Looking for molecular switches

The molecular biology of the process of development has been enlivened, in the past few years, by several novel clues. But there is still a long way to go.

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NATURE'S conference here last week on genes and systems of development, organized with the generous assistance of the University of California, San Francisco, turned out, perhaps as much by accident as design, to be as good a survey of the molecular biology of development as any. What follows is not a formal report of the meeting, but an inexpert account of what it now seems possible to say about the way in which organisms acquire different functions as they mature. Ontogeny is the fashionable synonym.

At meetings such as this, the starting assumption is that the genetic endowment of each embryo of every species contains not merely the genes that will function at the several stages of the development of the maturing organism but also those that determine the broad pattern of development, the sequence in which different sets of genes come into play. This does not, however, imply that all organisms are hard-wired and rigorously predetermined as in the nematode *Caenorhabditis elegans*; the observation that the visual system of mammals such as cats remains malleable, and affected by early experience, is a sufficient proof of that. The circumstances in which gross features of earlier stages in development are susceptible to external influences remain, for the most part, to be defined. Little is known of the mechanisms responsible, although it is clear that the development of the nervous system has a high intrinsic interest for other reasons as well.

Outsiders must also learn not to be confused that the pursuit of an understanding of development entails the use of model systems which are very much more particular than the grand name *ontogeny* would suggest are appropriate. That, however, is the spirit in which people at last week's conference (and elsewhere) are concerned with phenomena such as how yeast cells switch between one mating type and another, how white blood cells of different kinds, all descended from the same race of precursor cells, acquire their special properties and how the different kinds of cells in the nervous system differentiate from what is, to begin with, a more or less uniform collection of cells. Development, the argument goes, is a succession of differentiations, steps in which cells become specialized. The objective is to identify the switching mechanism, the genetic switches and the molecules that actuate them, presumably themselves products of the genes.

This is the sense in which the ever more elaborate, but also elegant, model of lambda-bacteriophage infection of *Escherichia coli* developed by Dr Mark Ptashne (Harvard) is relevant to the issue of the development of much grander organisms. For this is a set of identified genetic switches and actuating molecules, protein molecules in this case, which account for the interaction of the bacterial virus with its host. The obvious question is the extent to which this may be a general model for the switching that occurs during differentiation. Opinion seems to be veering towards the view that the actuator molecules are less likely to be molecules of messenger RNA than protein. But some switches are clearly not on/off switches as with lambda phage but genetic rearrangements. Most probably there will be quite a long catalogue of different kinds of switches before very long.

The great excitement about homoeotic genes in the past year seems an obvious way to extend the present catalogue. The opportunity, now well publicized, is that a set of genes known (from the study of mutations) to determine the body plan of *Drosophila* is distinguished by a certain nucleotide sequence, about 180 basepairs long, which also crops up in other organisms, *Xenopus* (the African clawed toad), mice and also human beings. The inference, but perhaps it is only a hope, is that the "homoeoboxes" that occur in organisms other than *Drosophila* also mark out genetic switches that control the process of development. But it now seems that people are on the point of being able to demonstrate directly, and not merely infer, that the products of the homoeobox-containing genes regulate other genes and constitute components of genetic switches. The more teasing question of what these same genes do in other organisms remains unclear, although the similarity with the switch part of the mating-type genes in yeast is suggestive. No doubt there will also have to be a search for further kinds of genetic switches in other organisms: so far, only five genes with homoeoboxes have been found in the human genome.

Inevitably, these developments (and new technology, such as the easy availability of monoclonal antibodies) have been a stimulus for what might be called the classical embryology of *Drosophila* and other insects whose larvae consist of segments which carry different undeveloped parts of the mature creature. Here as in other organisms, development at the earliest stages of an embryo appears to be determined not merely by the genes but also by the cytoplasm of the fertilized egg, hence current interest in maternal effects — "maternal" because sperm contributes next to nothing to the yolk. The objective, now, is to tell what kinds of molecules are responsible.

Oncogenes also, but inevitably, play a part. Cells with the carcinogenic forms of oncogenes escape the usual constraints on growth and are developmentally abnormal, so may it be supposed that the proto-oncogenes from which the cancerous forms derive play a part in the regulation of normal development? (Or are they Jekyll and Hyde genes, as the question was put by Dr Michael Bishop (UC San Francisco)?) Now that it seems that the proteins derived from these normal cellular genes are expressed differently in different tissues, and at different stages of development, at least in mice and *Drosophila*, there is some excitement that it may soon be possible to tell how their normal function is regulated, perhaps by molecular influences outside the cell. Much the same is true of the search for the mechanisms by which cells recognize contact with others, and to the presumably molecular influences that guide neuronal projections to the places at which they belong.

So, it seems, there is progress on a broad front towards an understanding of development, largely with the help of several novel techniques and molecular clues (of which the homoeoboxes are only the most dramatic).

But even in the simplest of all the workhorses of development, the presumably hard-wired nematode *C.elegans*, puzzles persist. Why should some cells be programmed to die, for example? And in spite of the attention that has been lavished on the genes known to regulate development in *Drosophila*, there are so many of them, and their functions are so likely to overlap, that it will be a long time before people attempt a full listing of them, with an accompanying chronology showing when they are switched off and on. The obvious difficulty is that such a task is no simpler than that of describing how cells function as biochemical networks. But at least, now, there is movement.

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