17 WEST, J. D., FRELS, W. I., CHAPMAN, V. M. & PAPAIOANNOU, V. E. (1977). Preferential expression of the maternally derived X chromosome in the mouse yolk sac. *Cell* **12**, 873–882.
18 TAKAGI, N. & SASAKI, M. (1975). Preferential inactivation of the paternally derived X chromosome in the extraembryonic membranes of the mouse. *Nature* **256**, 640–641.
19 HARPER, M. I., FOSTEN, M. & MONK, M. (1982). Preferential paternal X inactivation of extraembryonic tissue of early mouse embryos. *J. Embryol. exp. Morph.* **67**, 127–135.
20 RASTAN, S., KAUFMAN, M. H., HANDYSIDE, A. H. & LYON, M. F. (1980). X chromosome inactivation in extraembryonic membranes of diploid parthenogenetic mouse embryos demonstrated by differential staining. *Nature* **288**, 172–173.
21 ENDO, S. & TAKAGI, N. (1981). A preliminary cytogenetic study of X chromosome inactivation in diploid parthenogenetic embryos from LT/Sv mice. *Jap. J. Genet.* **56**, 349–356.
22 LYON, M. F. & RASTAN, S. (1984). Parental source of chromosome imprinting and its relevance for the X chromosome inactivation. *Differentiation* **26**, 63–67.
23 PAPAIOANNOU, V. E. & WEST, J. D. (1981). Relationship between the parental origin of the X chromosomes, embryonic cell lineage and X chromosome expression in mice. *Genet. Res.* **37**, 183–197.
24 RASTAN, S. & CATTANACH, B. M. (1983). Interaction between the *Xce* locus and imprinting of the paternal X chromosome in mouse yolk-sac endoderm. *Nature* **303**, 635–637.
25 WAKASUGI, N. (1974). A genetically determined incompatibility system between spermatozoa and eggs leading to embryonic death in mice. *J. Reprod. Fert.* **41**, 85–96.
26 SILVER, L. M. (1981). Genetic organisation of the mouse *t* complex. *Cell* **27**, 239–240.
27 JOHNSON, D. R. (1974). Hairpin-tail: a case of post-reductional gene action in the mouse egg? *Genetics* **76**, 795–805.
28 MCGRATH, J. & SOLTER, D. (1984). Maternal T^{hp} lethality in the mouse is a nuclear, not cytoplasmic, defect. *Nature* **308**, 550–551.
29 WILSON, A. C., MAXSON, L. R. & SARICH, V. M. (1974). Two types of molecular evolution. Evidence from studies of interspecific hybridization. *Proc. Natl. Acad. Sci. USA* **71**, 2843–2847.

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PROBLEMS AND PARADIGMS

Homoeotic Selector genes – A Working Definition

Peter A. Lawrence

There is a great deal of difference between an abstract concept and a working definition of it. In embryology such differences have always been the source of controversy and confusion; for example, cell determination is a widely understood idea, but diverse operational criteria have been used by different workers and this has led to many disputes. Some concepts can become provisionally accepted without any working definition but as evidence and information accumulates one becomes necessary. An example is the idea of a homoeotic 'selector gene'.[1]

Homoeotic genes are a motley group of genetic loci which, when mutated, affect the developmental pathways followed by growing groups of cells and result in the transformation of one part of the body pattern into a part normally found elsewhere (such as leg into antenna). Although homoeotic mutations are known in several insect species it is only in *Drosophila* where there seems much immediate hope of a deep understanding. At least one clear homoeotic gene has been identified in the nematode *C. elegans*.[2] If homoeotic genes exist in vertebrates it is not clear whether we could recognize mutants in them for they would probably be lethal and, in any case, it is not clear what would be transformed into what. Our interest in these genes comes from the expectation that understanding them will open up some developmental code and explain how body pattern is controlled.

Homoeotic transformations can probably be caused by defects of different kinds that operate at diverse levels. Some genes may have a role rather remote from pattern formation itself and yet may have homoeotic alleles – in these cases homoeosis may be a secondary consequence of the mutations. Earlier reviews on homoeotic genes in *Drosophila* had been primarily concerned to list the bizarre phenotypes of mutants and to make vague suggestions as to how these phenotypes might be caused. But Garcia-Bellido, in his imaginative paper (1975), attempted to understand homoeotic genes by concentrating on the function of their *wild-type* alleles. He built on the discoveries that each body segment of the epidermis is bipartite and is made by all the descendants of two founder groups of cells with precisely positioned and absolutely restrictive boundaries separating the cell populations – one at the segment border and one at the interface between anterior and posterior groups of cells in the middle of the segment.[3, 4] Each subsegment is defined by its cell lineage and is called a developmental compartment. One compartment boundary delimits the realm of effect of two well-known homoeotic mutations in the bithorax complex (Lewis[5] and many of his earlier papers, also reviewed in ref. 6) and it was this that suggested to Garcia-Bellido and his colleagues that compartments might be units of gene action. Garcia-Bellido proposed that the pattern of a compartment depends on the continual activity within all its cells of genes whose role is to select the pathway of development. He called this rather special class of homoeotic genes selector genes, and suggested that they would be small in number and would act in combination. Although the idea that body pattern might depend on a small number of genetic units acting combinatorially had been proposed earlier by Lewis (Table 1 in ref. 7) and later by Kauffman,[8] Garcia-Bellido's hypothesis linked this with the cell lineage of the developing fly in a precise way. Garcia-Bellido also suggested that there would be another class of homoeotic gene (activator genes) whose wild-type role would be to activate – or inactivate – the selector gene in the correct groups of founder cells. These gene functions would only be required early in development and, presumably, would be dispensable later.

Like most deep insights the idea of a selector gene has led to experimental tests; in most cases these have supported the concept. Just briefly, there are homoeotic genes which are active in

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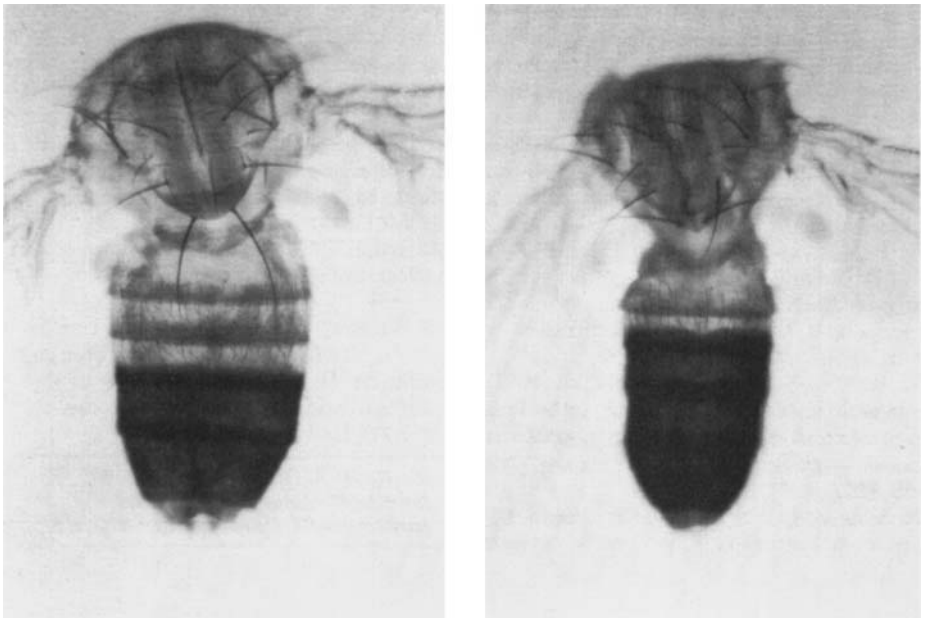

Fig. 1. *An abdominal homoeotic segment transformation produced by inappropriate expression of a selector gene. On the left is shown a male wild-type fruit fly; on the right, a male fly carrying the dominant mutation* Mcp (Miscadestral pigmentation),[5] *which produces a fifth abdominal segment phenotype in the fourth abdominal segment.*

groups of compartments and their products are required for normal development of pattern in those compartments only. These genes appear to work in a combination which we call the 'genetic address'.[9] For example, two genes of the Antennapedia complex[10] *Antp*$^+$ and *Scr*$^+$ appear to combine with *Ubx*$^+$ (from the bithorax complex) to direct the proper development of the thoracic segments. If a 'nonsense' combination of these genes, that is not found anywhere in the wild-type fly, is generated artificially the body pattern made in that region is found to be a messy mixture of the pattern specified by related genetic addresses.[11] Candidates for selector genes are the elements of the bithorax and Antennapedia complexes, *engrailed*, and some of the sex determining genes (the latter reviewed in reference 12). A selector gene-mediated transformation is shown in Figure 1. However, there are a large number of other homoeotic genes (e.g. *Polycomb*, *trithorax* and *wingless*) which are less well understood and it is clear that we now need a working definition to enable us to classify them. This should clarify thinking about these genes and be useful in practise; when a decision to clone a homoeotic gene is made, it makes sense to try to deduce the type of gene first, as many men-and-women lab-years will be committed before that gene is understood. Garcia-Bellido[1] did not explicitly provide a working definition for a selector gene, but now that we know more I suggest the following three criteria which have the advantage that they can be easily tested. A selector gene should be

(1) homoeotic,
(2) required only in a subset of developmental compartments,
(3) required throughout much of development.

Consider the application of these criteria to *Ubx*$^+$. By genetic tests this gene is required in parts of the thorax and abdomen but not in the head. The gene is transcribed in a specific subset of segments.[13] Removal of *Ubx*$^+$ from cells in these specific parts at different stages results in homoeotic transformation which shows that gene function is necessary until late in development. Removal of *Ubx*$^+$ from parts where it is not required (like the first thoracic segment or the head) has, of course, no effect (reviewed in reference 6). Similar experiments show that *Antp*$^+$ fits these criteria and that this gene is also required only in some mouthpart segments and in the thorax and abdomen.[10, 14, 15]

Note that the criteria do not include the requirement that removal of the gene results in a perfect transformation. Such a requirement would not be sensible because, as we have seen, removal of a selector gene can produce an unnatural 'nonsense' combination. Consider *engrailed*$^+$. This gene is required in posterior compartments but not anterior ones and is required throughout development.[16] Posterior clones of cells homozygous for the strongest alleles available do not give a perfect transformation to anterior.[17, 18] This could be because *engrailed*$^+$, and one or more other selector genes active only in posterior compartments, would be together required to give the complete genetic address for 'posterior'. Or, it could be because these mutant alleles still leave other parts of the *engrailed*$^+$ gene intact. In practise it is not easy to find out which of these alternatives is true and therefore such matters should not be part of an operational definition.

These criteria can be applied to other genes. For example, *transformer*$^+$ is required in the female somatic cells but not in the germ cells (which could be regarded as the first compartment to be defined in the developing egg) nor anywhere in the male. It decides between alternate paths of development and therefore could be described as homoeotic. It is required until late in development[12] and is therefore a selector gene. By contrast, *extra sex combs*$^+$ is probably required everywhere and the requirement is almost exclusively limited to early development.[19] It is not therefore a selector gene and could be called an activator gene. The *Polycomb*$^+$ gene is required until late in development but the phenotype of mutant larvae suggests it is required everywhere. It is also probably not a selector gene.

There may be many other selector genes, some unidentified, some described but unrecognized. There may be selector genes responsible for differences between dorsal and ventral ectoderm, between mesoderm and ectoderm and between other portions of the body pattern. I hope these working criteria, which may well be superseded when we know more, will help us identify these missing selector genes.

REFERENCES

1 GARCIA-BELLIDO, A. (1975). Genetic control of wing disc development in *Drosophila*. In *Cell Patterning* (ed. S. Brenner). Associated Scientific Publishers. Amsterdam, Oxford, New York. *Ciba Foundation Symposium* **29**, 161–182.

2 GREENWALD, I., STERNBERG, P. W. & HORVITZ, H. R. (1983). The *lin*-12 locus specifies cell fates in *Caenorhabditis elegans*. *Cell* **34**, 435–444.

3 GARCIA-BELLIDO, A., RIPOLL, P. & MORATA, G. (1973). Developmental compartmentalization of the wing disk of *Drosophila*. *Nature New Biol.* **245**, 251–253.

4 LAWRENCE, P. A. (1973). Clonal analysis of segment development in *Oncopeltus* (Hemiptera). *J. Embryol. Exp. Morph.* **30**, 681–699.

5 LEWIS, E. B. (1978). A gene complex

controlling segmentation in *Drosophila*. *Nature* **276**, 565–570.
6 LAWRENCE, P. A. & MORATA, G. (1983). The elements of the bithorax complex. *Cell* **35**, 595–601.
7 LEWIS, E. B. (1963). Genes and developmental pathways. *Amer. Zool.* **3**, 33–56.
8 KAUFFMAN, S. A. (1973). Control circuits for determination and transdetermination. *Science* **181**, 310–317.
9 GARCIA-BELLIDO, A., LAWRENCE, P. A. & MORATA, G. (1979). Compartments in animal development. *Sci. Am.* **241**, 102–110.
10 WAKIMOTO, B. T. & KAUFMAN, T. (1981). Analysis of larval segmentation in lethal genotypes associated with the Antennapedia gene complex in *Drosophila melanogaster*. *Develop. Biol.* **81**, 51–64.
11 STRUHL, G. (1982). Genes controlling segmental specification in the *Drosophila* thorax. *Proc. Natl. Acad. Sci. U.S.A.* **79**, 7380–7384.
12 BAKER, B. S. & BELOTE, J. M. (1983). Sex determination and dosage compensation in *Drosophila melanogaster*. *Ann. Rev. Genet.* **17**, 345–393.
13 AKAM, M. (1983). The location of *Ultrabithorax* transcripts in *Drosophila* tissue sections. *EMBO J.* **2**, 2075–2084.
14 STRUHL, G. (1981). A homeotic mutation transforming leg to antenna in Drosophila. *Nature* **292**, 635–638.
15 HAFEN, E., LEVINE, M., GARBER, R. L. & GEHRING, W. J. (1983). An improved *in situ* hybridization method for the detection of cellular RNAs in *Drosophila* tissue sections and its application for localizing transcripts of the homeotic *Antennapedia* gene complex. *EMBO J.* **4**, 617–623.
16 LAWRENCE, P. A. & MORATA, G. (1976). Compartments in the wing of *Drosophila*: A study of the *engrailed* gene. *Develop. Biol.* **50**, 321–337.
17 KORNBERG, T. (1981). *engrailed*: a gene controlling compartment and segment formation in *Drosophila*. *Proc. Natl. Acad. Sci. USA.* **78**, 1095–1099.
18 LAWRENCE, P. A. & STRUHL, G. (1982). Further studies of the *engrailed* phenotype in *Drosophila*. *EMBO J.* **1**, 827–833.
19 STRUHL, G. (1981). A gene product required for correct initiation of segmental determination in *Drosophila*. *Nature* **293**, 36–41.

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CHALLENGES

Molecular Medicines for Tropical Diseases: Bio-technological Future or Poor Man's Dream?

Kunthala Jayaraman

The ramifications of tropical diseases are far-reaching for countries in which these diseases are endemic. While the major epidemics such as smallpox and cholera have been eradicated or are under control all over the world, the situation is nowhere close to an abatement with several tropical diseases. The cost involved in prevention and curative measures drain most of the finance of the health care programmes, with no guarantee of any success. Since most of the countries located in the tropical belt of the world are either under-developed or developing, the economic constraints prevalent on the health care programmes render it almost impossible to usher in new areas of research.

The current methods of identifying the parasites or the vectors transmitting the diseases prior to epidemics are inadequate and usually only post-mortem epidemiological surveys are made. Expensive and often ineffective, drug-oriented approaches have so far dominated the area of control of the parasites. Similarly, vector control programmes have largely emphasized the use of polluting chemical insecticides. With the emergence of the insecticide-resistant forms of the vectors on one hand, and the drug-resistant forms of the parasites on the other, we are facing a crisis situation with respect to several diseases today.

The development of newer and effective chemotherapeutic agents for the tropical diseases is slow on account of the considerable expense involved in research and the limited market potentialities (not in terms of numbers, of course!). On the other hand, the development and marketing of newer pesticides never seems to stop and is an area coveted by multinationals.

Fortunately, the information explosion in molecular biology, especially in genetic engineering and molecular immunology, has also had an impact on the programme of research in tropical diseases. Today the genomic library of the various parasitic organisms is being studiously built. The protein components are being dissected and screened for the detection of gene products that render them different from the invaded host tissues and hence most vulnerable for attack. Thus along with the glamour products like insulin, Interferon, clotting factors, etc., development of immunotherapeutic and diagnostic agents made through the engineered genes for the control of tropical diseases is well under way. Monoclonal antibodies that can recognize and immobilize the invasive forms of the malarial and filarial parasites are currently on trial.

However, much of the excitement generated by research in these areas is still felt mainly in the laboratories in the developed nations, where enthusiasm for newer systems of study or possible application is motivating scientists. These research workers nevertheless lack adequate infective materials and often have to resort to model systems of infection in animals or tissue cultures. A close interaction of the basic biomedical scientists in developed nations with those working with the different aspects of parasitic infections in endemic areas is vital for rapid and meaningful progress in this area. In tropical countries, where the availability of disease material is unfortunately plentiful, the research workers are often inadequately trained in modern techniques and the programmes often concentrate on mere epidemiological surveys.

The UNDP/World Bank/WHO special programme for Research and Training in Tropical diseases (TDR) has emerged as a major force in refocusing the existing *modus operandi* and drawing the attention of the scientific community to new approaches in tackling these problems. Scientific working groups for the six major diseases (malaria, schistosomiasis, filariasis, trypanosomiasis (including Chagas' disease), leishmaniasis and leprosy) have been set up to identify