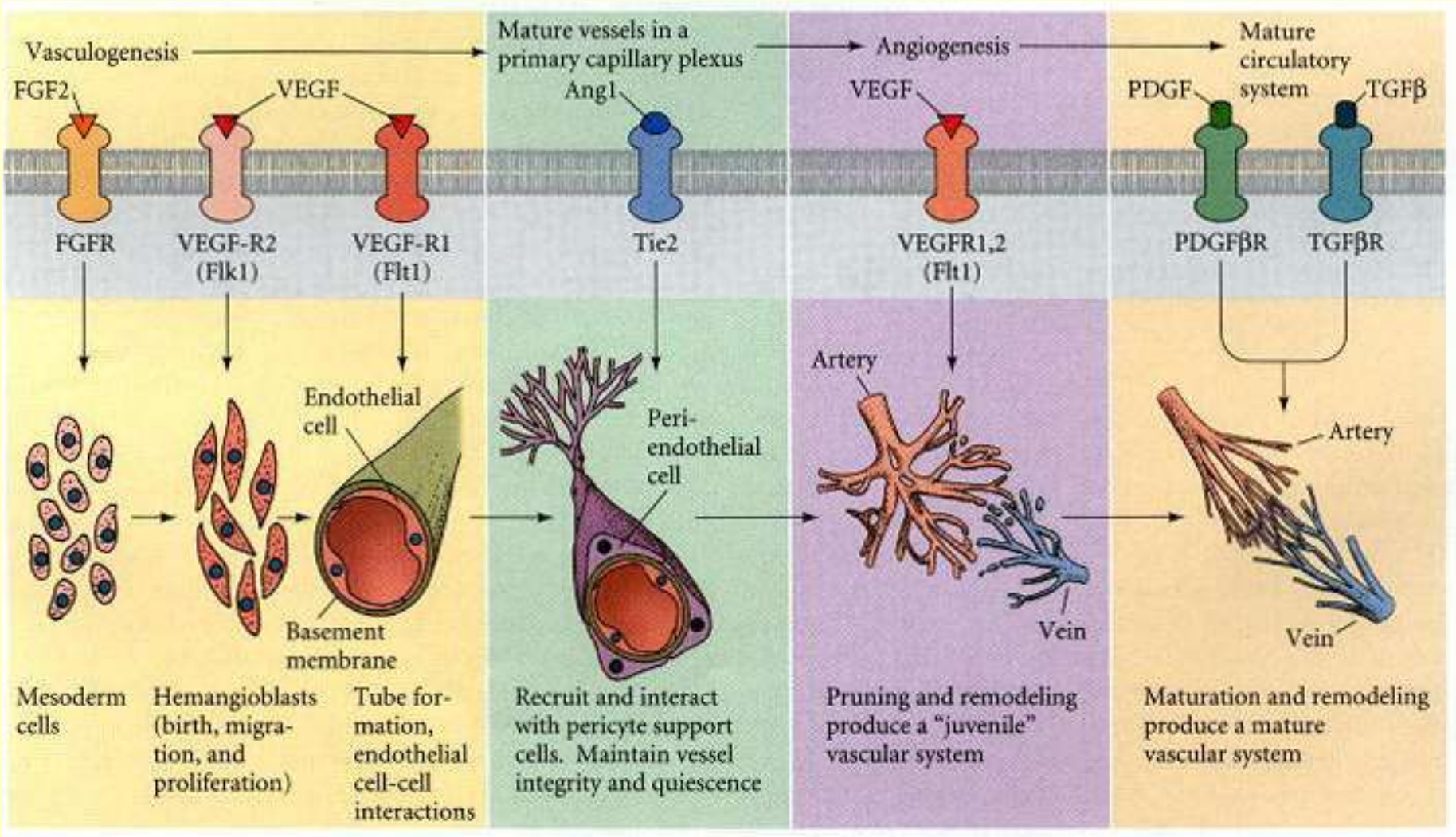


Jopling, *et al.*, 2010 Nature

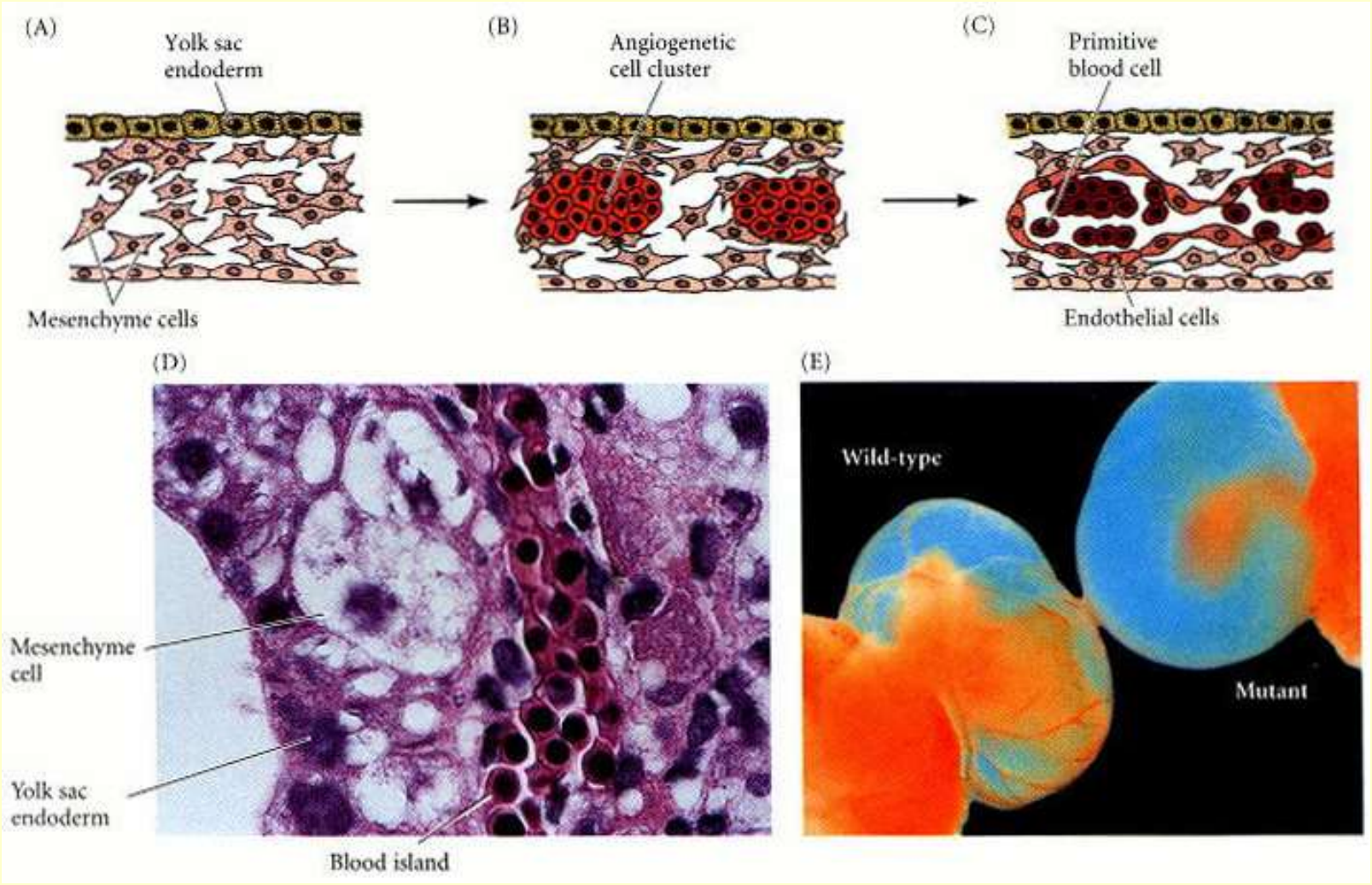
Hemangioblast (血管、血液前体细胞)

De Val & Black, 2009

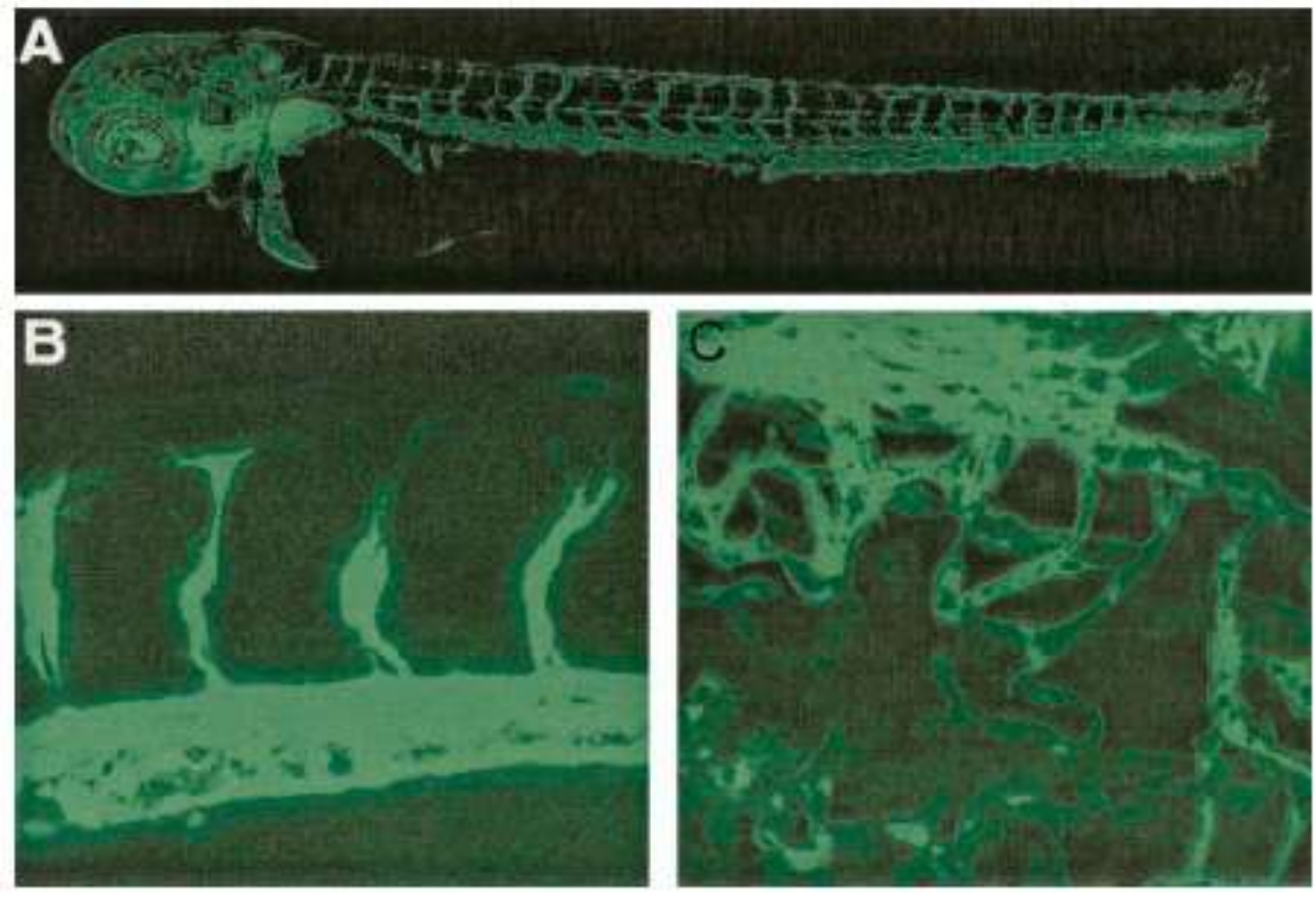
Blood vessel (血管) formation: Vasculogenesis and angiogenesis



Vasculogenesis （初级血管形成）

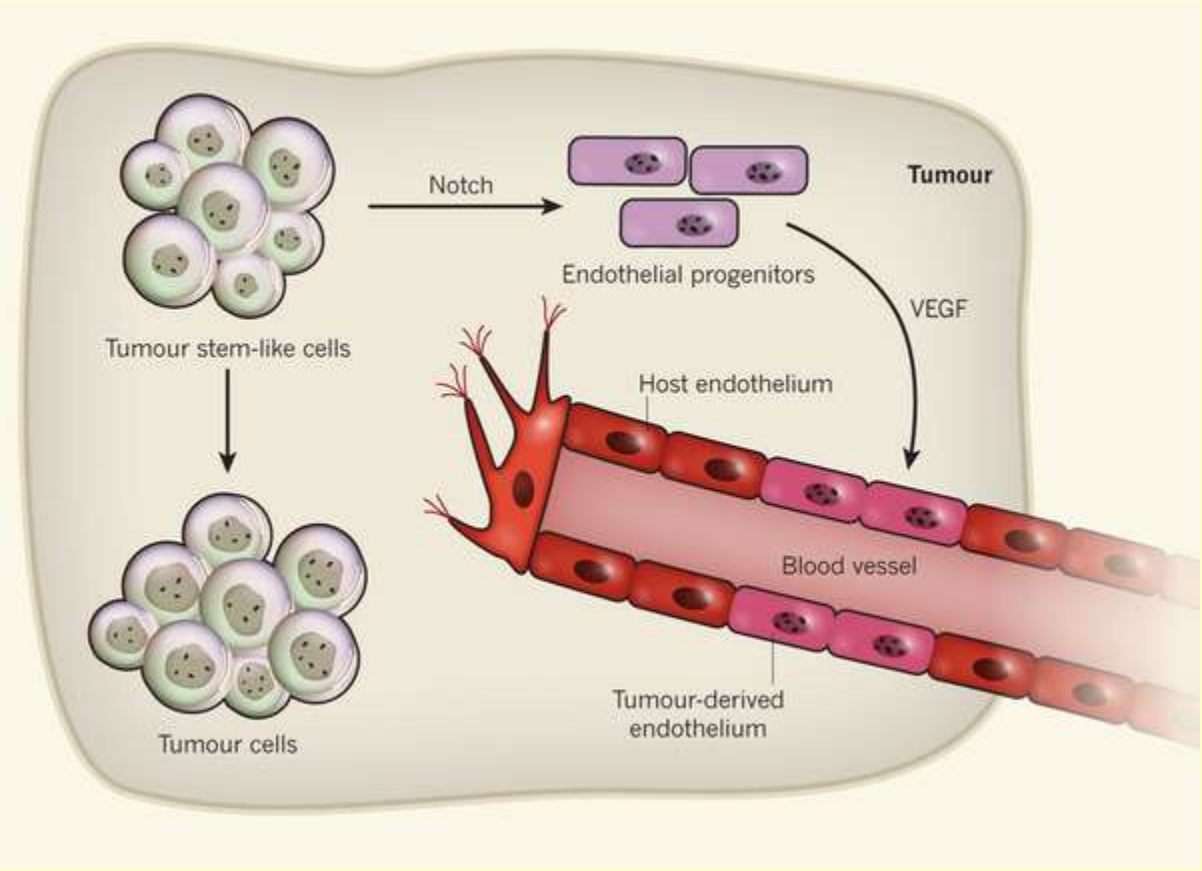


Blood vesscle (血管) in zebrafish (Fli:EGFP)



Angiogenesis （次级血管形成）in zebrafish

Angiogenesis and cancer



Blood vessel (血管) specification in zebrafish embryo

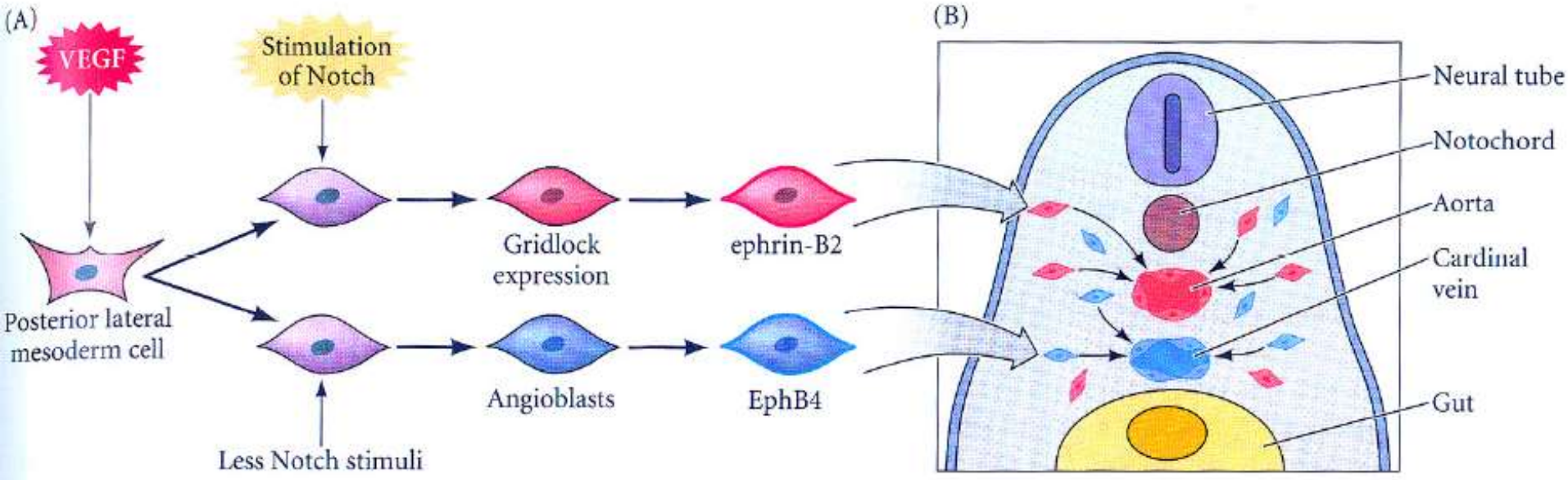
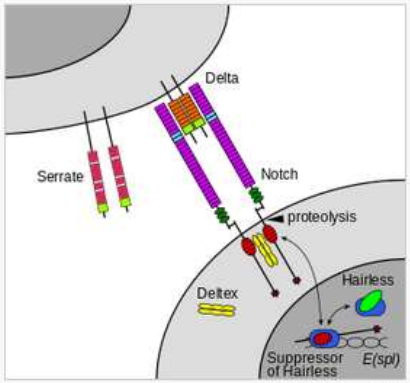


Figure 15.17
Blood vessel specification in the zebrafish embryo. (A) Angioblasts experiencing activation of Notch upregulate the Gridlock transcription factor. These cells express ephrin-B2 and become aorta cells. Those angioblasts experiencing significantly less Notch activation do not express Gridlock, and they become EphB4-expressing cells of the cardinal vein. (B) Once committed to forming veins or arteries, the cells migrate toward the midline of the embryo and contribute to forming the aorta or cardinal vein.

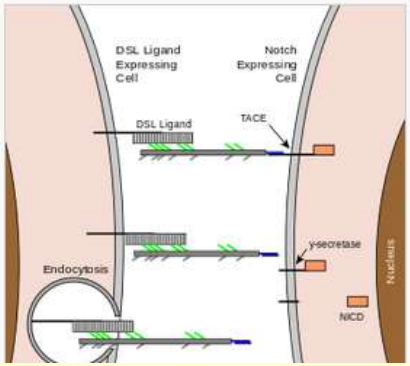
Notch signaling in wikipedia

Contents [hide]

1 Discovery
2 Mechanism of action
3 Function
4 Pathway
5 Notch signaling in embryogenesis
  5.1 Notch signaling in embryo polarity
  5.2 Notch signaling in somitogenesis
6 Notch signaling in central nervous system development and function
  6.1 Notch signaling in neuron cell differentiation
  6.2 Notch signaling in neurite development
  6.3 Notch signaling in gliogenesis
  6.4 Notch signaling in adult brain function
7 Notch signaling in cardiovascular development
  7.1 Notch signaling in cardiac development
    7.1.1 1. Notch signaling in atrioventricular (AV) canal development
    7.1.2 2. Notch signaling in ventricular development
    7.1.3 3. Notch signaling in ventricular outflow tract development
  7.2 Notch signaling in angiogenesis
8 Notch signaling in endocrine development
  8.1 Notch signaling in pancreatic development
  8.2 Notch signaling and intestinal development



Notch-mediated juxtacrine signal between adjacent cells.



Blood cell formation

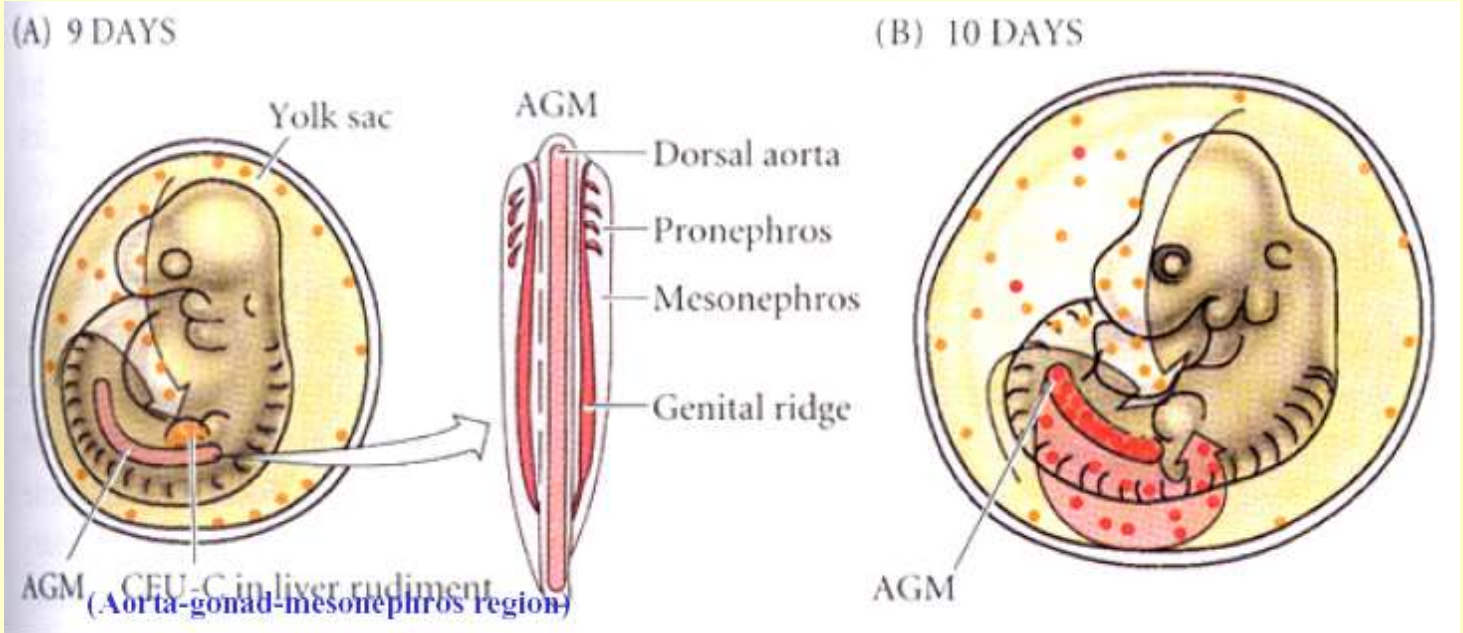
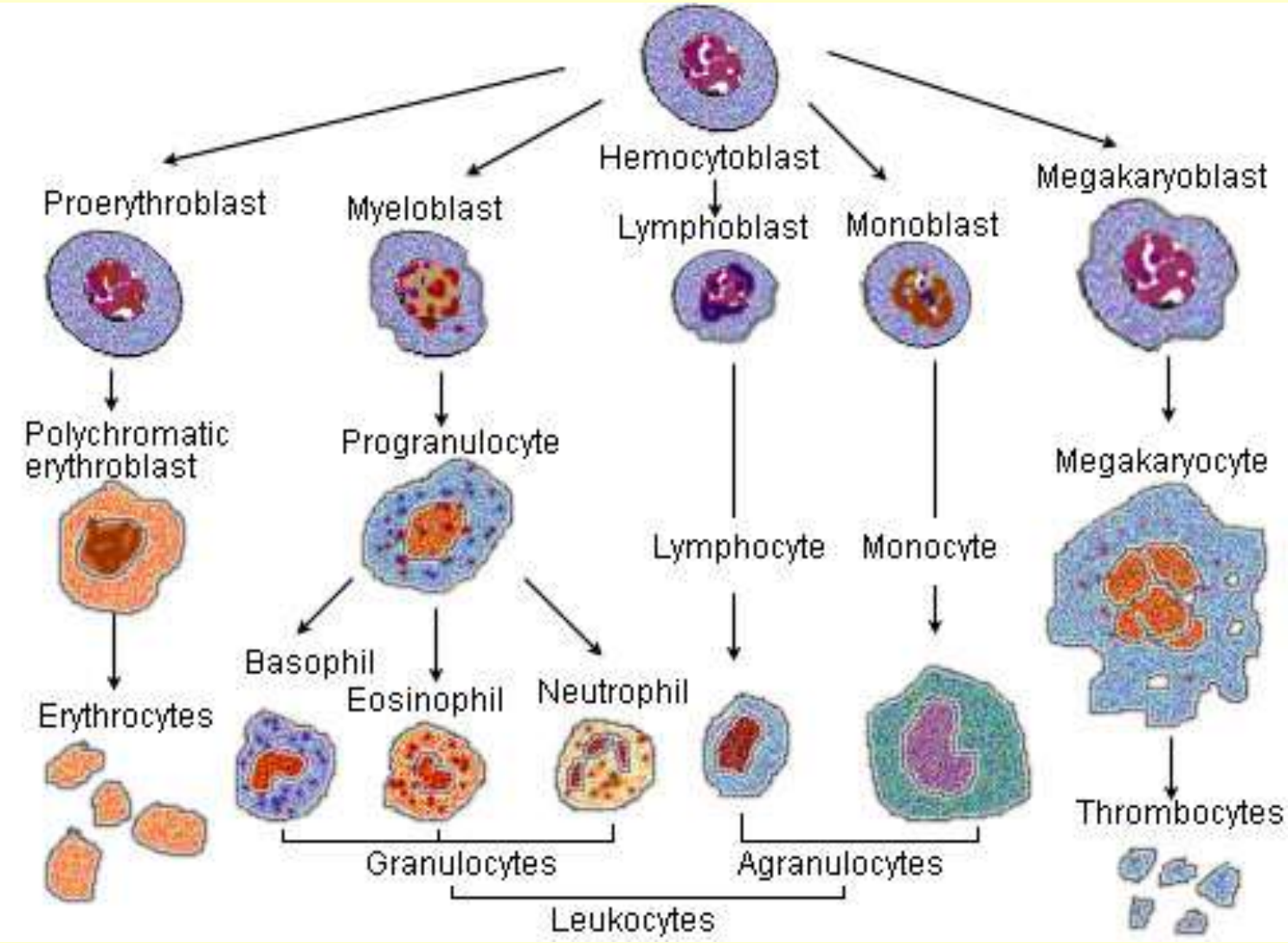


Figure 15.24
Colonization of the mouse liver by two waves of hematopoietic stem cells. The two main sources of hematopoietic progenitor cells are the yolk sac and the AGM region. (A) At day 9, the yolk sac contributes an early line of CFU-C cells that probably does not last long after birth, and which makes a population of predominantly red blood cells. This cell population is thought to be the major source of the first wave of hematopoiesis in the liver. (B) At day 10, the AGM-derived cells provide CFU-S cells and pluripotential hematopoietic stem cells. These constitute the major cells of the second wave. (After Dzierzak and Medvinsky 1995.)

哺乳动物造血器官：胚胎卵黄囊→胎儿**AGM**→成年个体骨髓和脾脏。

鱼类造血器官：胚胎**ICM**→成年肾脏。

Blood cell lineage



summary

- Key word:

  Vasculogenesis, Angiogenesis, VEGF, blood cell formation

- Event and mechanism

outline

- Ectoderm

  1) neural tube formation and differentiation

  2) eye development

- Mesoderm

  1) paraxial mesoderm: somite

  2) intermediate mesoderm: kidney

  3) lateral plate mesoderm: heart, blood vessels, blood cells

- Endoderm

  gut, lung