Neural crest and its derivatives.

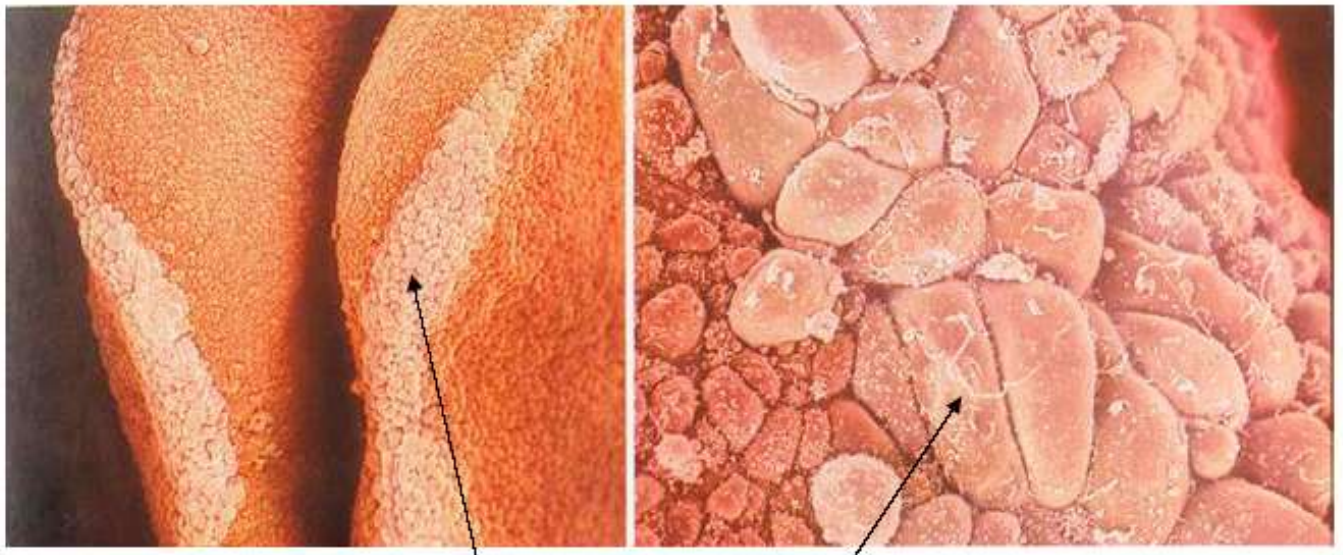
Dr. Nandor Nagy

Semmelweis University

Neural crest cells are a unique population of cells that arise from the dorsal part of the forming neural tube during neurulation and gives rise to a diverse cell lineage including : myofibroblasts, fibroblasts, cartilage, bone, melanocytes, endocrine cells, peripheral neurons, glial cells

.

3 weeks old human embryo

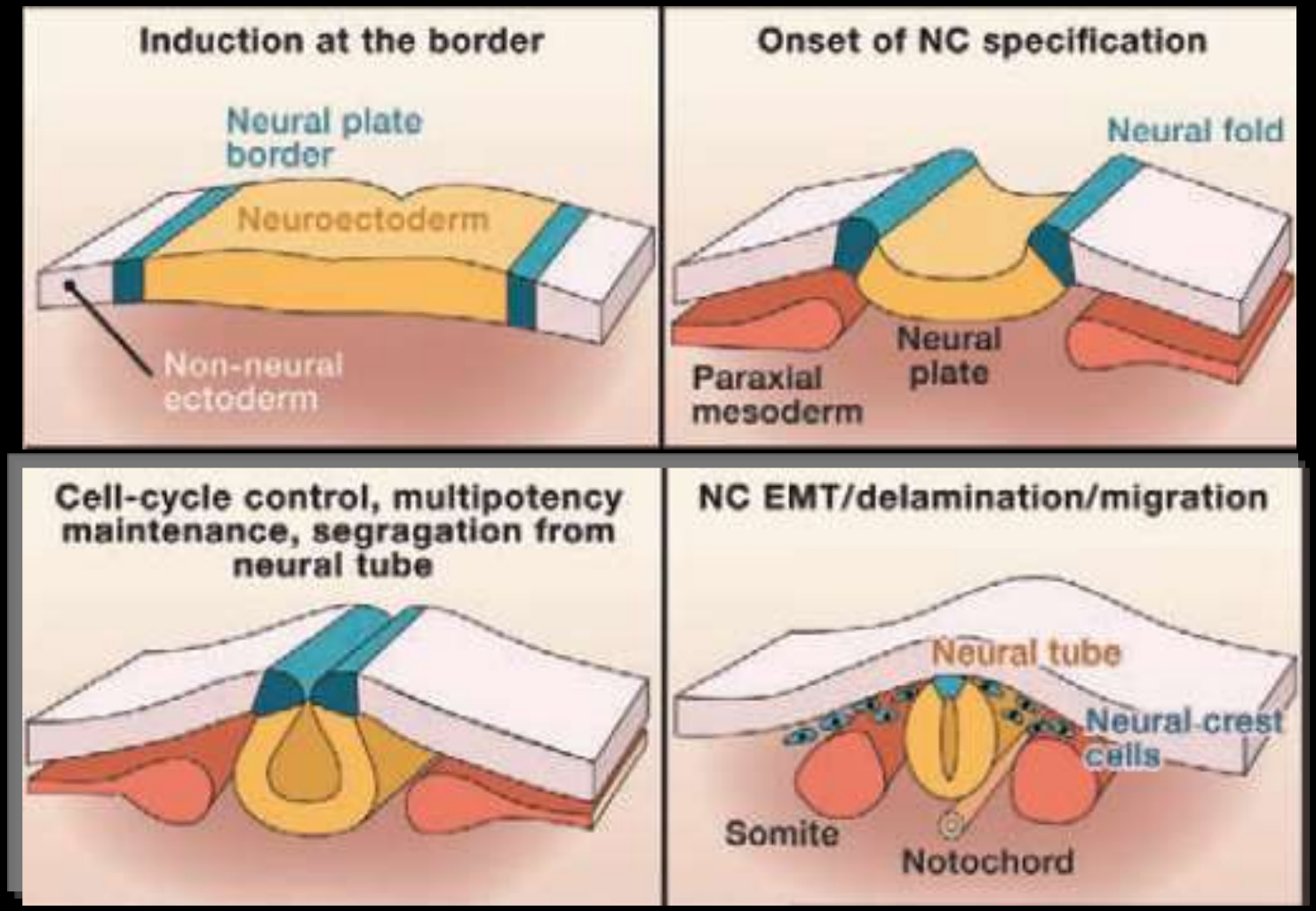


Some of these will become Neural Crest

Neural Crest Derivatives

Derivative	Cell type or structure derived
Peripheral nervous system (PNS)	Neurons, including sensory ganglia, sympathetic and parasympathetic ganglia, and plexuses Neuroglial cells Schwann cells
Endocrine and paraendocrine derivatives	Adrenal medulla Calcitonin-secreting cells Carotid body type I cells
Pigment cells	Epidermal pigment cells
Facial cartilage and bone	Facial and anterior ventral skull cartilage and bones
Connective tissue	Corneal endothelium and stroma Tooth papillae Dermis, smooth muscle, and adipose tissue of skin, head, and neck Connective tissue of salivary, lachrymal, thymus, thyroid, and pituitary glands Connective tissue and smooth muscle in arteries of aortic arch origin

Source: After Jacobson 1991, based on multiple sources.



The **NC cells** undergo an **epithelial-to-mesenchymal transformation** as they detach from the neural tube.

Ganglionléc fejlődése

1. indukció
2. delamináció
3. migráció
4. differenciáció

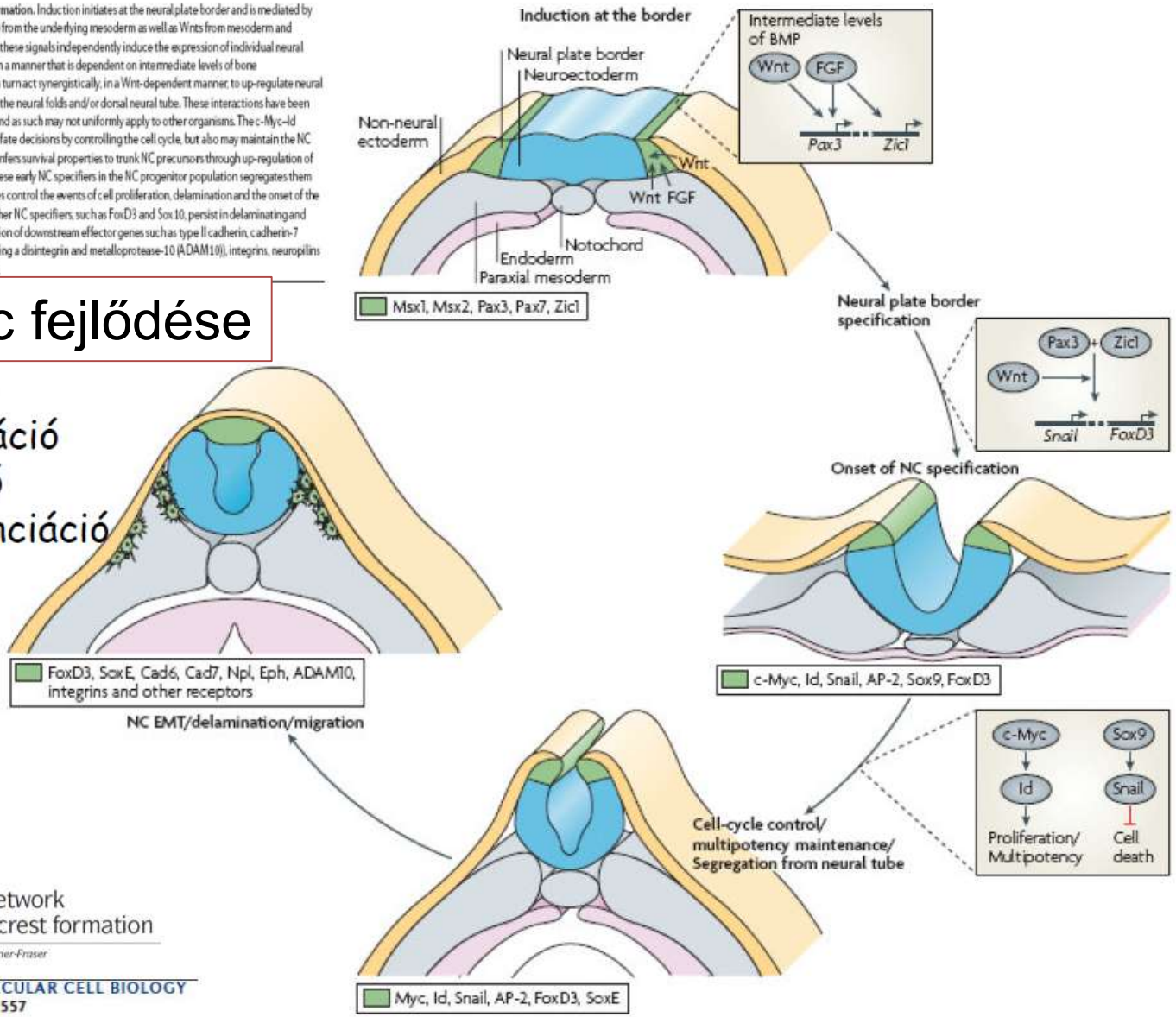


Figure 1 | **Regulatory steps in neural crest formation.** Induction initiates at the neural plate border and is mediated by signals including fibroblast growth factor (FGF) from the underlying mesoderm as well as Wnts from mesoderm and adjacent non-neural ectoderm. One or both of these signals independently induce the expression of individual neural plate border specifiers, such as *Pax3* and *Zic1*, in a manner that is dependent on intermediate levels of bone morphogenetic protein (BMP). Pax3 and Zic1 in turn act synergistically, in a Wnt-dependent manner, to up-regulate neural crest (NC) specifiers such as *Snail* and *FoxD3* in the neural folds and/or dorsal neural tube. These interactions have been primarily derived from work in *Xenopus laevis* and as such may not uniformly apply to other organisms. The c-Myc–Id cassette is a network switch that mediates cell-fate decisions by controlling the cell cycle, but also may maintain the NC progenitor pool in a multipotent state. Sox9 confers survival properties to trunk NC precursors through up-regulation of Snail, an anti-apoptotic factor. Expression of these early NC specifiers in the NC progenitor population segregates them from the dorsal neuroepithelium, as these genes control the events of cell proliferation, delamination and the onset of the epithelial to mesenchymal transition (EMT). Other NC specifiers, such as FoxD3 and Sox10, persist in delaminating and migrating NC cells, where they control expression of downstream effector genes such as type II cadherin, cadherin-7 (Cad7), matrix metalloproteases (MMPs; including a disintegrin and metalloprotease-10 (ADAM10)), integrins, neuropilins (Npl), Eph and other transmembrane receptors.

A gene regulatory network orchestrates neural crest formation

Tatjana Sauka-Spengler and Marianne Bronner-Fraser

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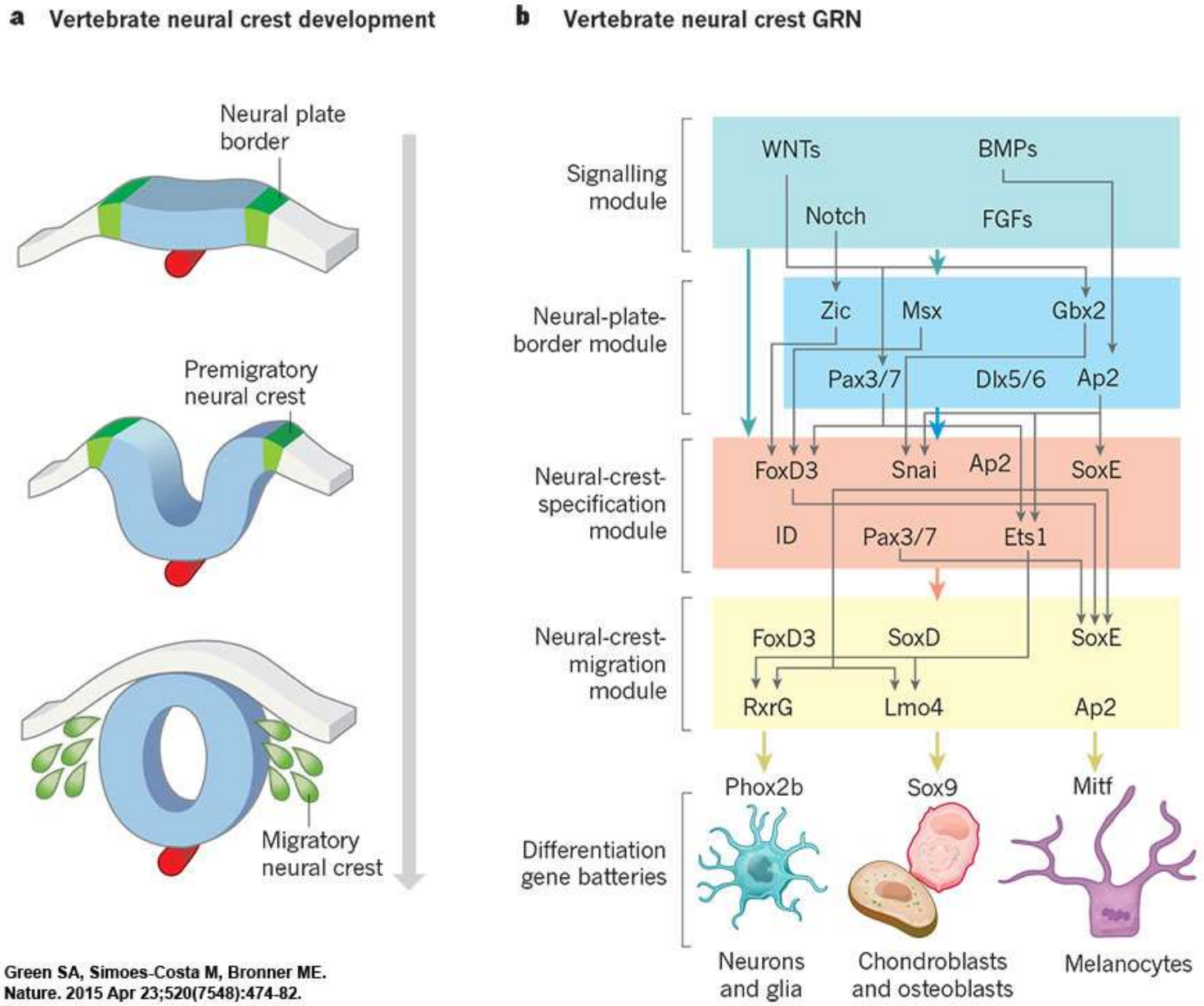
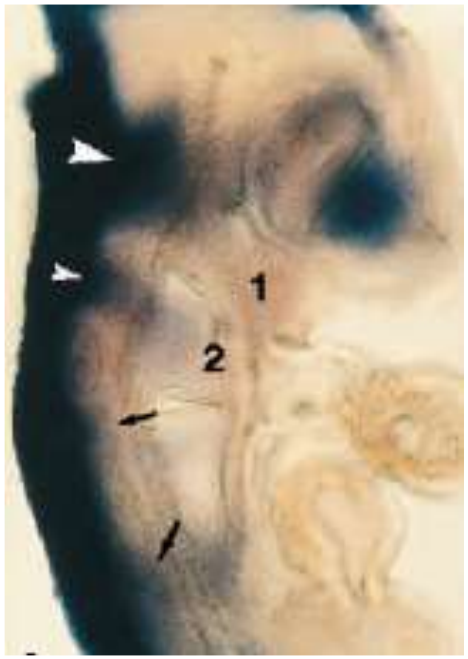
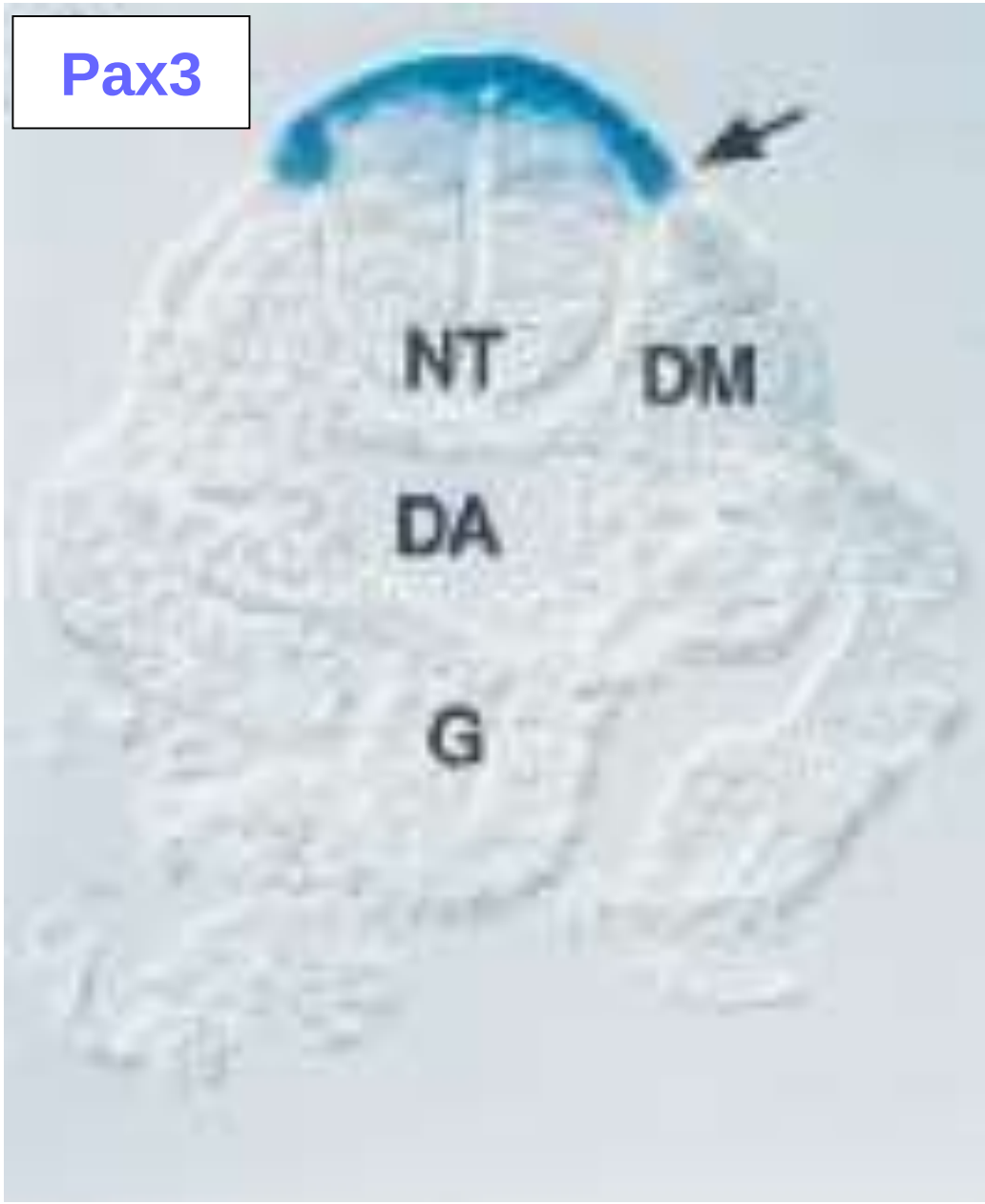


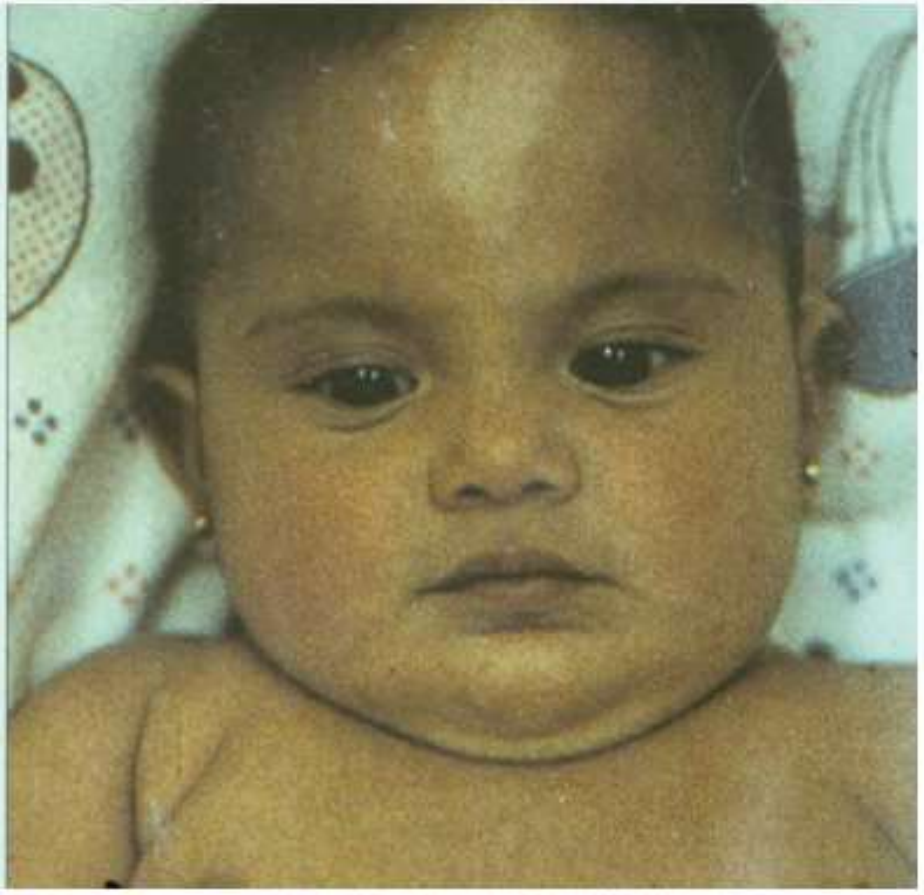
Green SA, Simoes-Costa M, Bronner ME.
Nature. 2015 Apr 23;520(7548):474-82.





Migration pathways are controlled by **extracellular matrices** and by chemotactic factors
- permissive and instructive signals
- negative signals also

Mutations in the *Pax3* or *Mitf* genes cause Waardenburg Syndrome; melanocyte migration defects, congenital deafness



Factors Influencing the Migration of Crest Cells

Permissive molecules

dissociation of lamina basalis of neural tube:
plasminogene activator

ECM components:
laminin, fibronectin, tenascin, collagene typ. IV

Cell adhesion molecules:
(cadherin)

Growth factors: Mash1, endothelin-3, neurogenin, GDNF.

Inhibitory molecules

F-spondin
(thrombospondin)

ECM components:
chondroitin-sulphate, aggrecan, versican, collagene typ. IX

Ephrin-proteins
(Ephrin B2 and B1)

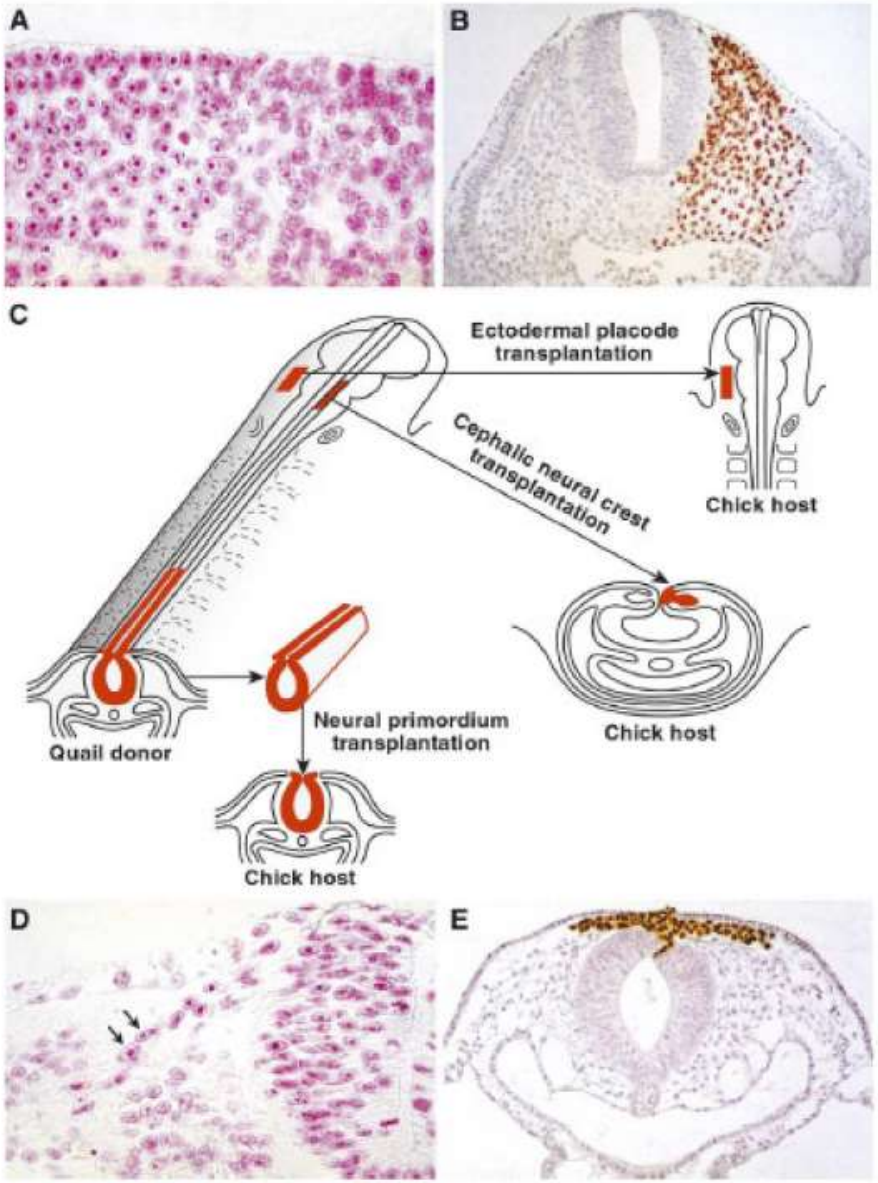
on Eph receptors

csirke-fürj kimérák

- eltérő heterokromatin szerkezet (fürj kondenzáltabb)
- QH1: fürj-specifikus magmarker

Development and evolution of the neural crest: An overview

Marianne E. Bronner *, Nicole M. LeDouarin



- NC-specifikus promoterek és markerek: Sox10, P0, Wnt1, FoxD3, $p75^{NTR}$....
- indukálható expresszió: Cre-lox, Dox, tamoxifen (ER).....
- P0-Cre/CAG-CAT-EGFP, Wnt1-Cre/FloxedEGFP, PLP-CreERT2/R26YFP, stb

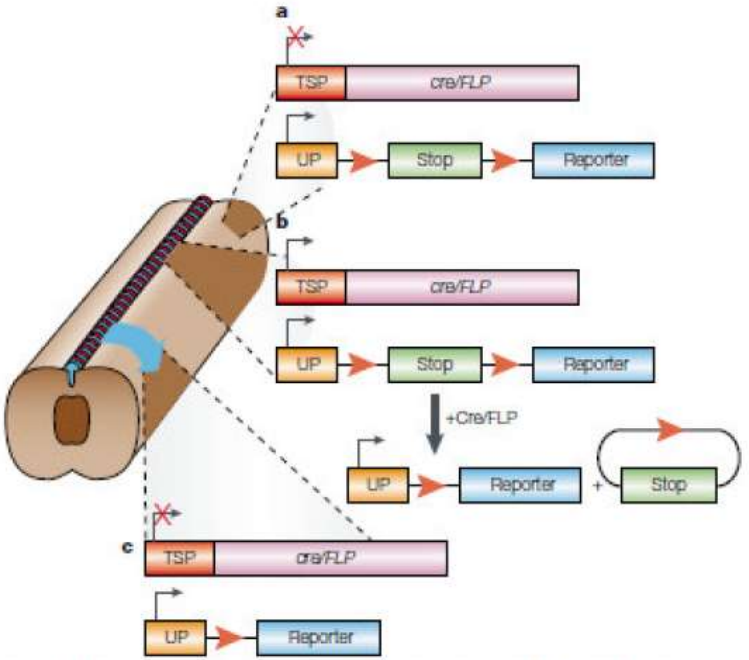


Figure 4 | **Fate mapping the descendants of a gene-expression domain.** In this example, a tissue-specific promoter (TSP) (for example, the *Wnt1* promoter) controls the expression of a *cre* or *FLP* transgene. **a** | The *cre* (or *FLP*) transgene is not expressed outside the dorsal neural tube. A reporter transgene is transcribed from a ubiquitous promoter (UP), but no functional gene product is produced outside the dorsal neural tube because Cre (or Flp)-mediated recombination is required to remove the floxed (or flirted) Stop sequences that separate the promoter from the reporter coding sequences (red arrowheads, *loxP* or *FRT* sites). **b** | Cre activity in the dorsal neural tube (red) results in the removal of the Stop sequence and reporter activation (blue). **c** | Migrating neural-crest cells (blue arrow) no longer express *cre* or *FLP*, but the reporter remains activated (blue).

CONDITIONAL CONTROL OF GENE EXPRESSION IN THE MOUSE

Mark Lewandoski

NATURE REVIEWS | GENETICS

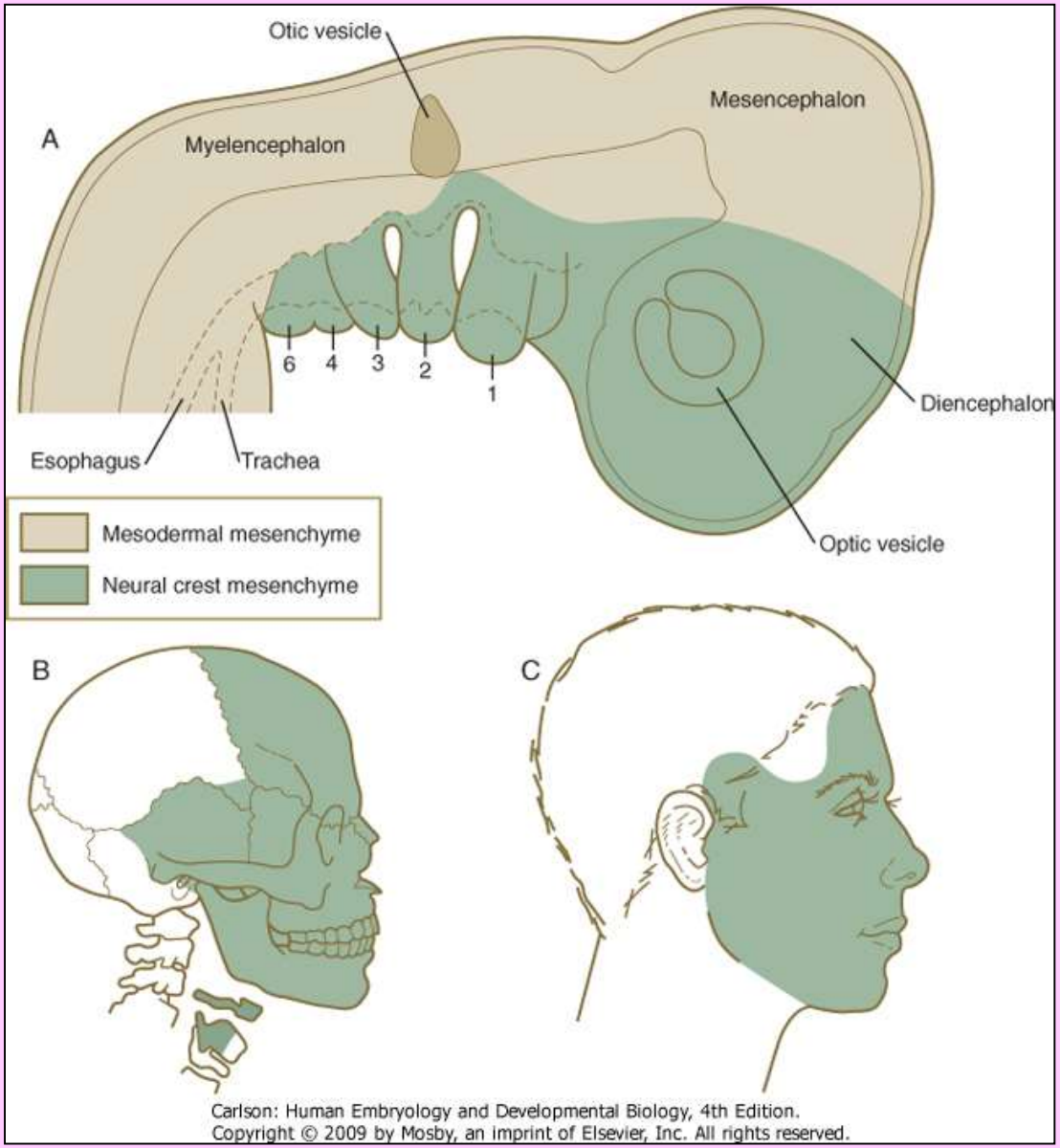
Development of neural crest along the rostro-caudal axis

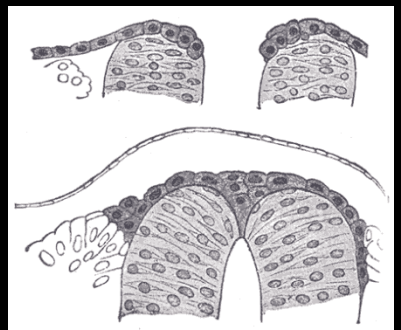
Neural crest cells are traditionally grouped into four cranial-caudal subdivisions

1. **cranial NCC** (caudal forebrain to the level of rhombomere 6 of the myelencephalon)
2. **vagal NCC**(level of somites 1 to 7
3. **trunk NCC** (level of somites 8 to 28)
4. **sacral NCC** (level caudal to somite 28).

Distribution of Cranial Neural Crest Cells (Ecto-mesenchyma) in the Skull and Face

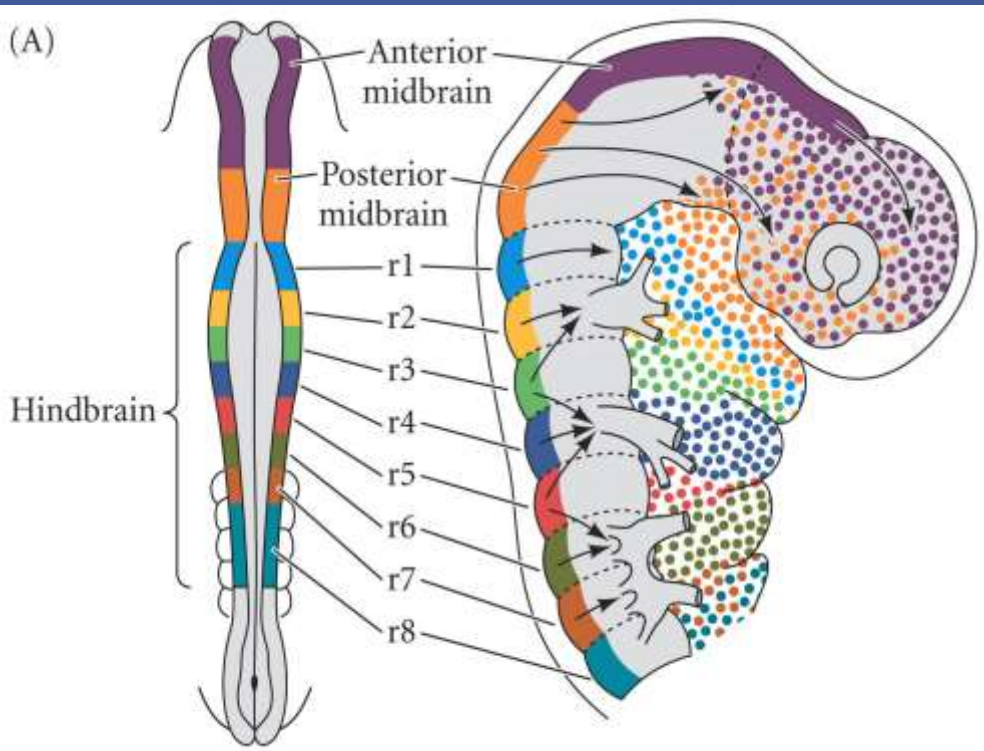
Neural crest forms the connective tissues, cartilages and bones, as well as the „boot-stretcher” of glands, muscles of pharyngeal arch.





cranial crest

craniofacial (ecto-) mesenchyma, cartilage, bone, connective tissue, nerve, glia



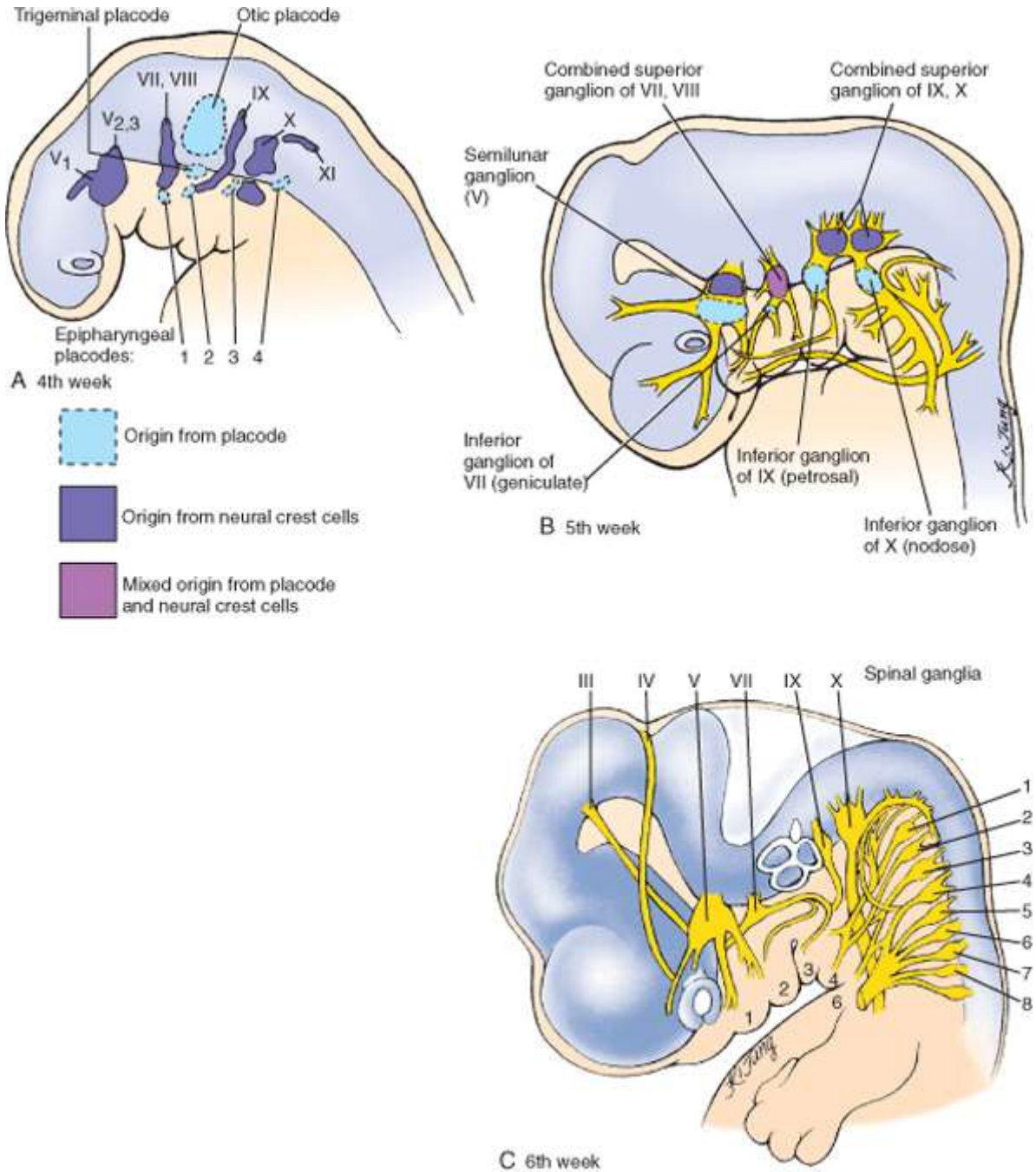
Major source to form the cranial neural crest

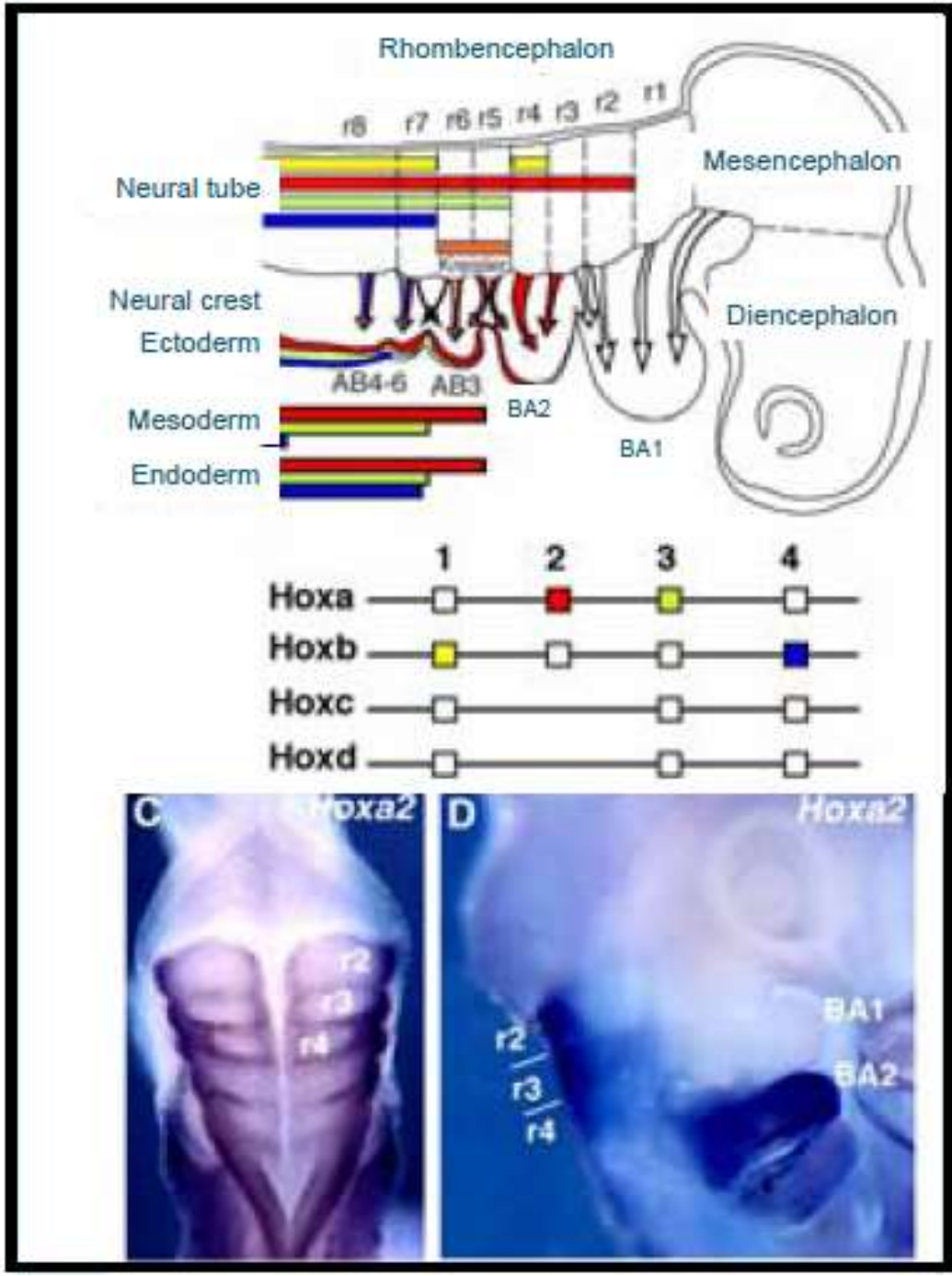
- **Midbrain and rhombomere 1 & 2**: the first pharyngeal arch (jaw bone and middle ear bones (incus and malleus)), trigeminal ganglion (teeth and jaw), ciliary ganglion (ciliary muscle of the eye), frontnasal process (facial skeleton); **Non-Hox expressing NC**

- Rhombomere 4: the second pharyngeal arch (hyoid cartilage of the neck) and stape bone of the middle ear, facial neurons; Hoxa2 expressing NC

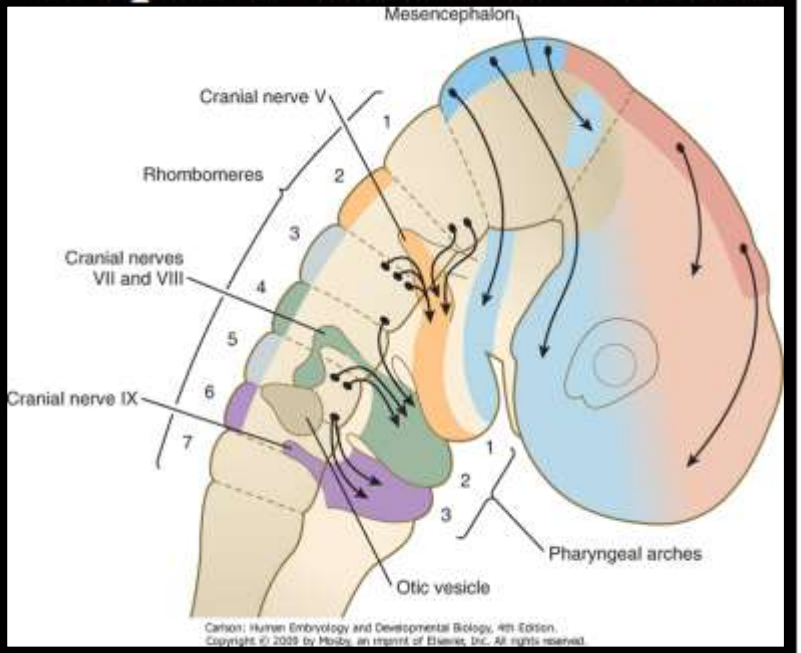
- Rhombomere 6 - 8: the third and fourth pharyngeal arches and pouches – thymus, parathyroid and thyroid

- Rhombomere 3 & 5: do not migrate through the neighboring mesoderm, but enter the stream of rhombomere 2 or 4 and 4 or 6, respectively



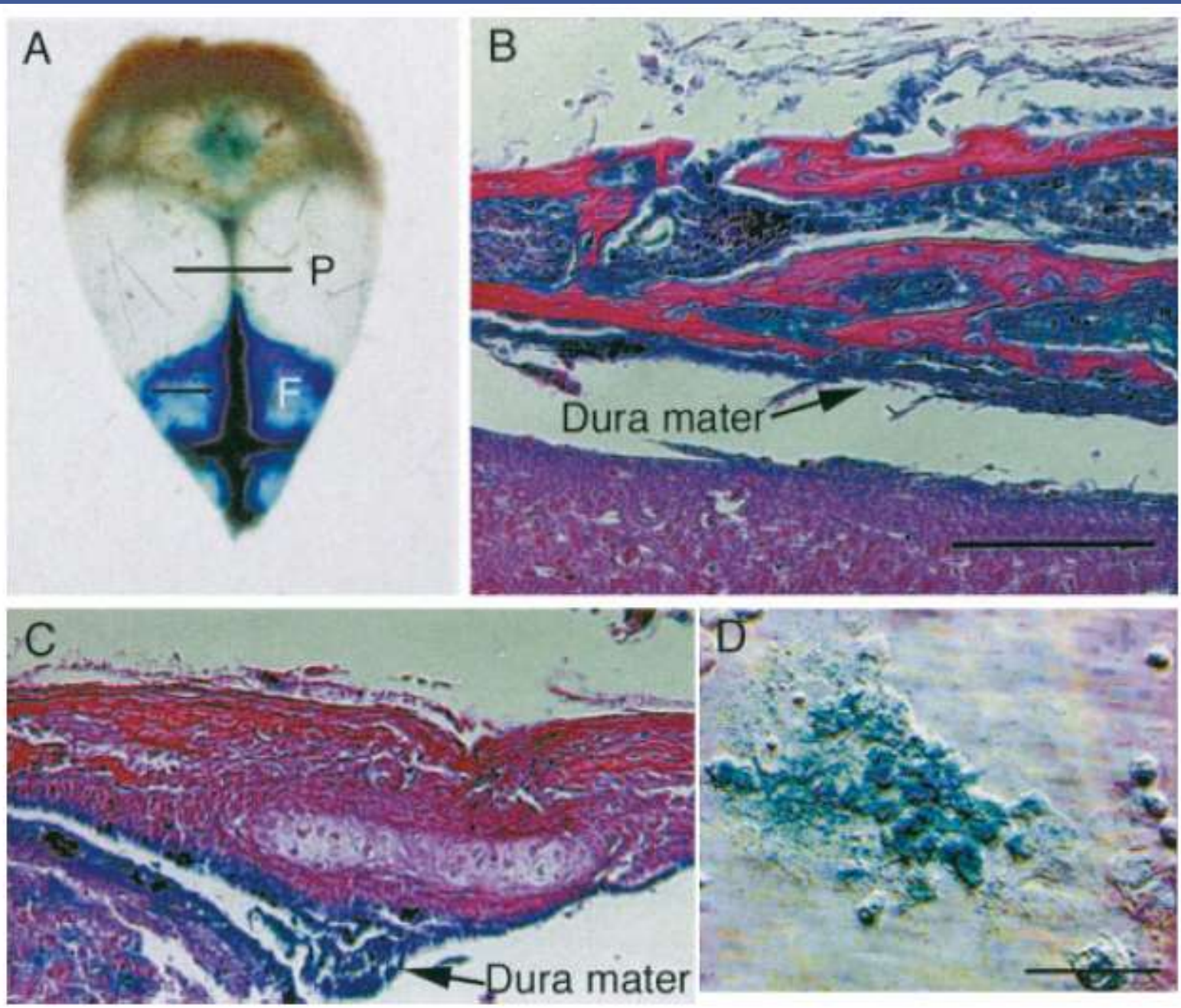


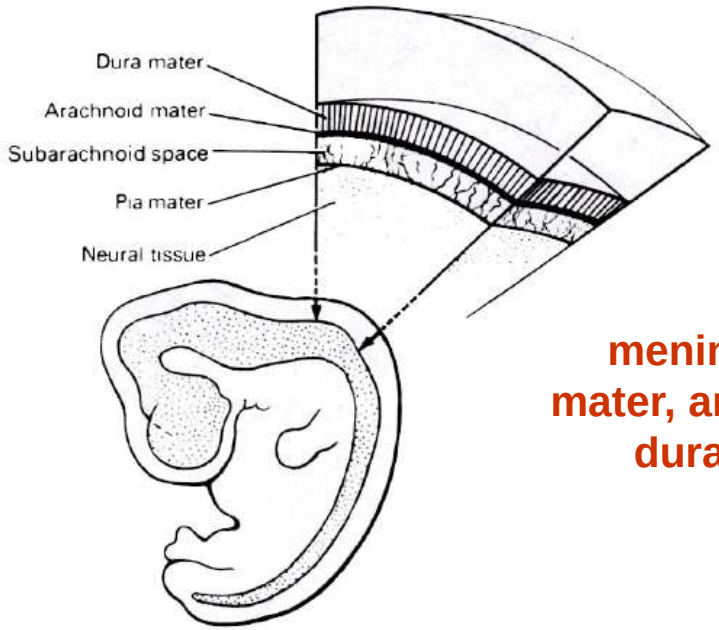
Hox gene expression in cephalic Neural Crest Cells



NC cells contribute:

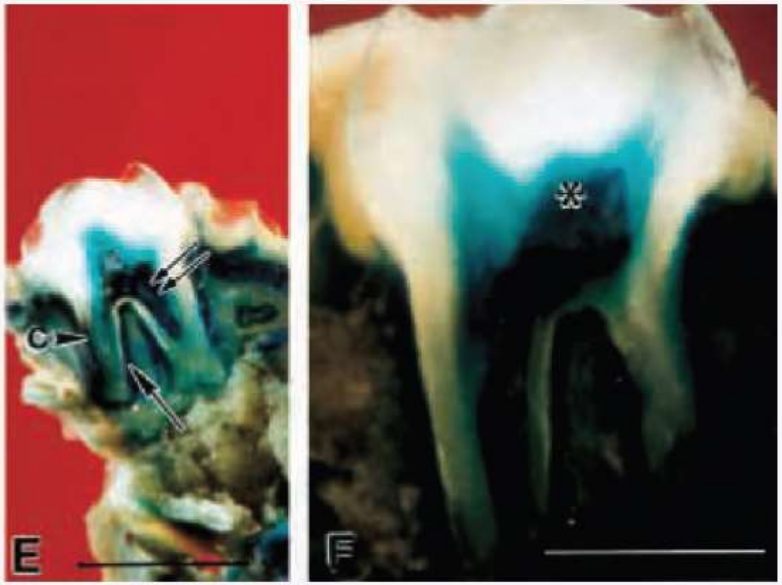
- skeletal elements (face, hyoid, etc.)
- cartilage elements (e.g. in trachea)
- inner ear bones
- cranial nerves (V, VII, IX, X,)

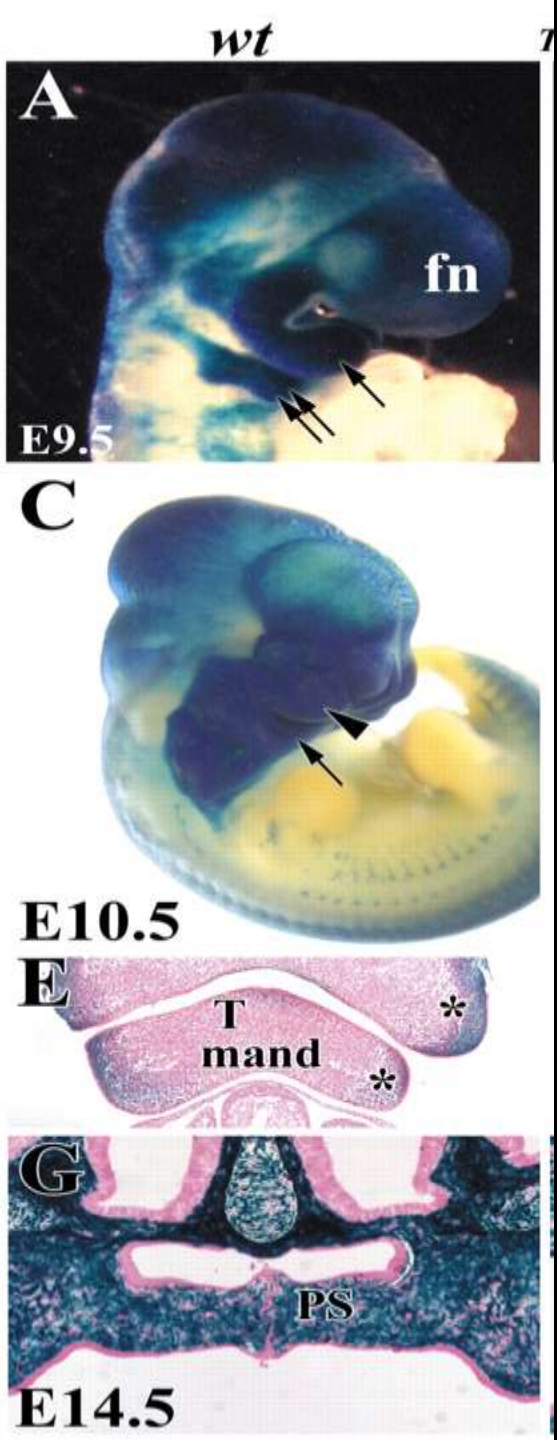

A
P
F
B
Dura mater
C
Dura mater
D

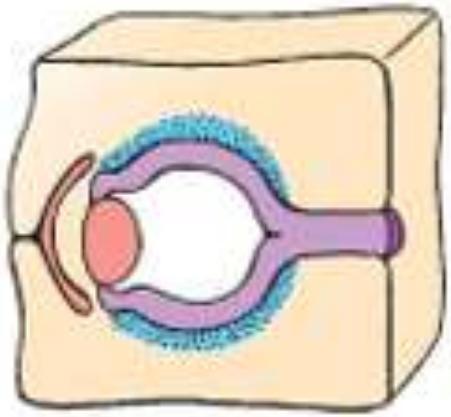


meninges (pia mater, arachnoidea, dura mater)

Cranial NC contributes to meninges of brain and spinal cord, dermis of the scalp and teeth







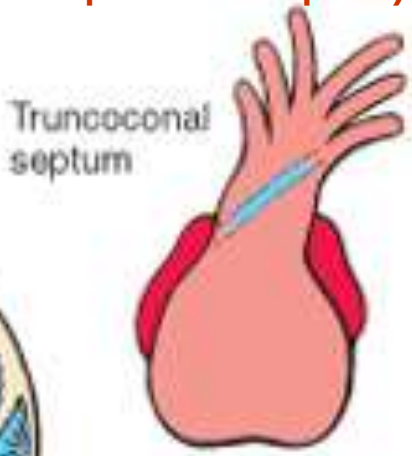
Components of eye

eye (sclera and ciliary muscle)

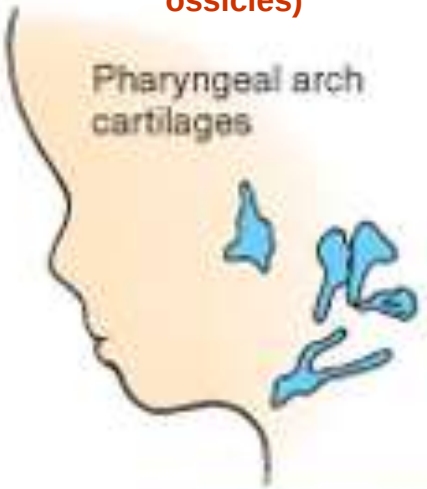
bone (desmal bones of skull)

Dermal bones of skull

heart (aortico-pulmonal septum)

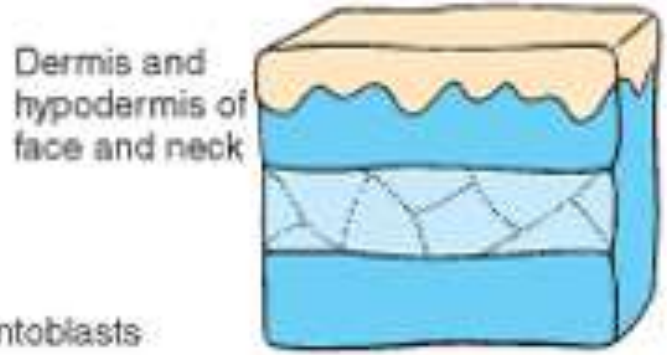


connective tissue (cartilages of arches, stroma of glands, auditory ossicles)

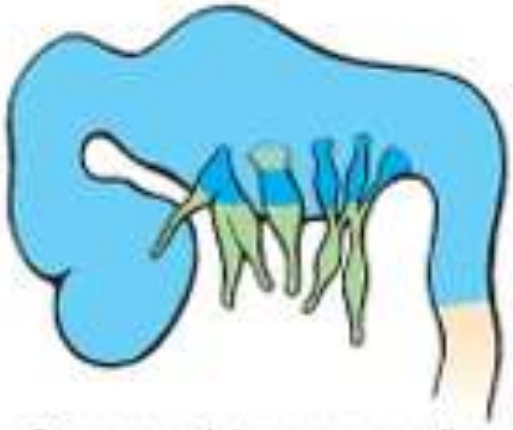


Odontoblasts

teeth



skin



Some cranial nerve ganglia

meninges (pia mater, arachnoidea, dura mater)

Non-neural Derivatives of Cranial Neural Crest

Cardiac neural crest (ant. rhobmencephalon-somite 3.)

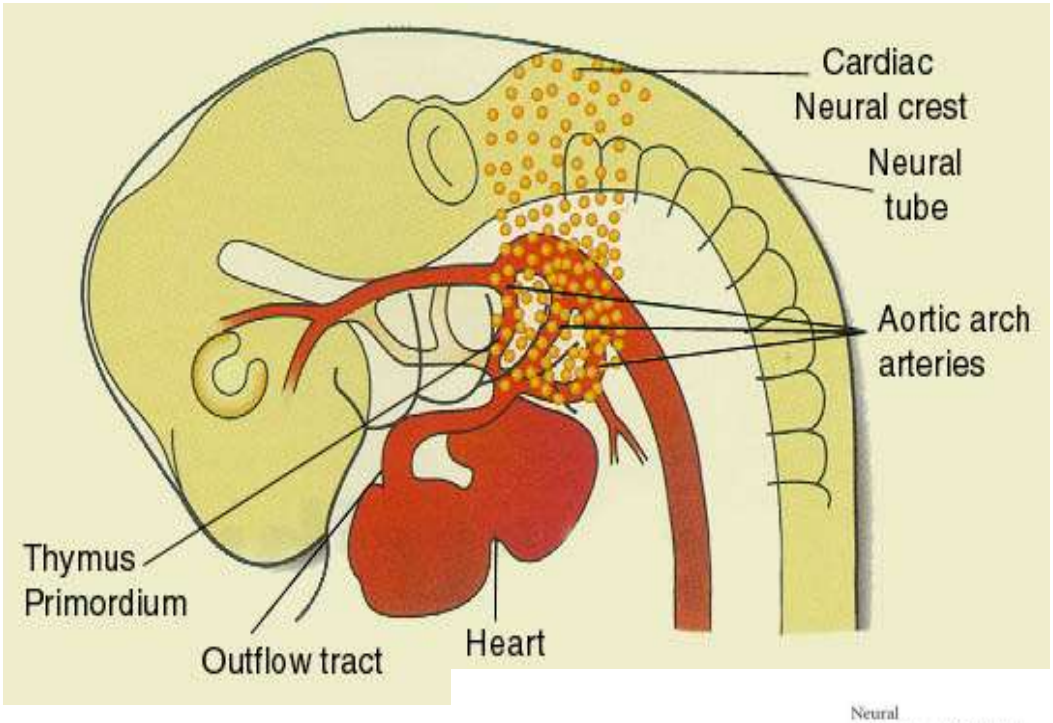
The **cardiac neural crest** overlaps the vagal neural crest and migrates to populate the pharyngeal arches 3, 4 and 6 (producing structures in the head) and to the heart, forming connective tissue that separates the great vessels of the heart.

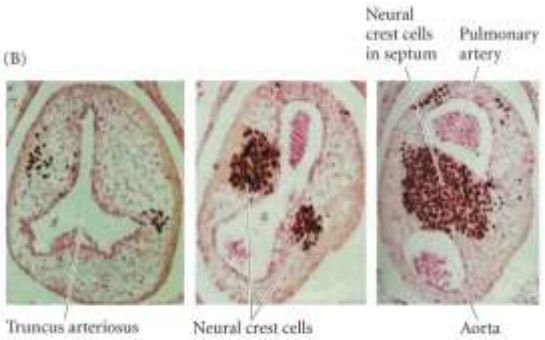
Other Migration Locations:

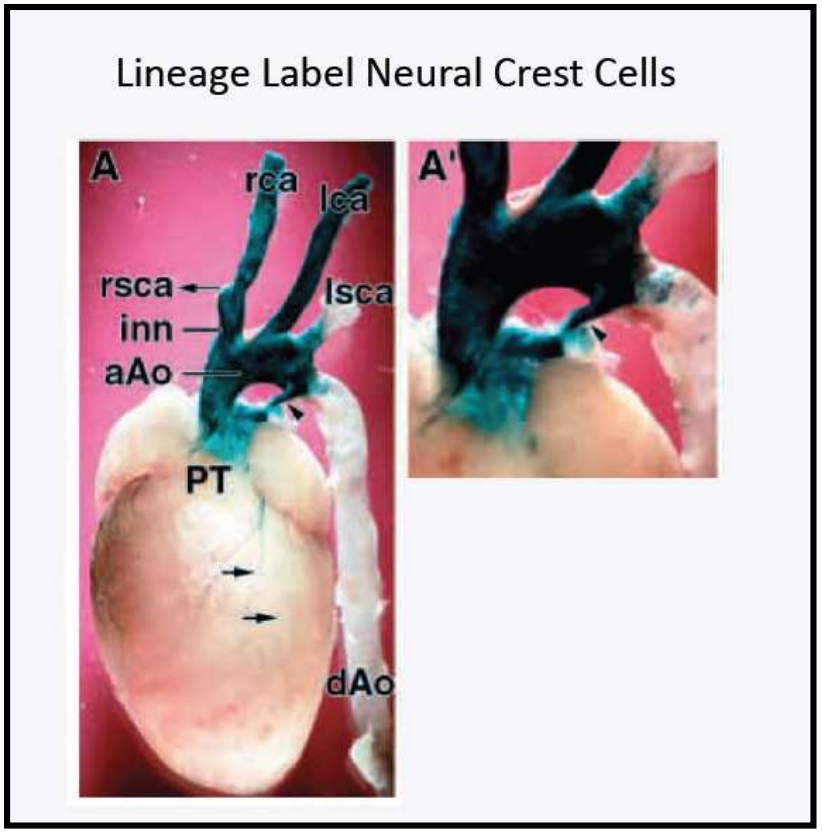
Into the pharyngeal arches and Truncus arteriosus (embryology), forming the aorticopulmonary septum and the smooth muscle of great arteries.

Anterior of the aorta to become the four pre-aortic ganglia (celiac ganglion, superior mesenteric ganglion, inferior mesenteric ganglion and aortical renal ganglia)

The septa that separate the truncus arteriosus into the pulmonary artery and aorta form from cells of the **cardiac neural crest**





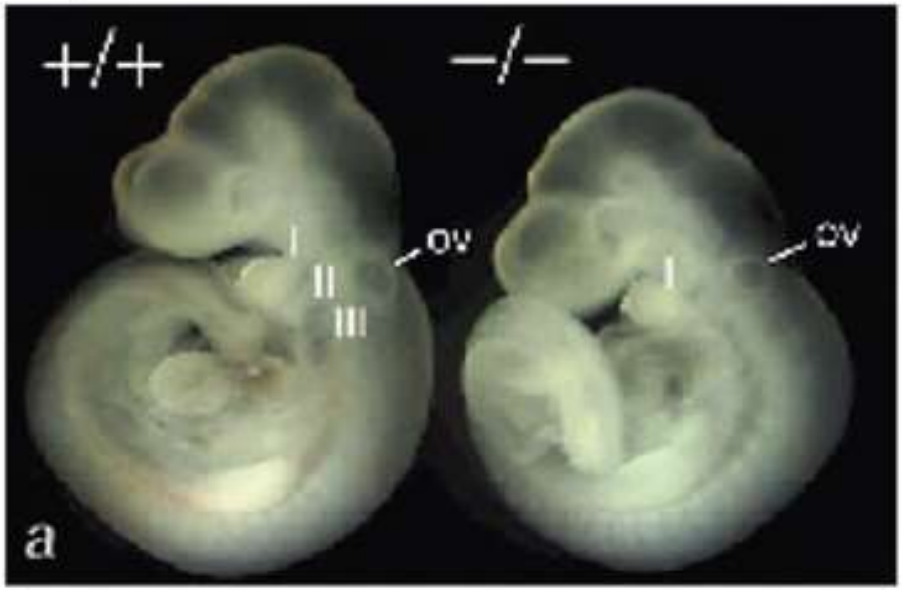


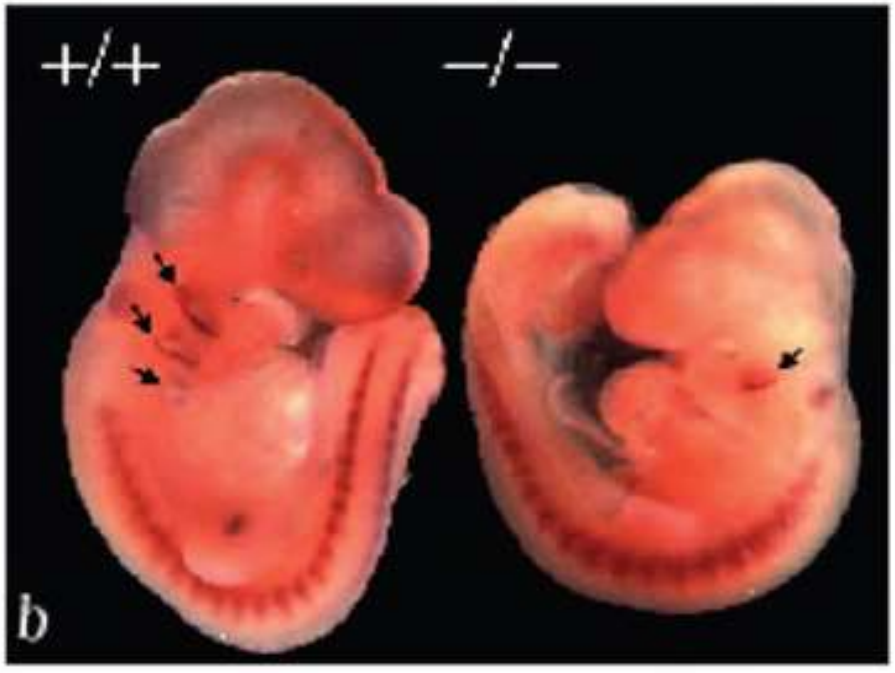
DiGeorge Syndrome

Defects in cranial and vagal neural crest; glandular deficiencies, craniofacial abnormalities, heart defects.

-aplasia of thymus and parathyroid gland

Mutations in *Tbx1* (transcription factor) is responsible for this syndrome.

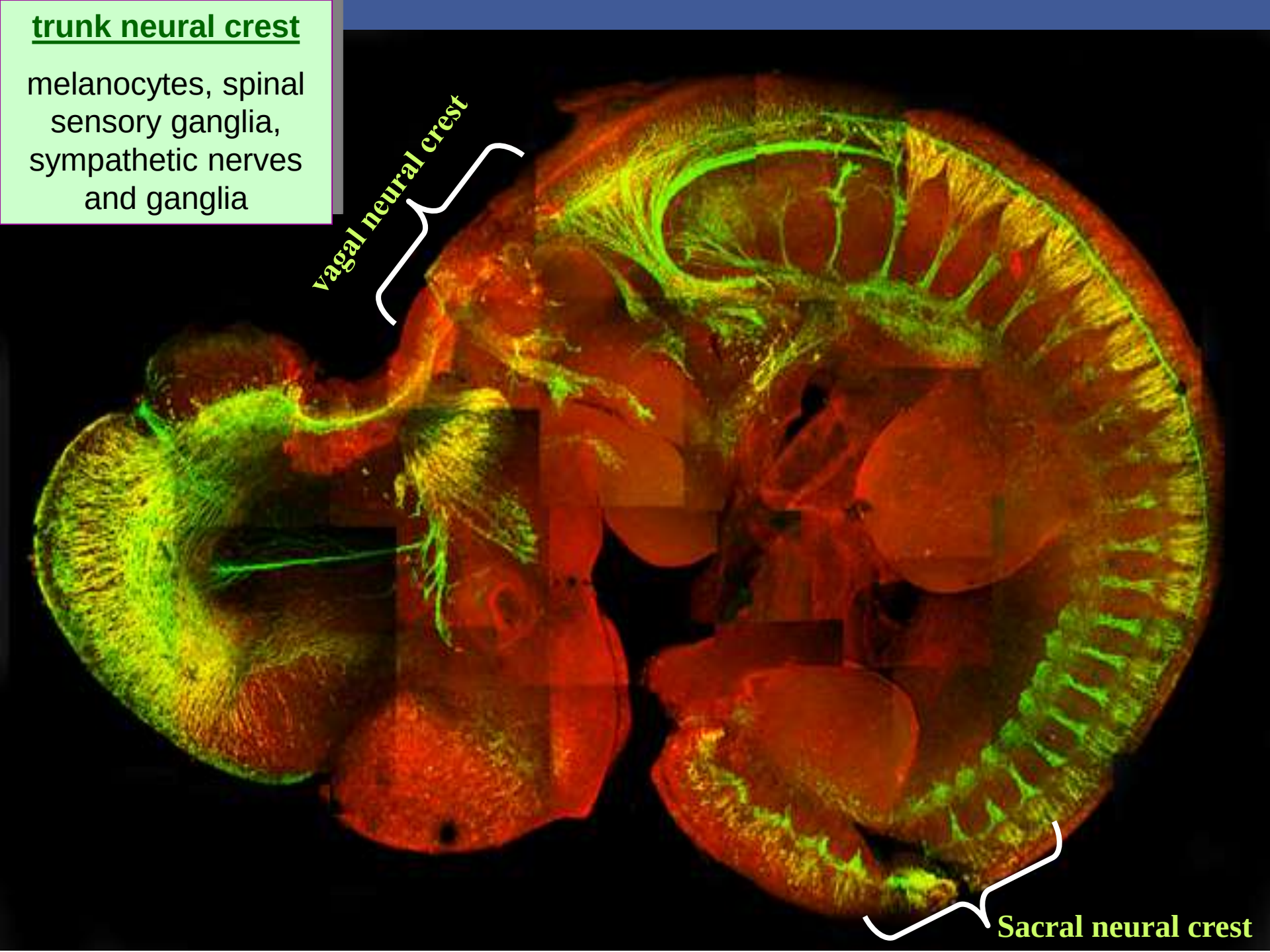




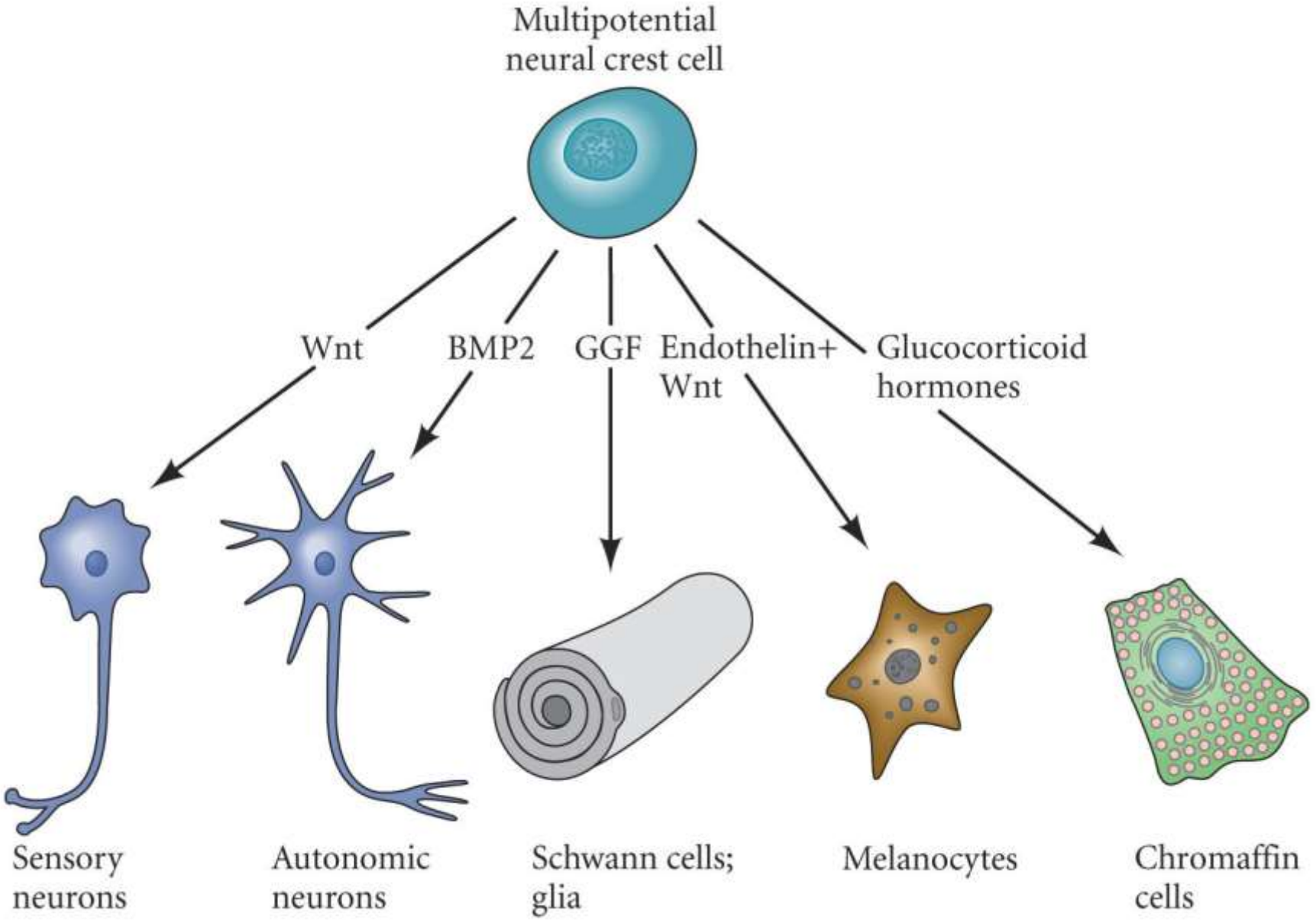
is associated with a deletion on chromosome 22, is characterized by hypoplasia and reduced function of the thymus, thyroid, and parathyroid glands and cardiovascular defects, such as persistent truncus arteriosus and abnormalities of the aortic arches.

trunk neural crest

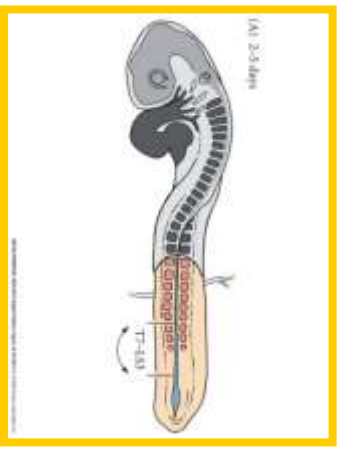
melanocytes, spinal sensory ganglia, sympathetic nerves and ganglia



Paracrine factors encountered in the environment help specify the different neural crest-derived lineages in the trunk



Neural crest cell migration in the trunk



Thrombospondin is expressed in the anterior section of sclerotomes, and cooperates with fibronectin and laminin to promote NC migration

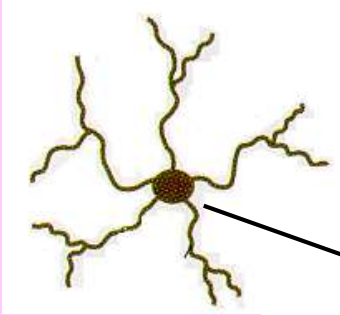
Migratory Pathways and Neurogene Derivatives of the Truncal Neural Crest

endothelin-3

↓

pigment cells (melanocytes)

dorsolateral pathway (1)



neural crest

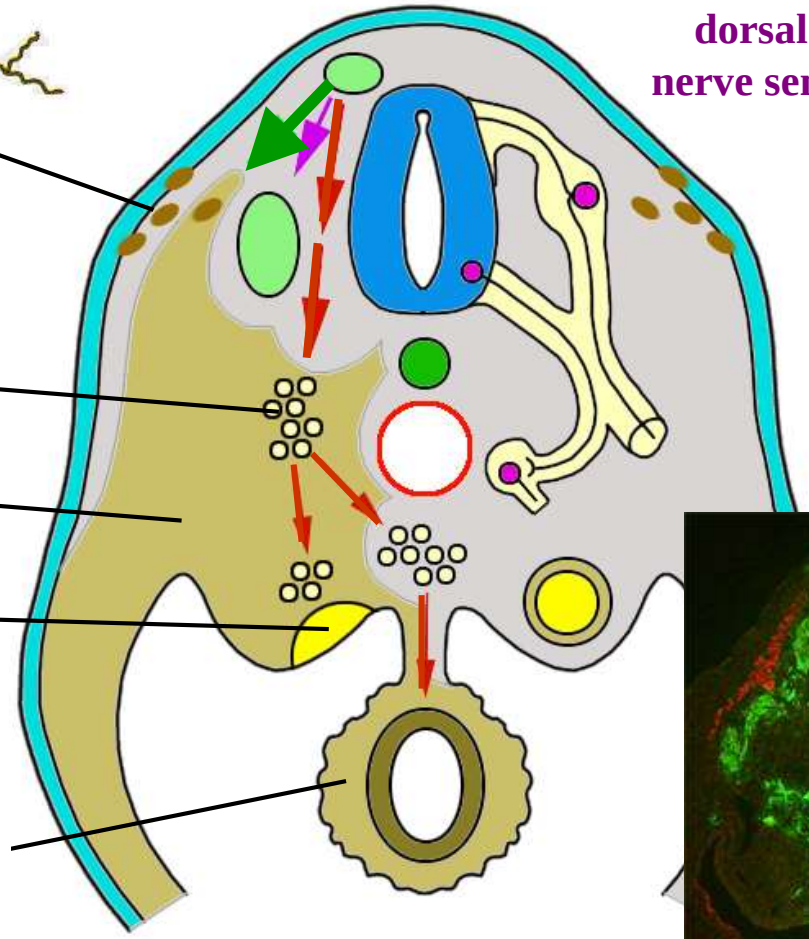
dorsal root, cranial nerve sensory ganglions

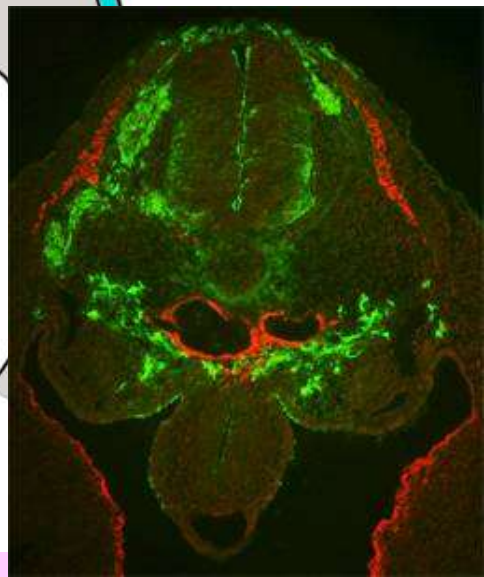
ventrolateral pathway (2)

parasympathic and sympathic ganglions

mesoderm

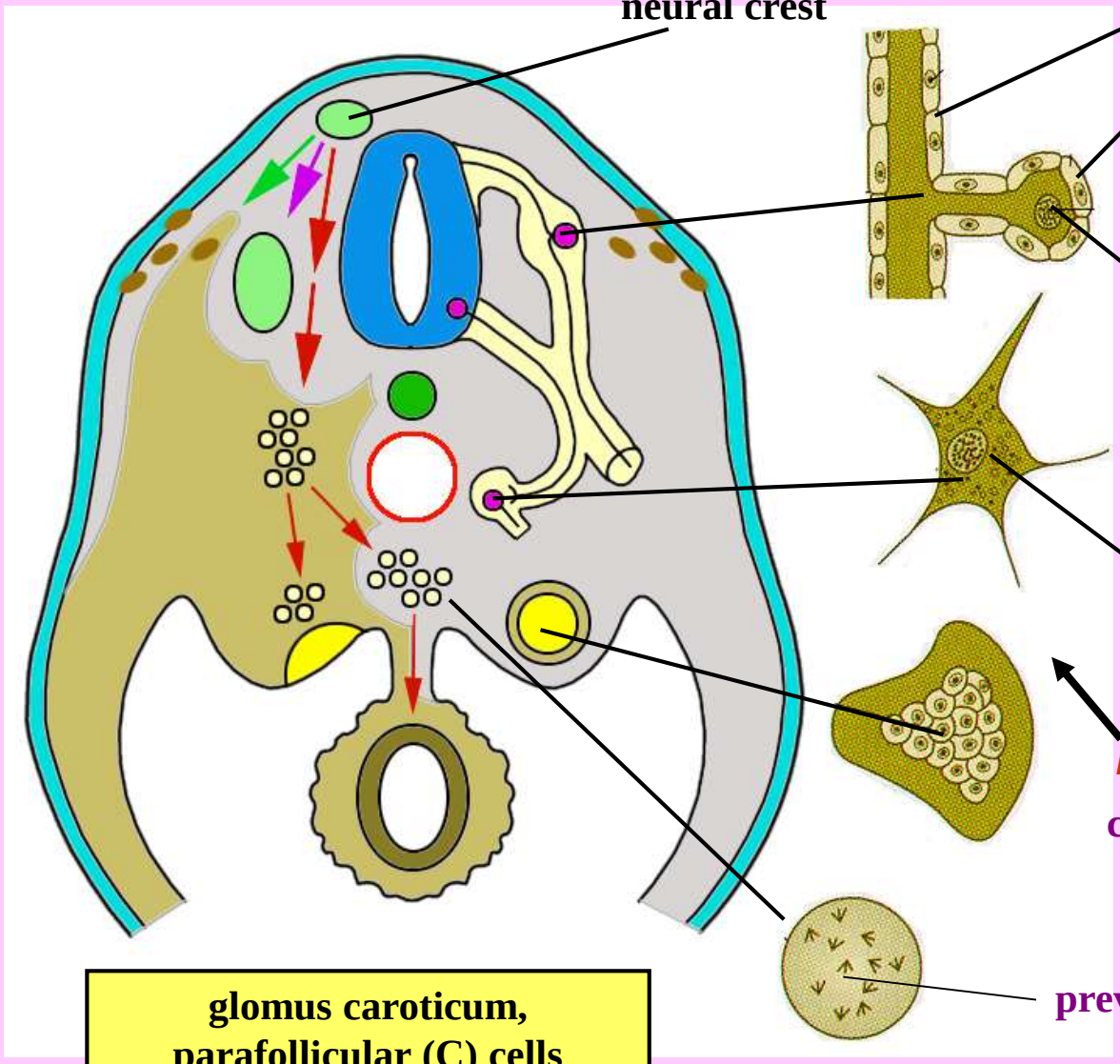
developing adrenal gland

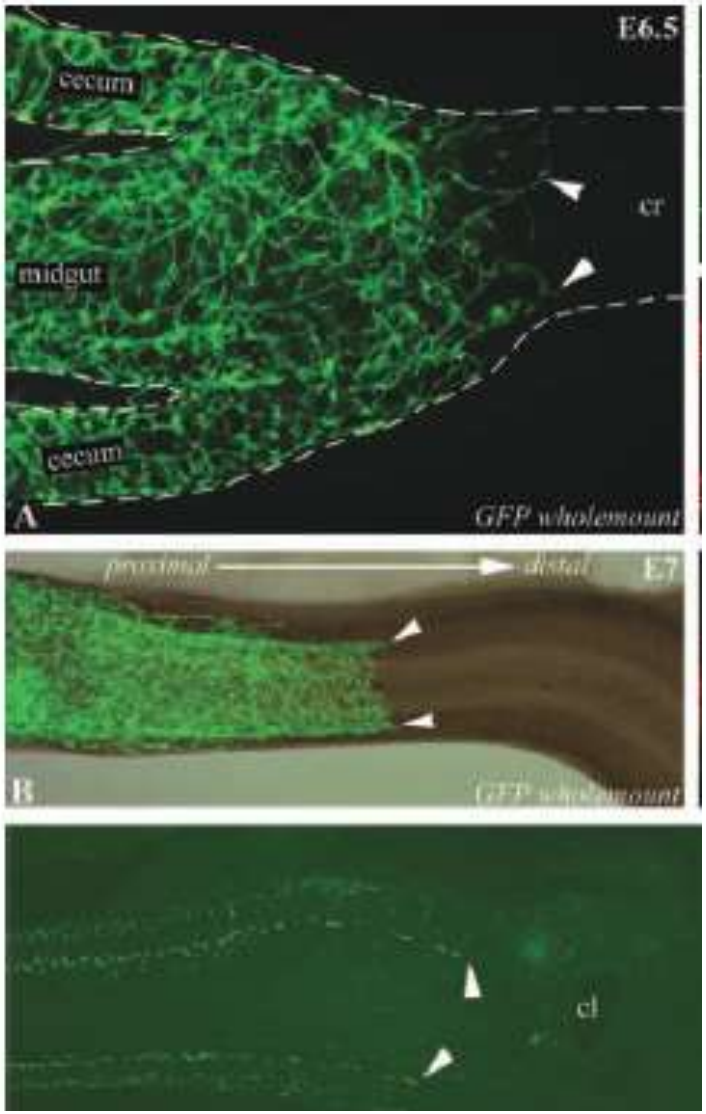




Migratory Pathways and Neurogene Derivatives of the Truncal Neural Crest

ventrolateral pathway





DEVELOPMENTAL DYNAMICS 241:842–851, 2012

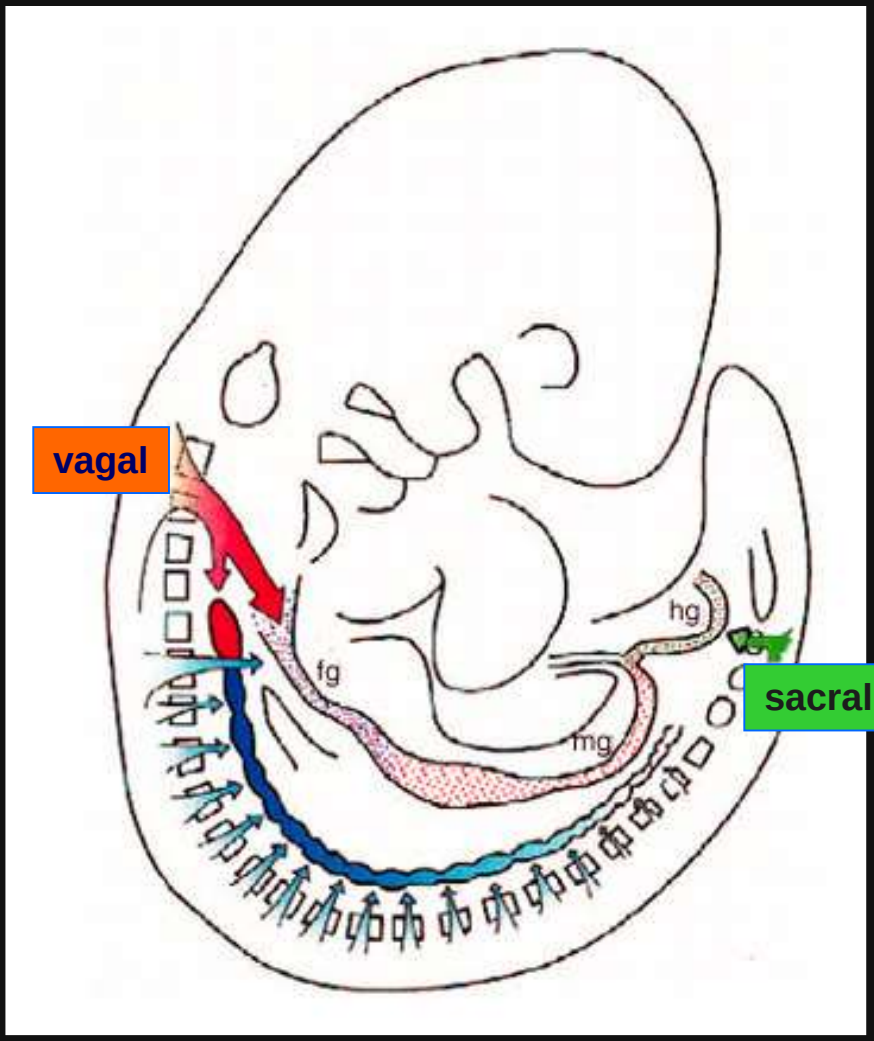
RESEARCH ARTICLE

Immunophenotypic Characterization of Enteric Neural Crest Cells in the Developing Avian Colorectum

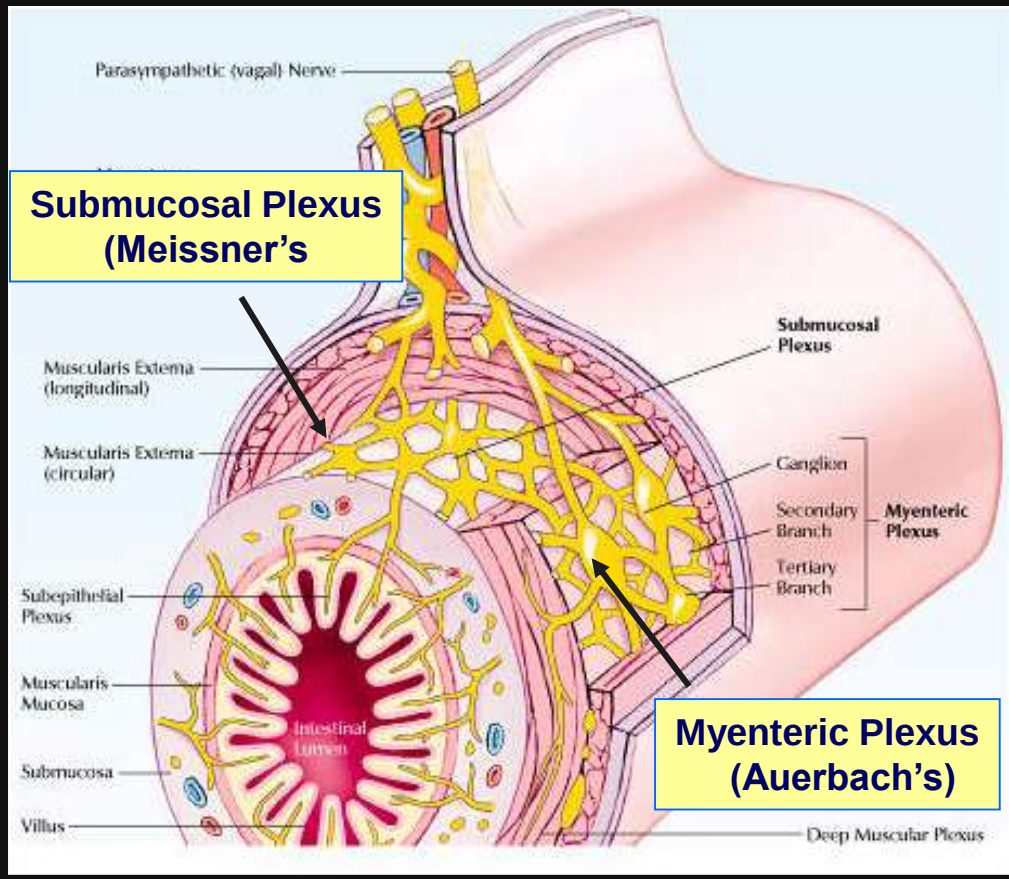
Nandor Nagy,[1,2] Alan J. Burns,[3] and Allan M. Goldstein[1]*

12 week old human embryo colon
Cover image by Nagy N and Goldstein A.M, 2010

Vagal and sacral neural crest cells generate the **parasympathetic (enteric) ganglia** of the gut



Enteric Nervous System originates from vagal and sacral neural crest

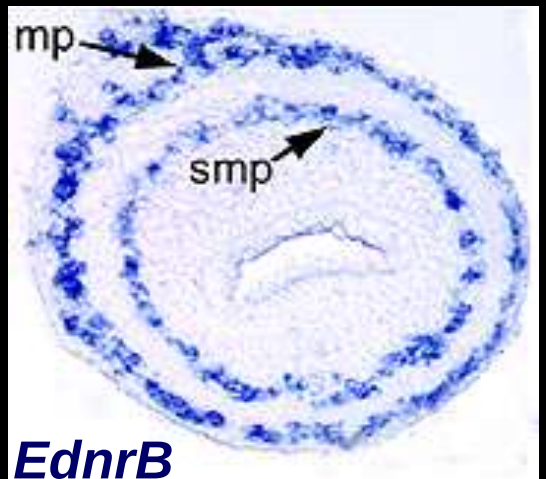


ventral pathway

- Ret (receptor tyrosine kinase)
- **Gdnf (glial-cell line derived neurotrophic factor)**

- **Et3 (endothelin-3)**
- EdnrB (endothelin receptor B)

- Sox10, Phox2b, BMP-4, Hedgehog proteins



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Endothelin-3 regulates neural crest cell proliferation and differentiation in the hindgut enteric nervous system

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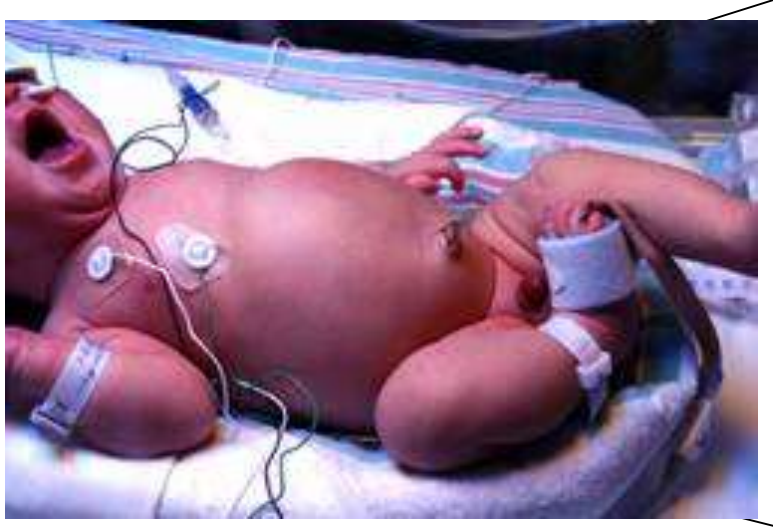
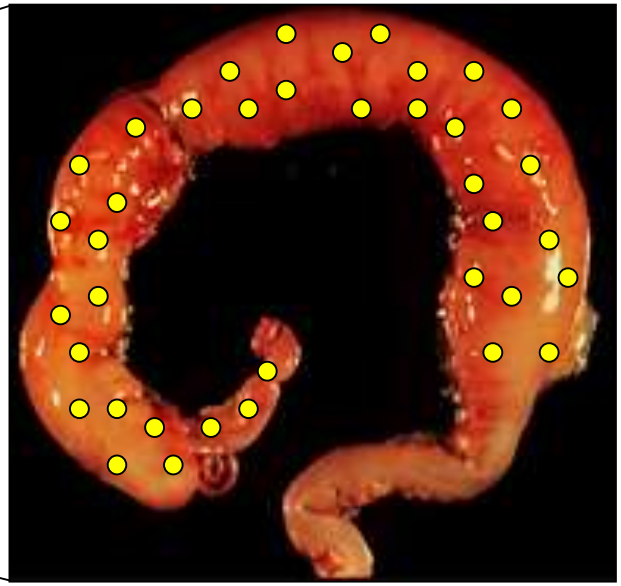
Hirschprung's disease (megacolon congenitum aganglionare)

-developmental anomaly; Affects 1:5000 human infants.

- complete absence of ENS in the distal bowel 90% are diagnosed as newborns. Proximal colon becomes distended
- Failure to pass stool within 1st 2 days of life, abdomen distended, vomiting





- Short segment HSCR –80%
- colon – 20%

Mesenchymal Derivatives of Cephalic and Cardial Crest

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

Neural Derivatives of Truncal and Vagal Crest Cells

Organ	*Cell type*	*Neurocristopathy*
Cortex of andrenal 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	entericus nerve cells, (enterochromaffine cells)	carcinoid tumors
(Truncal crest)	periferal nerves	neurofibromatosis (von Recklinghausen's disease)

Cranio-sacral vegetative system

Postganglionic parasympathetic neurons derive from occipito-cervical (vagal) and sacral crest.

The cranial cells bring about vegetative ganglia (ciliary, submandibular, pterygopalatinine, otic ganglia) that are bound to cranial nerves (III., V., VII.)

After the migration the cells stop in the wall of the internal organs (enteric ganglia).