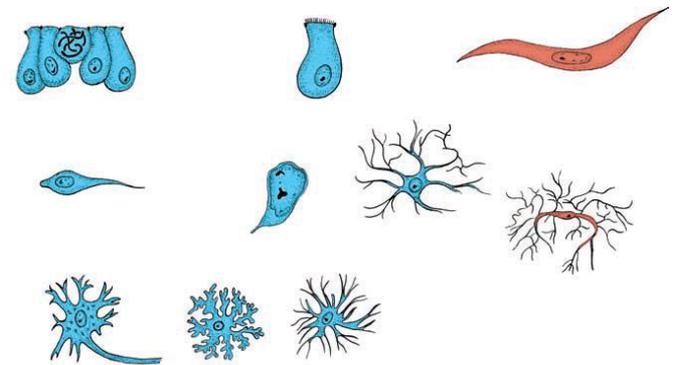
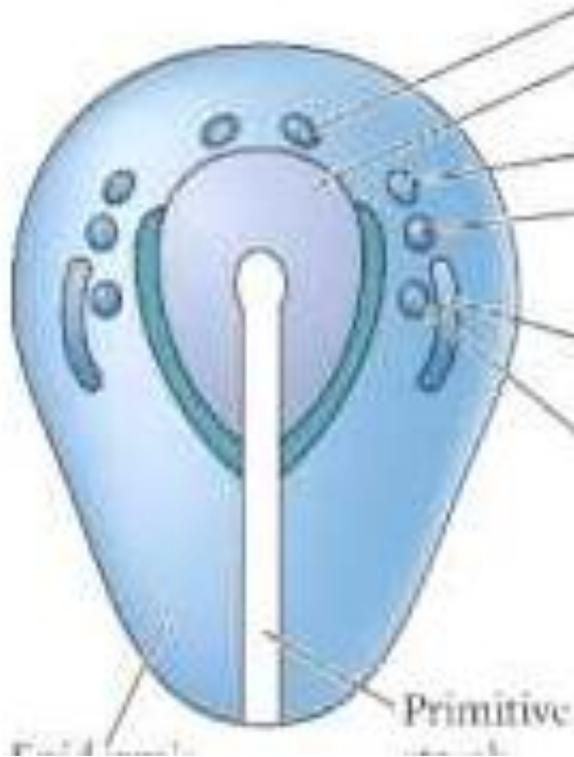


Dr. Andrea D. Székely

# Differentiation of the Placode Ectoderm Neural Crest Derivatives



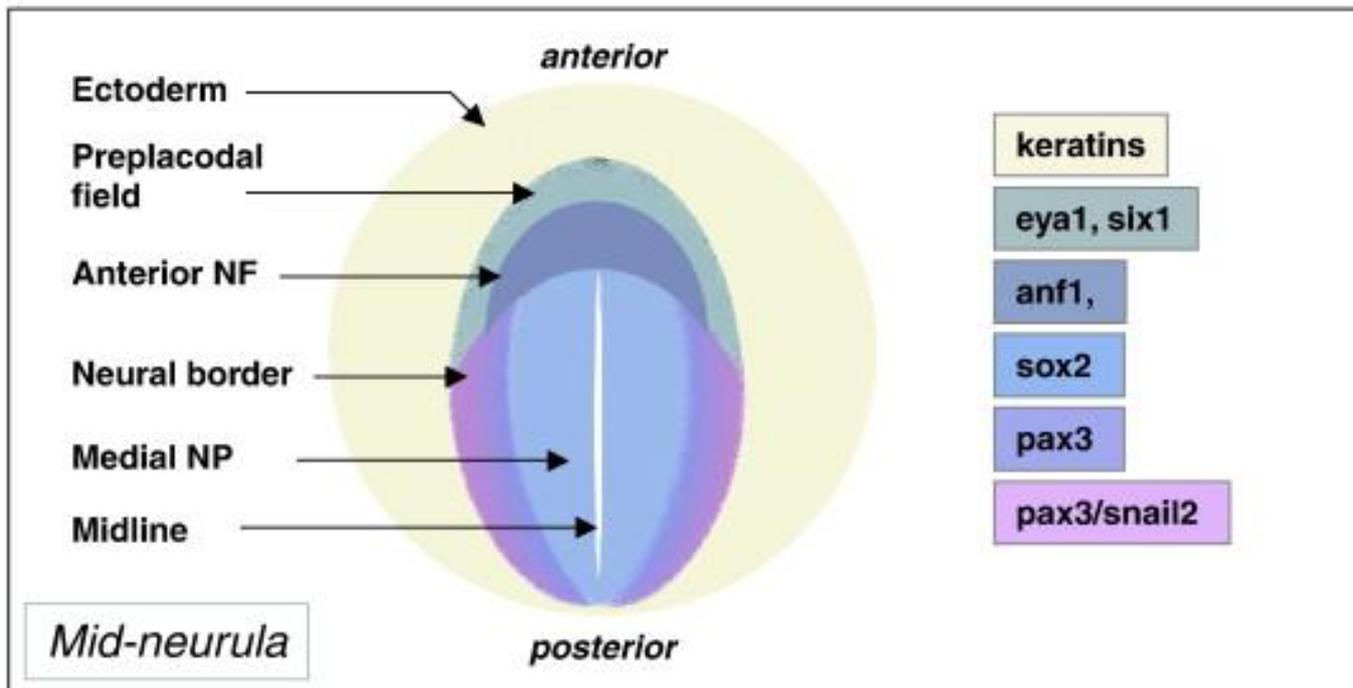
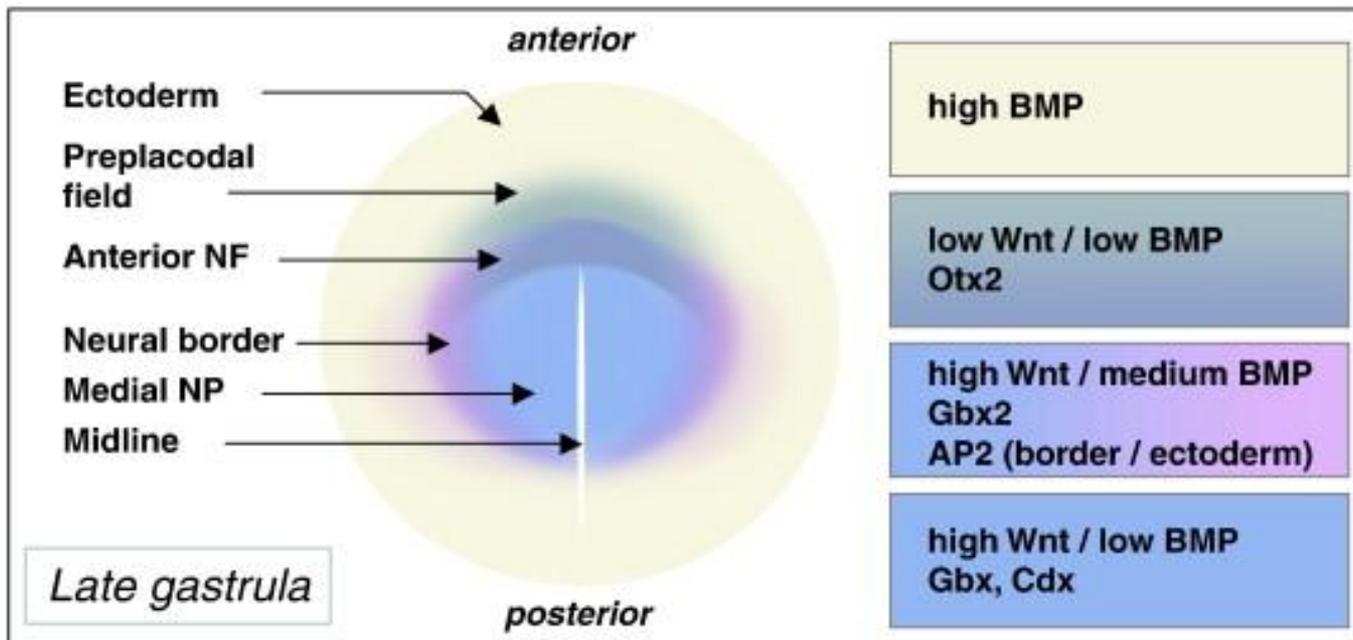
*Acknowledgements to*

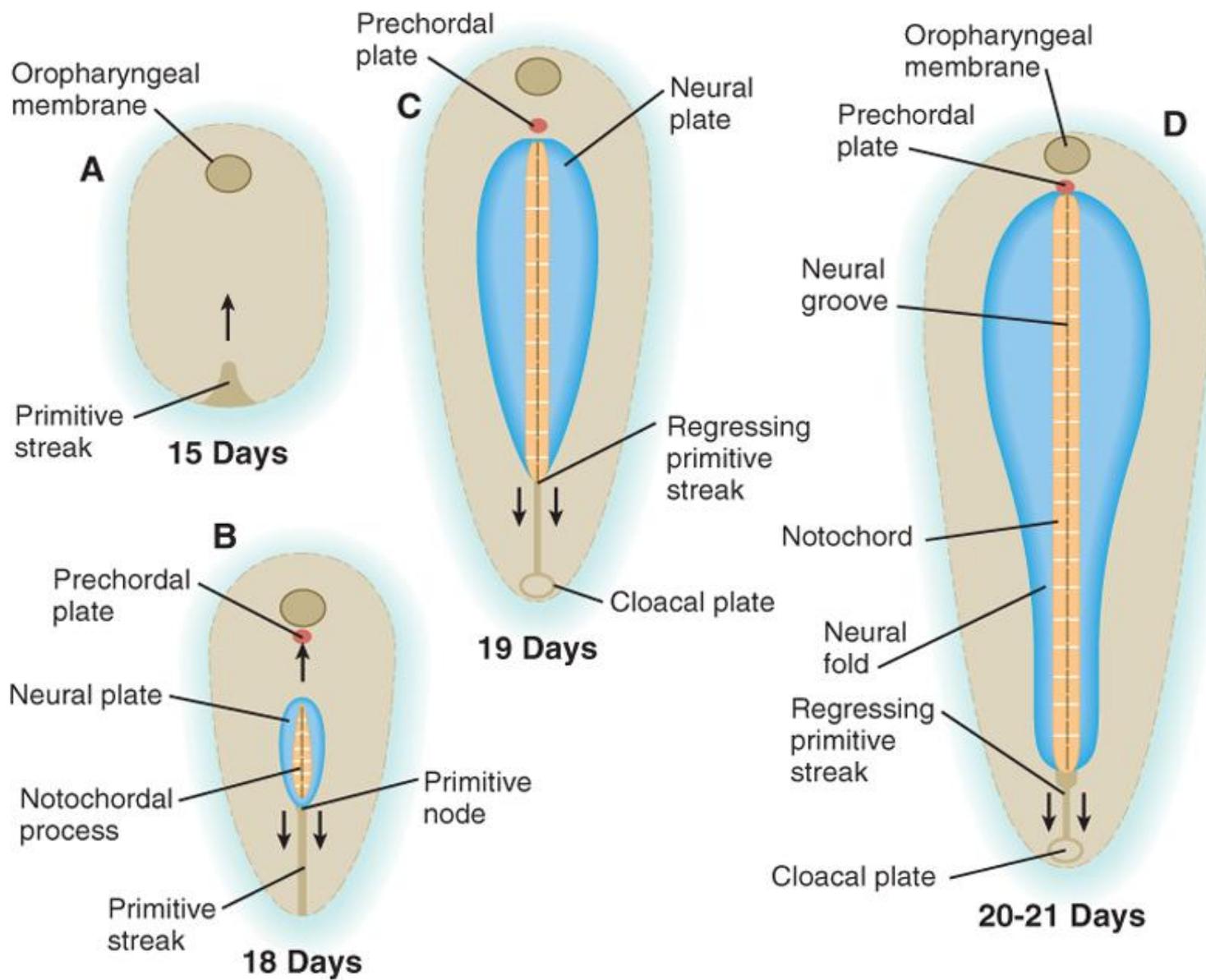
*Dr Károly Altdorfer  
Dr Nándor Nagy*

# EARLY DEVELOPMENT

The *neural crest* and *craniofacial placodes* are two distinct progenitor populations that arise at the *border* of the vertebrate neural plate.

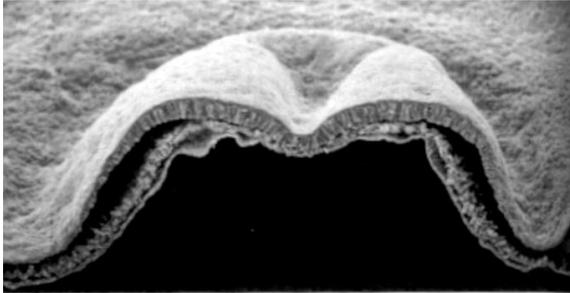
This border region develops through a series of inductive interactions that begins before gastrulation and progressively divide embryonic ectoderm into neural and non-neural regions, followed by the emergence of neural crest and placodal progenitors.





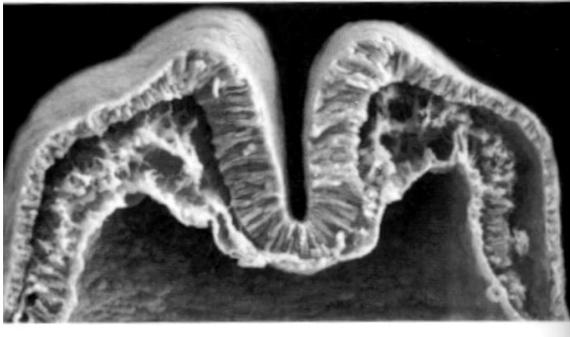
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# PRIMARY NEURULATION

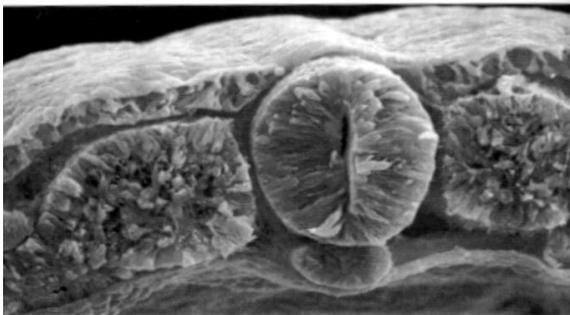


Neural induction and neurulation

Specification of neural fate and formation of the neural tube.

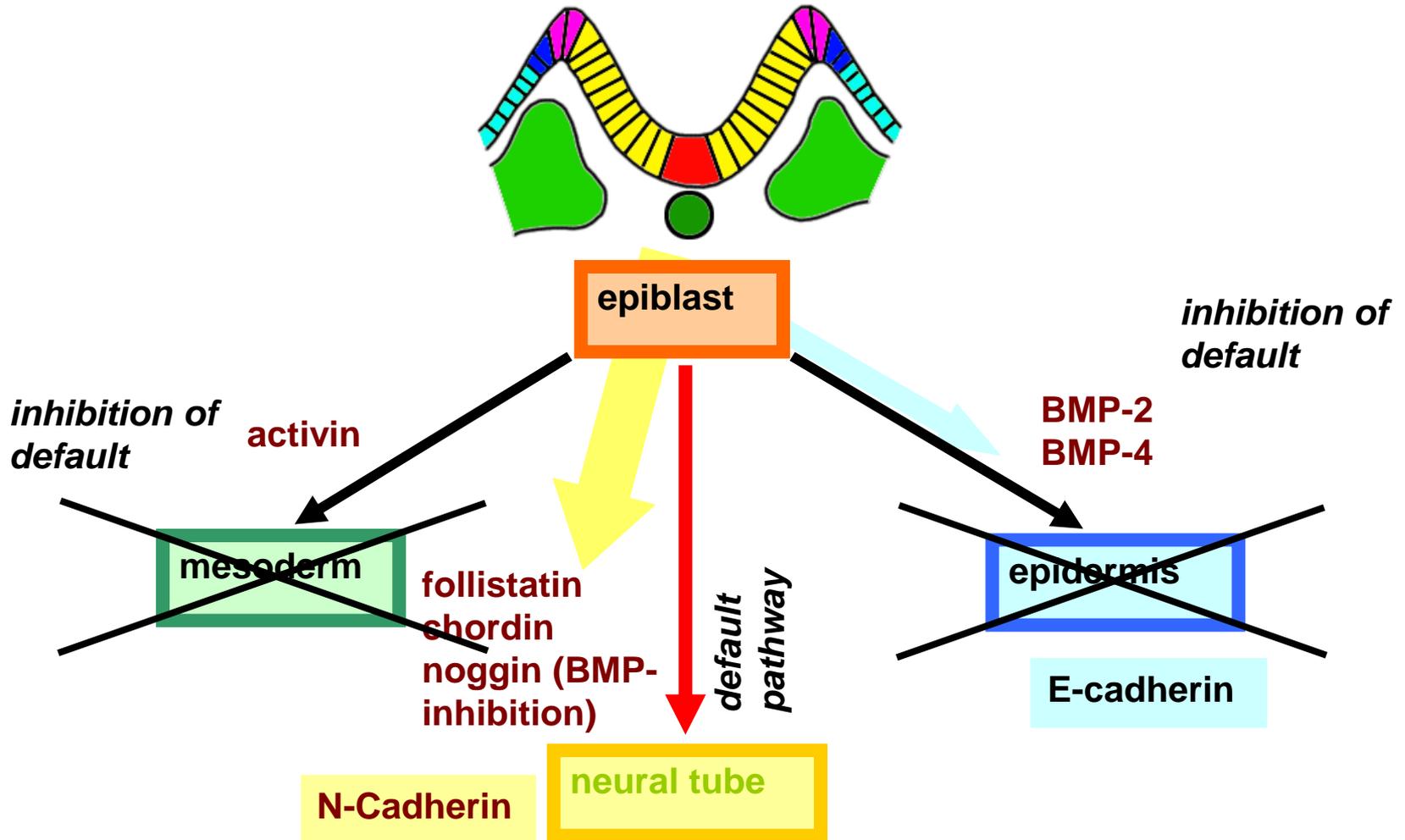


**NEURAL INDUCTION** : the delineation of ectodermal cells to the neural fate



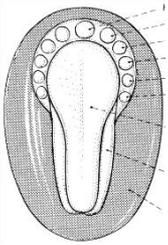
**NEURULATION**: the process in which the ectoderm of the future brain and spinal cord - the neural plate – develops, folds and forms the **neural tube**

# INDUCTION OF THE NEURAL TUBE



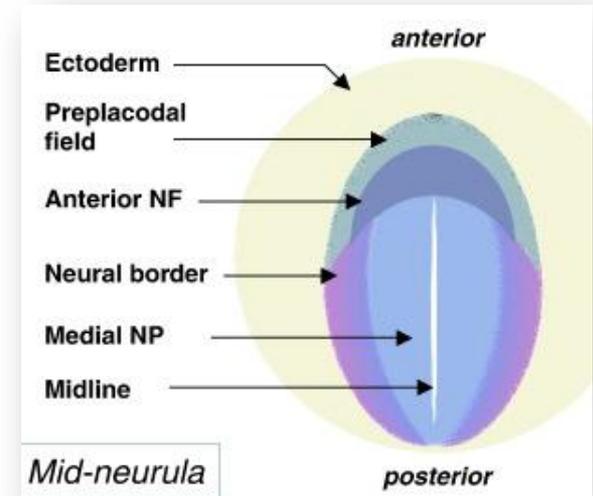
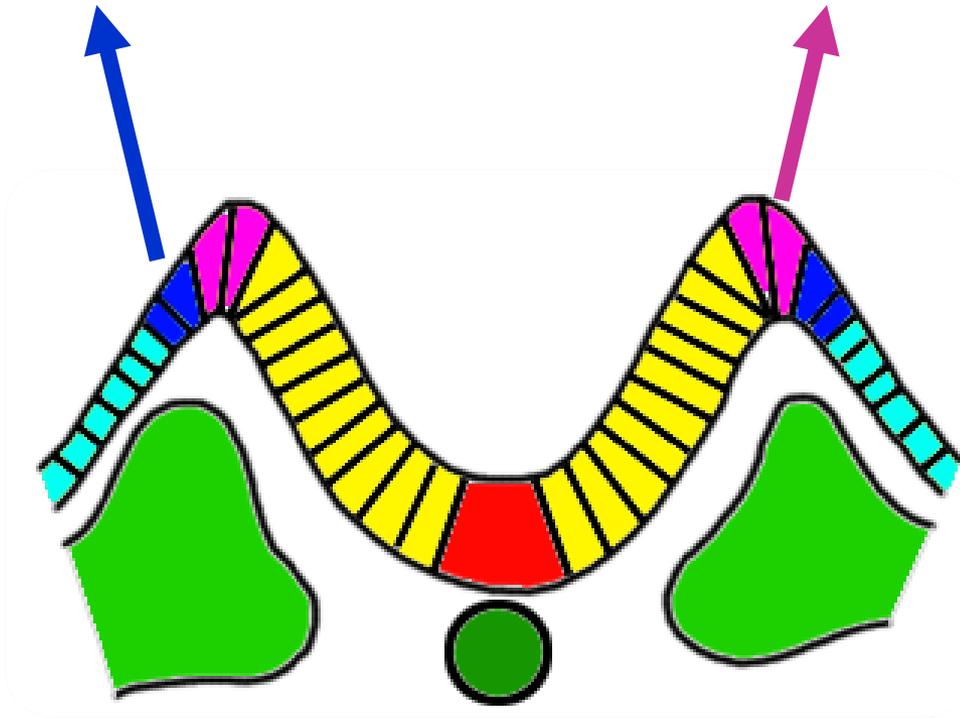
Numerous signal proteins inhibit the activity of BMP/Activin, thereby maintaining the default mechanism ( neural tube )

# DIFFERENTIATION



**Placode:** cranial and/or lateral epithelial thickenings may form vesicles

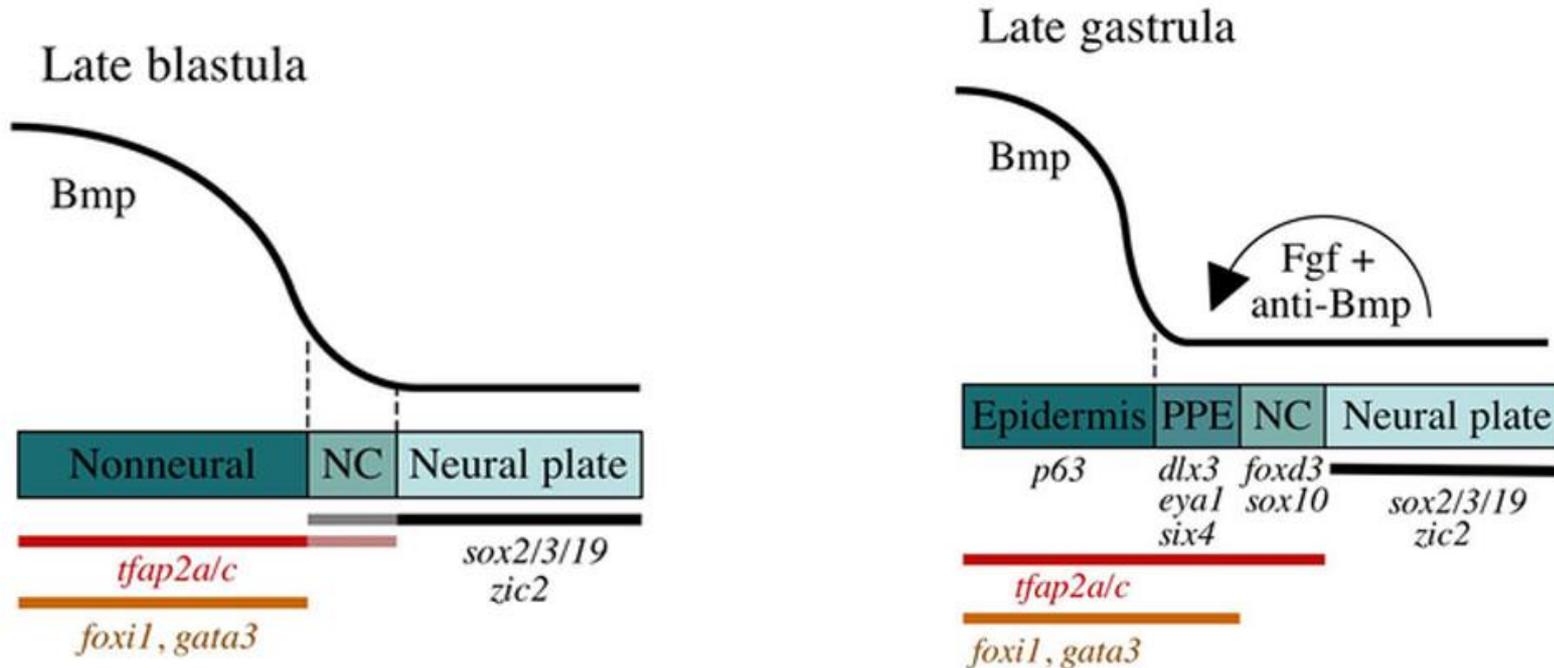
**Neural crest:** caudal and medial region may induce epithelio-mesenchymal transition



# PLACODE

Placodes are **localized regions of columnar epithelium** that develop from ectoderm between the 10- and 30-somite stage at the **border** between **neural plate/neural crest and the future epidermis.**

# PREPLACODAL DEVELOPMENT MODEL



***Bmp acts as a morphogen that specifies neural crest (NC) within a narrow but low range of signalling.***

***Preplacodal ectoderm (PPE) fate is specified in competent cells near the neural-nonneural border by dorsally expressed Bmp antagonists, Fgf and Pdgf.***

***Changing levels of Bmp do not distinguish preplacodal from epidermal potential.***

***Complete attenuation of Bmp is required for PPE specification.***



## NEUROGENIC PLACODES

### DORSOLATERAL PLACODES

- **trigeminal** placode, which consists of ophthalmic and maxillomandibular parts, and gives rise to the cells of the trigeminal ganglion
- **otic** placode forms the otic pit and the otic vesicle, giving rise eventually to organs of hearing and equilibrium.

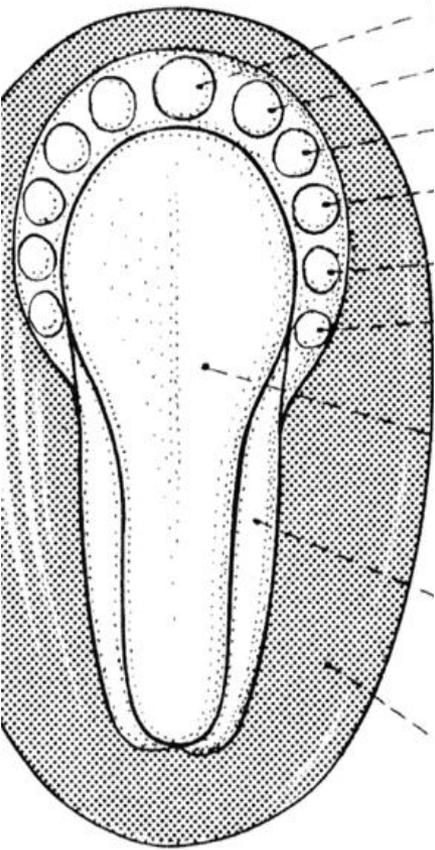
**EPIBRANCHIAL** or *epipharyngeal* placodes generate the distal portion of the ganglia of cranial nerves VII, IX and X:

- **geniculate** placode, associated with the first branchial cleft generates the geniculate ganglion and distal parts of cranial nerve VII
- **petrosal** placode, associated with the second branchial cleft generates the glossopharyngeal ganglion, and distal parts of cranial nerve IX
- **nodosal** placode, associated with the third branchial cleft, generates the nodose ganglion and distal parts of cranial nerve X
- **olfactory** placode (or *nasal placode*<sup>(1)</sup>) gives rise to the olfactory epithelium

### NON-NEURAL PLACODES

- **lens** placode under the direction of the optic vesicle gives rise to the lens of the eye.
- **adenohypophyseal** placode, which forms the anterior lobe of the pituitary gland.

# CRANIAL PLACODES

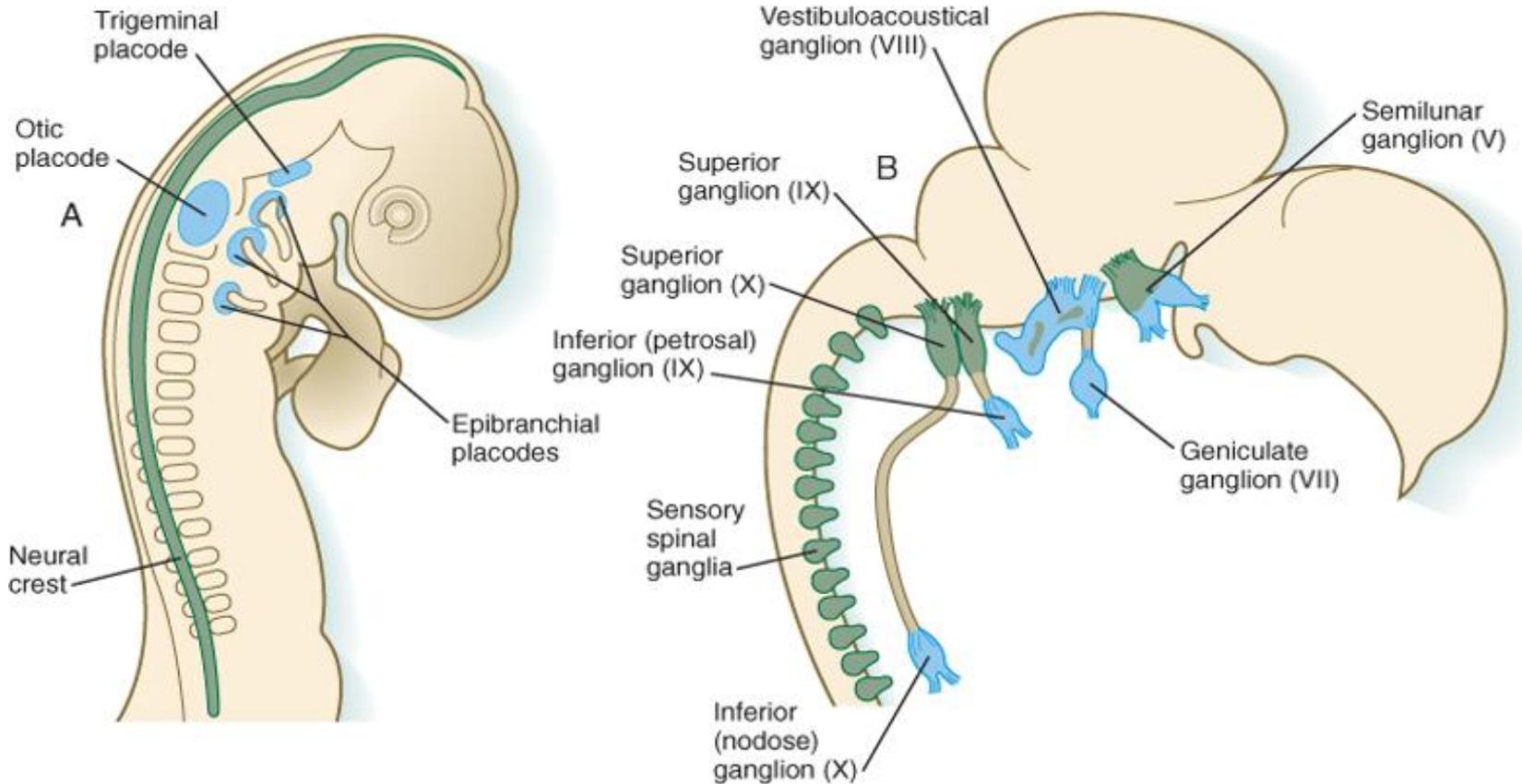


<b>Hypophyseal</b>	<i>Rathke's pouch</i> → Adenohypophysis
<b>Olfactory</b>	<i>Olfactory epithelium</i>
<b>Lens</b>	<i>Lens</i>
<b>Trigeminal</b>	<i>Trigeminal ggl. (partially)</i>
<b>Otic</b>	<i>Otic vesicle</i> → membranous labyrinth, spiral+vestibular ggl(CN8)
<b>Epibranchial</b>	<i>Epibranchial</i> → taste buds, geniculate ggl.(CN7.), inf ggl (CN9, 10)
<b>Neural plate</b>	→ CNS
<b>Neural crest</b>	→ Ganglia etc.
<b>Ectoderm</b>	→ Epidermis etc.

# CRANIAL PLACODES IN THE CHICK EMBRYO

Neural crest

Placode



# NEURAL CREST

The neural crest are **bilaterally paired** strips of cells arising in the ectoderm at the **margins of the neural tube**.

These cells **migrate** to many different locations and **differentiate** into many cell types within the embryo.

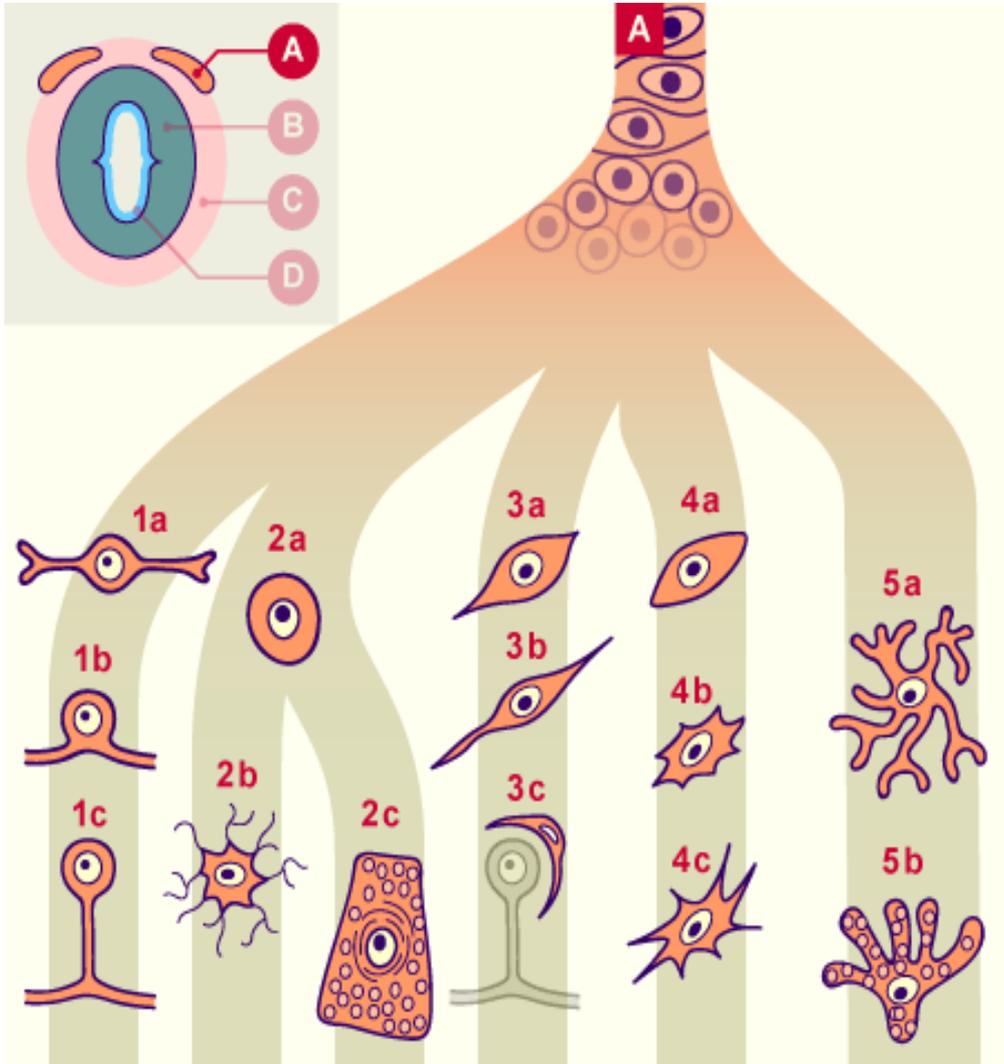
# THE NEURAL CREST

The neural crest is a *transient* and *multipotent* cell population arising at the *edge of the neural plate* in vertebrates.

Recent findings highlight that *neural crest patterning is initiated during gastrulation*, i.e. earlier than classically described, in a progenitor domain named the neural border.

**The rostral forebrain DOES NOT form neural crest cells**

# DERIVATIVES OF THE NEURAL CREST



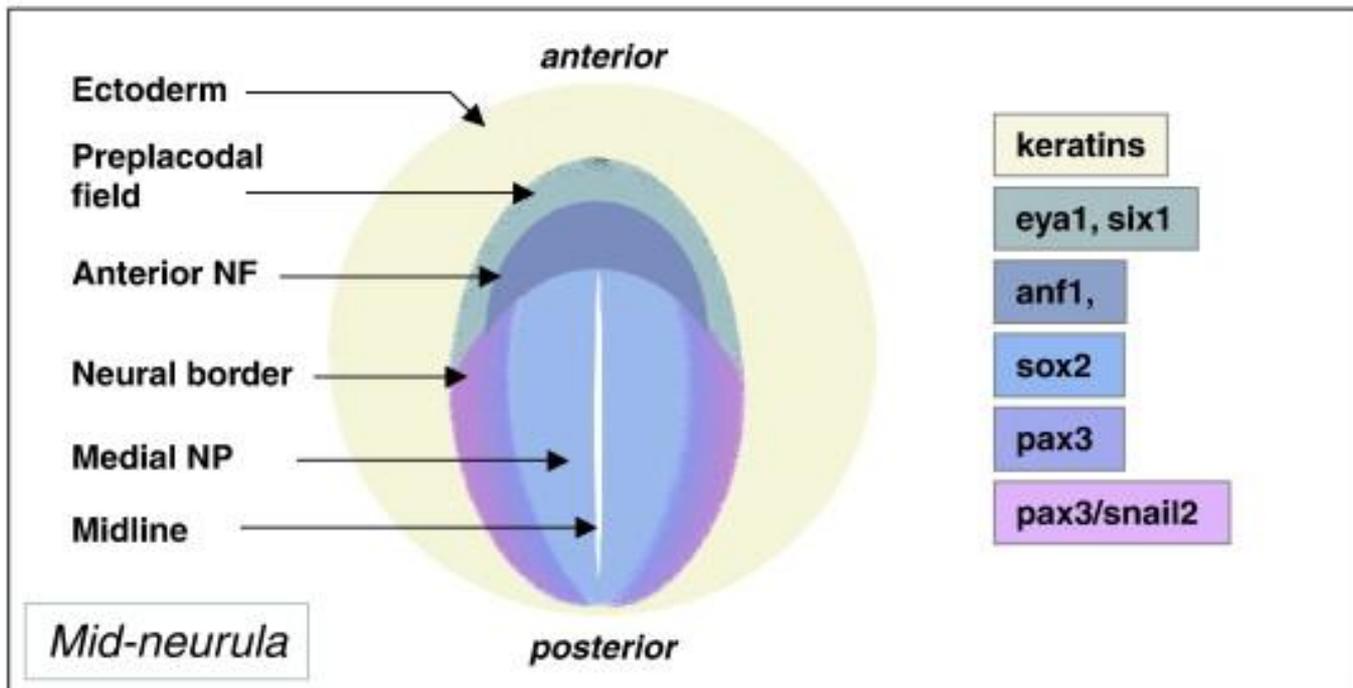
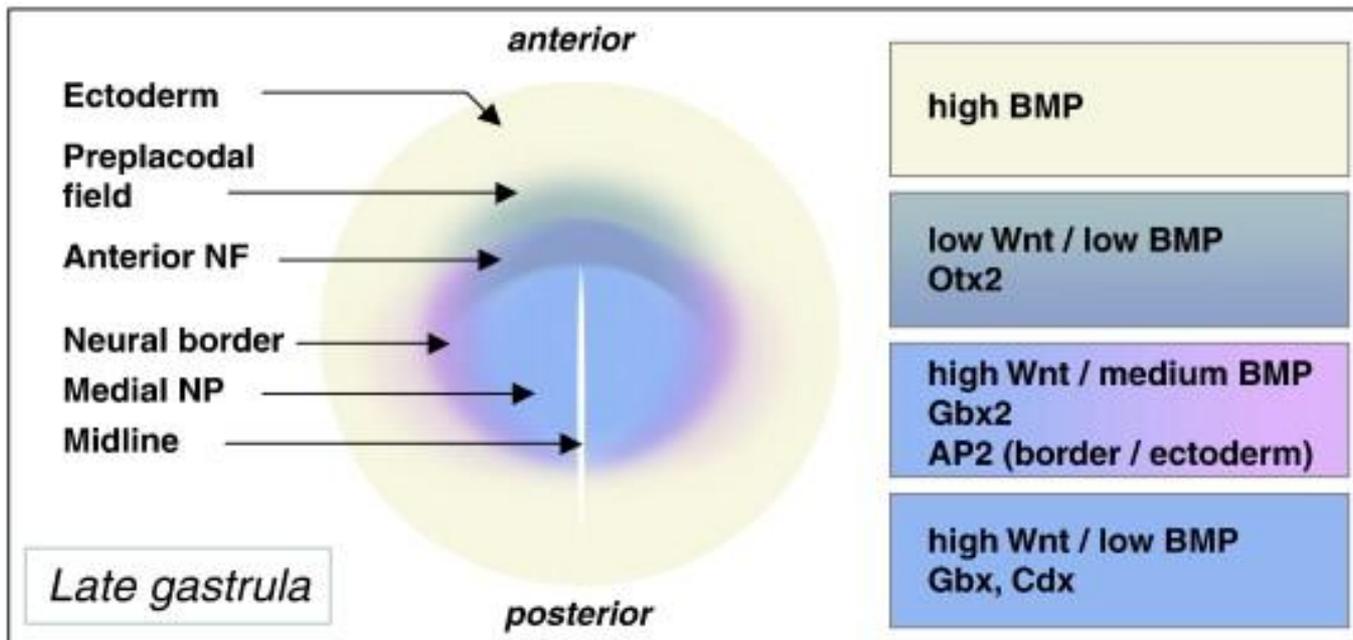
1a bipolar neuroblast  
 1b differentiating neuroblast  
 1c pseudounipolar sensory neuron

2a unipolar neuroblast  
 2b vegetative ganglion cells  
 (multipolar)  
 2c adrenal medulla - chromaffin cells

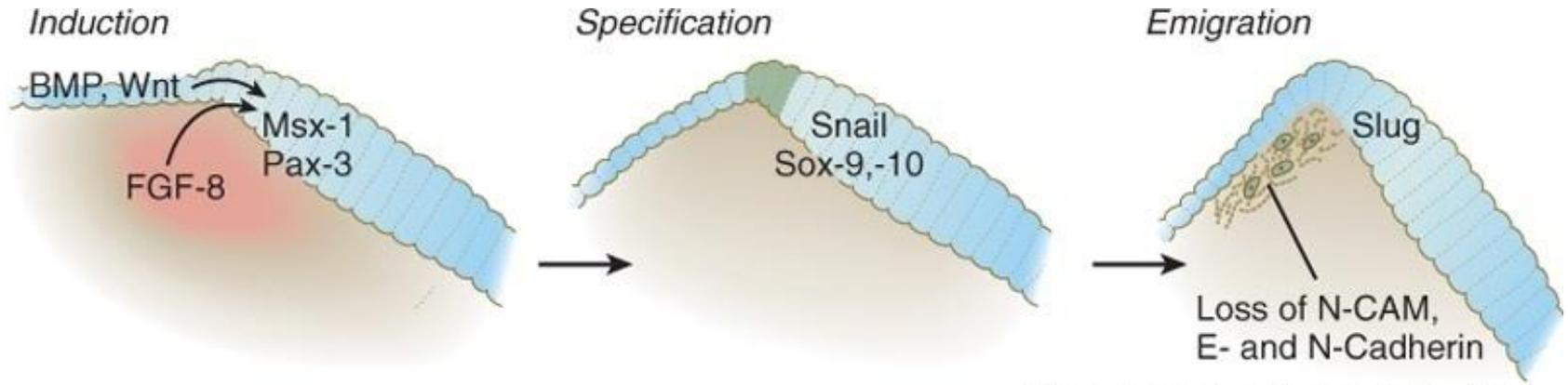
3a glioblast  
 3b Schwann cells  
 3c satellite cells

4a mesenchymal cells  
 4b leptomeningeal cells  
 4c ectomesenchymal cells

5 pigment cell  
 5b melanocyte



# NEURAL CREST INDUCTION



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## MOLECULAR REGULATION

**ectoderm:** BMP, Wnt

**mesoderm** FGF-8 (amphibian data)

*epidermal ectoderm* - high concentration of BMP

*neural ectoderm* - low concentration of BMP

*neural crest* - medium concentration of BMP

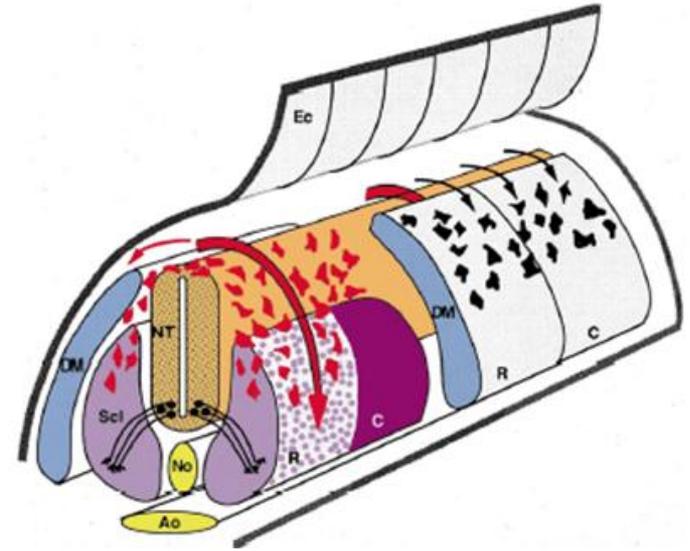
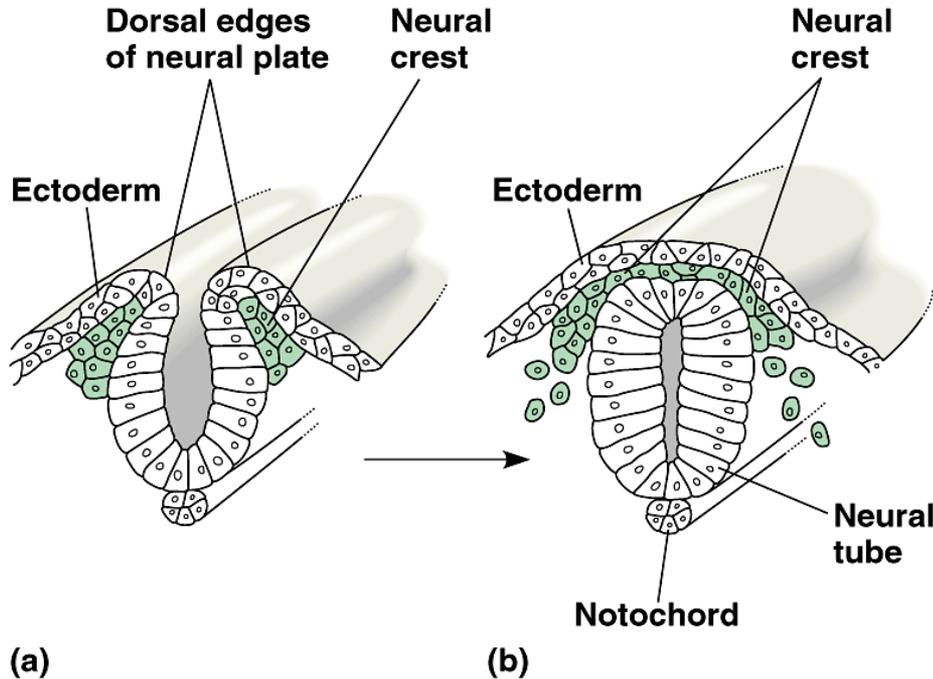
Msx-1, Pax-3 expression starts (characteristic for NC cells)

snail-1 and slug (snail-2) expression is needed for EMT

**slug** is expressed at gastrulation as well

Changes in adhesion properties (adhesion molecules)

# DERIVATIVES OF THE NEURAL CREST



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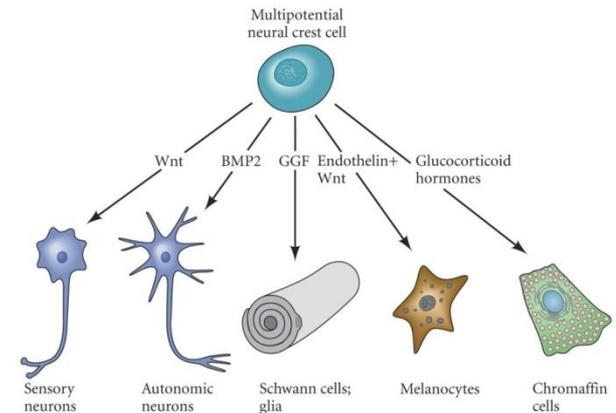
(b)

Migration into the mesenchymal layer

**Craniocaudal streams**

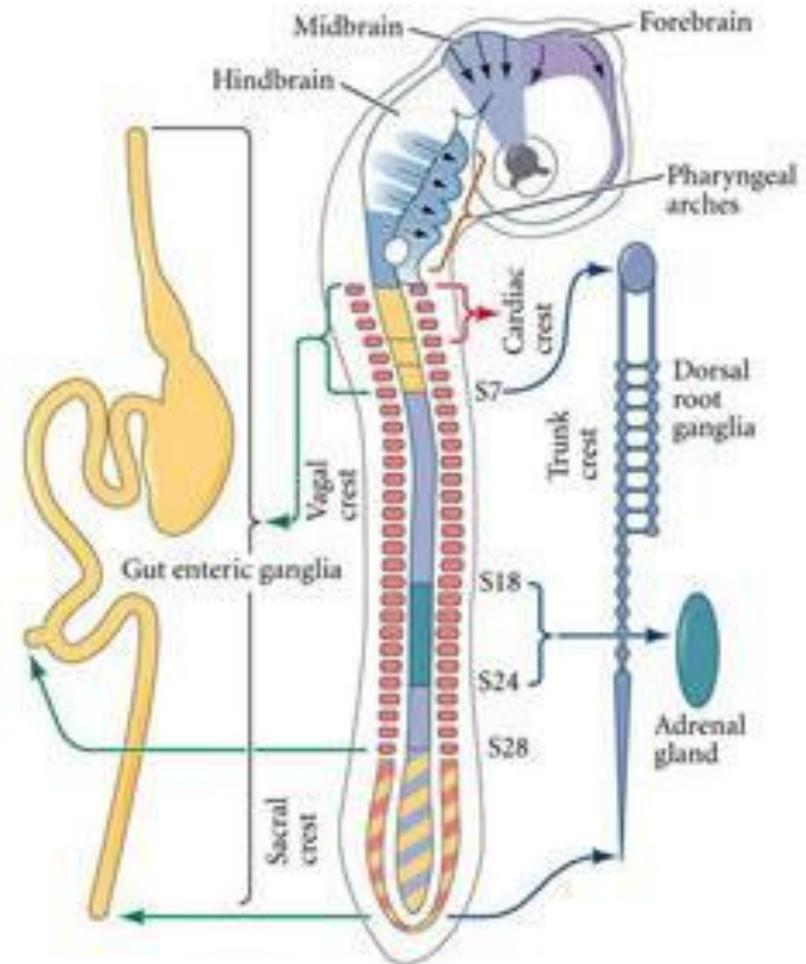
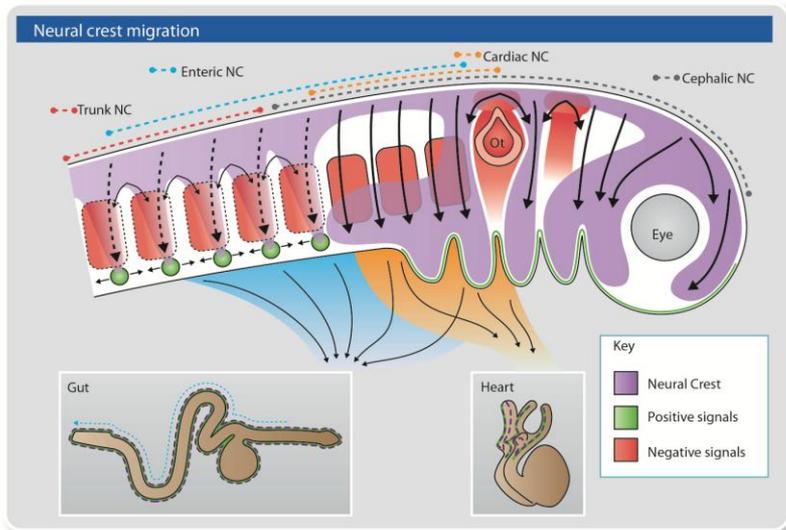
EMT - Epithelial – to - mesenchymal transformation

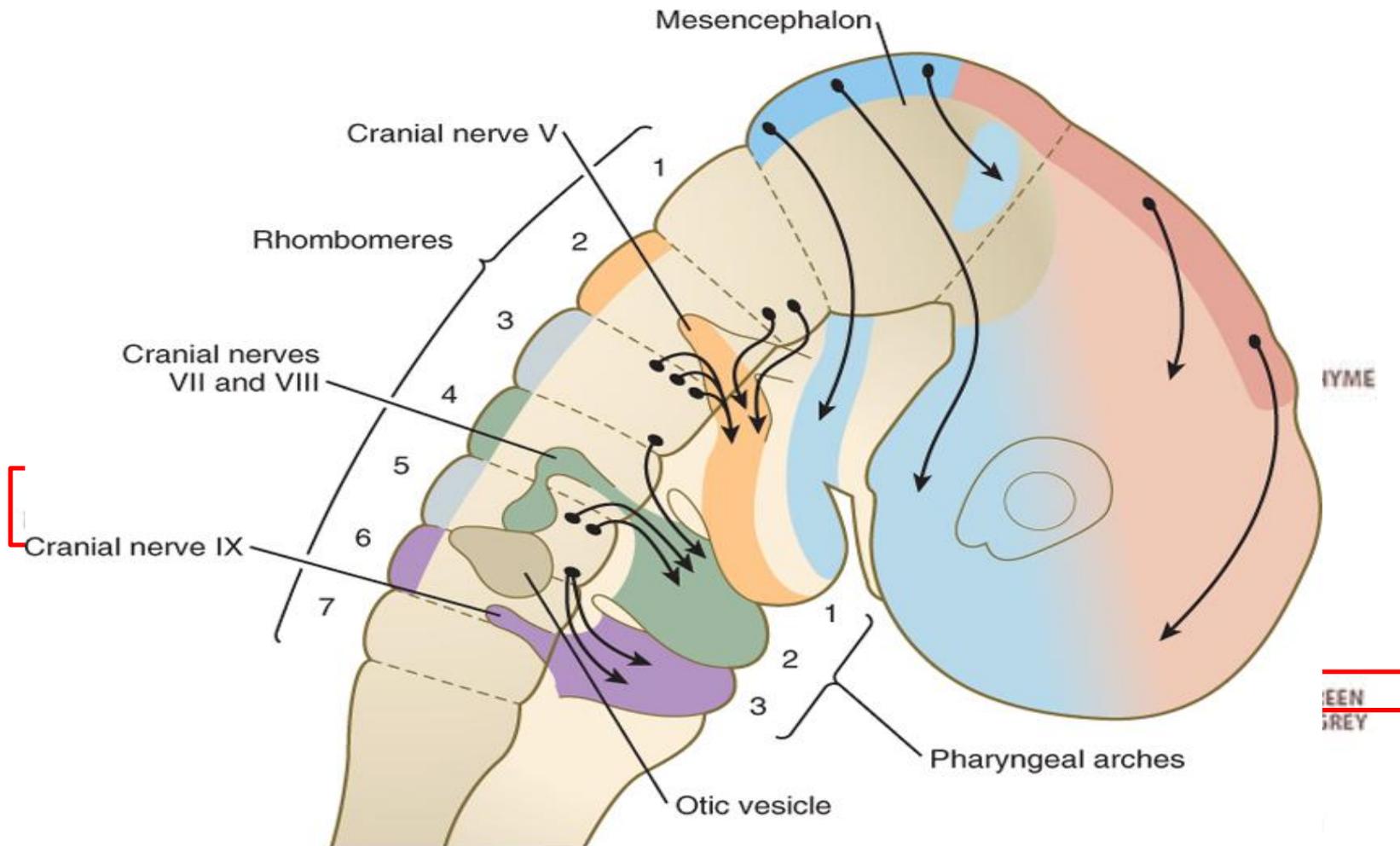
Influenced by: ECM molecules, growth factors



# REGIONS OF THE NEURAL CREST

- Cranial (caudal to the forebrain until the 6th rhombomere)
- Vagal (between somites 1-7)
- Truncal (somites 8-28)
- Lumbosacral (caudal to somite 29)





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Rhombomeres

1,2,(3) →

Rhombomeres

(3),4,(5) →

Rhombomeres

(5),6,7,8 →

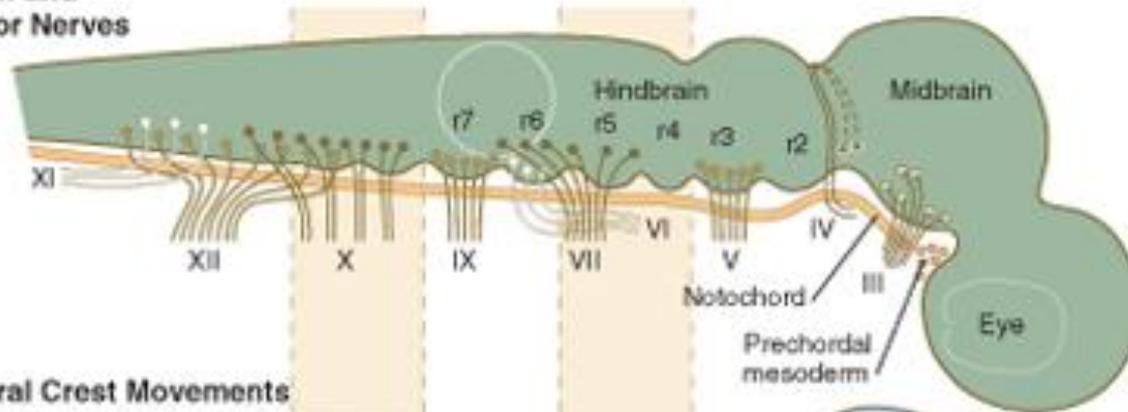
NC cell migration in 3 streams:

- 'trigeminal' – around 3 divisions of CN V. (1st branchial arch\*+frontonasal process)
- 'hyoid' – into 2. branchial arch
- 'postotic' (= behind otic vesicle) – into branchial arches 3-6.

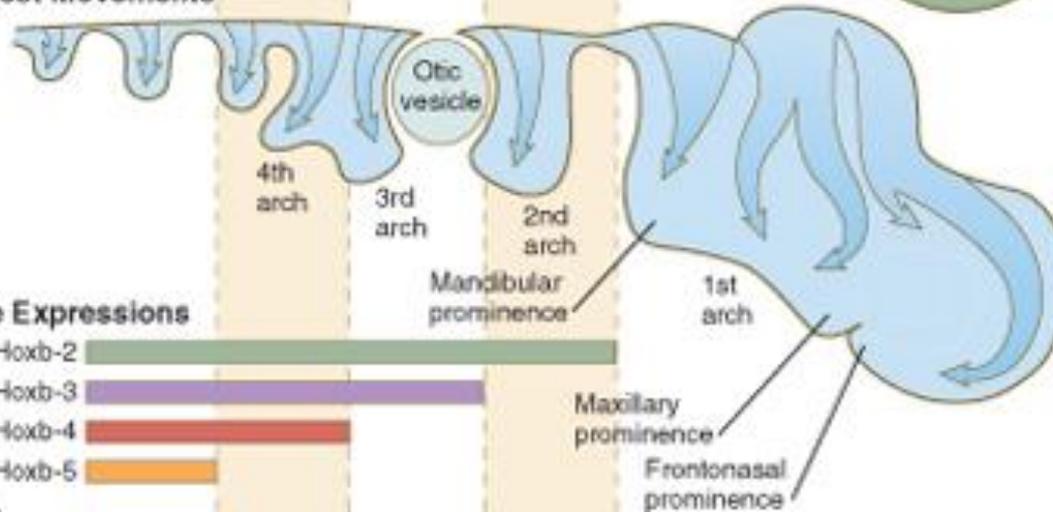
**Ectomesenchyme:** bones, cartilage, connective tissue, vessels

\* 2 of 3 auditory ossicles, jaw (Meckel's cartilage)- skull - new head"

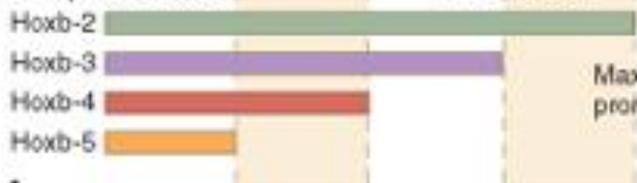
**Brain and Motor Nerves**



**Neural Crest Movements**



**Hox Gene Expressions**



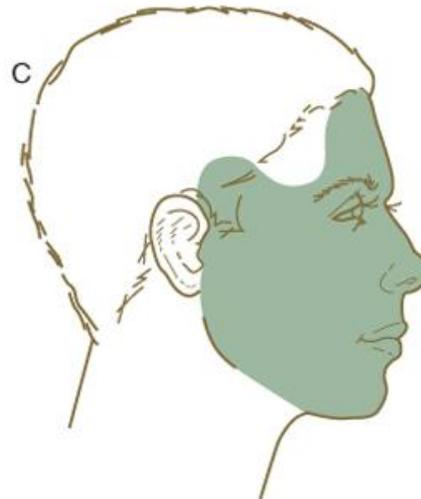
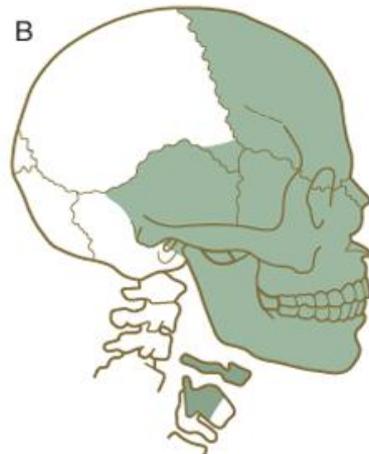
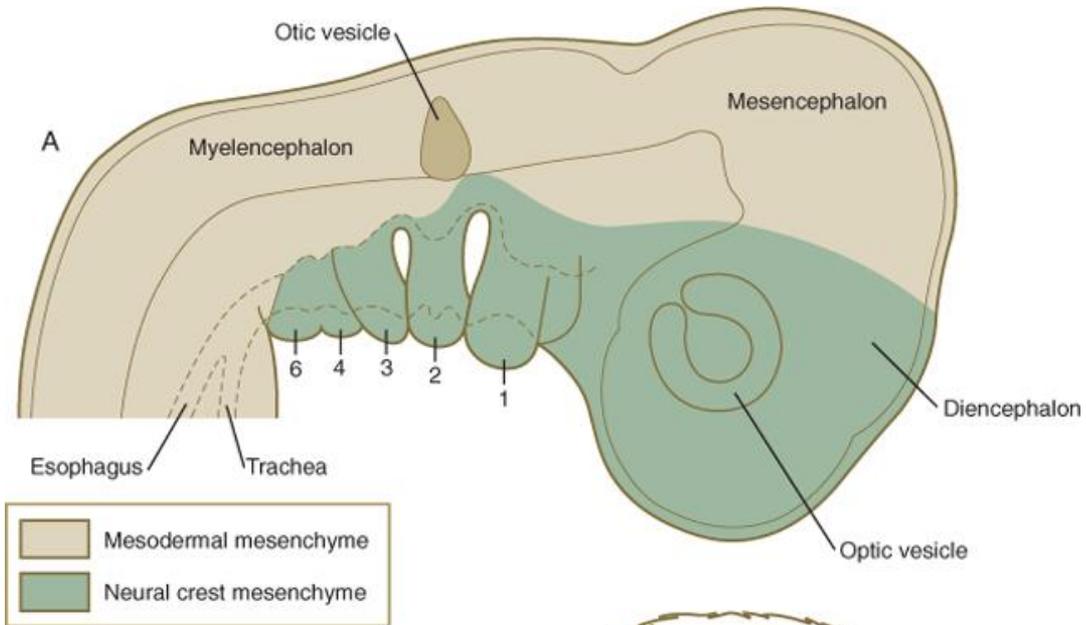
*5th and 6th prosomere levels do not give rise to neural crest*

*NC from hindbrain levels colonise the 1st-3rd pharyngeal arches.*

*Each rhombomeric and mesencephalic crest cell „remember” to the segmental code.*

*In the pharyngeal region, the pathways of crest cell migration are in close relation with HOXB gene expression*

*Cells of the cranial crest may be patterned with level –specific instructions, the trunk crest regulation seems to be different.*



# NEURAL CREST - HEAD REGION

## *NEURAL DERIVATIVES*

### *general sensory ganglia*

- superior ganglia of CN 9 and CN 10
- part of the trigeminal ganglion (+ from placode)

### *autonomic ganglia*

- ciliary (CN 3)
- pterygopalatine, submandibular (CN 7), otic (CN 9) ganglia  
*all from the 2nd rhombomer*  
*(arising from the vicinity of CN 5 branches)*

# NEURAL CREST - HEAD REGION

## *ECTOMESENCHYMAL TISSUE*

***bones of the skull*** (frontal, parietal, temporal squama, nasal, vomer, palatine, maxillae, mandible)

***meninges*** (choroid and sclera )

***dentin***

***glandular connective tissue*** (lacrimal, nasal, labial, palatine, oral, salivary , thyroid, parathyroid, thymus)

***connective tissue of the head*** (melanocytes, cartilage, ligaments, tendons)

***conotruncal septum*** (tunica media of the outflow tract of the heart and the great vessels )

# NEURAL CREST - TRUNK REGION

1 - cells which migrate through the *dorsal pathway*, differentiate to *melanocytes* in the skin and hair follicles

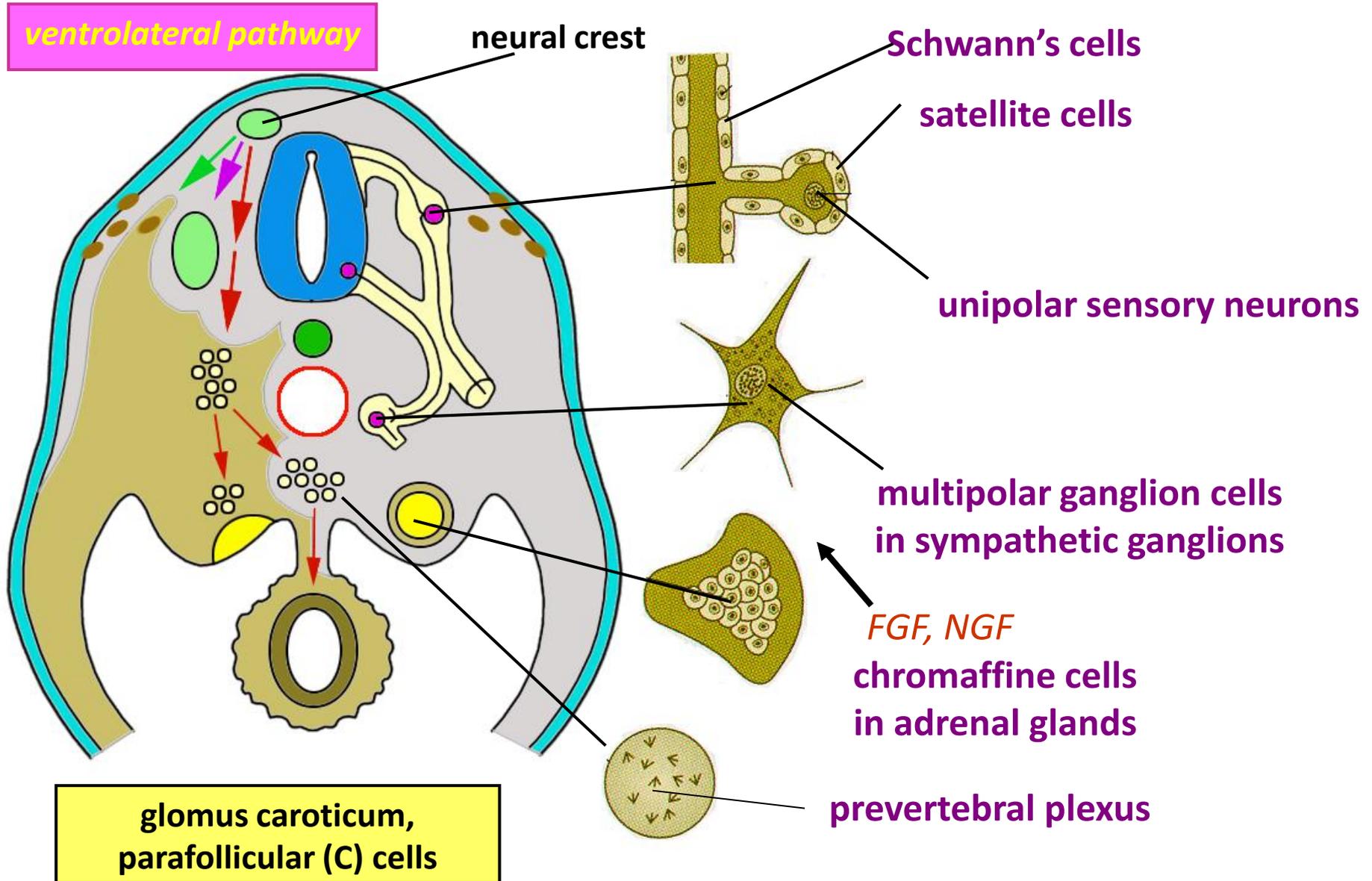
2 - cells which migrate through the *ventral pathway* may choose between two fates

*ventrolateral migration* between the dermatomyotome and sclerotome form *sensory ganglia* and the accompanying *glial satellite cells* and *Schwann cells*

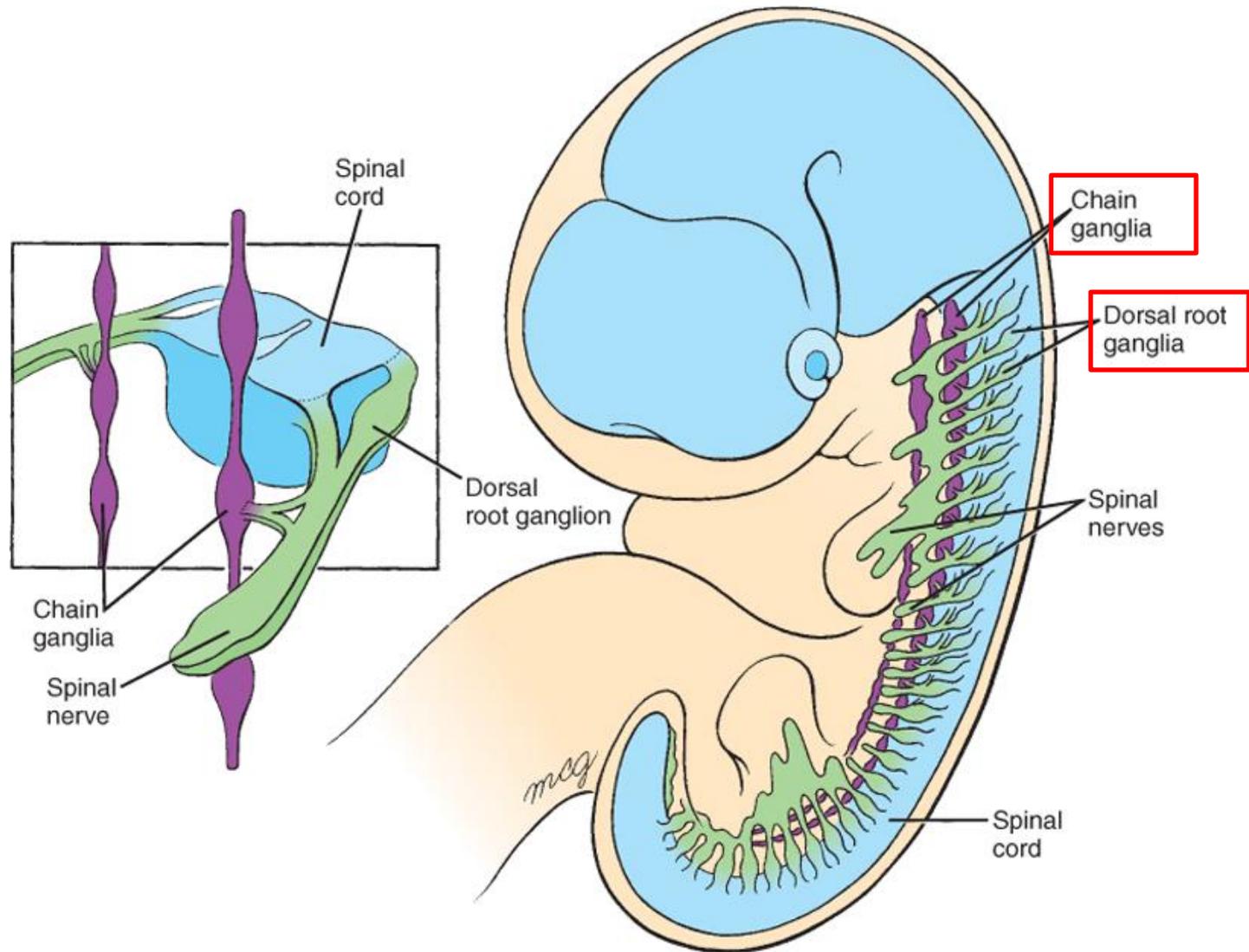
*ventromedial pathway* between sclerotome and neural tube form *sympathetic and enteric neurons, satellite cells, Schwann cells*, and cells of the *adrenal medulla*.



# NEURAL DERIVATIVES OF THE TRUNCAL NEURAL CREST



# PERIPHERAL NERVOUS SYSTEM



# SYMPATHETIC PREVERTEBRAL GANGLIA

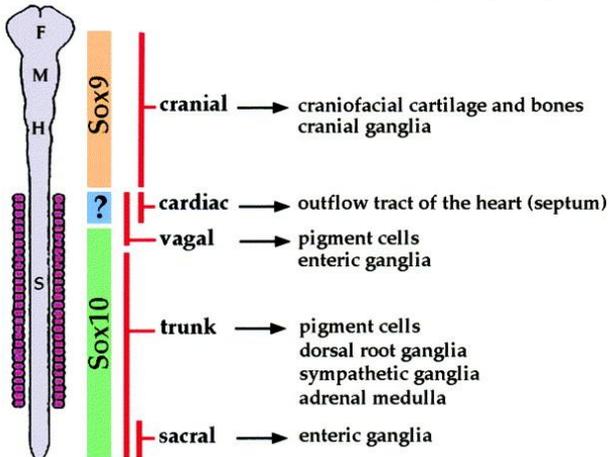
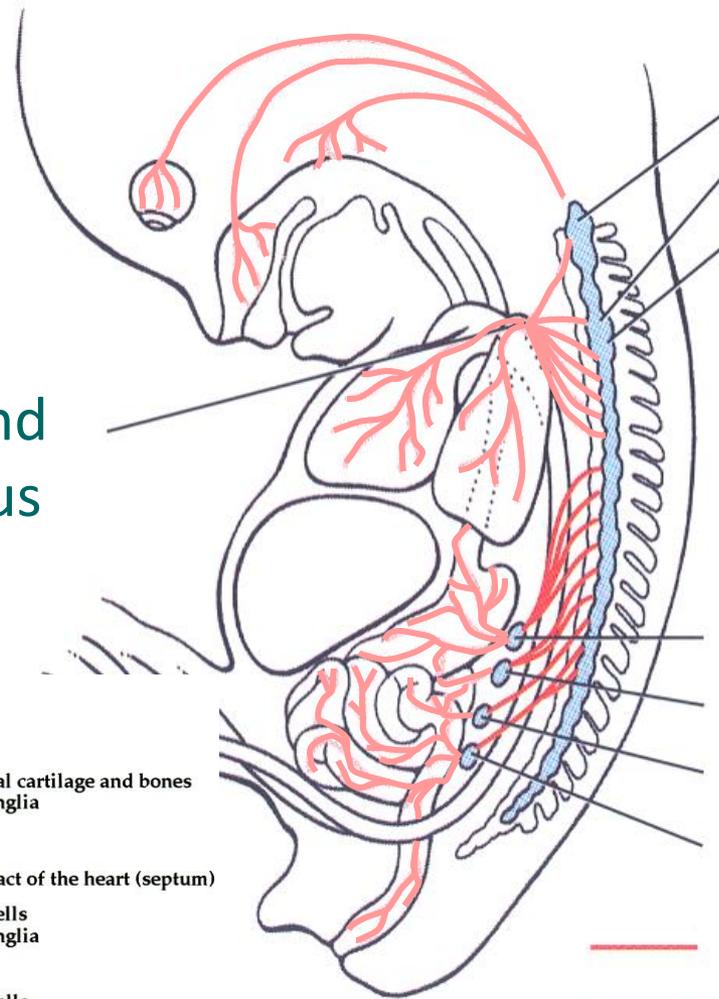
T1-T4

Superior & middle cervical & stellate ganglion

T5-L2

Celiac ganglion  
 Sup. mesenteric ggl.  
 Aorticorenal ggl.  
 Inf. mesenteric ggl.  
 Preganglionic fibers  
 Postganglionic fibers

Cardiac and lung plexus



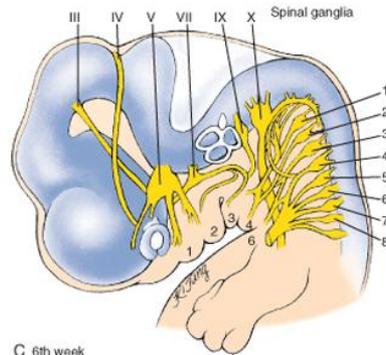
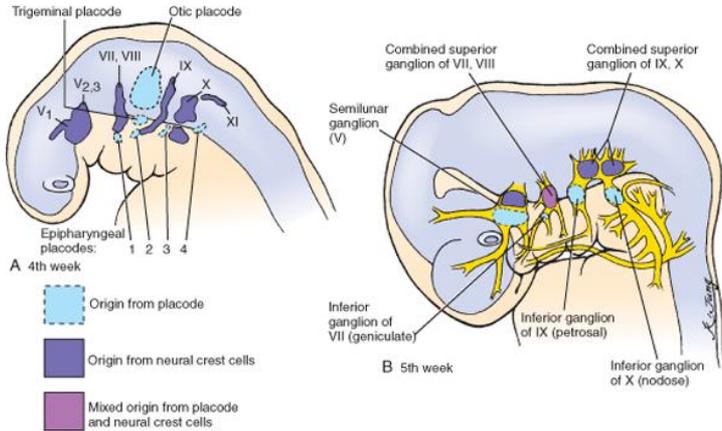
# MESENCHYMAL DERIVATIVES OF CEPHALIC AND CARDIAC CREST

<i>Tissue type</i>	<i>Organ, structure</i>	<i>Neurocristopathia</i>
<b>Bones</b>	frontal, parietal, temporal (squamous part), vomer, nasal, palatine bones, maxilla, mandibula, etc.)	palatine clefts, frontonasal dysplasia, choanal atresia
<b>Meninges</b>	pia mater, arachnoidea, dura mater (?)	
<b>Eye (connective tissue, smooth muscle)</b>	iris (stroma), choroid, ciliary body, sclera, orbit, ciliary muscles	hypertelorism, coloboma, other eye malformations
<b>Connective tissue</b>	cartilages, ligaments, tendons of the head	cleft lip
<b>Connective tissue of glands</b>	lacrimal, salivary, nasal, palatine, labial, oral glands, thyroid, parathyroid glands, thymus	DiGeorge syndrome (hypoparathyroidism, immune deficiency, thyroid tumors)
<b>Teeth</b>	odontoblasts (dentin)	dental malformations
<b>Heart</b>	outflow tract, aorticopulmonary septum, tunica media of vessels	septum defects, aortic arch defects

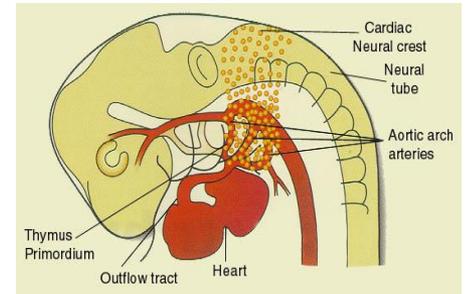
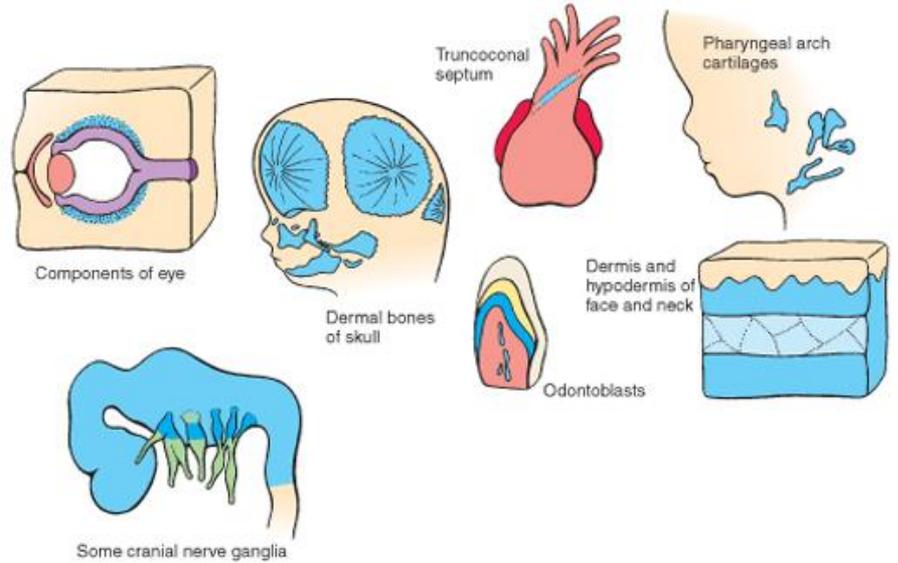
# NEURAL DERIVATIVES OF TRUNCAL AND VAGAL CREST CELLS

<i>Organ</i>	<i>Cell type</i>	<i>Neurocristopathy</i>
Cortex of adrenal gland	tumor of adrenal gland or ganglion	neuroblastoma
Cortex of adrenal gland	tumors of chromaffine tissue or adrenal gland	phaeochromocytoma
Skin	melanocytes	Waardenburg syndrome, albinism
Colon (vagal crest)	intramural ganglion cells of colon	Hirschsprung's disease (megacolon congenita)
Small intestine	enteric nerve cells, (enterochromaffine cells)	carcinoid tumors
(Truncal crest)	periferal nerves	neurofibromatosis (von Recklinghausen's disease)

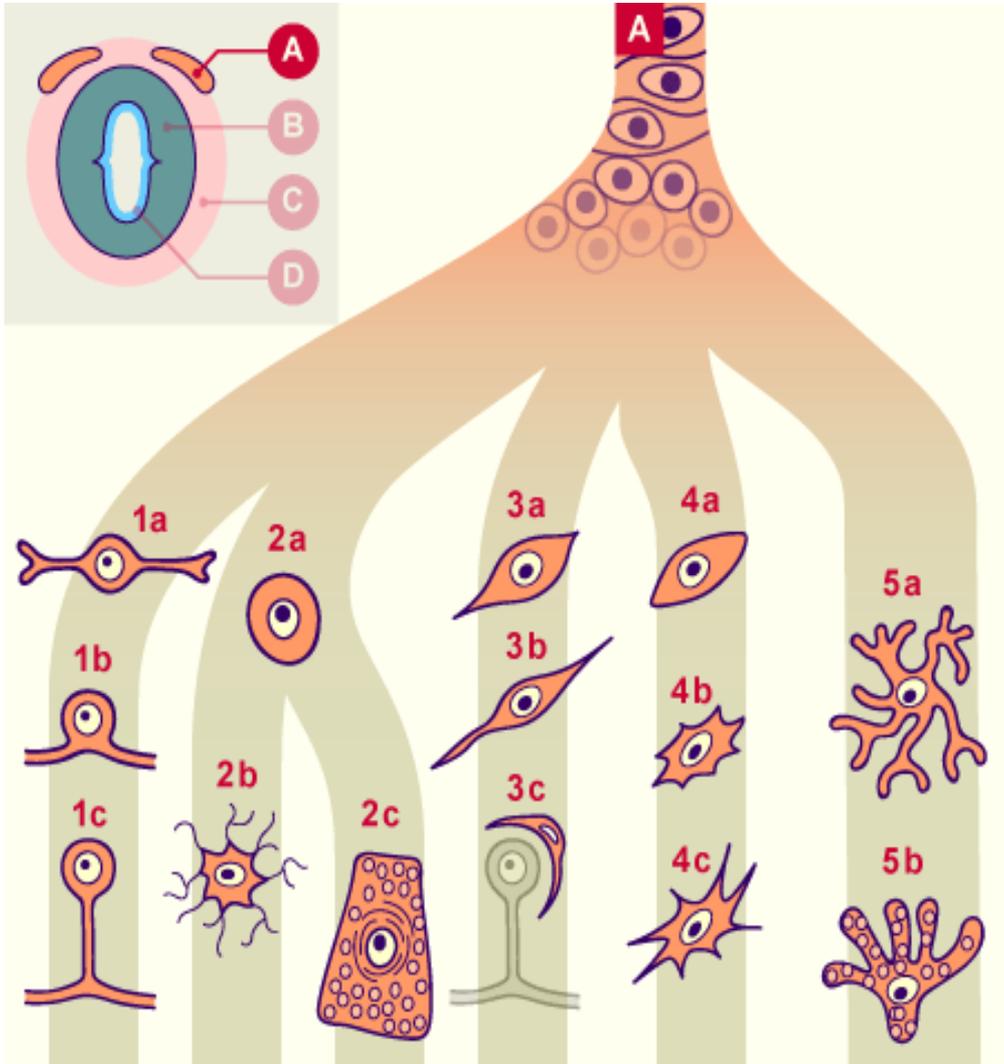
# NEURAL AND NON-NEURAL DERIVATIVES OF THE CRANIAL NEURAL CREST



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# DERIVATIVES OF THE NEURAL CREST



1a bipolar neuroblast  
 1b differentiating neuroblast  
 1c pseudounipolar sensory neuron

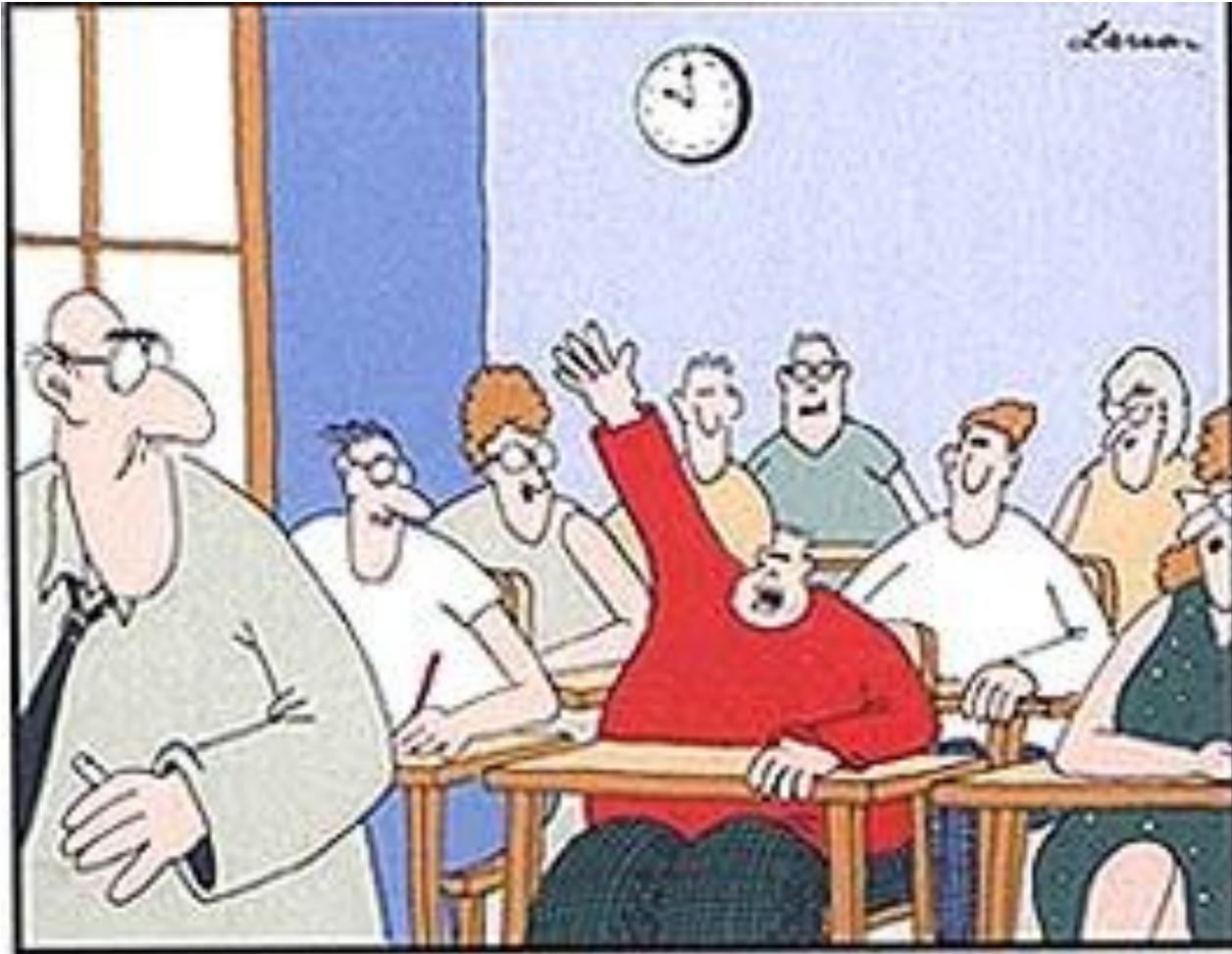
2a unipolar neuroblast  
 2b vegetative ganglion cells  
 (multipolar)  
 2c adrenal medulla - chromaffin cells

3a glioblast  
 3b Schwann cells  
 3c satellite cells

4a mesenchymal cells  
 4b leptomenigeal cells  
 4c ectomesenchymal cells

5 pigment cell  
 5b melanocyte

Thank you for your attention!



**"Mr. Osborne, may I be excused?  
My brain is full."**

# Neural Crest Cells

- These processes are known collectively as the **dorsal sensory root of the spinal nerve**. *The peripherally growing processes join fibers of the ventral* motor roots and thus participate in formation of the trunk of the spinal nerve.
- Eventually these processes terminate in the sensory receptor organs.
- Hence, neuroblasts of the sensory ganglia derived from neural crest cells give rise to the **dorsal root neurons**.
- In addition to forming sensory ganglia, cells of the neural crest differentiate into sympathetic neuroblasts, Schwann cells, pigment cells, odontoblasts, meninges, and mesenchyme of the pharyngeal arches.

