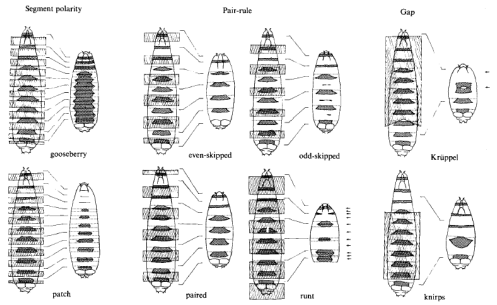
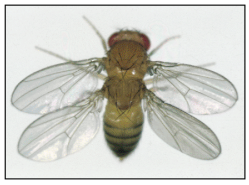
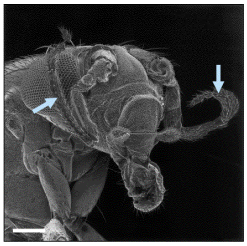


Homeotic mutation (Bateson, 1894):
A mutation in which one normal body part is replaced with another

Some of the famous ones…



Ultrabithorax (Ubx)



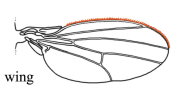
Antennapedia (Antp)

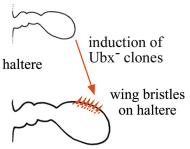
The *Hox* genes specify the identity of a field (segment), not the formation of the field.

Contrast this to the segmentation genes, which establish the segments themselves.

The *Hox* genes act cell autonomously, working within cells to select their developmental fate.

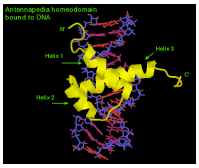
Thus they are sometimes called "selector" genes—they select the future developmental path of the segment, controlling whole later developmental programs



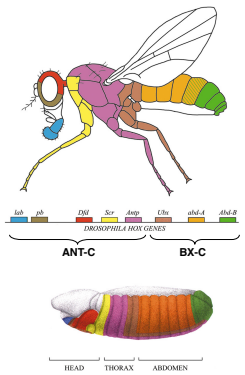


The *Hox* genes are all *transcription factors* and are related in their DNA binding domains, the *homeobox*

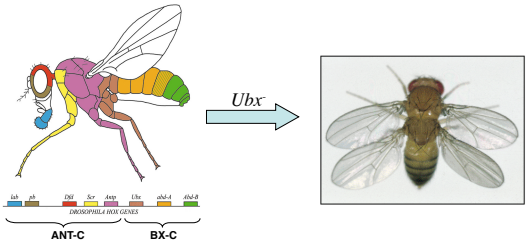
```
lab     NNSGRTNFTNKQLTELEKEFHFNRYLTRARRIEIANTLQLNETQVKIWFQNRRMKQKKRV
pb      PRRLRTAYTNTQLLELEKEFHFNKYLCRPRRIEIAASLDLTERQVKVWFQNRRMKHKRQT
Dfd     PKRQRTAYTRHQILELEKEFHYNRYLTRRRRIEIAHTLVLSERQIKIWFQNRRMKWKKDN
Scr     TKRQRTSYTRYQTLELEKEFHFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKEH
Antp    RKRGRQTYTRYQTLELEKEFHFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKEN
Ubx     RRRGRQTYTRYQTLELEKEFHTNHYLTRRRRIEMAHALCLTERQIKIWFQNRRMKLKKEI
abd-A   RRRGRQTYTRFQTLELEKEFHFNHYLTRRRRIEIAHALCLTERQIKIWFQNRRMKLKKEL
abd-B   VRKKRKPYSKFQTLELEKEFLFNAYVSKQKRWELARNLQLTERQVKIWFQNRRMKNKKNS
```



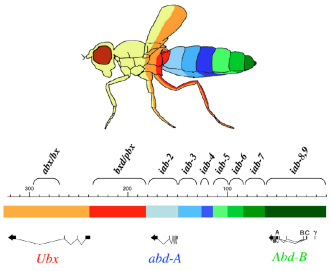
In the fly, there are two main clusters of *Hox* genes: the Antennapedia Complex (ANT-C) and the Bithorax Complex (BX-C). Strikingly, their order on the chromosome is identical to their order of expression in the A/P axis.



In a *Ubx* mutant, Antp expands into T3, causing a homeotic mutation of T3 into T2 (which has wings). More posterior segments are unaffected due to repression of Antp by Abd-A

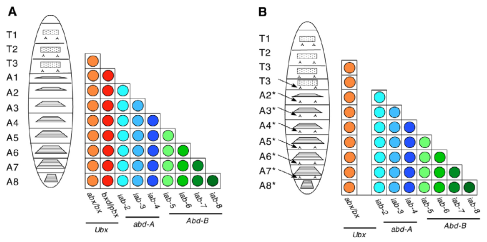


Although there are only 3 genes in the BX-C, there is a complex regulatory structure that causes segment-specific phenotypes in various mutants.

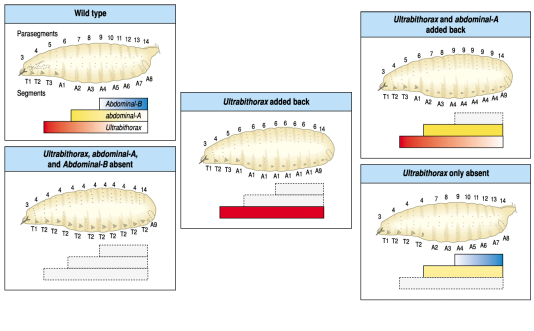


Maeda and Karch 2006

For example, the *bxd/pbx* mutation causes a transformation of A1-> T3 and a partial transformation of more posterior segments.



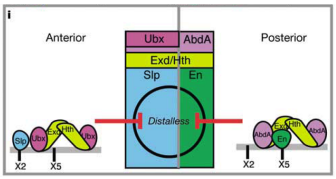
Maeda and Karch 2006



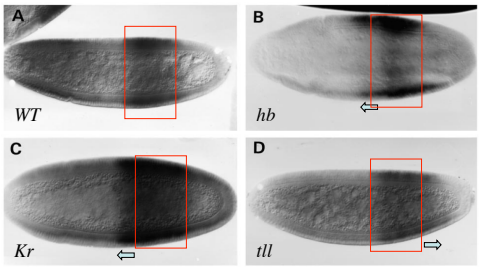
The Hox genes control the expression of important segment-specific and organ-specific genes, usually other transcription factors, which in turn control whole developmental programs.

For example, Scr **activates** the *forkhead* tx factor, which controls development of the salivary gland.

Ubx and *Abd-A* **repress** *distal-less* in abdominal segments, preventing the development of appendages. This also requires segmentation gene input.



Initial expression depends on gap and pair-rule genes



Abd-A in situ hybridization

Casares and Sanchez-Herrero 1995

Maintenance of expression is via epigenetic mechanisms.

Polycomb group (Pc-G) genes keep homeotic genes repressed in segments where they were not intially activated.

Trithorax group (trx-G) genes maintain the expression of the homeotic genes in their appropriate segments.

Both groups act by modifying chromatin conformation. PcG complexes promote H3K27 tri-methylation. TrxG complexes can promote H3K4 methylation. Many details remain to be established.

In this way, patterning information conveyed by the early activity of the segmentation genes is preserved throughout the life cycle.

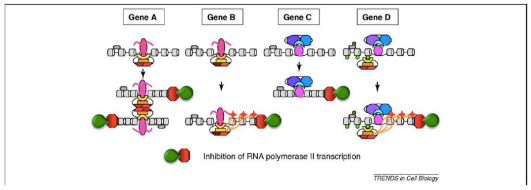
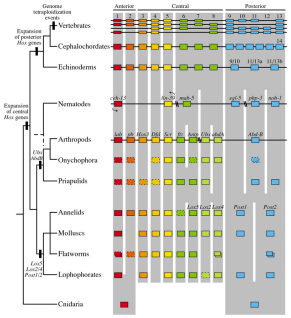


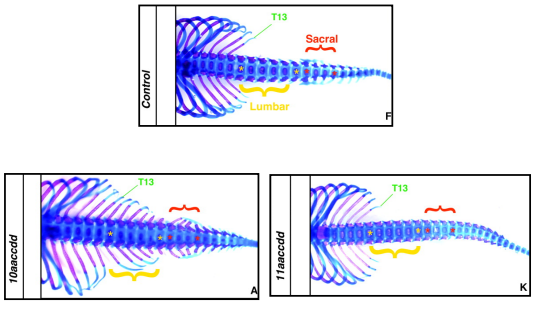
Figure 3. Proposed mechanisms for gene repression by PcG proteins. Chromatin compaction by either PRC1 (Gene A) or PRC2 (Gene C) could produce a chromatin configuration that blocks (red octagon) transcription by RNA polymerase II (green wedge). Alternatively, or in addition, histone H2A K119 ubiquitination (red star) by PRC1 alone (Gene B) or by PRC1 in association with PRC2 (Gene D) could block RNA polymerase II. Other potential mechanisms of gene repression by PcG proteins, including modifications of the transcription machinery, are not shown.

Kerppola (2009) Trends Cell Biol. 19:692-704

The *Hox* genes appear as far back as the *Cnidaria*. In vertebrates, there are four copies of the *Hox* cluster. Not every gene is maintained in each cluster.

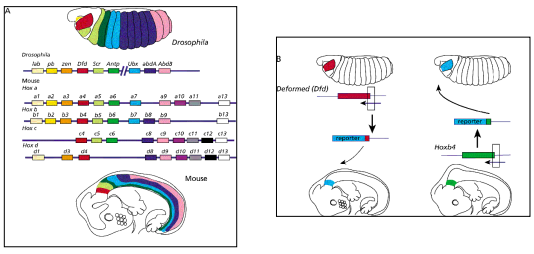


Similar homeotic effects are seen in vertebrates:



Wellik and Capecchi 2003

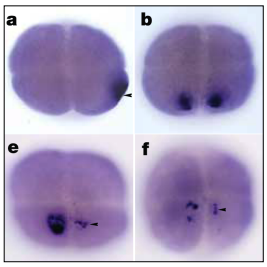
Function is conserved between fly and mouse:



Strategies for Patterning

- ubiquitous receptor, localized activation of ligand (dorsal/ventral system, terminal system)
- localized RNA (anterior/posterior)
- translational inhibition (posterior)
- morphogen gradients (d/v, a/p)
- mutual repression (segmentation)
- cell-cell signaling (segment polarity)
- chromatin remodeling (Hox genes)

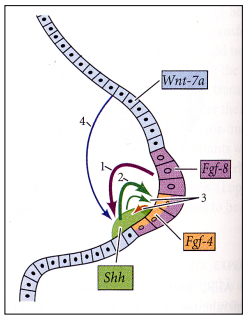
Maternal localization of *sqt* RNA in zebrafish presages the dorsal axis



Gore et al. 2005

The developing vertebrate limb

- Interactions between Wg (Wnt) and HH (Shh), like we saw in the fly embryo



Some major players in human disease

- Wg: Wnt/β-catenin/APC (oncogenes)
- Dpp: TGF- β (oncogene)
- Dorsal: rel/NFκB/TLR/IL-1 (immune response)
- Ras (oncogene)
- HH/ptc/smo/gli (cancer, birth defects)
- Runt (hematapoesis, leukemias)
- Hox cluster (various birth defects)

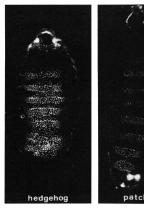
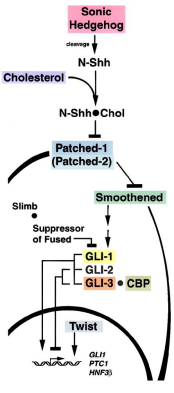


Table 1 Loci affecting segmentation in *Drosophila*

Locus	Map position*	No. of alleles†
cubitus interruptus^{D} (*ci*^{D})	4-0	(2)
wingless (*wg*)	2-30	6
gooseberry (*gsb*)	2-104	1
hedgehog (*hh*)	3-90	2
fused (*fu*)‡	1-59.5	(9)
patch (*pat*)	2-55	8



Holoprosencephaly

Smith-Lemli-Opitz

Gorlin Syndrome
Basal Cell Carcinoma
Medulloblastoma
Trichoepithelioma
Esophageal SCC
Bladder Transitional CCa

Basal Cell Carcinoma
Medulloblastoma

Basal Cell Carcinoma
Medulloblastoma

Basal Cell Carcinoma
Glioblastoma
Rhabdomyosarcoma
Osteosarcoma
Predicts Sarcoma Grade

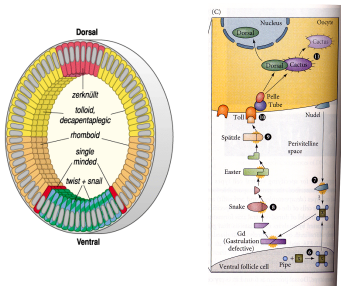
Greig Syndrome
Pallister-Hall Syndrome
Postaxial Polydactyly A
Preaxial Polydactyly IV
Postaxial Polydactyly A/B

Rubinstein-Taybi

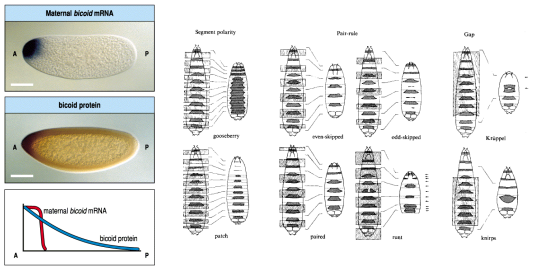
Saethre-Chotzen

We’ ve now seen:

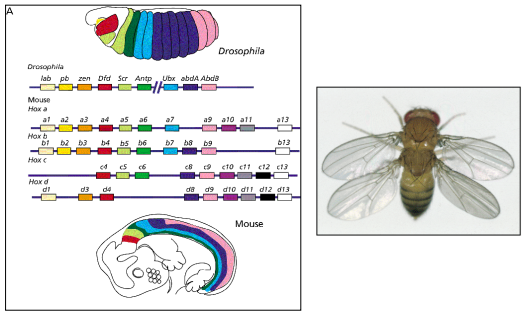
Dorsal-Ventral Patterning:



Anterior-Posterior patterning and Segmentation:

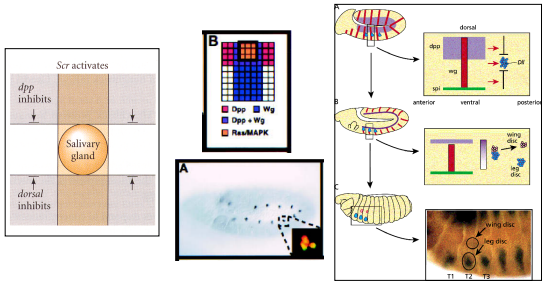


Segment Identity specification:

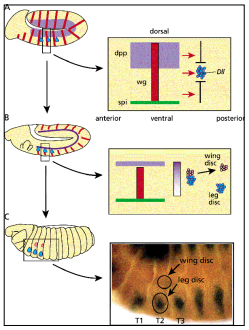


What does this mean for organogenesis?

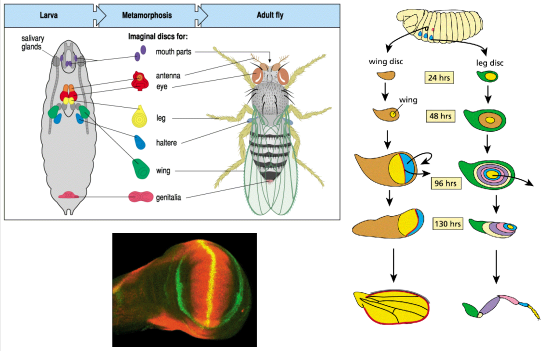
- These early axial patterning and segmentation events set up a coordinate grid on which organs are built

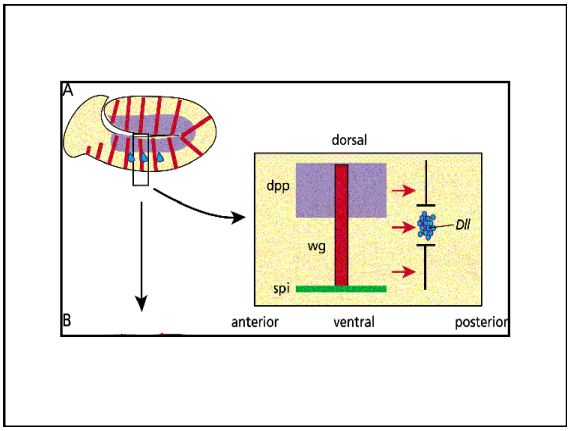


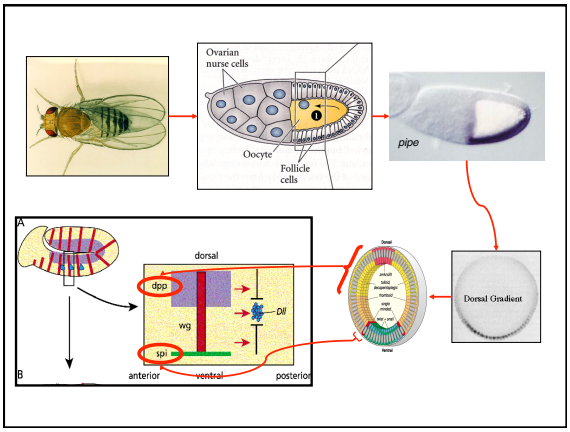
Let’ s look at wing and leg imaginal disc formation:

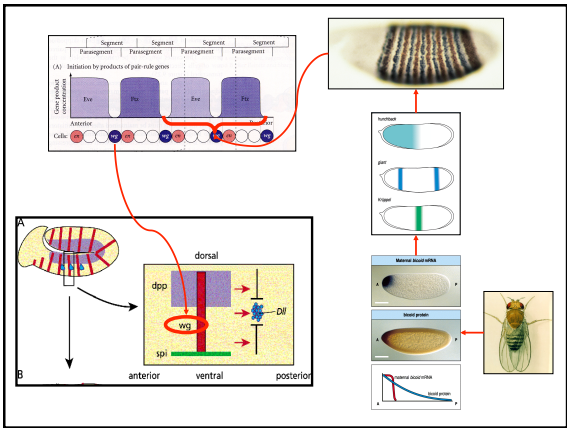


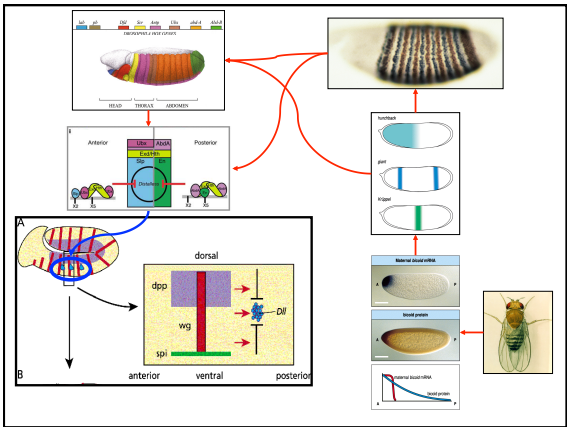
Imaginal Discs



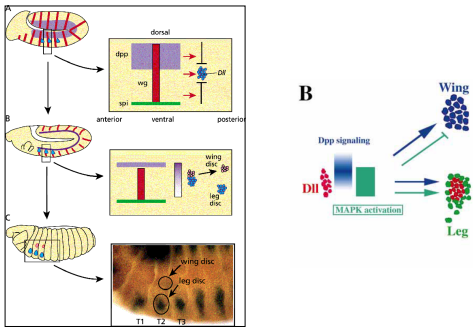




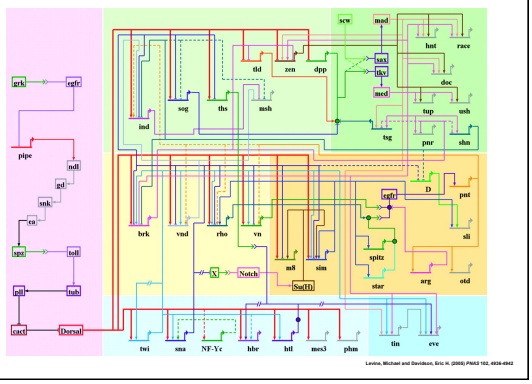




wing and leg imaginal disc formation: 2nd phase



Here's a partial view of the Dorsal-Ventral network:



Muscial Interlude

Regulatin' Genes

(http://www.youtube.com/watch?v=9k_oKK4Teco&feature=youtu.be)