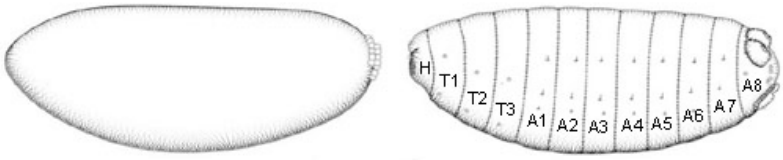
Drosophila: the genetics of segmentation (WR lecture 2)



In the previous lecture we covered the Drosophila life cycle from developing oocyte to the newly-cellularized blastoderm. At this stage (left), the embryo is shaped like a slightly bent rugby ball with about 6000 cells distributed around the surface. There are very few recognizable surface or internal features, but the future body plan is already mapped out through the expression of a set of genes known as the segmentation genes. This expression pattern - which defines a series of 15 stripes around the embryo - is a "molecular blueprint" that specifies the larval and adult segments. In this lecture we learn about the molecular events that subdivide the embryo into stripes (known as parasegments in the embryo). The key players in this process were identified during a genetic screen that was carried out by Christiane Nusslein-Volhart, Eric Wieschaus and their collaborators. Their groundbreaking effort was rewarded in 1995 by the award of the Nobel prize in Physiology and Medicine, which they shared with Ed Lewis for his work on homeotic mutants (next lecture). All animals, whether flies or humans, are constructed according to a fundamental repeated pattern so this work in Drosophila lays the foundation for understanding development of all animals.

1. Three sets of maternal effect genes define the anterior-posterior axis. These are the anterior group, the posterior group and the terminal group genes (the latter determine structures at the extreme front and back ends of the fly - the telson at the back and the acron at the front).

The main player in the anterior group is *bicoid*, mRNA for which is localized at the anterior end of the oocyte and is translated into protein (a homeodomain transcription factor) that diffuses posteriorly to set up an anterior-posterior (high-low) concentration gradient. This serves as a morphogen gradient that helps to specify positional information along the AP-axis. The other members of the anterior group genes (e.g. *exuperantia* and *swallow*) are required to localize *bicoid* mRNA at the anterior pole - by binding the 3'-UTR of the mRNA.

The main player in the posterior group is *nanos*, which forms a posterior-anterior (high-low) gradient of protein by a similar mechanism involving other members of the group such as *oskar* and *staufen*. The protein product of nanos is NOT a transcription factor but works by inhibiting the translation of mRNA encoding a homeodomain transcription factor Hunchback in the posterior region (so setting up a gradient of Hunchback which acts as a morphogen in the posterior part of the embryo).

The terminal group genes (e.g. *torso*) work in a quite different manner.

2. The gap genes are activated in broad domains along the A-P axis by different concentrations of the polarity gene products. The gap genes include *hunchback*, *kruppel* and *knirps*, which define relatively broad regions of the embryo - two to four future segments. If a gap gene is mutated (inactivated), the corresponding broad region of the embryo does not develop and a "gap" in the pattern results. The Gap genes encode transcription factors of the zinc-finger class. They are expressed in relatively broad bands in the embryo, the boundaries of which are "sharpened" by regulatory interactions among the gap genes themselves as well as with the maternal effect genes (see above). Furthermore, the gap genes regulate the next lower group of gene in the hiearchy, the pair-rule genes (see below).

3. The pair-rule genes are activated in a series of seven separate stripes around the embryo. The different members of the pair-rule group are expressed in non-coincident but overlapping domains so that, at any particular position along the A-P axis within each future segment, the nuclei express a characteristic cocktail of genes. If a pair-rule gene (e.g. *even-skipped, odd-skipped, hairy, fushi-tarazu, paired*) is mutated, then every other segment in the larva is missing - hence their name. The pair-rule genes are regulated by the gap genes together with the maternal effect genes. They mostly encode transcription factors of the homeodomain variety.

4. The segment-polarity genes are activated in every segment (14 in all) and define the anterior and posterior of each individual parasegment. Some key players are engrailed, hedgehog and wingless. Engrailed is a transcription factor that controls expression of hedgehog, which is a secreted protein that regulates wingless expression in neighbouring cells. Wingless itself is a secreted protein that regulates gene expression in surrounding cells. Both hedgehog and wingless act as morphogens to control cell fates within the parasegment.

Thus, segmentation is a stepwise exercise that divides the embryo up into ever smaller units. This is rather like what you might do if asked to cut a cake into a large number of equal slices; first you would cut it into large chunks then progressively cut each chunk into smaller slices.

Dorsal-ventral axis

The dorsal-ventral axis is also set up by a separate set of genes. Key players here are *snake, easter, spatzle, toll, cactus* and *dorsal*, among others. Dorsal is a transcription factor that is normally excluded from the nucleus by virtue of binding to Cactus in the cytoplasm. However, at the future ventral side of the embryo, activation of Toll, a transmembrane tyrosine kinase receptor, by its ligand Spatzle, releases Dorsal from Cactus and allows it to enter the nucleus to activate downstream genes.

Reading:

Wolpert, 2nd Edition chapter 5, pp143-190 (don't worry too much about mitotic recombination and compartment boundaries).

Gilbert, 8th Edition chapter 9, pp267-283. Strongly recommended - excellent photographs and diagrams.

Lawrence PA, Struhl G (1996) Morphogens, compartments, and pattern: lessons from Drosophila? Cell 85:951-61.

Anderson KV (1998) Pinning down positional information: dorsal-ventral polarity in the Drosophila embryo. Cell 95:439-42