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The genetic analysis of cell lineage in *Caenorhabditis elegans*

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The genetic control of cell lineage has been studied extensively in *Caenorhabditis elegans*. In this paper, three studies of cell lineage mutants are reviewed: the isolation of mutations affecting vulval cell lineages, and the analysis of two 'control genes', *lin-12* and *lin-14*. In addition, certain logical features of the genetic programme, as inferred from or illuminated by the study of cell lineage mutants, are discussed: the concepts of 'control genes' and developmental subprogrammes, and the organization of the lineage into a hierarchy of binary decisions.

Introduction

A cell lineage is a pattern of cell divisions and cell fates. The cell lineage of *Caenorhabditis elegans* is essentially invariant from zygote to adult and has been completely described (Sulston & Horvitz 1977; Kimble & Hirsh 1979; Sulston *et al.* 1983). Any cell can be described both in terms of its ancestry (that is, by its descent from a particular embryonic founder cell or postembryonic blast cell) and its subsequent cell fate (which may be to differentiate into a particular cell type or to express a subsequent cell lineage). Thus, cell lineage defects in developmental mutants of *C. elegans* can be precisely described, and alterations can be understood in terms of altered developmental decisions in individual cells (Sulston & Horvitz 1980; Chalfie *et al.* 1981; Greenwald *et al.* 1983; reviewed in Horvitz *et al.* 1983 and Sternberg & Horvitz 1984). Despite the relative simplicity of form and the large degree of intrinsic developmental programming that has been demonstrated experimentally (Sulston & White 1980; Sulston *et al.* 1983), events in *C. elegans* development also require the cell–cell interactions and positional information thought to be so important in the development of more complex organisms (Sulston & White 1980; Kimble 1981; Sulston *et al.* 1983; Kenyon, this symposium; P. Sternberg, personal communication).

C. elegans is extremely tractable to genetic analysis (Brenner 1974): it is small, is easily cultured in the laboratory on Petri dishes seeded with *Escherichia coli*, and has a generation time of only 3.5 days at 20 °C. There are two sexes: hermaphrodites and males. Hermaphrodites are capable of reproducing by self-fertilization, which affords several advantages for genetic analysis, such as the ease of isolating homozygous recessive mutations and the tendency towards a uniform genetic background. Of particular relevance to studies of cell lineage is that self-fertilization facilitates the isolation and maintenance of mutations that result in severe developmental defects, many of which interfere with mating. However, because the essence of genetic analysis is the movement of mutations into different genetic backgrounds, the ability to cross-fertilize hermaphrodites by mating them with males is indispensable for genetic studies. Thus, the ability to produce both self- and cross-progeny provides maximum flexibility in the design and execution of genetic protocols.

Genetic studies of cell lineage mutants

How one initiates a genetic analysis of cell lineage is no different from how one initiates a genetic study of any other problem, that is, one isolates and characterizes mutants, in this case with abnormal cell lineage. One level of genetic analysis of a cell lineage (or any other process) is 'saturation genetics', that is, the isolation of mutations that define all genes required for a particular part or property of the cell lineage. Another level of genetic analysis is to study intensively individual genes that appear to be of particular interest. I shall give selected examples of these two approaches below; more complete reviews of the cell lineage mutants described to date may be found in Horvitz *et al.* (1983) and Sternberg & Horvitz (1984).

(*a*) *Isolation and characterization of mutations affecting vulva development*

The development of the vulva in wild-type hermaphrodites is represented schematically in figure 1. Six multipotential hypodermal precursor cells, P(3–8).p, are born in the L1 stage (Sulston & Horvitz 1977; Sulston & White 1980; Kimble 1981). Their developmental potential becomes restricted in the L3 stage (Greenwald *et al.* 1983; P. Sternberg and I. Greenwald, unpublished observations), when P(5–7).p express vulval cell lineages, generating 22 progeny

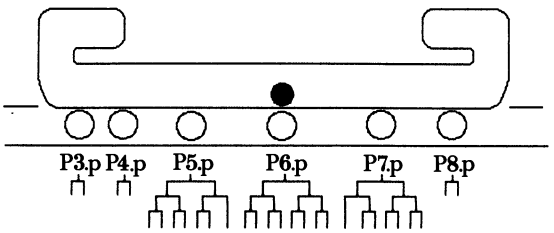

Figure 1. Vulva development in wild-type hermaphrodites. P(3–8).p, shown schematically as open circles, are multipotential hypodermal precursor cells whose developmental potential becomes restricted in the L3 stage: P(3,4,8).p divide to produce two progeny that join the hypodermal syncytium and P(5–7).p express vulval cell lineages, generating 22 progeny which undergo morphogenesis to form the vulva. The anchor cell, shown schematically as a black circle, is a gonadal cell that is required for the correct determination and execution of vulval cell lineages. Vulva development can be considered to proceed in five stages: (i) generation of P(3–8).p in the L1 stage; (ii) generation of an anchor cell; (iii) the determination of the fates of P(3–8).p in the L3 stage; (iv) the execution of P(3–8).p fates (vulval cell lineages); (v) morphogenesis (Sternberg & Horvitz 1984).

which undergo morphogenesis to form the vulva. A specialized gonadal cell, the anchor cell, is required both for expression of vulval cell lineages and for proper morphogenesis (Kimble 1981). Interactions between the anchor cell and the ventral hypodermal cells P(3–8).p may be sufficient to specify P(3–8).p cell fates, which then may be executed cell-autonomously (P. Sternberg and H. R. Horvitz, personal communication). Vulva development therefore is a microcosm of fundamental developmental processes: induction, cell–cell communication, cell type determination, cell fate execution, and morphogenesis.

The genetic analysis of vulva development has been extensive (Horvitz & Sulston 1980; Sulston & Horvitz 1981; Sternberg & Horvitz 1984; Ferguson & Horvitz 1985; P. Sternberg, E. Ferguson and H. R. Horvitz, personal communication). There are two features that render the vulva so amenable to study. First, the vulva is a non-essential structure. Its normal functions, as a passageway through which male sperm enter the uterus and through which eggs are laid, are both dispensable: in a hermaphrodite that lacks a functional vulva, self-fertilization occurs normally; the fertilized eggs hatch internally and the larvae devour their mother, forming a

'bag of worms', and eventually disperse. The 'bags of worms' are easily scored, enabling the isolation of mutants displaying abnormal vulva development among the progeny of mutagenized hermaphrodites. Second, the vulval cell lineages are relatively easy to study: only P(3–8).p normally have the potential to express vulval cell lineages (Sulston & White 1980), which entail three rounds of cell division that take only about 5 h (Sulston & Horvitz 1977).

Over 95 mutations have defined 22 genes that are involved in vulval cell lineages (Ferguson & Horvitz 1985). There are multiple alleles of most of these genes, suggesting that 'saturation' for fertile and viable mutations has been attained (most genes with sterile or lethal pleiotropies probably would not have been identified). Vulval mutants were analysed systematically to determine: (i) the nature of the mutation (null, reduction-of-function, gain-of-function) that resulted in the vulval defect; (ii) cell lineage alterations; (iii) the tissue (gonad or hypodermis) in which the mutation perturbs function; (iv) when possible, the temperature-sensitive period, and (v) epistatic interactions among the mutations (Sternberg & Horvitz 1984; Ferguson & Horvitz 1985; E. Ferguson, P. Sternberg and H. R. Horvitz, personal communication). The results of this analysis enabled the construction of a formal genetic pathway for vulva development (see figure 1). Null or reduction-of-function mutations defined genes that are required for the generation of P(3–8).p cells, for the correct specification of P(3–8).p cell fates. and for the correct execution of P(3–8).p cell fates.

Other genes that were defined originally by mutations that result in abnormal vulval cell lineages include *lin-12* and *lin-14* (Greenwald *et al.* 1983; Ambros & Horvitz 1985; Ferguson & Horvitz 1985). The characterization of these genes exemplifies the second approach to genetic analysis of cell lineage, that is, the detailed analysis of particular genes. The genes *lin-12* and *lin-14* appear to act as developmental 'control genes': differential gene activity appears to specify certain alternative cell fates.

(*b*) *lin-12 activity specifies certain cell fates as a function of position or ancestry*

Anatomical characterization of *lin-12* mutants revealed discrete and reciprocal homeotic transformations in the fates of certain cells (Greenwald *et al.* 1983). Two classes of *lin-12* alleles were examined: *lin-12(d)* alleles, which are semidominant, and *lin-12(0)* alleles, which are recessive. All transformations observed in *lin-12* mutants can be summarized schematically as shown in table 1, where a and b represent two cells of known ancestry that in wild type express different fates A and B, respectively.

TABLE 1. CELL FATES IN *lin-12* MUTANTS

	cell a	cell b
lin-12 (d)	A	A
lin-12(+)	A	B
lin-12(0)	B	B

The cell fates corresponding to A and B may be the expression of a specific cell lineage or the differentiation into a specific cell type. For example, a set comprising two gonadal cells (Z1.ppp and Z4.aaa) normally generates one anchor cell (a terminal differentiation) and one ventral uterine precursor cell (a blast cell) (Kimble & Hirsh 1979); in *lin-12(d)* mutants, both cells become ventral uterine precursor cells and in *lin-12(0)* mutants, both become anchor cells (Greenwald *et al.* 1983). Another example is shown in figure 2.

In hermaphrodites, at least six cells require *lin-12* activity for the correct expression of their

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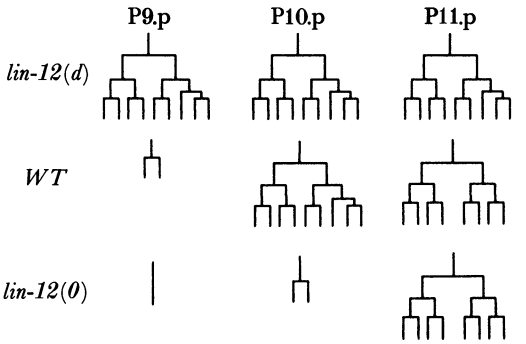

FIGURE 2. Cell fate transformations in the ventral hypodermis in *lin-12* mutant males. The fates of P(9–11).p are affected in *lin-12* mutants. P(9–11).p, like P(3–8).p (and like Z1.ppp and Z4.aaa, mentioned in the text), are multipotential in wild type and require cell–cell interactions for correct determination of their fates. P10.p is required to generate a distinctive structure, called a 'hook', that comprises neurons and hypodermal cells. Wild-type males each have a single hook; *lin-12(d)* males each have three hooks, and *lin-12(0)* males lack hooks (Greenwald *et al.* 1983).

fates; in males, at least seven cells require *lin-12* activity. These cells are born during four developmental stages (embryo–L3) and express very different cell fates (for example, neuroblast, myoblast). Many of the sets of cells affected in *lin-12* mutants require cell–cell interactions for correct determination of their fates (Sulston & White 1980; Kimble 1981; Sulston *et al.* 1983); most of the sets comprise homologues (that is, homologous progeny of related sublineages).

Genetic analysis of *lin-12* mutants indicated that *lin-12* controls certain binary decisions during development (Greenwald *et al.* 1983). First, by genetic criteria, *lin-12(d)* mutations appear to elevate *lin-12* activity, while *lin-12(0)* alleles eliminate *lin-12* activity. Thus, the level of *lin-12* activity is necessary for the expression of fate A, and an elevated level of *lin-12* activity is sufficient to result in the expression of fate A, suggesting that the level of *lin-12* activity (high or low) specifies the expression of cell fates (A or B). Second, the fates of certain sets of known multipotential cells are altered in *lin-12* mutants; the fates of these multipotential cells become specified at particular times during development, as ascertained by laser ablation (Kimble 1981; Greenwald *et al.* 1983; P. Sternberg and I. Greenwald, unpublished). The *lin-12* temperature-sensitive period coincides with the times that these cell fates are determined in wild type, suggesting that *lin-12* acts or is synthesized at the time cell fates are specified.

(*c*) *lin-14, a 'heterochronic gene', specifies cell fates as a function of time*

Mutations in four genes result in heterochronic developmental defects, that is, the timing of certain developmental events is altered relative to other events, which occur at their normal times (Ambros & Horvitz 1985). In 'retarded' mutants, events that normally occur only in an early larval stage are reiterated in subsequent larval stages, thereby retarding succeeding events. In 'precocious' mutants, events that normally occur in later larval stages occur in earlier stages, and the normal early events are skipped.

There are 'retarded' and 'precocious' alleles of one gene, *lin-14*, which result in discrete and opposite transformations in cell fate (for example, figure 3) (Ambros & Horvitz 1985). By genetic criteria, the retarded alleles (*lin-14(d)*), which are semidominant, result in elevation of *lin-14* activity, while the precocious alleles (*lin-14(r)*) result in loss or reduction of *lin-14*

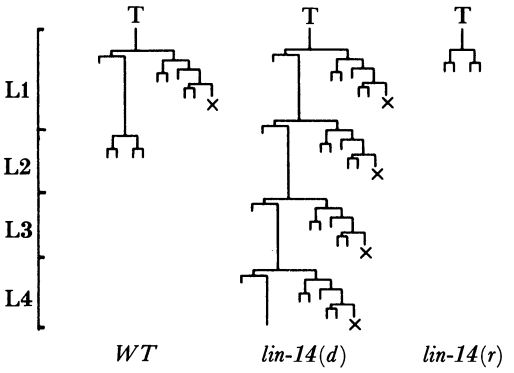

FIGURE 3. Cell fate transformations in the T lineage in *lin-14* mutant males. In *lin-14*(*d*) mutants, the L1 division pattern is reiterated in subsequent larval stages; in *lin-14*(*r*) mutants, this L1 pattern is deleted and is replaced by the L2 division pattern normally expressed by T.p (Ambros & Horvitz 1985).

TABLE 2. CELL FATES IN *lin-14* MUTANTS

	cell a	cell b
lin-14(*d*)	A	A
lin-14(+)	A	B
lin-14(*r*)	B	B

activity. Thus, we can summarize the fates of cells in *lin-14* mutants as in table 2, where a is a cell born early in larval development and b is a cell born late in larval development, and A and B are the fates they normally express.

Consideration of the phenotypes of *lin-14* mutants and the genetic nature of the *lin-14*(*r*) and *lin-14*(*d*) mutations suggests that *lin-14* controls certain binary decisions: certain cells, which may be of equivalent and multiple developmental potential, are born during each larval stage, and the level of *lin-14* activity specifies their appropriate fates(Ambros & Horvitz 1985).

LOGICAL ORGANIZATION OF THE LINEAGE

(*a*) '*Control genes*'

Both *lin-12* and *lin-14* are considered to be 'control genes' which are important for determining the identity, as inferred from their fates, of certain cells. A 'control gene' is one that appears to control a binary decision, that is, the initial or essential difference between two cell types is the level (high or low) or presence (present or absent) of a particular gene activity. One cell identity is determined, then the appropriate fate is executed, presumably through the activity of other genes. The term 'control gene' encompasses the concepts of 'activator' and 'selector' genes (Garcia-Bellido 1975), or genes involved in 'establishment' and 'maintenance' (Herskowitz & Hagen 1980) of a determined state, but should not imply anything about the mode of action of the gene product.

In general, genes that are required for the determination of cell identity might be recognized by two criteria: (i) loss or reduction of gene activity should result in discrete transformation in cell fate (see also Hierarchy below); and (ii) expression or function should be required when cell fates are determined. However, not all such genes need be 'control genes': the product of a particular gene may be necessary for the execution of a cell fate but not sufficient for the

determination of that fate and hence does not play a controlling role in the decision process. The existence of dominant gain-of-function alleles that have opposite phenotypic effects from null or reduction-of-function alleles is a valuable clue for identifying putative control genes.

(*b*) *Subprogrammes*

An examination of the wild-type cell lineage suggested that some information might be organized into developmental 'subprogrammes' that can be used to execute certain cell fates (Sulston & Horvitz 1977; Sulston *et al.* 1983). Three observations were suggestive: (i) bilaterally symmetrical precursor cells tend to express the same fates; (ii) non-homologous analogues, which are cells of unrelated ancestry that nevertheless express the same developmental fate, occur often, particularly in the embryonic lineage; (iii) sets of blast cells that express the same developmental fates ('repeating sublineages') occur often in postembryonic development.

Different cells that express the same fate could conceivably use different genes to get to the same end or alternatively could use a single genetic 'subprogramme' whenever a particular pattern is required. In principle, these alternatives might be distinguishable genetically: if corresponding pattern elements are independently mutable, one might infer that different genes are used to effect the same outcome. Or, if a single mutation coordinately alters corresponding pattern elements, one might infer the existence of genetic 'subprogrammes'.

There are no straightforward examples thus far of independent mutability of corresponding pattern elements. Mutations that coordinately alter the execution of the fates of bilaterally symmetrical precursor cells have been isolated (Sulston & Horvitz 1981; Chalfie *et al.* 1981). Other single mutations coordinately alter repeating sublineages (Horvitz *et al.* 1983; Sternberg & Horvitz 1984). Interestingly, most of these mutations appear likely to affect the determination of precursor cell identity rather than of cell fate execution *per se* (for example, *lin-22*, described below).

Programmed cell death provides perhaps the most striking example of a genetic subprogramme. Cell death is a common cell fate in nematode development (Sulston & Horvitz 1977; Sulston *et al.* 1983; reviewed in Horvitz *et al.* 1982): during hermaphrodite development, 1090 cells are born, but only 959 survive, that is, 131 cells die. The study of mutations that affect programmed cell death suggests that death results from the execution of a genetic subprogramme that results in cell suicide (Horvitz *et al.* 1982; H. Ellis and H. R. Horvitz, personal communication).

Mutations in the gene *ced-3* prevent cell suicides: cells that normally die instead survive. The 'undead' cells in *ced-3* mutants not only survive; many differentiate into recognizable cell types (Horvitz *et al.* 1982; H. Ellis and H. R. Horvitz, personal communication). For example, in wild-type males, two cells die that in hermaphrodites survive and differentiate into the HSNs (which are neurons required for egg-laying). In *ced-3* mutants these cells survive and differentiate into recognizable HSN-like neurons (H. Ellis, S. McIntyre and H. R. Horvitz, personal communication) (table 3). In contrast, a dominant mutation in the gene *eg1-1* results specifically in HSN death in hermaphrodites and hence is egg-laying defective (Trent *et al.* 1983). This specific death is blocked in the *ced-3*; *eg1-1* double mutant, which lays eggs normally (Trent *et al.* 1983) (table 3).

Because *ced-3* appears to be required for the onset of all cell suicides, and because the 'undead' cells can differentiate, a reasonable explanation is that *ced-3* is required for the initiation or early stages of a death subprogramme. Genes such as *eg1-1* might reveal how such a subprogramme is invoked during development.

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(*c*) *Hierarchy*

The cell lineage mutants analysed thus far suggest that an important aspect of the *C. elegans* cell lineage is that it is organized as a hierarchy of binary decisions. This inference is derived from the observation that most cell lineage mutations result in discrete transformations in cell fate, resulting in the deletion of pattern elements and their replacement by pattern elements normally found elsewhere (see, for example, Horvitz *et al.* 1983; Sternberg & Horvitz 1984), and that, in some cases, different mutations alter different steps in the lineage. For example, *lin-22* appears to be required for the correct determination of the fates of the lateral ectoblasts V1–V4: recessive mutations in *lin-22* cause the homeotic transformation of V1–V4 so that they express the cell fate normally associated only with V5 (figure 4) (Horvitz *et al.* 1983; W. Fixsen and H. R. Horvitz, personal communication). In wild type, V5 generates one postdeirid, which is a sensillum that contains a single dopamine neuron; *lin-22* mutants have multiple postdeirids, each containing a single dopamine neuron. Recessive mutations of *unc-86* appear to alter the execution of the V5 fate: in *unc-86* mutants, V5.paap acquires the fate normally expressed by V5.paa, so that multiple dopamine neurons are produced (figure 5) (Chalfie *et al.* 1981). The double mutant *unc-86*; *lin-22* has multiple postdeirids, each containing multiple dopamine neurons (Horvitz *et al.* 1983; W. Fixsen and H. R. Horvitz, personal communication). These results suggest that *lin-22* and *unc-86* participate in different decisions during the development of the lateral ectoderm: *lin-22* appears to be required for correct V1–V4 identity (that is, V1–V4 *versus* V5 identity), and *unc-86* is required for the correct execution of the V5 cell fate.

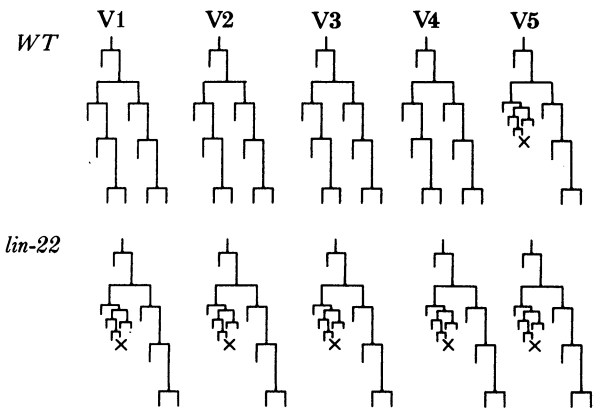

FIGURE 4. Cell fate transformations of the lateral ectoblasts V1-V4 in *lin-22* mutants (Horvitz *et al.* 1983; W. Fixsen and H. R. Horvitz, personal communication).

TABLE 3. HSN SURVIVAL IN CELL DEATH MUTANTS

genotype	hermaphrodites	males
wild type	+	−
ced-3	+	+
eg1-1	−	
ced-3; eg1-1	+	

+, ABp^{l}_{r} apppappa survives and differentiates into a morphologically recognizable HSN, −, cell death. (Trent *et al.* 1983; H. Ellis and H. R. Horvitz, personal communication).

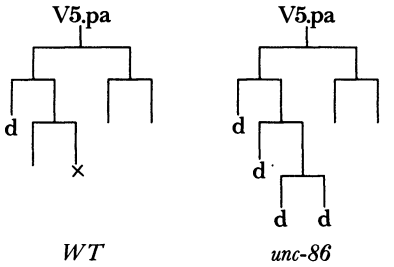

FIGURE 5. Aberrant execution of the V5. pa lineage in *unc-86* mutants (Chalfie *et al.* 1981).

Some of the cells in the lineage are relatively better characterized than others: they are found at starting points (the embryonic founder cells or the postembryonic blast cells), or at the termini (where the ultimate progeny of the lineage are differentiated). However, any cell in the lineage, no matter how transient its existence, has an identity that can be inferred from its fate. Many cell lineage mutants, as described above, display discrete transformations in cell fate; the cells that appear to be transformed need not be at the starting points of a sublineage. If many binary decisions were necessary to determine cell fate, then the failure to express the appropriate cell fate should lead to an 'identity crisis', resulting in an indeterminate or unrecognizable cell type, rather than in the expression of a discrete alternative cell fate, which is generally the effect observed in mutants.

(*d*) *Pleiotropy*

Most cell lineage mutations isolated thus far are pleiotropic, that is, many cell lineages are altered. Thus, the same genes are used by different cells to effect different fates, although a given gene is generally used by different cells in a consistent manner. For example, *lin-12* is required for correct expression of the fates of homologous cells that adopt different fates: most of the sets of cells known to be transformed in *lin-12* mutants comprise homologues. In addition, the defects observed in *unc-86* mutants suggest that *unc-86* is required to prevent stem cell-like divisions in several lineages (Chalfie *et al.* 1981). Presumably the restricted choice of cell fates available for consideration at each decision reflects the state of the cell (for example, the differential activity of other genes), which is likely to have been determined historically (that is, as a consequence of cell ancestry). For example, in the hermaphrodite gonad, *lin-12* controls the decision between the anchor cell and ventral uterine precursor cell fates and in the mesoderm, *lin-12* controls the decision between the coelomocyte and sex mesoblast cell fates (Greenwald *et al.* 1983).

CONCLUSIONS AND PROSPECTS

The genetic analysis of cell lineage in *C. elegans* has involved the isolation and characterization of many mutants with altered patterns of cell divisions and cell fates. Examination of these mutants has revealed features of the genetic programming, some of which were discussed above: the use of developmental subprogrammes, the hierarchical decision structure, and the use of the same genes for different developmental decisions. Most of the mutants that have been characterized to date have primarily postembryonic cell lineage alterations (Sulston & Horvitz 1981; Chalfie *et al.* 1981; Greenwald *et al.* 1983; Horvitz *et al.* 1983; Sternberg & Horvitz 1984;

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Ambros & Horvitz 1985; Ferguson & Horvitz 1985). Continued work on these mutants and others (E. Hedgecock and C. Kenyon, personal communication) should provide perspective on points addressed in this paper and illuminate other features of *C. elegans* development. In addition, work on embryonic cell lineage mutants is rapidly progressing (Denich *et al.* 1984; J. Priess, K. Kemphues, H. Schnabel, R. Schnabel, personal communication) and is expected not only to complement work on postembryonic cell lineage, but also to provide insight into other processes and problems encountered in embryonic development. Ultimately, an understanding of the molecular basis for the specification of cell fate is desirable. The recent isolation of DNA sequences from *lin-12* (I. Greenwald, unpublished observations) and *lin-14* (G. Ruvkun, V. Ambros and H. R. Horvitz, personal communication) is the necessary first step towards this goal.

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