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Eric Wieschaus' Lecture Part 3:
The Evolution of Bicoid-based Patterning

Teaching Tools were prepared by Eric Wieschaus and Oliver Grimm.

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1. Discussion Questions

1. Bicoid provides dipteran (fly) embryos with positional information such that target genes are expressed at the correct position. Outside the dipterans there is no Bicoid. How are those embryos provided with positional information? Do you expect to find a gene like bicoid (eg a morphogen)? Alternatively, how else could positional information be provided? Do you think there could be a gene like bicoid that controls early development in humans? What feature of human development would argue for or against the existence of such a gene?

2. The expression patterns of zygotic genes (hunchback, etc) scale with egg length. How could scaling be achieved, and how is it actually achieved? For the characteristic length of the Bicoid concentration profile (l) to scale with egg length, what do you predict for either the diffusion coefficient D or the life-time of Bicoid in different eggs?

3. How could the life-time of Bicoid change from species to species? What do you know about degradation of proteins in general? Are there motifs (sequences) that render a protein stable/unstable? How can you identify these motifs? Could you engineer (and how) a Bicoid with a different lifetime? Assume you had succeeded in obtaining a short-lived and a long-lived version of Bicoid. What do you predict the resulting gradient would look like? What would the gap gene expression pattern look like?

4. If the lifetime of Bicoid was solely determined by a degradation motif, what would you expect by expressing Bicoid from a big species in a small one? What was actually found? How do you explain the finding?

2. Answers to Discussion Questions

1. If we assume that morphogen gradients form by diffusion with uniform degradation, we need to consider the time over which the gradient forms and the size of the tissue that is provided with positional information. In the case of Drosophila, early development takes less than 3 hours and the embryo is 500µm long so that we can expect a gradient to form (assuming reasonable diffusion coefficients for a protein of Bicoid's size and the viscosity of cytoplasm). In contrast, mouse embryos are much larger and so it seems less likely that a single morphogen patterns the whole embryo. However, individual tissues are small enough such that the existence of a morphogen gradient is reasonable. For example, the neural tube in vertebrates is patterned by the sonic hedgehog (shh) morphogen.

2. Scaling could be achieved if, for example, the gene regulatory region of hunchback from different species had a different affinity for Bicoid. Thus, in bigger species hunchback would be induced at lower concentrations of Bicoid and thus further from the source. However, it turns out that the Bicoid gradient itself scales and this could be achieved if either the diffusion coefficient or the lifetime changed such that l increases with increasing egg size.

   Diffusion in eggs of different sizes is roughly similar and therefore (within the framework of the simple model) for the length constant l to scale, the life-time of Bicoid has to increase with the size of the eggs. On the other hand, for the gradient to be at steady-state, the life-time has to be much smaller than the interval between fertilization and the time at which the gradient is utilized. Use the numbers for D, l and life-time given in Wieschaus' presentation and in the literature and show the limits to scaling.

   This goes back to the problem mentioned above (l = square root (DT)). For the gradient to be at steady state, the life-time has to be much smaller than the time over which the gradient forms, T_2/sec. For the bigger species the diffusion coefficient would have to be even greater.

3. Many proteins are degraded by the ubiquitin proteasome pathway. Often proteins carry a conditional degradation signal (activated, for example, by phosphorylation). Such signals can be identified by either deleting them (the protein should be stabilized) or by fusing them to an otherwise stable protein (the resulting fusion protein should be unstable). One could delete the degradation signal of Bicoid (if there is one) or attach a known degradation signal to it (if Bicoid is stable). Let's assume that normal Bicoid is short-lived and the normal gradient is, therefore, at steady state. By deleting the putative degradation signal, the engineered Biocid should be stable (long life-time) and therefore the gradient more extended. Consequently, the expression of hunchback should be shifted posteriorly and the expression boundary might be shallower.

4. The Bicoid gradient would have the exact same length constant irrespective of egg size. However, Bicoid of a big-egg species scales with egg length when expressed in smaller eggs suggesting that it is some characteristic of the egg itself that causes scaling.