

Molecular biology

Genetics of development elucidated by nematodes

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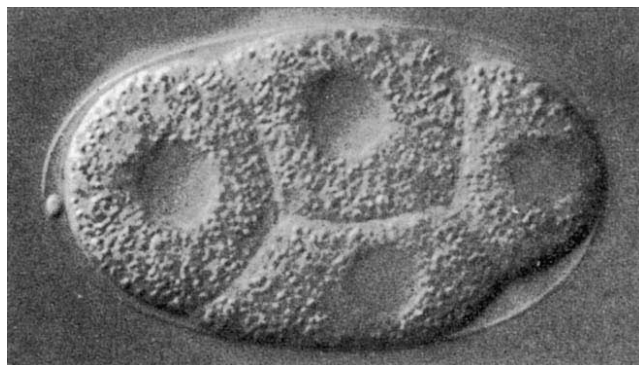
THE molecular mechanisms responsible for development of metazoan pattern and form are largely unknown. Embryos have been described and experimentally manipulated for more than a century, but only in the past few years have some of the genes and proteins that influence, and perhaps govern, development been isolated and scrutinized. These genes, cloned chiefly from the fruitfly *Drosophila melanogaster*, constitute the 'nuts-and-bolts' of developmental decision-making. The challenge to developmental biologists today is to understand the functions of these genes and to describe developmental decisions in biochemical terms. Results reported at a recent meeting* indicate that some elucidation of development at a molecular level will emerge from investigations of the nematode worm *Caenorhabditis elegans*.

Two important developments are responsible for the transition of research on *C. elegans* from traditional to molecular-genetic analysis. First, reliable methods for molecular cloning of *C. elegans* genes are now available, and second, a method of reintroducing cloned genes into the *C. elegans* germ line has now been developed. The ability to clone, manipulate and transform *C. elegans* genes offers great power and promise for unravelling genetic regulatory mechanisms.

A mechanism for determination of lineages that is often considered, but rarely explored, is chromosome imprinting (see the article by Monk on page 203). Such a mechanism predicts that parental DNA strands segregate to specific blastomeres in the embryo. The invariant cell lineage of *C. elegans* makes it a particularly attractive organism in which to investigate this mechanism. In an elegant series of experiments (K. Ito, Univ. Calgary), either oocyte or sperm DNA strands were marked in a manner that allows their segregation to be followed during embryogenesis. The cellular destination of individual chromosomes turns out to be random, a result suggesting that chromosome imprinting is not significant in early cell determination.

The cloning and molecular analysis of developmental regulatory genes was, arguably, the dominant theme of the meeting. Two general methods for cloning

genes were evident. First, techniques of 'transposon-tagging' are now well developed. Many spontaneous mutations are caused by transposition of the highly active *Tc1* family of transposable elements, and such mutations allow cloning of the affected genes. In addition, two new genetically active families of transposons (J. Collins, Univ. Wisconsin; J. Yuan and M. Finney, MIT) should facilitate the cloning of additional genes. Second, an ordered set of overlapping cosmid clones, representing about 95 per cent of the *C. elegans* genome, has been assembled (A. Coulson and J. Sulston, MRC Cambridge). As the gaps in this ordered cosmid library are relatively small, chromosome walking — even over very long distances — is relatively painless. The importance of these



Photomicrograph of a *C. elegans* embryo at the four-cell stage (courtesy of J. Austin).

two techniques was apparent in many presentations. Genes representing the rich variety of *C. elegans* developmental genetics have now been isolated. Of special excitement are genes involved in the determination of cell fate (S. Kim and M. Finney, MIT; J. Way, Columbia Univ.; I Greenwald, Princeton Univ.); sex determination (T. Rosenquist and P. Okkema, Univ. Wisconsin); programmed cell death (Yuan); developmental timing (G. Ruvkun, Harvard Univ.); and establishment of cellular asymmetry during cleavage (D. Stinchcomb, Harvard Univ.).

What is to be done with these genes when cloned? A direct and powerful approach is to manipulate them *in vitro*, to return them *in vivo* by DNA transformation and to evaluate their function in the resulting animal. Transformation and expression of five different cloned genes was described (A. Fire, Carnegie Institute, Baltimore; Way; T. Blumenthal, Indiana Univ.). Transformed genes retain their proper tissue-specific expression, but they integrate into the chromosome in

a non-homologous manner (Fire). In this respect, transformation in *C. elegans* resembles that of mammalian cells in culture.

Until recently, there was little evidence to suggest that interactions between cells are involved in early development of the nematode. The few cell interactions that were known influenced chiefly post-embryonic events. This result has been interpreted to indicate that ancestry is the primary determinant in nematode embryogenesis. At the meeting, evidence was reported for important interactions between early blastomeres. One particularly dramatic example, revealed by blastomere removal experiments, may be analogous to embryonic induction in vertebrates. An interaction between early blastomeres induces a mesodermal lineage (muscles of the anterior pharynx) from a precursor cell that primarily makes ectoderm (J. Priess, MRC Cambridge). Unexpectedly, mutations in a single gene, *glp-1*, affect both the early interaction involved in embryonic induction of the pharynx and a post-embryonic cell interaction controlling germ cell proliferation (J. Austin, Univ. Wisconsin; Priess). This finding suggests that these apparently distinct developmental events share common elements of control.

The mechanisms of gene expression in *C. elegans* hold some surprises. A compelling case was presented that trans-splicing is a regular feature of *C. elegans* messenger RNA processing (M. Krause, Fred Hutchinson Cancer Center). The 5' termini of certain mRNAs appear to be encoded in the genome as a separate leader sequence that is added post-transcriptionally during processing of the pre-mRNAs. The clearest example involves the actin gene family. Of four different nematode actin genes, three do not encode the 22 nucleotides at the 5' terminus of the mature mRNA. Rather, these nucleotides are encoded as part of an abundant, non-polyadenylated RNA that is about 100 nucleotides long. The 5'-terminal 22 nucleotides of this small RNA are attached to the actin mRNAs as an untranslated leader sequence.

The nematode phenomenon, therefore, is very similar to trans-splicing of trypanosome mRNAs. In *C. elegans*, however, not all mRNAs are trans-spliced. The fourth actin gene and the *unc-54* heavy-chain gene are not trans-spliced. The functional significance of these differences is unknown. □

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