Development of the nervous system - I

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Early embryonic development

- Development of the nervous system begins after gastrulation
- Nervous system and skin develop from ectoderm
Stages of neural development

- Neural induction
- Birth and differentiation of neurons
- Polarity, segmentation of nervous system
- Migration of neurons to their final position
- Growth of axons and axon guidance to their post-synaptic targets
- Changes in synapses
Model systems for studying development

C-elegans

Drosophila

Xenopus

Chicken

Zebra fish

Mouse
Hydra (diploblast)- neurons develop from a precursor in the epidermis - interstitial cell

- Molecular mechanisms poorly understood
C-elegans - development of nervous system

- ~1000 cells
- 302 neurons and 56 glial cells
C-elegans

- Endoderm and mesoderm precursors migrate inward - end of gastrulation
- Proliferation phase
- Ventral indentation - start of morphogenesis - 4 molts
- Neurons form and migrate inward
Drosophila - neurons generated from ventrolateral part of embryo (ectoderm)

- Cellularisation results in cellular blastoderm
- Ventral furrow marks start of gastrulation
- Mesoderm invagination
- Ventral midline - future site of neurogenesis
Drosophila

- Continuation of neurogenic region into anterior region gives rise to brain
- Neuroblasts delaminate
- Divide into GMC and Nb
- GMC gives rise to neurons or glia
- Larval nervous system
- Morphogenesis - additional neurogenesis
Frog

- Blastopore - small invagination - point of initiation of gastrulation
- First cells to invaginate occur at the dorsal side of blastopore - opposite to sperm entry point
- Spemann's organiser
- Involuting marginal zone - first cells form head, last form tail (mesoderm)
- Neural plate
Frog

- Neural plate folds over to form neural tube
- Gives rise to neurons and glia of CNS
- Neural crest - junction between neural tube and ectoderm
- Unique to vertebrates - gives rise to PNS
Zebra fish - small differences in gastrulation due to differences in amount of yolk

- Epiboly
- 50% epiboly marks start of gastrulation at future dorsal margin - shield
- Mesoderm delaminates, moves inside
- Neural plate forms
Chick - “yolky” egg

- Blastodisc floating on yolk
- No epiboly
- Mesoderm invagination in this disc through blastopore-like primitive streak
- Hensen's node - posterior end of primitive streak - like dorsal lip of blastopore
Human - no yolk

- Inner cell mass of blastula gives rise to embryo
- Primitive streak - line of cells migrating into blastocoel to form mesoderm
- Overlying ectoderm induced to form neural tube
- Tube rolls up and forms brain and spinal cord
Involuting mesoderm “induces” overlying ectoderm to form neural tissue

- Culture each part of embryo separately to determine time of fate determination
- Frog
- Hans Spemann
Spemann and Mangold identify Spemann organizer

- Dorsal lip of blastopore can induce formation of second body axis including second brain and spinal cord
- Host and donor cells contribute to new axis
- Dorsal lip - Spemann organizer - not only neural inducer but also organizes body axis
- Who organizes Spemann organizer?
Spemann organizer organized by Nieuwkoop center

- Nieuwkoop found that mesoderm is induced at the junction of animal cap (ectoderm) and vegetal cap (endoderm)
- Dorsal-most part of vegetal pole can induce Spemann organizer
- Possibly β-catenin
- But, again, how is this setup - sperm entry, cortical rotations, gray crescent, etc...
Induction of neural tissue - studying it with the isolated animal cap assay

- Do candidate factors induce neural tissue directly or indirectly?
- Assay looked for increased expression of neural genes without increased expression of mesoderm genes
Noggin is a secreted molecule that can induce neural tissue

- Ventralized and hyperdorsalized embryos
- cDNA from dorsal lip (Spemann organiser) was divided into smaller and smaller collections to rescue UV treated embryos
- Noggin mRNA expressed in gastrulating embryos by cells of dorsal lip of the blastopore
- Richard Hartland's group
Chordin identified as another molecule secreted by organizer

- DeRobertis' group
- Identify genes that were expressed in the organizer region
- Chordin a secreted molecule expressed when neural induction occurs
- Overexpressing results in formation of second axis just like noggin
Neural fate is the default for endodermal cells

- Noggin, chordin - not clear what they were doing
- Melton's lab
- Identified follistatin as a potential neural inducer
- Known to inhibit activin, a TGF-B family member
- Was actually studying the role of follistatin in mesoderm induction
- Truncated activin
- No mesoderm
- Also lots of neural tissue despite the absence of mesoderm!!
More experiments to show that neural fate is default for animal cap cells

- Dissociated animal cap cells form neural tissue
- Follistatin also expressed in the organizer region at the time of neural induction
Vertebrate embryos are inverted insect embryos!

- **sog** (like **chordin**) inhibits **dpp** (like **BMP4**) in Drosophila to induce neural tissue - only on the ventral side

- Different neural inducers antagonize BMP signaling

- **BMP4** inhibits neural tissue formation in animal caps (dissociated animal cells too) - even with **noggin**, **chordin**, **follistatin**

- Antisense BMP4 RNA - neural tissue forms without addition of inducers
Wnt and BMP signaling pathways - two that are important for development
All three neural inducers block BMP signalling in a similar fashion

- Noggin and chordin bind to BMP4 directly
- Follistatin binds to related BMP7 and activin
Inhibiting BMP signaling - not enough in mammals

- Deletion of noggin and chordin affect head formation and cerebral hemisphere formation
- Some neural tissue does form
Current understanding of neural induction

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Next step - formation of neuroblasts

- Drosophila, proneural clusters
- achaete-scute complex genes expressed by clusters of proneural cells before delamination
- One neuroblast develops from each cluster
Achaete-scute complex genes are required for formation of the one neuroblast

- Only one of the proneural cells becomes a neuroblast in a normal fly
- Flies mutant for proneural genes like achaete scute - neuroblasts don't form
- Flies mutant for notch or delta - multiple neuroblasts form
These genes are basic-helix-loop-helix transcription factors
Delaminating neuroblast inhibits neighbouring cells from becoming a neuroblast

- Ablation of a delaminating neuroblast makes the neighbouring ectodermal cell become a neuroblast
- Neuroblast inhibits neighbouring cells from becoming neuroblasts
Notch signaling pathway is involved in lateral inhibition