INDUCTION

lat. *inductio*

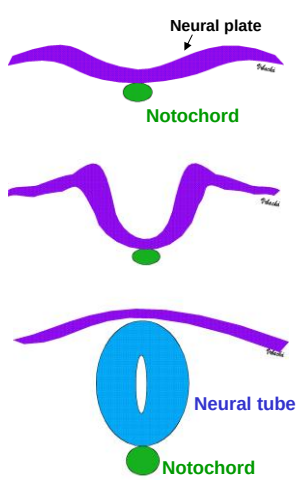
= Interaction of tissues, in which one tissue (the inductor or organizer) directs the development of another adjacent tissue to differentiate in a way it otherwise would not (i.e. it generates new cell types). Induction occurs only for a limited time during early development. As differentiation of cells proceeds, tissues lose their ability of induction or their ability to respond to inductive signals.

Inductor must be close to but not necessarily in contact with the tissue to be induced.

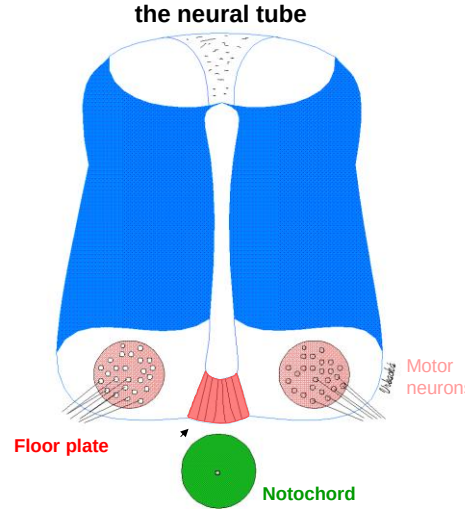
Example: **Motoneurons have been induced by a diffusible factor from the notochord or the floor plate, whereas dopaminergic neurons require cell - cell contact with floor plate cells.**

Example: The developing notochord (axial mesodermal tissue) induces the overlying ectoderm to form the neural plate (primary induction).

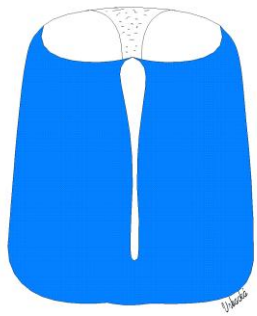
Induction of the neural tube by the notochord



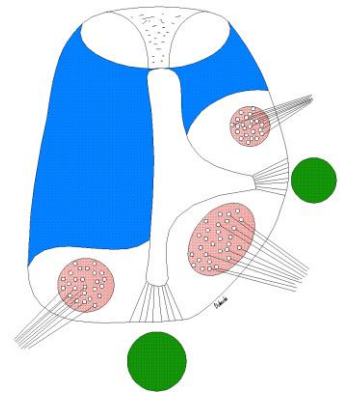
Regionalization of the neural tube



In the **absence** of any outside inductor, the pluripotent c. of the neural tube will spontaneously express a dorsal fate, ie. no floor plate of motoneurons will differentiate.



An **ectopic** notochord placed lateral to the neural tube triggers induction of an extra floor plate and extra motoneurons.



The notochord and the ventral floor are responsible for regionalization of the neural tube in the transverse plane.

The **notochord** instructs the most ventrally located cells of the neural tube to become the **floor plate** (primary induction).

The notochord and the floor plate induce neural precursor cells of the neural tube to assume fates of **ventral neurons** (eg. motor neurons of the spinal cord, serotonergic neurons of the hindbrain or dopaminergic neurons of the ventral mesencephalon) - secondary induction.

Induction is performed through the action of chemical substances transmitted from one tissue to another. EGF,

TGF-beta, FGF and others may act as inductive signals (morphogens) during early development.

Example:

• Extra limbs can be induced from the flank of the chick embryo by implantation of beads soaked in FGF.

• bFGF is capable of inducing gastrula ectoderm cells of *Xenopus laevis* to produce CNS neurons and melanophores

Primary organizers **establish the basic embryonic plan, and then the chain of secondary, tertiary or other inductions occur. By a series of successive inductions, it is possible to generate many different kinds of tissues.**

Examples:

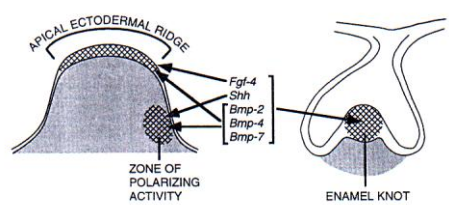
- **The adjacent mesoderm induces formation of optic vesicles from the wall of the prosencephalon (secondary induction).**
- **The optic cup (that develops from the optic vesicle) induces the generation of the lens placode from the adjacent ectoderm (tertiary induction).**
- **The lens vesicle induces the adjacent epidermal epithelium to transform into the cornea (quartery induction).**

INDUCTION REGULATORY FACTORS

	EK	AER	ZPA	Noto-chord	Floor plate
Shh	+		+	+	+
Bmp2	+	+	+		
Bmp4	+	+	+		
Bmp7	+	+	+		
Fgf4	+	+			
Fgf9	+	+			
Msx2	+	+			

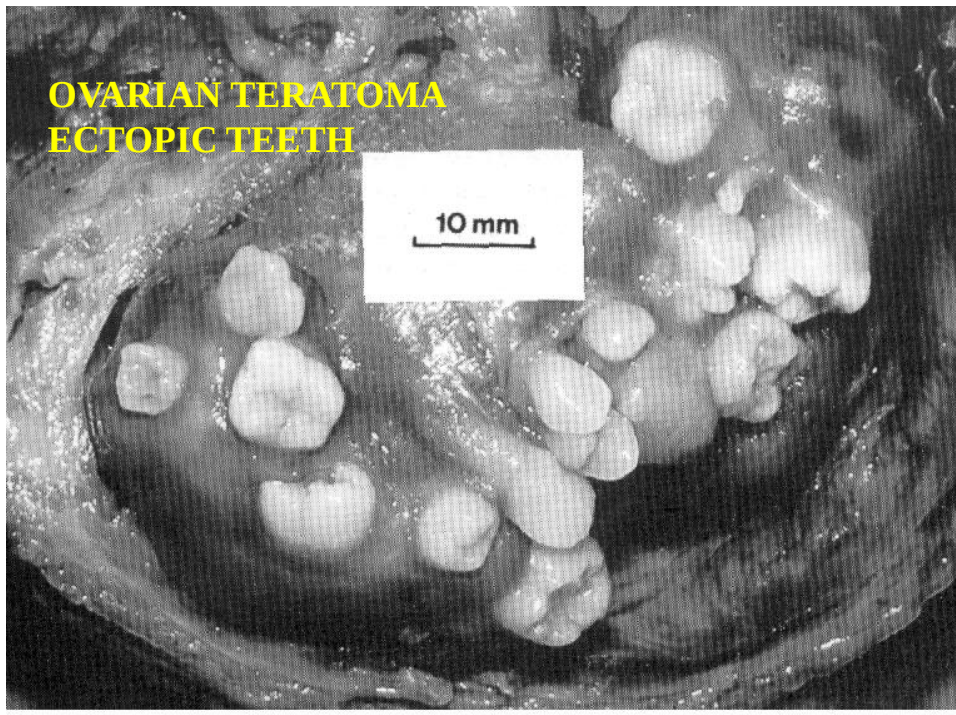
LIMB **TOOTH**

In developing limb bud, regulatory factors are localized in 2 regions: AER and ZPA.



In developing tooth, all factors are expressed by the enamel knot only.

Interaction between dental papilla nad ectodermal epithelium is necessary for a proper development of the tooth (incl. formation of its shape).



MIGRATION lat. *migratio*

= the active passage of cells from one site, eg. site of their origin, into another.
(x passive movement - erythrocytes in the blood stream, movement of cells after mitosis)

Example:

- **Cells of the intraembryonic mesoderm migrate from the primitive pit and groove between the layers of epiblast and hypoblast**
- **Cells of ventromedial parts of somites migrate to the notochord to form the sclerotome.**
- **Migration of neural crest cells in embryonic jaws → odontoblasts etc. (c. migrating in a new microenvironment are exposed to influenco of new inducing signals, which generate a new phenotype.**
- **Primordial germ cells (primitive sex cells) migrate from the wall of the yolk sac, yolk stalk and allantois along the dorsal mesentery of the hindgut to the coelomic epithelium of the gonadal ridges**
- **Two successive migrations during the development of the telencephalon:**

I) Cells from the **ventricular zone** migrate into the **intemediate zone**
II) neuroblasts migrate from the intemediate zone into the marginal zone – **cortical plate**

Infiltration of the tissue by migratory cells is a determining condition for further successful development of a particular organ. Interruption of migration leads to malformations (polymicrogyria - ectopic neurons lying in the white matter). Migratory cells compete for reaching their destination (competition). Unsuccessful cells are eliminated by apoptosis. After cells reach their destination, they lose the ability to migrate.

The process of migration is strictly controlled via variety of different mechanisms:

- **Matrix glycoproteins help to define cell migration pathways**
- **Chemoatractans - eg. vascularization of organs with the help of VEGF**
- **Radial glia fibers (processes) guide migrating neuroblasts**
- **Adhesion molecules, eg. astrotactin of migrating neuroblasts form the migration junction with the ligand expressed in endothelial c. enable transit of leukocytes from the blood stream into lymphatic organs**
- **Movement of migrating cells is performed by contractile cytoplasmic proteins (eg. actin)**
- **Proteinases make the passage through extracellular matrix possible**

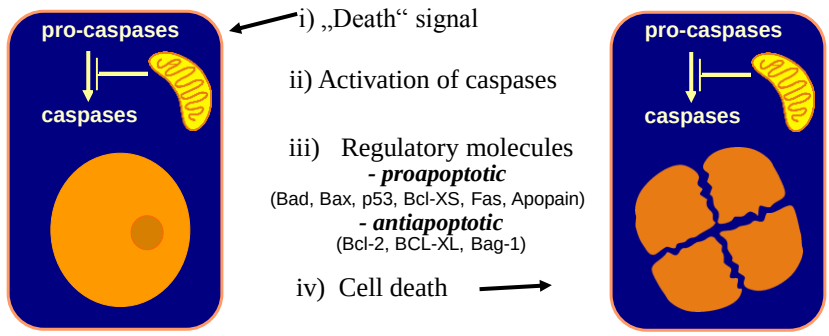
Migration of synapses, neurites - attractants and repelents (diffusible and membrane-bound)

APOPTOSIS (programmed cell death)

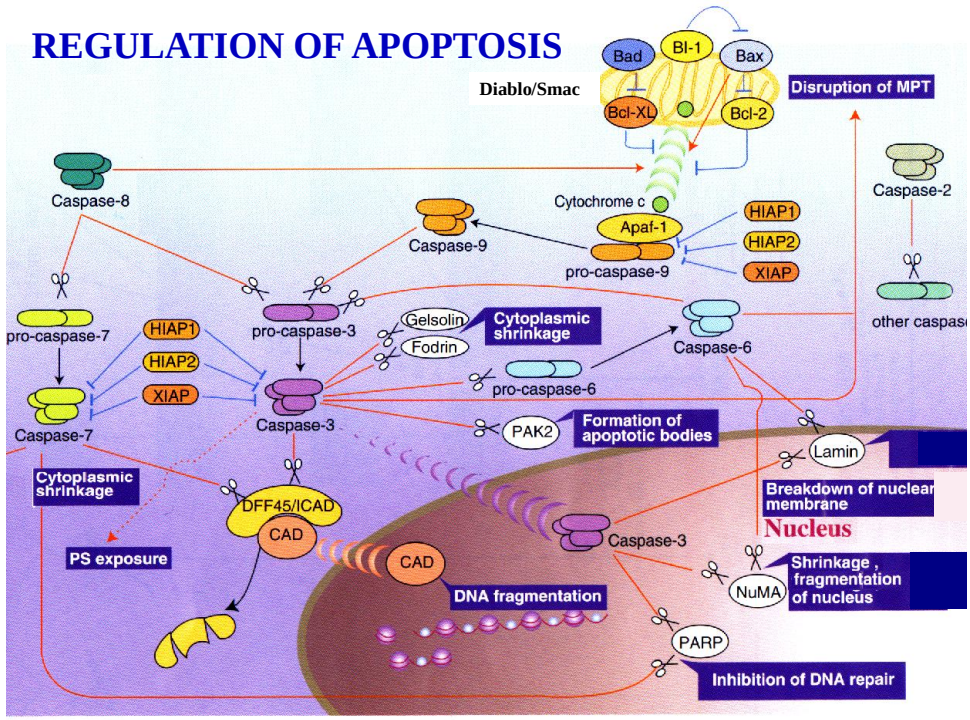
from Greek: *apoptosis* ("falling off" of leaves from trees)

= autodestructive programme leading to fragmentation of the nuclear DNA and decay of the cell into many tiny apoptotic bodies

REGULATION OF APOPTOSIS

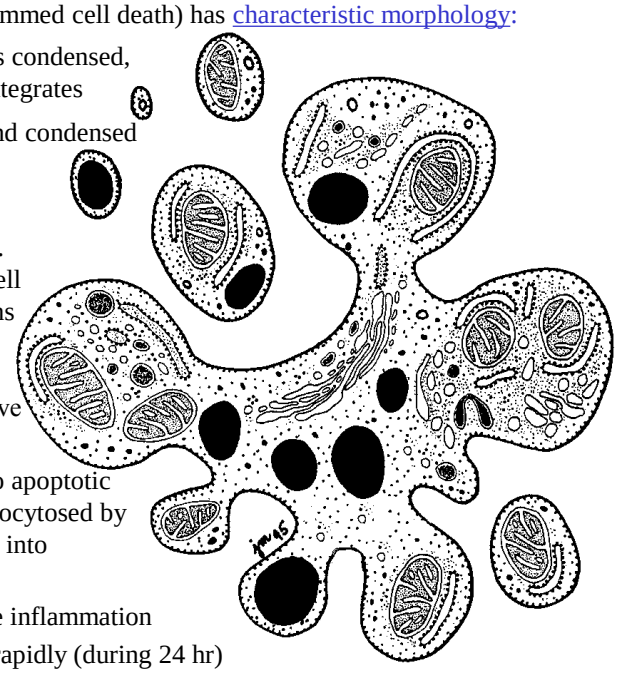


During evolution, apoptosis developed probably as an efficient protection of multicellular organisms against viral infections.



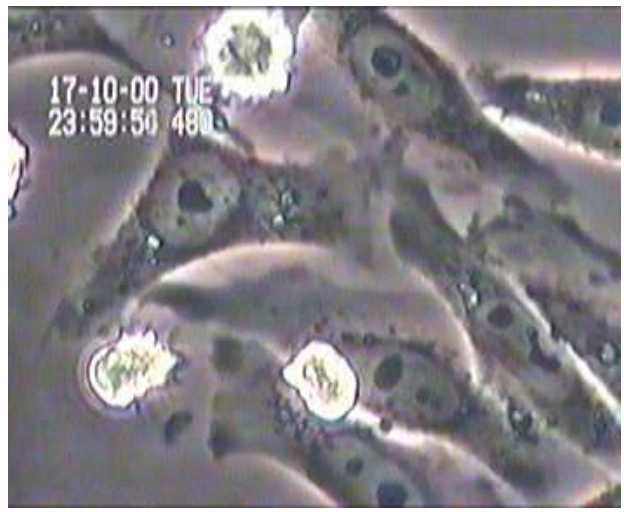
APOPTOSIS (programmed cell death) has characteristic morphology:

- nucleus of the cell becomes condensed, shrinked and it finally disintegrates
- cytoplasm is also shrunk and condensed
- organelles remain intact
- several molecules are lost from the plasmalemma (eg. adhesion molecules); the cell is released from connections with neighbouring cells; plasma membrane forms "membrane buds" which give rise to apoptotic bodies
- the cell is disintegrated into apoptotic bodies, which may be phagocytosed by adjacent cells or shed away into the lumen of hollow organs
- the process does not induce inflammation
- the process proceeds very rapidly (during 24 hr)



APOPTOSIS (PROGRAMMED CELL DEATH)

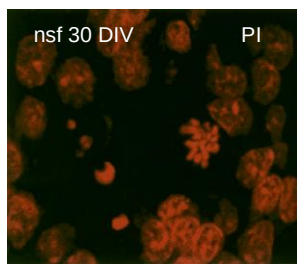
in stabilized cell line from cervical carcinoma Hep-2
induced by topoisomerase II inhibitor Etoposide (10 μg/ml)

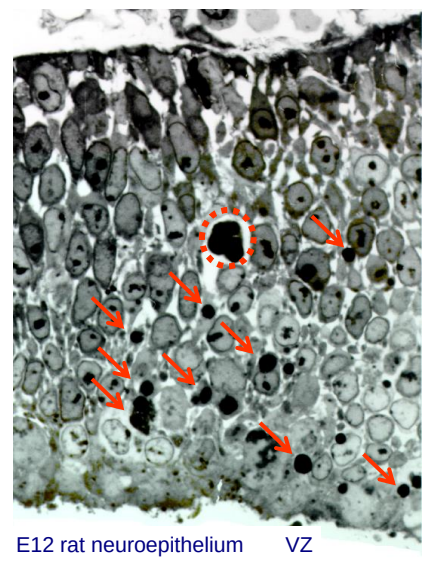


Authors: M. Červinka, E. Rudolf, J. Cerman (Hradec Králové)

CHARACTERISTIC MORPHOLOGY

- cell rounding
- blebbing
- eosinophilic cytoplasm
- echinoic spikes
- intact organelles
- pycnosis
- karyorrhexis
- apoptotic bodies
- emperipolesis





E12 rat neuroepithelium VZ

During ontogenesis, this mechanism enables the organism to eliminate those cells from the tissue that are mispositioned or already accomplished their transient role. Apoptosis does not induce damage to neighbouring cells.

Examples:

Formation of amniotic cavity.

Primary enamel knot is destroyed (via apoptosis) after approx. 2 days from the developing tooth; inducing factors are also lost at the cap stage (expression of BMP-4 → *Msx-2*).

Formation of tubular structures, eg. lumen of the intestinal tract or cavities

Perforation of membranes (oronasal, pharyngeal, urogenital or anal membranes)

Formation of slits between fingers

During neurogenesis, superfluous neurons are generated.

Neurons that became mispositioned or did not form synapses with their target tissue are eliminated by apoptosis.

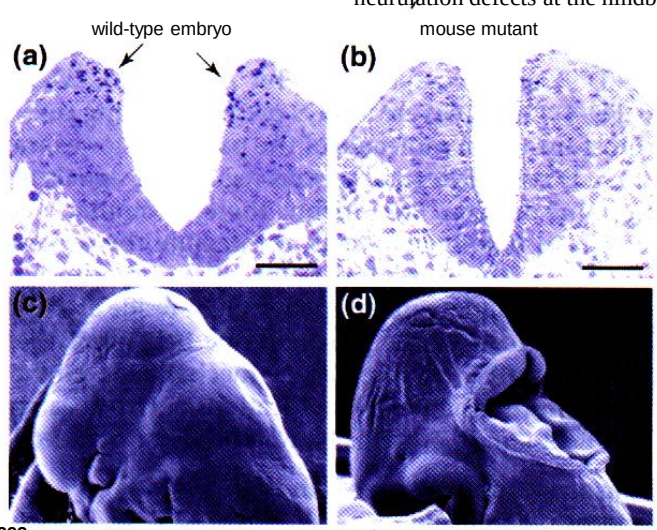
Separation of neural folds from the ectoderm.

If the number of eliminated cells prevails over the number of newly generated cells, eg. as a result of teratogens, congenital malformations develop.

Apoptosis is required for the closure of the hindbrain neural tube.

Pycnotic cells located at the lateral edges of the neural tube prior to closure.

In mouse mutants (deficient in both Jnk1 and JNK2 protein kinases), reduction of region-specific apoptosis causes neurulation defects at the hindbrain (d).



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Neurotrophic hypothesis: Neurons that form synapses with their target tissue are protected against programmed cell death by a trophic factor that is produced by the target tissue.

NGF - trophic effect on sympathetic and cholinergic neurons
BDNF (brain-derived neurotrophic factor) supports motor neurons
CNTF (cilliary neurotrophic factor) supports survival of motor neurons and parasympathetic nn.
FGF: endothelial cells
IL-5 (interleukin-5): eosinophilic granulocytes

As the number of target cells is limited, neurons must compete to get their trophic support (competition)

In the adults, apoptosis takes part in:
- balance of tissue homeostasis
- elimination of autoreactive lymphocytes
- involution of the endometrium or *corpus luteum*