Lectures 39 and 40 – Developmental genetics

I. Developmental genetics
   A. requirements for development
      1. cell proliferation
      2. mechanisms for generating cell differences
         a. specification – cell fates become restricted
            - early \( \rightarrow \) pluripotent
            - later \( \rightarrow \) more restricted in developmental potential
         b. two general mechanisms
            i. asymmetric segregation of determinants
            ii. cell-cell signaling

B. Drosophila early development – A-P axis patterning
   1. Why Drosophila?

   2. fly development in overview:
      - nuclear proliferation
      - nuclear migration
      - cellularization
      - segmentation
      - e.g. T2 = wings, T3 = halteres

   A-P axis patterning
   - Notum
   - Haltere (rudimentary wing)
   - A5-A8
   - A1

   Segmentation:
   - head
   - thorax
   - abdomen
   - 3 segments
   - 3 segments
   - 8 segments
3. anterior-posterior body axis – concentration gradient of key transcription factors that act as morphogens
   - morphogen –

   BCD protein
   bcd mRNA
   bcd/bcd- lack anterior structures
   bcd mRNA
   BCD gradient

   HB-M
   gradient

   hb mRNA
   HB protein
   hb mRNA

   nos mRNA
   NOS protein
   NOS regulates HB
   nos/nos- lack posterior structures
   nos mRNA

4. proteins expressed in gradients regulate expression of next level of patterning, the gap genes

   protein level
   BCD
   HB
   NOS

   KRUPPEL

   mutations in gap gene results in loss of region of embryo

   KNIRPS

   - gap genes divide embryo into distinct domains
   - adjacent gap gene expression often overlaps

5. gap genes regulate pair-rule gene expression
   - pair-rule genes specify alternating segments

   FTZ
   Eves

   mutation in pair-rule gene result in loss of alternate segments

   - pair-rule gene regulation is complex
     - eg: eve in stripe 1 activated by hi HB, in stripe 2 activated by low HB and hi Kruppel

6. pair-rule genes regulate expression of segment polarity genes
   - segment polarity genes regulate A-P identity of cells in each segment
7. what regulates identity of individual segments?
   a. gap genes regulate homeotic gene complexes
      - homeosis

   - all contain homeodomain, act as transcription factors
   - ANT-C proteins regulate segment identity in anterior regions
     - antp specifies one of thoracic segments
     - antp gain-of-function mutations transform antennae to legs
   - BX-C proteins regulate segment identity in posterior
     - btx mutations transform 3<sup>rd</sup> thoracic segment into 2<sup>nd</sup> thoracic segment

   b. mutations in homeotic gene alter identity, but # segments is same

8. summary – cascade of regulatory proteins patterns A-P axis

C. what about dorsal-ventral body axis?
   1. established later, when cellularized
      a. cell-cell signaling via secreted ligands
      b. ligands bind cell surface receptors
   2. control of D-V axis via Dorsal transcription factor
      a. 2 forms of DL, inactive cytoplasmic or active nuclear
      b. dl mRNA and DL protein uniform along D-V axis
      c. signaling induces change →DL active, nuclear
D. ensuring at least one cell adopts appropriate fate
   - *C. elegans* vulval development
     1. 6 cells have potential to adopt any of 3 different fates
     - to form vulva, 1 cell must adopt 1° fate, 2 must adopt 2° fate and rest must adopt 3° fate
     2. signal from anchor cell determines fates

- how it works in some detail

**How was the vulval development pathway deciphered?**
Genetic screens for mutations that produce vulvaless (Vul) or multivulva (Muv) phenotypes
II. Summary
   A. gradient of morphogens establishes initial differences within egg
      - gradient of morphogen may be within syncitium (A-P patterning) or
        extracellular (D-V patterning)
   B. initial gradients regulate expression of downstream components to divide embryo
      into ever smaller regions
      - homeotic genes provide regional identity
   C. many cell-cell signals regulate cell fate
III. Who cares about fly or worm development, what about mammals?
   A. homeotic genes conserved from worms to mammals
      - mammals have many more homeotic genes
   B. vulval signaling molecules function in mammals
   C. homologous molecules have same/similar function in mammals
   D. basic principles are universal