Development of the Muscle and Nerve

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Development of Nerves

This is an image from Dr. Kathy Sulik’s website showing the trilaminar embryo with the midline notochord and neural tube. Somites are located lateral to the neural tube.
In this image of the embryo before lateral body folding the point is made that the neuroectoderm develops as levels of FGF increase thereby inhibiting the levels of BMP. Low levels of BMP permit the differentiation of nervous tissue.
This slides review the point that FGF induces Noggin and Chordin and that Noggin and chordin inhibit BMP.

Ectoderm will become nervous tissue if protected from BMP.
Lateral Body Folding
Review of Early Development

1. The notochord develops in the midline and induces the overlying ectoderm to form the neural tube.
As the third week comes to an end, the neural folds become prominent and they approach one another in the cervical region.
The neural tube is first formed in the cervical region. It then continues to form in a cephalic and caudal direction.
The last two areas to fuse are the cranial neuropore cephalically and the caudal neuropore caudally.
The neural tube in blue consists of a central canal which is surrounded by neuroepithelial cells. The central canal has two lateral sulci which form the sulcus limitans on each side. The sulcus limitans designates the dorsal and ventral parts of the neural tube.
Neural induction which converts ectoderm into neuroectoderm is regulated by the coordinated actions of BMP, Wnt and FGF signaling pathways. Neuroectodermal cells are undifferentiated dividing neuroepithelial cells that will latter differentiate into neurons (neurogenesis period) and in a second phase into glial cells (gliogenesis period). Among the factors that control the selection of neuronal progenitors from the neuroectodermal cells and their commitment to differentiate along the neuronal lineage are the proneural bHLH genes. In vertebrates, proneural bHLH genes are first expressed in the neuroectodermal cells, already committed to the neural fate. The neuronal progenitors have a limited mitotic potential. Differentiation occurs in a defined temporal sequence, neurons being generated first, followed by glial cells. The switch from neurogenesis to gliogenesis is controlled by both extrinsic and intrinsic signals and is the result of changes in the progenitor properties within the same pool of neuronal progenitors. (B). In ESC neural induction and specification of ES-derived neural progenitors follow the same cues as in the embryo to give rise to populations of neurons and glial cells. Black curved arrows indicate self-renewing cells. Abbreviations; BMP, Bone Morphogenetic Protein; bHLH genes, basic Helix-loop-Helix genes; ESC, embryonic stem cell, NSC, Neural stem cell.

Catherine Leclerc, Isabelle Neant, Marc Moreau Early neural development in vertebrates is also a matter of calcium Biochimie Volume 93, Issue 12 2011 2102 – 2111 http://dx.doi.org/10.1016/j.biochi.2011.06.032
Fig. 3  Schematic diagrams of the temporal development of neural progenitors in the early stages of CNS formation. (A) Early neuroepithelial progenitors of the ventricular zone are columnar cells self-renewing by symmetric divisions. These cells can generate some neurons. (B) As neurogenesis proceeds, neuroepithelial cells are transformed into radial glial cells which ultimately will give rise to neurons and glial cells. Radial glia cells can undergo either symmetric divisions, generating two progenitors or asymmetric divisions, producing a neural progenitor and a neuron. Also illustrated is the interkinetic nuclear migration of the nuclei during the cell cycle in the VZ. The nucleus of a single neuroepithelial cell moves during the G1 phase, from the ventricular surface to the border of the VZ where it enters S phase. During G2, the nucleus moves down to the ventricular surface where it enter mitosis (M phase). Interkinetic nuclear migration in radial glial cells is confined to the VZ portion, does not extend to the border of the MZ. (C) In the cerebral cortex a second proliferative zone, the subventricular zone (SVZ), appears adjacent to the VZ; the postmitotic neurons and glia arise from both the ventricular and the subventricular zones. In the SVZ interkinetic nuclear migration does not occur, mitotic cells are found throughout the SVZ. Abbreviations; CNS, central nervous system; IZ, intermediate zone; MZ, marginal zone; SVZ, subventricular zone; VZ, ventricular zone.

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• From Kathy Sulik’s website. Note the neural tube has a ventricular layer, a mantle layer and a marginal layer. Also see are neural crest cells.
The mantle layer is then subdivided into three divisions:
1. Alar plate - the sensory region (blue)
2. Basal plate - the motor region (red).
3 An intermediate autonomic region (black).
cranial ganglia and nerves
sensory ganglia and nerves
autonomic ganglia and nerves
medulla of adrenal gland,
melanocytes
branchial arch cartilages,
head mesenchyme
Dentin
Cementum
Periodontal ligament
Alveolar bone
Conotruncal septum
Schwann cells

central nervous system
motor neurons
preganglionic autonomic
neurons
retina,
pineal body,
posterior pituitary
glial cells
Intermediate levels of BMP will lead to the formation of neural crest cells from the ectoderm.
Intermediate levels of BMP

FGF
WNT

PAX3

FOXD3

Neural Crest cells

migration

SLUG
Neural crest differentiation into trunk sensory neurons. (A) Wnt1Cre;R26R<sup>lacz</sup> labels all of the migrating neural crest cells (NCCs) at E10.0. (B) A cross section through the trunk reveals the ventromedial path of NCC migration that populates the dorsal root ganglia (DRG). Differentiation of NCC during and postmigration leads to formation of three morphologically distinct types of sensory neurons: small-diameter nociceptive (peptidergic and nonpeptidergic) (shown in yellow) and large-diameter mechanoreceptors (red) and proprioceptors shown in red and (pink), respectively. (C) Trunk sensory neurogenesis occurs in two waves, both of which are directly or indirectly dependent on canonical Wnt signals emanating from the dorsal neural tube. (C-1) During the first wave of sensory neurogenesis, Wnt signals act on migratory NC cells to induce the expression of Neurogenin2 (Ngn2). Ngn2 expression biases the neural crest fate toward sensory neurogenesis. Postmigratory cells of the first wave express Bm3a and differentiate into large-diameter proprioceptor (TrkC<sup>+</sup>, shown in red) and mechanoreceptor (TrkB<sup>+</sup> or Ret<sup>+</sup>, shown in purple) neurons. Runx3 plays an important role in formation of TrkC<sup>+</sup> proprioceptors, whereas Shox2 has an important role in regulating expression of TrkB in mechanoreceptors. (C-2) The second wave of neurogenesis occurs subsequently in embryogenesis and gives rise to nociceptor neurons. Neurogenin1 and Bm3a expression in the postmigratory second-wave cells marks them for sensory differentiation. Bm3a directly activates TrkA in these cells, which then, based on the differential expression of Runx1, differentiate into nonpeptidergic (Runx1<sup>+</sup>;Ret<sup>+</sup>) and peptidergic (TrkA<sup>+</sup>) nociceptor neurons (peptidergic cells are shown in yellow). E, Embryonic day; P, postnatal day; NT, neural tube; no, notochord; DRG, dorsal root ganglion; NCC, neural crest cell. (Figure adapted and modified based on Marmigere and Ernfors 2007.)
Signals and switches regulating cranial neural crest cell differentiation. Schematic representation of the signals and switches that govern neural crest cell segregation from a stem or progenitor cell into neuroglial or ectomesenchymal cells. This is then followed by differentiation of ectomesenchymal cells into an osteochondral progenitor cell and then bifurcation of potential into chondroblasts/chondrocytes or osteoprogenitors/osteoblasts.
<table>
<thead>
<tr>
<th>Event</th>
<th>Regulatory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>BMP, Wnt, FGF</td>
</tr>
<tr>
<td>Neural plate border</td>
<td>Pax3, Zic</td>
</tr>
<tr>
<td>Neural crest</td>
<td>Snail, FoxD3, cMyc</td>
</tr>
<tr>
<td>Cell proliferation/</td>
<td>Id, Snail, Myc,</td>
</tr>
<tr>
<td>Delamination/migration</td>
<td>Sox10, Integrins,</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Sox9/10, FoxD3</td>
</tr>
</tbody>
</table>
cranial ganglia and nerves
sensory ganglia and nerves
autonomic ganglia and nerves
medulla of adrenal gland,
melanocytes
branchial arch cartilages,
head mesenchyme
Dentin
Cementum
Periodontal ligament
Alveolar bone
Conotruncal septum
Schwann cells

central nervous system
motor neurons
preganglionic autonomic
neurons
retina,
pineal body,
posterior pituitary
glial cells
Neural Crest Gene Regulatory Network
<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>Microcephaly, blindness, mental retardation</td>
</tr>
<tr>
<td>Varicella virus</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Hydrocephalus, cerebral calcifications</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Mental retardation and deafness</td>
</tr>
</tbody>
</table>
An MRI scan of a brain with hydrocephalus (left) and a normal MRI scan (right). The large dark area on the left is the ventricles, made bigger by a build-up of CSF.
Microcephaly
Physical Agents causing Neural Defects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays</td>
<td>Microcephaly, Spina bifida</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Anencephaly, spina bifida, mental retardation</td>
</tr>
<tr>
<td>Agent</td>
<td>Defect</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Anticonvulsants for epileptics</td>
<td>Mental retardation, Neural tube defects.</td>
</tr>
<tr>
<td>Anticoagulant Warfarin</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Microcephaly, Behavioral abnormalities</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Fetal Alcohol Syndrome, Mental retardation.</td>
</tr>
<tr>
<td></td>
<td>Alcohol is the leading cause of mental retardation.</td>
</tr>
<tr>
<td></td>
<td>Fetal alcohol syndrome and fetal alcohol spectrum disorder occurs in 1:100 live births.</td>
</tr>
<tr>
<td>Organic mercury</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Lead</td>
<td>Neurological disorders</td>
</tr>
</tbody>
</table>
Fetal Alcohol Syndrome

- These are some of the characteristic facial features of infants born with fetal Alcohol Syndrome.
  - Small eyes
  - Smooth philtrum
  - Thin upper lip

- To view these features you can go to The FAS Diagnostic and Prevention Network website.
Other causes of Neural defects

<table>
<thead>
<tr>
<th>condition</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal diabetes</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>Maternal obesity</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>Normal Glucose</td>
<td>Elevated glucose levels</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Pax3 levels increase</td>
<td>Pax3 levels decline</td>
</tr>
<tr>
<td>P53 protein decreases</td>
<td>P53 protein increases</td>
</tr>
<tr>
<td>Cardiac neural crest and neuroepithelium proliferate</td>
<td>Cardiac neural crest and neuroepithelium arrested</td>
</tr>
<tr>
<td></td>
<td>Programmed cell death</td>
</tr>
<tr>
<td>Normal crest migration</td>
<td>Crest cells not present</td>
</tr>
<tr>
<td>Outflow tract and neural tube normal</td>
<td>Outflow tract and neural tube defects.</td>
</tr>
</tbody>
</table>
Development of Vertebrae

In this image the paraxial mesoderm on either side of the neural tube has developed into the somite.
Somites give rise to skeletal muscle.

Splanchnic mesoderm gives rise to smooth muscle and cardiac muscle.
Sulik Embryology Website
• Somitomeres 1 and 2 - eye muscles innervated by cranial nerve 3
• Somitomere 3 - superior oblique innervated by cranial nerve 4
• Somitomere 4 - all muscles of mastication plus two tensors and two others innervated by cranial nerve 5.
• Somitomere 5 - lateral rectus innervated by cranial nerve 6
• Somitomere 6 - All muscles of facial expression plus three others innervated by cranial nerve 7
• Somitomere 7 - stylopharyngeus innervated by cranial nerve 9
• Occipital somite 1 - muscles of the pharynx and larynx innervated by the vagus.
• Occipital somite 2 - muscles of the larynx innervated by the recurrent laryngeal branch of the vagus.
• Occipital somites 3 and 4 - intrinsic muscles of the tongue.
In the neck and trunk there are:

42 - 44 paired somites

42 - 44 paired somites

4 occipital
8 cervical
12 thoracic
5 lumbar
5 sacral
8(10) coccygeal

Myotomes develop into muscles
Sclerotomes develop into vertebra
The somite gives rise to a dermatome, myotome and sclerotome. The myotome gives rise to the skeletal muscles of the trunk and extremities.
• The somite gives rise to cartilage, bone and other connective tissue constituents as well as smooth and skeletal muscle.
Development of Vertebrae & Ribs

- The formation of bone involves:
  1. the mesenchymal cells differentiating and migrating from the sclerotome to the region of the presumptive vertebrae and ribs;
  2. the mesenchymal cells round up and form a precartilage mass
  3. cartilage is formed
  4. the formation of the bone by the replacement of the cartilaginous model with bone tissue.
Vertebra Formation

- Sclerotome cells surround the
  - notochord
  - neural tube
• SHH induces PAX1 which forms in scleretome to aid in formation of the vertebrae.
• WNT from dorsal spinal cord induces Myf5 in myotome to aid in the formation of back muscles.
• WNT from body wall ectoderm induces lateral myotome to express myoD for the formation of anterior and limb musculature.
Vertebra Formation

• Sclerotome around the notohord forms the vertebral body.
• Sclerotome around the neural tube forms the vertebral arch.
• Chontroitin sulfate is secreted by the notochord and important in cartilage formation during vertebral body development.
Neural Tube Defects

Spinal bifida occulta

Dermal sinus

Sinus with squamous plug

Fat pad overlying spina bifida occulta. Tuft of hair or only skin dimple may be present, or there may be no external manifestation. Dermal sinus also present in this case (arrow)

Types of spina bifida aperta with protrusion of spinal contents

Meningocele

Meningomyelocele
Neural Tube Defects

- Occipital encephalocele
- Frontal encephalocele
- Anencephaly
Meningomyleocele
Meningomyleocele

- Incidence 1 in 1000 live births
- Defect in the base of the spinal cord
  - protrusion of spinal cord or meninges through the skin
- Condition often associated with hydrocephalus
- Extensive lesions can result in lower limb paralysis and bowel and bladder dysfunction