FOUNDATION IN NEUROSCIENCE I

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Neural Development

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Outline and Objectives

• The early embryo and Neurulation
  – Know the 3 primitive germ layers and able to give examples of their derivatives
  – Body axis establishment
  – Origin of the central vs. peripheral nervous system

• Molecular basis of neural induction
  – Families of molecules signaling in reciprocal gradients

• Major brain subdivisions
  – Primary and secondary brain vesicles
  – Ventricular system

• Neurogenesis and neuronal diversity
  – Cell division at the ventricular zone
  – Key players in neuronal vs. glial differentiation

• Neuronal migration
  – Cortical lamination
  – Tangential migration
Gastrulation

- Will not cover fertilization
- Gastrulation begins when this single sheet of cells began to divide and invaginate at the midline resulting in 3 primitive germ cell layers:
  - Ectoderm:
  - Mesoderm:
  - Endoderm:
- As a result of the position of the 3 germ layers, gastrulation as defines the midline and establishes the basic body axes:

Moving towards the midline is **medial** and away from the midline is **lateral**

Diagram:

- **Back**
- **Head**
- **Foot**
- **Front**
- **Dorsal**
- **Ventral**
- **Anterior**
- **Lateral**
- **Midline**
Gastrulation

- The notochord, defines the midline, a transient structure during development that is important later for neural induction. Mesodermal derived.

The beginning of neurulation...

- Formation of all the above structures
- Thickening of the midline ectoderm to form the neural plate
Neurulation

- At around 20 days of gestation, the neural plate begins to fold inward.

**Non-neuronal tissues:**
- Floorplate
- Roofplate

**Somites:** paraxial mesoderm,
- **Sclerotome** → vertebrae and skull
- **Myotome** → skeletal muscles
- **Dermatome** → dermis

**Neural crest:**
Neurulation

Neural tube closure abnormalities:
- Anencephaly
- Hydrocephalus
- Spina bifida
Scanning EM of Neural Tube Folding
Neural Tube Closure Defects

Anencephaly: failure of the neural tube to close anteriorly/rostrally (in the future head region). This will result in no brain, fatal.

Spina bifida: failure of the neural tube to close posteriorly or caudally (in your rear end region).
- *Spina bifida occulta* —

- *Spina bifida cystica* —
Neural Crest?

- Specialize ectoderm at the most dorsal part of the neural fold.
Neural crest derivatives

- Visceral motor ganglia (autonomic nervous system)
- Enteric nervous system
Molecular basis of neural induction

• How do cells know their identity (cell fate)?
• How does one achieve cellular diversity?

Molecular players:
• Retinoic acid (vitamin A derivative)
• Fibroblast growth factors (FGFs)
• Transforming growth factor (TGF) superfamily of proteins, including the Bone morphogenetic proteins (BMPs)
• Sonic hedgehog (Shh)
• Wnt family proteins

Gene regulation
• Inhibitory SMADs: SMAD6 and 7.
• Chordin and noggin are antagonists of BMPs, they dorsalize the mesoderm, important in cartilage and bone patterning and rescue the neuroectoderm from the fate of becoming epidermis tissues.
Inhibition of BMP Signaling by Noggin and Chordin

Noggin and Chordin do not bind the BMP receptors, but rather binds the BMPs thus preventing them from signaling.
• Sonic hedgehog (Shh):

• Shh was discovered as a morphogen:

• Recently, Shh have been found to also act as an axonal guidance cue.
Combination of signaling molecules give cellular diversity in the developing spinal cord.
The Development of the Brain

(Figure 1)
Development of the Brain

(c) Secondary brain vesicles

<table>
<thead>
<tr>
<th>Telencephalon</th>
<th>Mesencephalon</th>
<th>Diencephalon</th>
<th>Metencephalon</th>
<th>Myelencephalon</th>
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</table>

(a) 5 weeks

- Anterior (rostral)
- Posterior (caudal)
- Flexures
- Midbrain
- Cervical
- Spinal cord

(b) 13 weeks

- Cerebral hemisphere
- Outline of diencephalon
- Midbrain
- Pons
- Medulla oblongata
- Spinal cord

(c) 26 weeks

- Cerebral hemisphere
- Cerebellum
- Pons
- Medulla oblongata
- Spinal cord

(d) Birth

- Cerebral hemisphere
- Diencephalon
- Cerebellum
- Brain stem
- Midbrain
- Pons
- Medulla oblongata

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Basic Organization of the CNS
Epithelia cells line the entire surface of the ventricle known as the epithelia membrane, within this membrane are specialized epithelia cells called ependymal cells that form a thin tissue called the choroid plexus, which secretes fluids into the ventricle. This fluid is called the cerebral spinal fluid (CSF).
Hydrocephalus
Neurogenesis

Ventricular Zone

1. In $G_1$, nucleus is near ventricular surface.
2. During S stage, nucleus and surrounding cytoplasm migrate toward the pial surface and DNA replicates.
3. During $G_2$, cell grows and nucleus migrates toward lumen again.
4. In mitosis, cells lose their connection to pial surface and divide. Symmetrical divisions generate two neural stem cells. Asymmetrical divisions generate a neuroblast and a progenitor cell with limited mitotic potential.
Neuronal diversity

1. Neural induction
   - Ectoderm
   - BMPs
   - Noggin/chordin
   - Epidermis

2. Organizer centers
   - Neuroectoderm
   - Ventricles
   - TGF-βs
   - Sonic hedgehog
   - Roofplate
   - Floorplate

3. Neural patterning
   - Neural tube

4. Neurogenesis
   - Proneural bHLHs
   - Notch/Nrg
   - Astrocyte precursors
   - Astrocytes

5. Oligodendrogensis
   - Proneural bHLHs
   - Olig1/2 Nkx2.1
   - Oligodendrocyte precursors
   - Oligodendrocytes

6. Astrogliogenesis
   - Proneural bHLHs
   - Notch/Nrg
   - Astrocyte precursors
   - Astrocytes

7. Ependyma
   - Proneural bHLHs
   - Notch/Nrg
   - Astrocyte precursors
   - Astrocytes
Neuronal birth dating

- A neuron is said to be “born” or “postmitotic” is when it undergoes its final mitosis (cell division).
- The cerebral cortex has 6 layers of neurons.

- Cortical layers are established in an “inside-out” fashion.
Neuronal migration

- Neuronal migration in the CNS:
- Radial glia:
- Newly born neurons:

Molecular cues regulating radial migration?
Abnormal cortical neuron migration due to lack of the reelin protein

• Reelin is a large extracellular matrix protein, expressed by the Cajal-Retzius cells during development. Receptors for reelin, VLDL and APOE2, are expressed by migrating cortical neurons. *Reeler* is the naturally occurring mutation that lacks reelin.

Sheldon et al., Nature 1997
Howell et al., Nature 1997
Trommsdorff et al., Cell 1999
Neuronal migration

- Tangential or long distance migration does not use radial glia.

Ventral forebrain
- Medial ganglionic eminence
- Lateral ganglionic eminence
Together these structures generate distinct classes of GABAergic interneurons and oligodendroglia in the cerebral cortex.
Cortical interneurons avoid the striatum in their migration to the cortex

O Marín et al. Science 2001;293:872-875
Ectopic expression of Sema3A and Sema3F blocks the migration of cortical interneurons

Sema3A and Sema3F are members of the semaphorin family of axonal guidance molecules, they have established roles in repelling axons during development.

O Marín et al. Science 2001;293:872-875
What happens to the neuronal connections in the brain of animals with neuron migration defects?
Wiring of the Nervous System
(The ultimate goal of proper neural development)

• Patterning of the nervous system
• Neuronal cell fate determination
• Neuronal differentiation
• Neuronal migration
  • Layer/lamina formation
• Axon guidance and pathfinding
• Dendrite development
• Map formation
• Synaptogenesis
• Synaptic competition, elimination
• Synaptic homeostasis, maturation
• Synaptic plasticity