DEVELOPMENTAL BIOLOGY

Wondrous transformation

Michael Akam

VERTEBRATES and insects have similar clusters of homeobox genes, the protein products of which play a crucial part in determining the course of development[1]; in insects at least, these proteins serve as labels that define a cell's position along the body axis[2,3]. Striking parallels between the vertebrate *Hox* and insect homeotic gene clusters suggest that they have a common origin, and may possibly retain vestiges of common function (see figure). That possibility has now been tested and confirmed in a series of audacious gene-swap experiments reported in *Cell* by McGinnis and his colleagues[4,5]. They have expressed in *Drosophila* the proteins encoded by two vertebrate *Hox* genes, and find that each of these proteins induces a specific developmental response characteristic of the product of the related gene in *Drosophila*.

The perfect way to test the functional equivalence of gene products in two different species is to place the coding sequence from one into the normal chromosomal environment of the other, under the regulation of an endogenous promoter. This is not yet possible for the homeotic genes. McGinnis and his colleagues have therefore placed the vertebrate *Hox* genes under the control of a heat-inducible promoter, and used a transposable P element to insert this construct into the fly genome.

Drosophila homeotic genes have previously been placed on similar constructs. When strains carrying such constructs are subjected to heat shock, the homeotic protein is transiently expressed at high levels in all cells of the developing embryo[6-8]. This does not mimic normal expression, but it does result in a suite of developmental changes that is specific for each protein and that is clearly related to the normal developmental effects of that protein. For example, the *Antennapedia* (*Antp*) gene is normally expressed in the thoracic segments, where it promotes the development of, amongst other things, legs. In a heat-shock-promoter/*Antp* construct, as in certain other *Antp* mis-expression mutants, the normal *Drosophila* protein is expressed in the head, causing the antennae to develop as legs[8]. When McGinnis uses the mouse *Hox-2.2* construct instead of the *Antp* gene, he sees the same transformation.

Antennapedia is not the only *Drosophila* gene that can induce antenna-to-leg transformations. Leg development can also be induced by expressing the Ultrabithorax homeoprotein in developing antennae[9], but the leg structure, and other transformations induced in the developing embryo, are different from those induced by the *Antp* product. *Hox-2.2* mimics at least some of these specific effects of *Antp*. An equally specific effect is seen when the human counterpart of the *Deformed* (*Dfd*) gene is expressed in flies — in this case an effect on head morphology, which closely mimics the original *Dfd* mutant[5].

There are two ways in which these effects may be brought about. The most obvious is that the induced vertebrate protein may interact with the normal downstream targets of the equivalent protein in *Drosophila*. However, an alternative mechanism is suggested by earlier work with the *Drosophila* heat-shock constructs[7]. The induced homeoprotein may activate the resident copy of the corresponding *Drosophila* gene, stimulating an autoregulatory pathway. This appears to be how a heat-induced pulse of the *Drosophila* Deformed protein affects development. In certain cell types, a brief pulse of Deformed protein is sufficient to turn the normal *Dfd* gene on inappropriately. It is in these cells that a homeotic transformation occurs.

The human counterpart to the Deformed protein, the product of the *Hox-4.2* gene, appears to work in the same way. It activates the *Dfd* gene in *Drosophila*, but it does not activate any of several other homeotic genes tested[5] (thereby further demonstrating the specificity of the heterologous interaction). Antennapedia[6,8] and its protein counterpart in the mouse do not seem to act in this way, for the effects of mis-expression are seen even in embryos that lack a normal copy of the *Antp* gene. Presumably in this case the vertebrate gene is able to interact with at least some of the normal downstream target genes. Why the responses to Deformed and Antennapedia protein should differ in this way is not clear but, in each case, the regulatory effects of the vertebrate products mimic those of their counterparts in *Drosophila*.

The clearest conclusion to be drawn from these experiments is that the structural similarities between the homeobox genes in vertebrates and those in insects do translate into similar regulatory specificities. This was not a foregone conclusion, for besides the homeobox and its immediately flanking sequences, only short peptide motifs are generally conserved between the proteins in *Drosophila* and vertebrates[10].

A distinct question is whether the similar vertebrate and insect proteins are functioning within a network of conserved regulatory interactions, in which both upstream regulators and downstream targets are the same in different species. The new results do not prove that, but as the extent of functional similarity between individual proteins is revealed, so the likelihood of such conservation is increased. It may be humbling to discover just how few changes nature has needed to mould man and fly from their common ancestor. □

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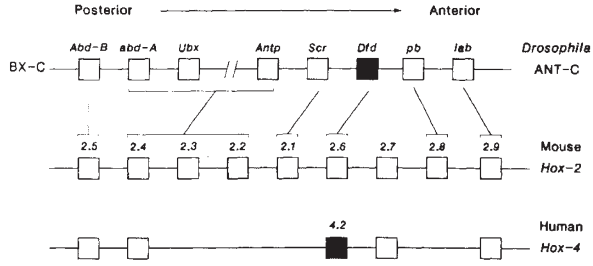

Drosophila genes and vertebrate *Hox* genes tested for function in the gene-swap experiments of McGinnis and colleagues[4,5]. The homeotic genes of *Drosophila* occur in two separate clusters on the third chromosome (ANT-C and BX-C), but probably derive from the splitting of a single ancestral cluster[11]. The chromosomal organization of the vertebrate *Hox* genes resembles that inferred for the ancestral insect cluster, but this ancestral unit appears to have been replicated in the lineage leading to mammals, so that each genome contains four clusters which have a similar overall structure[12-14]. (Specific genes appear to be missing or duplicated in individual clusters.) Two of the four clusters are shown here (modified from ref. 12). Genes at corresponding positions in each vertebrate cluster show extensive sequence similarities. These subsets are termed paralogous loci (examples are *Hox-2.6* and *Hox-4.2*). Comparisons of the sequences of the vertebrate and *Drosophila* gene products allow specific sets of paralogous vertebrate genes to be matched with a particular gene in *Drosophila*[10] (for example the *Hox-2.6* family with *Deformed*). In the diagram, lines connect the *Drosophila* genes with their counterparts in the vertebrate complexes. Such matching reveals that the linear order of the genes within clusters has been conserved between vertebrates and *Drosophila*. In both vertebrates and *Drosophila*, the genes of each cluster are activated in a series along the anteroposterior axis of the body. This series parallels the order of the genes on the chromosome, so a particular vertebrate gene resembles its equivalent gene in *Drosophila* not only in sequence, but also in being activated at a similar relative position along the body axis[12-14]. Shading marks the genes used in the gene-swap experiments described here.

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