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The Nematode *Caenorhabditis elegans*

CYNTHIA KENYON

In *Caenorhabditis elegans* patterns of cell division, differentiation, and morphogenesis can be observed with single-cell resolution in intact, living animals. Mechanisms that determine behaviors of individual cells during development are being dissected by means of genetic, cell biological, and molecular approaches.

THE NEMATODE *Caenorhabditis elegans* WAS ORIGINALLY selected for study as the result of a deliberate search for a multicellular organism that could be analyzed with the ease and resolution characteristic of studies of microorganisms (*1*). Features of the *C. elegans* life cycle facilitate genetic analysis, and features of its development and anatomy make it possible to analyze multicellular processes in the living animal at the level of individual cells. Since then a concerted effort has been made by members of the field to develop the system for studies of neurobiology, development, and cell biology. A detailed genetic map and methods for genetic analysis have been compiled (*1–3*), a complete cell-by-cell description of the development and anatomy of *C. elegans* has been achieved (*4–7*), and now a library of ordered cosmid clones representing the genome is nearing completion (*8*).

Caenorhabditis elegans is well suited to genetic studies for several reasons. First, it takes about 3 days to do a genetic cross in *C. elegans*; this is about the time required for genetic crosses in yeast. In addition, unlike many closely related nematode strains, *C. elegans* reproduces by self-fertilization. Self-fertilization allows new mutations to become homozygous automatically, without requiring brother-sister matings. The ability to freeze strains allows mutant stocks to be maintained indefinitely. Finally, genes defined by mutation can be cloned easily by transposon tagging or by injection of cloned DNA sequences from the genetic region of interest.

Each cell in the developing nematode is visible under the light microscope (Fig. 1). Furthermore, the entire cell lineage, from egg to adult, is essentially the same in each animal and is known precisely (*4, 5*) (Fig. 2). This means that any process involving the behaviors of individual cells in a multicellular context can be analyzed at the level of the single cell.

Finally, development of *C. elegans* appears to involve mechanisms that are conserved throughout the animal kingdom. When nematode lineages were found to be invariant, it seemed possible that much of nematode development would be controlled by mechanisms internal to individual lineages, and not by cell-extrinsic signaling, which plays such an important role in the development of higher organisms. Because the majority of *C. elegans* lineages are invariant, showing that cell-cell communication occurs is problematic. In order to show that cellular interactions influence cell fate, one must be able to alter a cell's behavior by changing its environment, for example by ablating other cells with a laser microbeam. By using this and other approaches, many examples of cellular interactions have now been discovered; it is clear that cell-cell communication plays a central role in *C. elegans* development (*9*). Furthermore, molecules that regulate *C. elegans* development have been found to contain homology to familiar vertebrate growth factor precursors and cell surface receptors (*10*), and to evolutionarily conserved homeodomains (*11*). Thus, with *C. elegans* it is possible to use genetics and single-cell analysis to dissect regulatory mechanisms of general significance and also to gain insights into how these mechanisms are modified to produce different kinds of animals.

We will first describe nematode development, then discuss experimental approaches available, and finally mention some current topics in *C. elegans* development, neurobiology, and cell biology. More comprehensive reviews are also available (*12–17*).

Overview of *C. elegans* Development

Caenorhabditis elegans adults are about 1 mm in length and live in the soil, feeding on microorganisms. They are sexually dimorphic, with hermaphrodites having two X chromosomes and males only one. Hermaphrodites have a total of 959 somatic nuclei (*5*), and a

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relatively simple 80,000-kb genome (*18*). After fertilization, the egg undergoes a series of asymmetric cleavages that produce six cells called founder cells. One founder cell gives rise to the germ line, another the intestine, and one makes only body muscle cells. The other founders generate predominantly ectodermal or mesodermal cell types. The cells divide rapidly for several hours, then the animal elongates and, 14 hours after fertilization, hatches. The juvenile proceeds to the adult stage via four molts. Of the cells generated during embryogenesis, roughly 10% divide after hatching. These postembryonic divisions generate additional epidermal cells, muscles, neurons, and nearly all the reproductive structures.

Techniques Used for Studying *C. elegans*

Genetic analysis. The isolation of mutants in *C. elegans* is a straightforward procedure because of its small size and short generation time, and because self-fertilization leads automatically to the segregation of recessive mutations in the homozygous form. The ease of isolating homozygotes also makes it possible to identify suppressors, secondary mutations that restore a mutant phenotype to wild ype. Suppression analysis can be used to identify genes that interact in a pathway (*19–21*). To isolate suppressors, the investigator simply mutagenizes a mutant strain and looks for wild-type animals among its progeny (for dominant suppressors) or its grandchildren (for recessive suppressors). Because it is often easy to see wild-type animals in the midst of mutants, a very large number of animals (as many as 10^8 in some cases) can be examined at one time. The ability to screen large numbers allows the isolation of rare suppressors, such as mutations that correct defective protein-protein interactions. Genes involved in sex determination, dosage compensation, cell lineage, and behavior have been identified by virtue of their being recessive suppressors of other mutations.

To map and complement new mutations, and to construct genetic regulatory pathways, mutations must be moved into other genetic backgrounds. For this, males are required. In *C. elegans*, males are produced at low frequency by spontaneous meiotic nondisjunction of the X chromosome, or at high frequency in certain mutants (*22*). XO animals are males, and will mate with the XX hermaphrodites. One half of the outcross progeny are males that now carry genes from the hermaphrodite and can be used to move these genes into other hermaphrodites. About 700 genes have now been identified and mapped to one of the five autosomes or the X chromosome (*23*). In addition, genetic analysis has been enhanced by the isolation of chromosome deficiencies, duplications, and translocations (*2*).

Given the prevalence of cell signaling systems in development, an important question is whether or not gene activity is cell-autonomous; that is, whether a gene's influence is confined to or extends beyond those cells that express it. This question can be answered in vivo by means of genetic mosaic analysis. Genetic mosaics are animals containing clones of mutant cells in a wild-type background. In *C. elegans*, they can be produced by the rare, spontaneous loss of chromosome fragments carrying wild-type genes in an otherwise mutant animal (*3*). Mutant cells are then examined to see whether they can develop normally despite the absence of the gene function of interest. As an example, the technique has been used to show that acetylcholinesterase, which inactivates the neurotransmitter acetylcholine at neuromuscular junctions, is made in muscle (*24*).

Single-cell analysis. The ability to analyze multicellular processes at the level of single cells is a great advantage of working with *C. elegans*. The complete cell lineage has been determined by direct observation of living animals with Nomarski optics (*4, 5*). Single-cell resolution is feasible because the animal is transparent, and because all but a few cells behave in the same way in every animal throughout development. Cell divisions, migrations, and morphogenesis can be observed and monitored precisely in the developing organism. Individual cells can be ablated with a laser microbeam in living animals in order to test for cellular interactions (*25*). To determine how genes influence cells in vivo, mutants can be compared to wild-type animals throughout development cell by cell. The point at which mutant cells first begin to behave differently from their wild-type counterparts can be identified, and the alternative fates expressed by the mutant cells—changes in division patterns, types of descendants, cell death, cell migration behaviors, altered sequences of morphogenesis—can be determined exactly by following cell lineages. This resolving power has allowed the identification of cell lineage and migration mutations whose phenotypes would have been uninterpretable otherwise. Furthermore, because the whole animal is accessible, it is possible to learn how gene functions are distributed among all cells in the developing organism.

Molecular genetics. A variety of new methods have streamlined molecular analysis in the nematode. In particular, J. Sulston and A. Coulson of the Medical Research Council (Cambridge, England) are assembling an ordered library of cosmid clones representing the genome. Overlapping cosmids are identified by the presence of common restriction fragments (*8*). At this time, cosmids representing about 95% of the genome have been analyzed. The map positions of sets of overlapping clones are known for about 50% of the genome (*26*). This means that for 50% of mapped genes, a set of

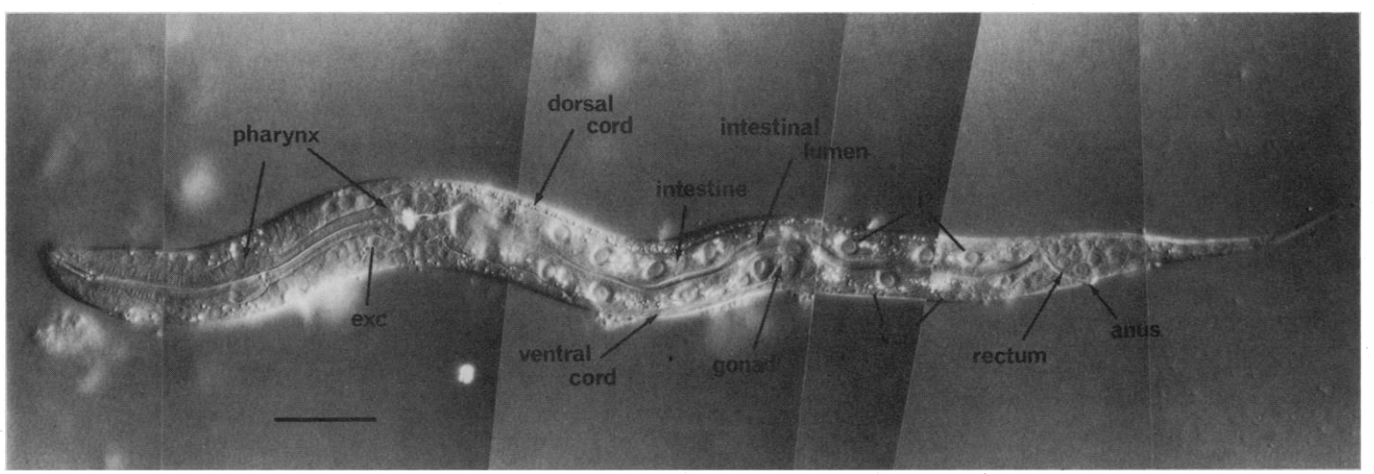

Fig. 1. A live, newly hatched hermaphrodite, as seen with Nomarski optics. Abbreviations: exc, excretory cell; i, intestinal nuclei; and vcn, ventral cord neurons. Scale bar, 20 μm [from Sulston and Horvitz (*4*)].

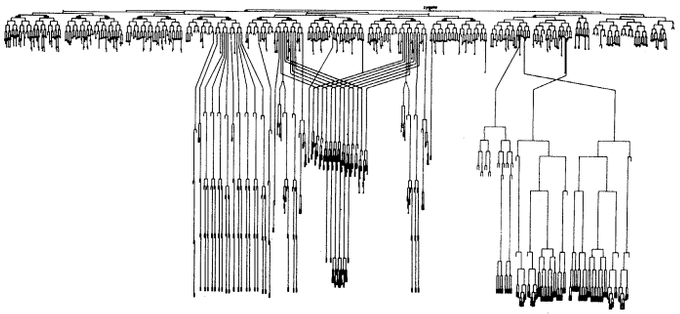

Fig. 2. The cell lineage of the *Caenorhabditis elegans* hermaphrodite. The rapid early divisions are embryonic, and generate the 558-cell juvenile. Fifty-five cells continue to divide after hatching, adding cells to existing tissues and also producing the reproductive system.

overlapping cosmids in the region is available on request. For cloning genes in locations not yet associated with sets of overlapping cosmids, the relevant set can generally be identified by finding a genetically linked DNA probe, as described below. Furthermore, because procedures for DNA transformation have been developed (*27*), genes are now being cloned simply by injecting cosmid clones known to map in the genetic region of interest into mutants and looking for phenotypic rescue (*28*). A. Fire has shown that the coupling of the β-galactosidase gene with the control sequences of a muscle-specific gene produces a transgenic animal with appropriate tissue-specific expression (*29*). Thus control sequences may be identified in this way.

The discovery of transposable elements, and their variable numbers and positions in different strains of *C. elegans* has further enhanced molecular genetic methods (*18, 30*). Strain-specific transposons occur approximately once every 120 kb (4 cosmid lengths). These create restriction site polymorphisms, and thus become physical markers for the genetic map. By finding polymorphic transposons linked to the gene of interest, it is possible to identify previously unmapped sets of overlapping cosmids likely to contain the gene. Even more powerful is the ability to create mutations by insertion of the transposon into the gene itself, thereby tagging the gene. The frequency of transposition is very high in certain strains, allowing mutants to be selected easily (*18, 31*). A number of genes involved in development, neurobiology, and muscle structure have now been cloned by transposon tagging (*10, 32*).

It is also possible to start with conserved molecules from other organisms, and obtain mutants in *C. elegans* to study their in vivo functions at the cellular level. Valuable initial information can be obtained about possible gene functions with antibodies (*33*) or in situ hybridization to RNA (*34–36*) to determine which cells express the gene of interest. The mapped cosmid library can be used to determine the genetic location quite precisely. To identify mutants, it is possible to examine known mutations and deletions in the region, or else isolate new mutations in the region, and identify those that alter the gene product. An essential function of a cloned myosin heavy chain gene has been identified by this approach (*37*).

Control of Cell Division and Differentiation

Embryonic cell patterning. Cellular asymmetries that arise early in development establish the future body plan of the animal. The first embryonic cleavage produces the cell AB (which generates most of the ectoderm) and the cell P1 (which generates the germ line, intestine, and much mesoderm). When these two blastomeres are separated from one another, they produce very different types of progeny, suggesting that regulatory molecules segregate asymmetrically at the first division (*5, 38*). In support of this interpretation, germ line–specific granules can be seen to move asymmetrically during the first few cleavages, until they enter the appropriate germ line precursor cell (*39*). Mechanisms for establishing asymmetries during the first embryonic cleavages are under investigation with genetic approaches and probes for the cytoskeleton. Studies with cytoskeletal inhibitors suggest that microfilaments, but not microtubules, are involved in the establishment of these early asymmetries (*39, 40*). Mutations that cause the AB and P1 blastomeres to behave similarly have been isolated as a means of identifying genes involved in generating embryonic asymmetry. Products of the *par* (*par*tition-defective) genes are particularly interesting, because in *par* mutants some or all manifestations of asymmetry are absent (*41*).

Caenorhabditis elegans embryos have classically been regarded as highly mosaic in character; that is, intracellular segregation of regulatory information has been thought to lead to embryonic cell patterning. However, recent experiments by J. Priess have shown that an extensive network of cellular interactions influences the fates of at least two-thirds of the cells in the embryo (*42*). In normal embryos, the daughters of the AB blastomere, ABa and ABp, generate different lineages and cell types. If the positions of ABa and ABp are switched, their fates are switched, and each cell generates the descendants normally produced by the other. Differences between the ABa and ABp lineages appear to arise by cellular interactions that occur at a later time during embryogenesis. By ablating individual cells with a laser microbeam, Priess has discovered an example of classic embryonic induction: cells derived from P1 induce three AB-derived cells to generate the anterior portion of the pharnyx (esophagus). Mutations in the gene *glp-1* (*g*erm *l*ine *p*roliferation) produce an animal specifically lacking the anterior pharynx, suggesting that the gene participates in this inductive interaction (*43*). The same gene also functions postembryonically. Here *glp-1* is required for developing germ cells to respond to a mitogenic signal from a nearby somatic cell.

Postembryonic cell patterning. How complex patterns of cell types form within initially uniform arrays of cells is a fundamental problem in development. Several examples in *C. elegans* are under investigation (*20*). Among the more intensively studied are the development of the vulva and the patterning of the antero-posterior body axis. The vulva is an epidermal structure generated by three ventrally located epidermal cells. If a cell in the overlying gonad (called the anchor cell) is ablated, the vulva is not formed; thus a signal from the anchor cell induces vulva formation (*44*). Laser ablation experiments also show that any of six epidermal cells is capable of participating in vulva formation, and that each can adopt any of three alternative vulval cell fates. Which fate each cell adopts depends on its distance from the anchor cell, and possibly also on signals from other epidermal precursor cells (*45*). An extensive search for mutations affecting vulva formation has led to the identification of 22 genes required for vulva development (*46*). These fall into several classes, including genes involved in the generation of the anchor cell, the generation of vulval precursor cells, the decision process that determines which of three fates the precursor cells adopt, and the generation of the corresponding vulval cell lineages. One of the genes involved in the choice between alternative precursor fates, *lin-12* (*lin*eage abnormal), is similar to the precursor of vertebrate epidermal growth factor and the low density lipoprotein (LDL) receptor (*10*). Like *glp-1, lin-12* mutations influence the fates of additional cells known to participate in cellular interactions. The mutation also affects cells whose fates are not changed by laser ablation of adjacent cells. Possibly further analysis of this gene will reveal still more cases of intercellular communication.

Many antero-posterior differences in body pattern arise after

hatching, and genes influencing patterning in the head (*16*), anterior body region (*47*), and posterior body region (*48*) have been identified. Raising or lowering the dosage of some of these genes can shift the boundaries between position-specific patterns toward the head or the tail, suggesting that these genes function to position cell types within the animal. The best characterized of these genes is *mab-5*, (*m*ale *ab*normal), which promotes posterior specialization in many cell types (*48*). The cells affected by *mab-5* are related only by position, not by lineage or cell type, suggesting that localized cell-extrinsic signals may be involved in patterning the body axis. The *mab-5* gene shares sequence homology with genes affecting pattern formation in Drosophila (*49*), again suggesting conservation of developmental mechanisms.

Temporal control of development. A set of genes called heterochronic genes controls the timing of developmental events (*50*). In heterochronic mutants, lineage patterns expressed at one developmental period appear at another period. In precocious mutants, cells in early larval stages express lineages characteristic of later stages. In retarded mutants the opposite is true, and cells adopt fates characteristic of earlier stages. The gene *lin-14* appears to play a regulatory role; high levels of *lin-14* activity specify cell fates characteristic of early larval stages, whereas low levels specify late cell fates (*51*). Most heterochronic mutations affect many cell types, but one, *lin-29*, affects only one tissue, the lateral epidermis (*50*). This gene may regulate lineage patterns in specific cells in response to more global regulatory signals.

Sex determination. Developing cells not only respond to spatial and temporal cues, but also to information that controls sexual development. Analysis of sex determination mutants has defined a complex regulatory network (*21*). In nematodes, as in Drosophila, the ratio of X chromosomes to autosomes (X:A) determines sex; a ratio of 0.5 leads to male development and a ratio of 1.0 to hermaphrodite development. However, the developmental machinery can discriminate between very fine differences in the X:A ratio; animals with a ratio of 0.67 are males, while those with a ratio only slightly higher, 0.75, are hermaphrodites (*52*). It will be interesting to see how such a fine discrimination can be made, and whether the mechanism has general significance. A number of sex determination genes have been placed into a formal regulatory pathway (*53–55*); upstream genes affect both sex determination and dosage compensation (a process that equalizes levels of X-linked gene expression in the two sexes), while downstream genes have more restricted effects. Much of the complexity of the pathway is thought to reflect a requirement for fine tuning. For example, the genes *fog-2* (*f*eminization *of g*erm line (*56*) and *tra-2* (*tra*nsformer) (*57*) permit XX animals to undergo a brief period of male gametogenesis, so that some sperm are produced and the animals become hermaphrodites instead of females. Together the sex determination genes appear to establish the state of the gene *tra-1* (*58*); if *tra-1* is on, somatic cells adopt hermaphrodite-specific fates, otherwise they adopt male fates.

The Nervous System

The nervous system of *C. elegans* contains a set of only 302 neurons, but this set is complex, and consists of 118 distinguishable cell types (*59*). A variety of neurotransmitters are represented among *C. elegans* neurons, including acetylcholine, GABA (γ-aminobutyric acid) serotonin, dopamine, octopamine, FMRFamide, and others. In order to facilitate studies of neurogenesis and behavior, the entire nervous system has been reconstructed from 20,000 electron micrographs taken of serial sections (*6, 59*). Some portions of the nervous system can be reconstructed quickly, which permits the isolation of mutations affecting synapse formation and synaptic specificity (*59*). Reconstructions of developing animals are currently under way; knowing the order in which processes extend and make interconnections will be quite informative. For example, neurons that first extend processes have been identified, and laser ablation studies have shown that they function to guide subsequent axons to their targets (*60*).

Knowledge of the complete structure should allow us to analyze behavior in a unique way, by simulating how it might be generated from the known neuronal network. For example, Chalfie and coworkers have identified neurons that mediate a response to mechanical stimulation by analyzing the wiring diagram and then ablating cells likely to mediate aspects of the behavior. Because of its small size, it is not yet possible to do neurophysiological experiments in *C. elegans*, so it is not possible to follow the flow of information directly. However, the structure and function of nervous system of the larger nematode *Ascaris* appears to be essentially the same as the *C. elegans* nervous system, and models about the *C. elegans* mechanosensory response are consistent with electrophysiological studies in *Ascaris* (*61*).

Many mutations affecting neurogenesis have been isolated by screening for animals with alterations in behaviors or in such cellular properties as transmitter production, drug sensitivity, or lineage alterations (*59*). Because the *C. elegans* lineages are known, and because many neural cell types can be distinguished, it is possible to ask how a neuronal cell type is specified genetically. For example, genes that specify the mechanosensory response have been identified genetically. The gene *lin-32* is required for many epidermal precursor cells to generate neuroblasts instead of additional epidermal cells (*62*), including neuroblasts that produce mechanosensory receptors. The gene *unc-86* (*unc*oordinated) is required at a later stage for the generation of complex neural cell lineages that generate mechanosensory receptors; in *unc-86* mutants, many neuroblasts undergo simple stem cell divisions instead of generating complex lineages (*63*). Further analysis of this gene may reveal whether (and if so how) cell-intrinsic events generate complex lineages. The gene *mec-3* (*mec*hanosensory) which has a homeobox and may therefore regulate gene expression, initiates differentiation of the mechanosensory neurons (*11*). Candidates for genes regulated by *mec-3* include the gene *mec-7*, a β-tubulin gene required for a mechanosensory cell–specific form of microtubules (*64*).

A total of 131 cells normally undergo programmed cell death during *C. elegans* development. The majority of cell deaths occur within neural cell lineages, and specifically require activity of the genes *ced-3* (*c*ell *d*eath) and *ced-4* (*65*). In the absence of either gene function, cells that would normally die differentiate into functional neurons (*65, 66*). A different class of genes that includes *mab-5* (*48*), specify some, but not all, cell deaths. This class of genes may be used to activate the death program, which can be considered a state of differentiation, in particular cells.

Caenorhabditis elegans is particularly well suited for learning how neural processes are guided to their destinations. Guidance mutants can be identified by staining fixed animals with neuron-specific antibodies, or better, they can be isolated by looking directly at axon placement in live animals. To see axons in living animals, Nomarski optics can be used to examine mutants in which processes are visible (*11, 67*), or else the animals can be soaked in fluorescent dyes that are taken up by many sensory neurons (*68*). Many guidance genes have been identified (*16*), and some of these are being analyzed at the molecular level.

In *C. elegans*, a small number of mesodermal and neural cells migrate for long distances. These migrations are easy to see in the light microscope in normal, untreated animals, and so the isolation and characterization of mutations affecting cell migration is possible. The problem of cell migration is not unlike that of axon guidance, so

it is not surprising that many mutations affect both. So far, mutations in approximately 30 genes disrupt the movements of cells or axons along the body wall (*16*). A particularly interesting set includes three genes affecting both cell migration and axon outgrowth along the dorso-ventral axis. One of these, *unc-6*, is required for all such migrations, while *unc-5* is required only for dorsalward movement, and *unc-40* is required only for ventralward migration. At least two of these genes are homologous to genes encoding known extracellular matrix proteins (*69*).

Muscle Assembly and Function

An important question in cell biology is how proteins such as muscle components assemble into machines capable of generating force. In *C. elegans*, muscle assembly and function is being dissected by means of the genetic approaches that have been so successful in understanding the related problem of bacteriophage morphogenesis. Mutations affecting muscle function can be isolated by looking for animals that move abnormally; mutants with remarkably subtle changes in the smooth sinusoidal pattern of movement can be detected. The development and structure of muscle fibers can be examined with polarizing optics in living animals and also by electron microscopy of fixed individuals. By analyzing uncoordinated (*unc*) mutants, about 30 genes encoding myosin isoforms, paramyosin, actins, and additional, possibly new, muscle components have been identified [reviewed in (*70*)]. The sequence of myosin heavy chain, first elucidated in *C. elegans*, has refined our conception of the two major myosin domains, the globular head region and the coiled-coil rod region. In particular, the repetitive coiled-coil sequence in the rod provided a structural basis for the periodicity of the thick filament. Fine structure genetic analysis is revealing structural and functional properties of the myosin domains. For example, all *unc* mutations known to affect the rod inhibit assembly, indicating that the rod functions in this process. All of these rod mutations have been deletions; one possibility for the failure to isolate missense mutations in this region is that the coiled-coils contain sufficient structural redundancy to withstand small perturbations. Surprisingly, some dominant mutations in the myosin head region also block muscle assembly, suggesting that this domain can also influence the assembly process (*70*). Body-wall thick filaments have been found to contain two myosin isotypes that have different locations and functions. The sequences responsible for these positional and functional differences can now be identified by constructing hybrid myosin genes and introducing them into the animal by DNA transformation.

The *unc* collection contains additional genes thought to encode thick filament proteins. One of these is a 500-kD protein with protein kinase homology (*71*). In addition, three genes with mysterious functions affect the dense body (the nematode equivalent of the Z line). Two of these are thought to bind actin filaments, and the third may anchor the dense body to the adjacent hypodermis. These gene products could help us understand how muscle filaments are positioned within a sarcomere, and how the force generated within the sarcomere is transduced to the body wall.

Other interesting topics, beyond the scope of this review, include aging (*72*); sperm morphogenesis (*73*); the dauer larva, an alternative developmental form that appears under conditions of stress (*74*); construction of the elaborate collagen-based cuticle; aspects of neuronal ultrastructure (*75*); and the role of the cytoskeleton in the elongation of the embryo (*76*). Also under study are aspects of DNA and RNA metabolism, including transposable elements (*30*) and the provocative phenomenon of trans-splicing (*77*), which is the post-transcriptional joining of separate RNA molecules.

Conclusions

Caenorhabditis elegans provides the experimental biologist with a powerful experimental system for the study of development and other complex systems in a multicellular animal. Its virtues are that the cellular plan and developmental lineages are essentially invariant and both have been determined completely; genetic analysis is extensive and now can exploit all the techniques of modern molecular genetics. In principle, in this organism the analysis of the genes and how their products work to implement the developmental process could be carried to completion.

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Drosophila melanogaster as an Experimental Organism

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The fruit fly *Drosophila melanogaster* has been used as an experimental organism in studies of genetics since the early 1900s. It is now widely used not only in classical and molecular genetics but also, with many new biochemical, cell biological, and physiological techniques, to research problems requiring a multidisciplinary approach, such as those of developmental biology and neurobiology.

MANY PROBLEMS IN EUKARYOTIC CELL BIOLOGY CAN BE most easily studied in unicellular organisms, such as yeast, or in cell cultures derived from multicellular organisms. Other problems, however, currently can be studied meaningfully only in intact animals. This may be because we do not know how to mimic crucial aspects of the organismal environment in vitro, because cell-cell interactions play an important role, or because the process under study involves a behavior that is not currently understood in terms of the properties of individual cells. Examples include pattern formation in the embryo and the development and function of organ systems, such as the nervous system. *Drosophila's* intermediate level of complexity, in combination with its sophisticated genetics, makes it particularly well suited for the study of basic problems in metazoan biology.

Drosophila melanogaster, the Most Genetically Manipulable Metazoan

The fruit fly has a small size and a short life cycle—features that make feasible the raising of large numbers of individuals for the many generations required for genetic analysis (Fig. 1). It also has a small genome, 1/20 the size of a typical mammalian genome, which facilitates molecular genetic analysis (*1*). Other organisms share these features, however, and they are not the primary reasons for *Drosophila*'s place in modern genetics. For this, credit must go to the hundreds of skillful and creative geneticists who have developed the wide range of tools available for use with this organism. Genetic studies with *Drosophila* began in T. H. Morgan's laboratory at Columbia University in 1909 (*2*). A year later, Morgan described the isolation of the first *Drosophila* mutant, *white eye*, and the observation that its inheritance was sex-linked (*3*). In 1915, Morgan, Sturtevant, Muller, and Bridges published their classic book *Mechanisms of Mendelian Inheritance* (*4*), establishing the relation between genes and chromosomes. Over the past 80 years, much of what we know about recombination, mutation, chromosome rearrangements, and other genetic phenomena has been discovered through the use of *Drosophila* as an experimental organism. It is important to remember that most of the techniques now used in genetic work with *Drosophila* were developed in the course of these efforts.

Use of Mutations to Dissect Complex Processes into Discrete Steps

In *Drosophila* it is possible to screen systematically for all genes that can mutate to produce a given phenotype. This phenotype can be any characteristic for which an assay can be devised, and a wide variety of such screens have been, and are being, carried out. Most common are screens for mutations affecting either viability or aspects of adult or embryonic morphology (*5*). Morphological analysis has advanced to the level of individual cells by the use of antibodies that allow the scoring of specific cells or cell types (*6*). In addition, screens for mutations affecting oogenesis (*7*), sex determi-

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