GENETIC CONTROL OF CELL INTERACTIONS IN NEMATODE DEVELOPMENT

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CONTENTS

INTRODUCTION ................................................................. 411
SUMMARY OF DEVELOPMENT OF C. ELEGANS ................. 412
CELL INTERACTIONS .......................................................... 413
  Identification of cell interactions ........................................ 413
  Distal tip cell control of germline proliferation ...................... 414
  Cell interactions that control vulval development ................. 415
  Interactions in the lateral hypodermis ................................. 417
  Other cell interactions ..................................................... 418
GENETIC CONTROL OF CELL INTERACTIONS ................... 419
  glp-1 and lin-12 ............................................................ 419
  Genes regulating the VH/SH decision ................................. 426
  pal-1 ........................................................................... 429
  Other genetic pathways .................................................... 430
CONCLUSIONS, SPECULATIONS AND PROSPECTS .............. 431

INTRODUCTION

Cell interactions are vital to the regulation of cell division, differentiation, and pattern formation during the development of most multicellular creatures. The nematode Caenorhabditis elegans is no exception to this rule. Like other
metazoans, this small worm relies heavily on cell interactions during development. With the powerful genetics of *C. elegans* and its relatively simple anatomy, researchers have been able to delineate the genetic mechanisms regulating cell interactions with an unparalleled degree of precision. In addition, as the analysis of cell fate regulation in *C. elegans* has advanced to the molecular level, it has merged to a remarkable degree with the rapidly expanding field of signal transduction biochemistry, which has been intensively studied in vertebrate cells. The conjunction of these two areas of research is certain to enhance our understanding of the mechanisms, regulation, and evolution of cell interactions during development.

In this review, we emphasize those interactions in *C. elegans* that have been best characterized genetically. These include examples of both induction and lateral signaling. Induction occurs between separate tissues, with one tissue regulating the fate of another, whereas lateral signaling occurs within a single tissue and results in the adoption of distinct fates by cells with equivalent developmental potential. In addition to our discussion of the genetics of these better characterized interactions, we briefly mention other cell interactions and other genetic controls that promise to provide special insight into how cell interactions influence cell fate.

**SUMMARY OF DEVELOPMENT OF C. ELEGANS**

Figure 1 diagrams the essential features of the development and anatomy of *C. elegans*. The development of *C. elegans*, which unfolds in about 3 ½ days, is known at the level of individual cells. For a detailed account of the development and anatomy of *C. elegans* see refs. (1, 16, 32, 44, 49, 74, 76, 77, 79); for extensive reviews see refs. (47, 75, 87, 88).

During early embryogenesis, the zygote generates five somatic founder cells (AB, MS, E, C, and D) and one germline founder cell P4 (Figure 1A). Most founder cells contribute to several tissues; moreover, most major tissues (e.g. hypodermis, nerve, muscle) arise from several founder cells. In contrast, the gut and germ line are each generated by clonal divisions of a single founder cell, E and P4, respectively (Figure 1A). In the first half of embryogenesis, the somatic founder cells generate 559 descendants by a fixed cell lineage, whereas P4 divides only once, producing two germline precursor cells. The second half of embryogenesis is characterized by extensive differentiation and morphogenesis, resulting in a tiny worm about 150 μm long. After hatching, the animal passes through four larval stages (L1, L2, L3, L4) to reach adulthood. During this period of postembryonic development, the somatic and germline tissues grow and mature sexually. Somatic development occurs by a nearly invariant lineage. Typically, each cell in *C. elegans* has a fate that is coupled to its position and ancestry. By cell fate, we mean either differentiation as a specific cell type (e.g. a neuron) or execution of a
Figure 1  A) An outline of the embryonic cell lineage of *C. elegans*. Beneath the name of each blast cell is a list of the tissues it generates. B) Major anatomical features of the adult *C. elegans* hermaphrodite.

particular pattern of divisions, generating a fixed number of cells with specific fates. In contrast to somatic development, the pattern of cell divisions in the germ line is variable.

CELL INTERACTIONS

In this section, we first describe methods by which cell interactions have been discovered, then discuss selected interactions that exemplify the types of interactions known to influence cell fate during development, and, finally, mention other interactions that are generally less well characterized.

Identification of Cell Interactions

Most cell interactions have been identified by observing the consequences of altering a cell’s environment during development. Three different experimental approaches have been developed. First, individual cells can be
killed. In larvae, laser microsurgery is extremely effective in eliminating cells with little or no damage to neighboring cells (80). However, in embryos laser ablation has been less effective (79). Yet early embryonic blastomeres have been successfully removed by extrusion through a punctured eggshell (60, 65) and the laser has been used to arrest cells in the embryo rather than killing them (66). After a cell is killed/removed, the fates of its neighbors are observed. If abnormalities are seen, it is likely that the removed cell influences the development of its neighbor(s). Second, the relative positions of blastomeres in the early embryo can be changed by micromanipulation (60, 89). Here again, if the predicted development is changed, the fates of the blastomeres are likely to be regulated by cell interactions. Third, some interactions have been discovered by the analysis of genetic mosaics (reviewed in ref. 30). In these experiments, an animal is generated with one group of wild-type cells and a second group of mutant cells. If the fate of a cell is affected by the genotype of its neighbor, these cells probably interact. These experiments have clearly demonstrated that cell interactions are critical to development in *C. elegans* from early embryogenesis through adulthood.

**Distal Tip Cell Control of Germline Proliferation**

The control of germline proliferation by the distal tip cell is an example of *induction*. The adult germ line is a syncytial tissue consisting of about 2500 P₄ descendants in hermaphrodites and about 1000 in males (32, 49). In hermaphrodites, the germline tissue is split into two ovotestes, each with a single somatic cell, called the distal tip cell, located at its apex (Figure 1B; 2. See also 44). In males, the germ line occupies a single testis with two distal tip cells at the end. Induction of the germline from two cells at hatching to the one or two thousand descendants in adults depends on the presence of the distal tip cell (Figure 2; 48). In either sex, if the distal tip cells are killed during larval development or adulthood, all germline nuclei that are in mitosis enter meiosis. In hermaphrodites, if a single distal tip cell is killed, germline mitoses are arrested only in the ovotestis to which that distal tip cell belongs. Therefore, the presence of the distal tip cell is essential for the larval mitotic divisions that generate the germline tissue and for the adult divisions that maintain a stem cell population in the mature gonad. A simple model to explain this phenomenon is that the distal tip cell signals germline nuclei to remain in mitosis.

Germline proliferation can also be stimulated by a second somatic gonadal cell, the anchor cell (68). Normally the anchor cell is separated from the germ line by other somatic gonadal cells. However, if these other cells are removed, the anchor cell induces germline mitoses in the proximal region of the ovotestis. This induction differs from the distal tip cell induction in that the continued presence of the anchor cell is not required to maintain proximal mitoses (68).
**Cell Interactions that Control Vulval Development**

The hermaphrodite vulva is an opening in the body wall through which insemination occurs and embryos are extruded (Figure 1B). The vulva is a specialization of the body wall epithelium, or hypodermis, that is controlled by specific nerves and muscles. Here we limit our discussion to those interactions required for development of the vulval hypodermis. These include both inductive and lateral signaling interactions. Recent reviews provide more comprehensive summaries of vulval development and its genetic control (34, 71).

**Vulval Induction**

The bulk of the hypodermis is syncytial, consisting of numerous nuclei in a common cytoplasm (87). However, in young larvae, six cells in the ventral hypodermis remain separate. These six cells are the vulval precursor cells (or VPCs). The vulva is produced by three of the vulval precursor cells, which generate a total of 22 vulval hypodermal (VH) descendants (77). One of the vulval precursor cells follows the VH1 fate, producing eight vulval hypodermal cells, and the two flanking vulval precursor cells each follow the VH2 fate, generating seven more vulval hypodermal cells on each side (Figure 3). The remaining three vulval precursor cells divide once and their descendants join the syncytial hypoderm (SH) (Figure 3).

Induction of the vulval hypodermal fates (VH1 and VH2) depends on the presence of a single cell, the anchor cell, in the somatic gonad (43). If the anchor cell is killed, all vulval precursor cells follow the SH fate and join the syncytial hypodermis (Figure 3B). Furthermore, if all somatic gonadal cells except the anchor cell are killed, vulval induction occurs normally (43). Therefore, the anchor cell regulates the VH/SH decision. This inductive interaction occurs just prior to the first division of the vulval precursor cells in the early L3 stage (43).
Two lines of evidence support the idea that the anchor cell induces vulval development at a distance. First, the anchor cell is normally positioned directly over the VH1 cell, but at some distance from the two VH2 cells. Since the anchor cell can induce VH2 at a distance, even when the cell normally adopting the VH1 fate is not present (72, 81), it seems likely that the anchor cell induces both VH1 and VH2 fates directly. Second, the anchor cell can induce vulva formation when positioned on the opposite side of the animal. In *dig-1* (for displaced gonad) mutants, vulval induction occurs even though the somatic gonad is located on the dorsal side of the animal (81). The most likely mechanism for anchor cell control is production of a diffusible signal. Yet it remains possible that the anchor cell extends a cellular process to induce VH fates at a distance or that it can act via the syncytial hypoderm. Identification of the anchor cell signal and electron microscopic analysis of the cellular contacts between the anchor cell and vulval precursor cells should distinguish among these possible mechanisms for action at a distance.

Based on a genetic mosaic analysis of *lin-15*, a gene essential to the VH/SH decision (see below), Herman & Hedgecock have proposed that the syncytial hypoderm surrounding the vulval precursor cells promotes the SH fate and/or inhibits the VH fates in the vulval precursor cells (31). This interaction was previously unknown, presumably because ablation of the syncytial hypoderm...
that surrounds the vulval precursor cells would cause lethality. Therefore, the vulval precursor cells appear to make the VH/SH decision by integrating the effects of two antagonistic inductive interactions, one with the anchor cell and the other with the surrounding hypoderm.

LATERAL SIGNALING AND VULVAL DEVELOPMENT  The correct specification of cell fates in the vulval hypodermis is dependent on lateral signaling within two sets of equivalent cells. Such arrays of cells with equivalent developmental potential are known as equivalence groups (46). The first group that we consider is the two-celled AC/VU equivalence group, located in the somatic gonad (Figure 3). Either member of this group can differentiate as an anchor cell (AC) or a ventral uterine precursor cell (VU) (43, 44). As described above, the anchor cell induces vulval development in the hypodermis. The VU cell, on the other hand, generates ten uterine cells (44). If either cell of the AC/VU pair is killed, the remaining cell becomes an anchor cell (43, 67). Therefore, the AC fate is known as primary. The VU fate is followed only when an anchor cell is present and therefore is known as secondary. If both cells of the AC/VU pair are left intact, one always becomes an anchor cell and the other always adopts the VU fate. One model to explain these results is that the anchor cell influences its neighbor to assume the VU fate, either by inhibiting the AC or promoting the VU fate. A second model is that the two cells of the AC/VU pair compete for some site or factor that promotes anchor cell differentiation. The first model is favored by the observation that both members of the AC/VU pair can assume the AC fate if the close association of the two cells is disrupted (28).

The six vulval precursor cells constitute the second equivalence group required for vulval development (Figure 3). As described above, the VH/SH decision among the vulval precursor cells depends on an inductive interaction with the anchor cell. However, each of the six vulval precursor cells follows one of three fates: VH1, VH2, or SH. These fates, like the AC and VU fates, can be placed into a hierarchy by laser ablation experiments: VH1 is primary, VH2 secondary, and SH tertiary (72, 80). A simple model to explain these results is that the cell determined to follow the VH1 fate signals its neighbors to adopt a different fate and, similarly, that cells determined to follow the VH2 fate signal their neighbors. However, competition for sites or factors that promote specific fates remains a formal possibility. Genetic evidence supports the idea of an interaction between VH1 and VH2, but not between VH2 and SH (73). Therefore, only one lateral signal, between VH1 and its neighbors, is diagrammed in Figure 3.

Interactions in the Lateral Hypodermis

In the L1 larva, there are seven lateral hypodermal cells distributed along the antero-posterior axis on each side of the animal (77). In males, the two most
posterior cells (V6 and T) give rise to sensory structures known as rays, while their anterior counterparts (V1–V4) generate seam cells (hypodermal cells that produce cuticular ridges called alae). The cell that lies between these two groups (V5) gives rise to both a seam cell and a ray. If T is killed, the lineages of V1–V6 are unaffected; however, if either V5 or V6 is killed, its anterior neighbor will shift to occupy the vacant position and assume the fate of the ablated cell (80). The decision to produce either rays or seam cells appears to be controlled by a combination of the position of a cell along the antero-posterior axis and signaling between neighboring cells (38, 85; see section below on pal-1).

Other Interactions

Other interactions in addition to those discussed above dramatically affect development in C. elegans. A detailed discussion of these interactions is beyond the scope of this review. However, we mention them briefly here and provide references for interested readers.

EMBRYONIC INDUCTION OF ASYMMETRY  Recent experiments involving micromanipulation and laser irradiation of blastomeres have demonstrated that cell interactions determine left-right asymmetry (89, 90) and possibly govern the establishment of the dorso-ventral axis (66).

EMBRYONIC INDUCTION OF THE ANTERIOR PHARYNX  The pharynx is a neuromuscular organ that pumps food into the intestine (Figure 1B). The anterior pharynx derives primarily from the AB blastomere and the posterior pharynx from EMS (Figure 1A; 79). If EMS is physically removed, AB no longer produces pharyngeal tissue (60). Therefore, EMS or one of its descendants is likely to induce pharyngeal development in AB or one of its descendants. Experiments involving the removal of EMS or its descendants at various times have demonstrated that this interaction must occur between the 4- and 28-cell stages of embryogenesis (60).

OTHER EQUIVALENCE GROUPS  Besides the AC/VU and vulval equivalence groups described above, several other equivalence groups have been revealed by laser ablation experiments (for review, see ref. 75). In each case, a hierarchy of fates has been established. Of particular note are equivalence groups that are affected by the genes discussed below. These include the G2/W pair, which generates one ectoblast and one neuroblast, the P11/P12 pair, which produces two different ectoblasts, two equivalence groups in the descendants of the B precursor cell that produce parts of the male copulatory apparatus (Bα/Bβ and Bγ/Bδ), and a three-celled equivalence group (P9.p, P10.p, and P11.p) located in the ventral hypodermis of the male, which also is responsible for generating specific cells of the male copulatory apparatus.
MIGRATIONS Although most cells in *C. elegans* stay where they are born, some cells migrate long distances to adopt new positions within the animal. For example, the somatic gonadal precursor cells migrate from their place of birth in the head to a ventral position midway along the animal’s antero-posterior axis (79). Similarly, the sex myoblasts migrate from the posterior region of the animal to the gonadal region, where they generate vulval and uterine muscles (77). Evidence is beginning to accumulate in support of long-range signaling as the mechanism that may direct these migrations (81).

In addition, axonal outgrowth and branching are dependent upon cell-cell and cell-extracellular matrix interactions (28, 53, 81). Mutants have been identified in which these interactions are likely to be perturbed. (For a recent review, see (29).)

CELL DEATH During male development, the programmed death of two different cells depends on specific interactions with an engulfing cell (76). This type of cell death differs from most other cell deaths in *C. elegans*. (For a review, see (17).)

OTHER TYPES OF CELL INTERACTIONS Some cells react to the deaths of their neighbors by altering their own morphology, generating additional descendants, or reversing their lineage polarity (75). A proliferative response has been observed specifically in the lateral hypodermis (80) and changes in lineage polarity have been seen in isolated cells of various tissues (11, 43, 80). An understanding of these “other” interactions requires a detailed description of the cellular morphology involved; since these changes remain largely unexplored genetically, we do not consider them further.

GENETIC CONTROL OF CELL INTERACTIONS

Among the genes known to regulate cell interactions in *C. elegans*, we focus on those that mediate induction and lateral signaling. First, we discuss *glp-1* and *lin-12*, homologous genes that mediate germline induction and lateral signaling, respectively. Second, we discuss genes that mediate the VH/SH decision during vulval development. Third, we describe the *pal-1* gene and its role in silencing an interaction. Finally, we mention two intensively analyzed genetic pathways for cell fate regulation that have recently become candidates for genetic models of signal transduction.

*glp-1* and *lin-12*

Two genes, *glp-1* and *lin-12*, control several distinct cell interactions in *C. elegans*. The *glp-1* gene mediates germline induction by the distal tip cell and induction of the anterior pharynx during embryogenesis (5, 59). In contrast, the *lin-12* gene primarily regulates cell fate decisions among members of
equivalence groups (e.g. the AC/VU and VH1/VH2 decisions) (22). These two genes are discussed together here, because it has become evident that the \textit{glp-1} and \textit{lin-12} proteins are remarkably similar in both structure and function (5, 51, 55a, 68, 91).

**MUTANT PHENOTYPE OF \textit{glp-1}** Null mutations of \textit{glp-1}, \textit{glp-1(0)}, severely curtail the mitotic proliferation of the germ line (4, 60). In \textit{glp-1(0)} mutants, the two germline precursor cells present at hatching undergo only one or two mitotic divisions and then enter meiosis. Yet, the distal tip cell is present and meiosis and gametogenesis appear to be unaffected. Therefore, the \textit{glp-1} product is required in the germ line for the decision between mitosis and meiosis. One class of \textit{glp-1(ts)} mutants has a germ line virtually identical to that of a null mutant when raised at restrictive temperature. However, when \textit{glp-1(ts)} mutants are raised at permissive temperature and then shifted to restrictive temperature as adults, a second phenotype, embryonic lethality, is seen (4, 60). The cellular defects observed in the dead embryos indicate that \textit{glp-1} is also required for the embryonic induction of the anterior pharynx and the development of the embryonic hypodermis (60). The expression of \textit{glp-1} is required zygotically for germline development and maternally for embryogenesis (4, 60). The maternal requirement for \textit{glp-1} is absolute: a wild-type allele introduced by mating does not rescue any aspect of the \textit{glp-1} embryonic lethality.

Five \textit{glp-1} mutations have unusual phenotypes (4, 55a, 60; V. Kodoyianni, E. M. Maine, J. Kimble, manuscript in preparation). Four have more severe effects on the embryo than the germ line. These mutations may identify regions of \textit{glp-1} specific for embryonic functions. Alternatively, the embryo may be more sensitive than the germ line to the level of \textit{glp-1} activity, in which case these alleles could simply be weak loss-of-function mutations. The other unusual mutation, \textit{glp-1(q35)}, causes both a recessive Glp and a dominant Muv phenotype; this allele is discussed further below.

**MUTANT PHENOTYPE OF \textit{lin-12}** Two classes of \textit{lin-12} mutations exist: dominant gain-of-function mutations, \textit{lin-12(d)}, and recessive loss-of-function mutations, \textit{lin-12(r)} (25). The \textit{lin-12(d)} alleles were identified by their Multivulva (Muv) phenotype and the \textit{lin-12(r)} have been obtained primarily as revertants of \textit{lin-12(d)}. Both genetic and molecular evidence support the notion that \textit{lin-12(r)} alleles cause a decrease in \textit{lin-12} activity, while \textit{lin-12(d)} alleles cause an increase (22, 25).

The \textit{lin-12(r)} and \textit{lin-12(d)} mutations transform cell fates in several equivalence groups and have reciprocal effects (25). Generally, equivalent cells follow a primary fate in \textit{lin-12(r)} mutants and a secondary fate in \textit{lin-12(d)} mutants. For example, in the AC/VU equivalence group (see section above on
vulval development), both cells follow the primary AC fate in lin-12(r), but the secondary VU fate in lin-12(d) mutants. In animals lacking lin-12, the anchor cell appears to be no longer able to signal its neighbor to assume the VU fate. In males, lin-12 mutations have comparable effects on the fates adopted by the cells of the P9.p, P10.p, P11.p equivalence group (25). A simple interpretation of these results is that the lin-12 product mediates lateral signaling (25, 70, 73).

Other effects of lin-12 mutations indicate that this gene plays a fairly broad role in controlling cell fates during development. First, in the G2/W equivalence group, the effects of lin-12 are opposite that described above (25). Both cells follow the secondary W fate in lin-12(r) mutants and the primary G2 fate in lin-12(d) mutants. This may be a case where lin-12 is required for reception of a signal that specifies the primary fate. Second, some pairs of cells that exhibit reciprocal fate transformations in lin-12(r) and lin-12(d) mutants do not change their fates in response to ablation (e.g. sex muscle and coelomocyte fates) (25, 80). This suggests that lin-12 may not always be required for cell interactions per se. An alternative mechanism, consistent with the molecular identity of lin-12 as a membrane protein (see below), invokes autocrine stimulation by these cells. Finally, in lin-12(r) mutants, germ cells in the proximal region of the gonad undergo ectopic mitotic proliferation (68). Therefore, the effects of lin-12 activity are not limited to somatic cells. However, Seydoux and colleagues have shown that this abnormal proximal germline proliferation occurs because lin-12 activity is lacking in the somatic gonad and suggest that lin-12(+) expressed on somatic gonadal cells normally blocks an interaction between the anchor cell and the germ line (68).

MOSAIC ANALYSIS AND TEMPERATURE SHIFT EXPERIMENTS WITH glp-1 AND lin-12 Genetic mosaic analyses of glp-1 and lin-12 have demonstrated that each is required in the receiving cell of its relevant cell interaction. Thus, glp-1(+) activity is required in the germ line but not the distal tip cell for germline induction (4) and lin-12(+) activity is required in the ventral uterine precursor cell but not the anchor cell for lateral signaling within the AC/VU equivalence group (67). In addition, temperature-shift experiments with glp-1(ts) and lin-12(ts) mutants have shown that each activity is required at the time when the relevant cell interaction occurs. Thus, glp-1 activity is required throughout postembryonic development for continued germline mitoses and only from the 4- to 28-cell stage for embryonic induction (4, 60). Similarly, lin-12 appears to act during the L2 stage for lateral signaling in the AC/VU equivalence group (25), just when the AC/VU interaction occurs (43).

MOLECULAR ANALYSIS OF glp-1 AND lin-12 The glp-1 and lin-12 genes appear to encode proteins that are similar to each other both in sequence and
overall organization (5, 22, 91, 92). The \textit{glp-1} and \textit{lin-12} proteins are 48% identical and 66% similar in amino acid sequence (V. Kodoyianni, personal communication) and have conserved exon/intron boundaries (91). Furthermore, the \textit{lin-12} and \textit{glp-1} genes are located very close to each other (approximately 20kb apart) on chromosome III (4). Therefore, these two genes are likely to have evolved by gene duplication.

The \textit{glp-1} and \textit{lin-12} proteins share the same structure (5, 91, 92). Both possess a putative signal sequence at the N-terminus and an internal hydrophobic region followed by positively charged amino acids that might function as a transmembrane domain. Therefore, these are likely to be transmembrane proteins. In addition, both are composed of the same types of structural motifs arranged in the same order. The predicted extracellular domain is composed almost entirely of two different types of cysteine-rich motifs. One motif is EGF-like and is repeated 13 times in \textit{lin-12} and 10 times in \textit{glp-1}; the other, the LNG motif (see below), is present in three copies in both \textit{lin-12} and \textit{glp-1}. Intracellularly, there are six copies of a motif observed originally (8) in two yeast genes, \textit{cdc10} (required in \textit{Schizosaccharomyces pombe} for initiation of the cell cycle) and SWI6 (required in \textit{Saccharomyces cerevisiae} for \textit{HO} gene transcription during G1). Recently, this repeat has been found in several other regulatory proteins, including the transcription factor NF-κB (40) and vertebrate erythrocyte ankyrin (54), a protein thought to attach cytoskeletal elements to the cell membrane. The structure of the \textit{glp-1} and \textit{lin-12} proteins is strikingly similar to that of the protein encoded by Notch (5, 39, 86, 91, 92), a \textit{Drosophila} gene that also is responsible for developmental cell interactions (52, 58). Moreover, vertebrate homologues with all the features of \textit{lin-12}, Notch, and \textit{glp-1} have recently been discovered (13; G. Lemke, personal communication; J. Sklar, personal communication). We call this group of genes the LNG gene family, for its founding members: \textit{lin-12}, Notch, and \textit{glp-1}.

The molecular characterization of \textit{glp-1} and \textit{lin-12} mutations provides critical information about the functional and regulatory domains of these proteins. For \textit{glp-1}, severe loss-of-function alleles are either nonsense mutations in the first half of the coding region or missense mutations in the EGF-like, LNG, or SWI6 repeats (V. Kodoyianni, E. Maine, J. Kimble, manuscript in preparation). For \textit{lin-12}, one loss-of-function mutant (\textit{n302n653}) carries a missense mutation in one of the SWI6 repeats (23). The \textit{glp-1(q35)} allele, which phenotypically mimics \textit{lin-12(d)}, is a nonsense mutant predicted to generate a protein lacking 122 amino acids from the C-terminus (55a). This terminal region is not highly conserved between \textit{lin-12} and \textit{glp-1} and may be required for somatic regulation of \textit{glp-1} activity. The other partial loss-of-function \textit{glp-1} alleles all map to the EGF-like repeats (V. Kodoyianni, E. Maine, J. Kimble, manuscript in preparation). The \textit{lin-12} gain-of-function alleles are all missense mutations in the extracellular region.
adjacent to the transmembrane domain (23). Because the analogous amino acids are highly conserved in glp-1, the two proteins are likely to be regulated by a similar mechanism. Based on experiments that indicate an interaction between lin-12 alleles, Greenwald & Seydoux (23) propose that the gain-of-function lin-12 mutations might promote dimerization. However, these mutations could equally well interfere with dimerization or disrupt any down-regulation of protein activity.

glp-1 and lin-12 overlap in function In addition to being similar in structure and function, the lin-12 and glp-1 proteins appear to be biochemically interchangeable. Three lines of evidence support this idea. First is the phenotype of the lin-12 glp-1 double mutant (51). Whereas both lin-12 and glp-1 single mutants usually reach adulthood, the lin-12 glp-1 double mutant invariably arrests in the first larval stage. Therefore, in glp-1 and lin-12 single mutants, the presence of the wild-type product of the other gene is essential for survival. Therefore, certain developmental processes must be able to rely on either glp-1 or lin-12 function. Second is the similarity in the effects of the lin-12(d) and glp-1(q35) mutations. Both cause a Muv phenotype that is anchor cell-independent (5, 25, 55a). Third is the effect of lin-12(r) on the germ line. In lin-12(r) mutants, mitotic germline nuclei are present at the proximal end of the gonad in addition to the normal site at the distal end (68). Seydoux and colleagues speculate that the anchor cell signal mimics the distal tip cell signal and that the positive regulatory signal normally received by lin-12 product may also activate the glp-1 protein.

The major differences between glp-1 and lin-12 may be regulatory in nature. The glp-1 gene is primarily responsible for germline-dependent interactions (embryonic induction of the pharynx depends on maternal glp-1 product, which is presumed to be produced in the germ line). Although glp-1 plays a role in the embryonic soma in the absence of lin-12, the lin-12 gene appears to be more critical to these decisions (51). The lin-12 gene, in contrast to glp-1, is primarily responsible for somatic interactions and specifically for lateral signaling. One simple mechanism to achieve such a disparity in the roles of functionally similar proteins is to confine the expression of each to a separate tissue. By Northern blot analysis, it has been shown that glp-1 RNA accumulates primarily in the germline (5). In addition, analysis of the glp-1(q35) mutation indicates that the somatic activity of glp-1 may be inhibited posttranslationally (55a). Therefore, two regulatory mechanisms have already been discovered that could explain the restriction of glp-1 activity to the germ line.

Genes acting with glp-1 and/or lin-12 In screens for mutants with the glp-1 and lin-12 mutant phenotypes, only glp-1 and lin-12 were discovered.
However, two other approaches have successfully identified genes that act with \textit{glp-1} and/or \textit{lin-12}.

\textit{The lag genes}  In screens for mutants with a larval-lethal phenotype similar to that of the \textit{lin-12 glp-1} double mutant, two genes, \textit{lag-1} and \textit{lag-2} (for \textit{lin-12} and \textit{glp-1}), were identified (51). For both \textit{lag-1} and \textit{lag-2}, the strongest alleles are probable null mutations and result in a phenotype that is virtually indistinguishable from that of the \textit{lin-12 glp-1} double mutant. Also, for each \textit{lag} gene, weak mutations exhibit postembryonic phenotypes diagnostic of \textit{lin-12} and \textit{glp-1} single mutants. Therefore, each \textit{lag} gene is involved not only in the embryonic functions of \textit{lin-12} and \textit{glp-1} but also in the postembryonic functions of \textit{lin-12} and \textit{glp-1}.

The roles played by \textit{lag-1} and \textit{lag-2} are not understood. Double mutant experiments have not been informative. Since the \textit{lin-12 glp-1} double mutant phenotype is the same as the \textit{lag-1} and \textit{lag-2} probable null phenotypes, epistasis analysis cannot establish their functional relationship. Furthermore, the double mutants that might have been useful, the \textit{lin-12(d); lag} double mutants, are Lag (E. Lambie, S. Christensen, J. Kimble, unpublished observations). This result does not distinguish among the various relationships that the \textit{lag} genes might have with \textit{lin-12/glp-1}. One or both might be an obligate positive regulator of \textit{lin-12/glpl}, act together with \textit{lin-12/glpl}, or function downstream of \textit{lin-12/glpl}. A combined mosaic and molecular analysis of the \textit{lag} genes will likely be required to understand their functional relationships.

\textit{The sog and sel genes}  Isolation of suppressors of \textit{glp-1(ts)} and \textit{lin-12(d)} mutations has revealed eight \textit{sog} (for suppressors of \textit{glp-1}) genes (E. Maine, J. Priess, personal communication) and six \textit{sel} genes (for suppressors/enhancers of \textit{lin-12}) (J. Thomas, I. Greenwald, personal communication). The \textit{sog} and \textit{sel} mutants have no visibly abnormal phenotype. Among the suppressors of \textit{lin-12(d)}, \textit{sel-3} mutations are now known to be dominant gain-of-function mutations of \textit{lag-2} (F. Tax, J. Thomas, R. H. Horvitz, personal communication). The \textit{lag-2/sel-3} locus was first identified in a screen for lethals and was originally called \textit{let-461} (37). Suppression of \textit{lin-12(d)} by \textit{lag-2(gf)} indicates an interaction between \textit{lin-12} and \textit{lag-2}, but the nature of that interaction is unclear.

\textit{Collagen suppressors of glp-1}  Mutations in eight genes required for the normal morphology of the animal act as recessive suppressors of \textit{glp-1} (55). These genes had been previously identified: \textit{dpy-1}, \textit{dpy-2}, \textit{dpy-3}, \textit{dpy-7}, \textit{dpy-8}, \textit{dpy-9}, \textit{dpy-10}, and \textit{sqt-1} (9, 15). Three of these genes have been sequenced and found to encode collagens (50; J. Kramer, personal com-
NEMATODE CELL INTERACTIONS

munication); the molecular identities of the others are not known. This finding suggests an interaction between the extracellular matrix and \textit{glp-1}. If the collagen mutations alter the structure of the gonadal basement membrane, this may lead to an increase in the availability of the \textit{glp-1} protein to receive the distal tip cell signal. This model requires that a partially functional \textit{glp-1} gene be present and explains the lack of suppression of null mutations (55).

MODELS FOR THE ACTION OF \textit{glp-1/lin-12}

Figure 4 presents a speculative model for regulation by \textit{glp-1}, based on the \textit{glp-1} mutant phenotype (4, 59), the requirement for \textit{glp-1} in the receiving cell (4), and the probable status of \textit{glp-1} as a transmembrane protein (5, 91; S. Crittenden, J. Kimble, unpublished). The \textit{glp-1} protein is proposed to be a receptor for a signal produced by the distal tip cell. Although the hypothetical signal is drawn as diffusible, a membrane-bound signal is equally possible. Furthermore, the \textit{glp-1} receptor is proposed to be activated by the signal and to generate an

![Figure 4](https://example.com/figure4.png)

**Figure 4** A model for the control of germline proliferation. The distal tip cell is shown as producing a diffusible signal that activates \textit{glp-1}, which is expressed on the surface of the syncytial germ line. The activation of \textit{glp-1} triggers a transduction pathway that results in mitosis. \textit{glp-1} is not activated in regions of the germ line that are more distant from the distal tip cell, resulting in the entry into meiosis.
intracellular second messenger, which in turn activates mitosis, e.g. by stimulating a p34/cdc2-like (56) activity. One simple modification of this general model incorporates the idea that the extracellular matrix may negatively regulate the glp-1 receptor (55). In this case, the primary function of the signal might be to interfere with the negative regulatory interaction between glp-1 and the extracellular matrix. Clearly the model of Figure 4 is speculative and other mechanisms are conceivable. For example, the glp-1 protein might act by stabilizing a receptor rather than by functioning as one itself. Alternatively, there may be no signal; the glp-1 protein might be in dynamic equilibrium between a free activated state and an inhibited state in which it is bound by a negative regulator (e.g. the extracellular matrix).

Given that lin-12 is so similar to glp-1 in structure and function, one might think that the model presented for induction in Figure 4 might also apply to lateral signaling. To some degree this is true, but lateral signaling differs from induction in an important way. In induction, the two interacting cells are distinct at the outset, whereas in lateral signaling, they are the same. Therefore, some additional mechanism must be postulated to generate two different cells. One such mechanism has been proposed by Seydoux & Greenwald (67), who suggest that each equivalent cell initially produces both the lin-12 receptor and a limited amount of signal, but not enough signal to activate lin-12. At some point, one of the cells begins to produce enough signal to activate lin-12 in the apposing cell, either because of random fluctuation or because of some bias imposed by position or lineage. The activated lin-12 stimulates a negative regulatory circuit that down-regulates its own signal production, resulting in the establishment of two distinct cell types.

**Genes Regulating the VH/SH Decision**

The genes that regulate the VH/SH decision can be placed in two categories based on the phenotypes of loss-of-function or reduced function alleles. First, mutations in six genes, lin-2, lin-3, lin-7 (35), lin-10, let-23 (18), and let-60 (7, 26), have a Vulvaless (Vul) phenotype. In Vul mutants, most vulval precursor cells follow the SH fate (78). Second, mutations in three genes, lin-1 (35), lin-13, and lin-15 (18), have a Multivulva (Muv) phenotype. In Muv mutants, most vulval precursor cells adopt a VH fate (either VH1 or VH2) (78). In strong Muv mutants, all vulval precursor cells execute VH fates, even in the absence of the anchor cell (20). In addition, recessive mutations in certain pairs of genes (e.g. lin-8 and lin-9) result in a Muv phenotype (see below); these are termed the SynMuv loci, because of the synthetic nature of the Muv phenotype (19, 35).

**MOSAIC ANALYSIS OF vul AND Muv GENES** Based on laser ablation experiments (43, 70, 80), the Vul and Muv genes might be predicted to act
either in the anchor cell as part of the signaling mechanism or in the vulval precursor cells as part of the receiving mechanism. Because the phenotypes of the Muv mutants are essentially anchor cell-independent (20), the prediction was that the Muv genes might act in the vulval precursor cells. To date this prediction has been tested for only one gene, lin-15, with surprising results. In a landmark study, Herman & Hedgecock found that expression of the wild-type lin-15 gene in the vulval precursor cells is neither necessary nor sufficient to rescue the lin-15 Muv phenotype (31). This result, in combination with an analysis of which cells do need to express lin-15 to ensure normal vulval development, led them to speculate that lin-15 is normally expressed within the syncytial hypoderm (hyp7), where it would act to repress the VH fates in the adjoining vulval precursor cells. By this model, the anchor cell would function by relieving repression from the surrounding hypodermis. The anchor cell could accomplish this by sending an overriding signal to the vulval precursor cells or by down-regulating lin-15 (and/or other Muv genes) within hyp7. An alternative model is that hyp7 might relay the inductive signal from the AC to the vulval precursor cells, in which case lin-15 would function by preventing expression/transmission of the inducing signal. Additional studies are needed to distinguish among these models.

SUPPRESSORS OF lin-15  In an effort to identify additional loci required for the VH/SH decision, suppressors of the lin-15 Muv phenotype have been isolated (7, 26). Among the lin-15 suppressors, alleles of let-60, a gene previously identified by recessive lethal mutations (12, 64), were obtained. Some lin-15 suppressor alleles are recessive Vul or recessive lethal (7) and others are both dominant Vul and recessive lethal mutations (7, 26). A separate class of dominant let-60 mutations [previously thought to define a separate gene, lin-34 (18)] cause a Muv phenotype (7). Together, these data suggest that the activity state of let-60 acts as a switch, with a high level being necessary and sufficient for the induction of VH fates and a low level resulting in the SH fate.

Weak alleles of let-23, another gene first identified by recessive lethal mutations (69), were also obtained as suppressors of lin-15 (3). These weak let-23 alleles have a Vul phenotype. Significantly, the dominant Muv alleles of let-60 are epistatic to the Vul let-23 mutations (26). The analysis of the coding sequences of let-60 and let-23 (see below) has provided a credible biochemical basis for this relationship.

MOLECULAR CHARACTERIZATION OF Vul AND Muv GENES Recent molecular data provide insight into the functions of two Vul genes. First, let-23 encodes a member of the EGF receptor subfamily of receptor tyrosine kinases (2). Although the tissue within which let-23 functions is unknown, an
exciting possibility is that *let-23* is the receptor for the anchor-cell signal. Second, the *let-60* gene encodes a protein homologous to mammalian *ras* (27). All five dominant Muv mutations of *let-60* are associated with a change in amino acid 13, which is comparable to one of the alterations of mammalian *ras* resulting in oncogenic activation (7). Because *let-60* dominant Muv mutations are epistatic to *let-23* Vul mutations (26), *let-60* is likely to function downstream from *let-23* in a pathway of signal transduction that specifies VH fates. Only one other Muv/Vul gene has been cloned and sequenced: *lin-10* encodes an apparently unique protein (41). Therefore, the analysis of these genes will provide more than a genetic model for known proteins. It will reveal new activities involved in either the function or regulation of well-known proteins such as *ras*.

A MODEL FOR VULVAL INDUCTION Classically, the functional relationships among regulatory genes have been deduced from double mutant experiments. However, in the case of the Muv and Vul genes, the interpretation of such experiments is considerably hampered by the inability to use null mutations (45). Certain Muv and Vul genes have a lethal null phenotype, which means that only partial loss-of-function or gain-of-function mutations can be used for epistasis. Other Muv and Vul genes have not been sufficiently characterized to know the nature of their mutations. Therefore, much of the double mutant data remains difficult to interpret, although certain double mutants (see below) have helped our understanding of how these genes may interact.

Figure 5 presents a speculative model for the genetic control of the VH/SH decision, based largely on proposals made by several investigators, notably Hedgecock, Herman, Horvitz, and Sternberg. The key results essential to the model are as follows: (a) all Muv mutants are anchor-cell independent (20) and thus these genes are unlikely to function as part of the mechanism by which the anchor cell signals the vulval precursor cells. (b) *lin-15* appears to act in hyp7 (31). Since the *lin-15* locus has components required for both functionally redundant Muv pathways identified by the SynMuv genes (19), we suggest in Figure 5 that all Muv genes (Muv and SynMuv) direct an interaction between hyp7 and the vulval precursor cells that normally promotes SH or inhibits the VH fates. Some Muv genes, e.g. *lin-15*, may act in hyp7 while others act in the vulval precursor cells. Indeed, some Muv genes (including *lin-15*) may act in both hyp7 and the vulval precursor cells. (c) *let-23* is similar to the EGF receptor, which stimulates proliferation in mammalian cells (2). This gene is therefore a good candidate for the receptor of the anchor cell signal and is placed in the vulval precursor cells as part of the mechanism for stimulating the VH fate. (d) Dominant gain-of-function mutations of *let-60* are epistatic to partial loss-of-function mutations of *let-23* (26). Therefore, *let-60* appears to act downstream of *let-23* in the pathway.
stimulating the VH fate. (e) Partial loss-of-function mutations of the Muv gene, *lin-15*, are epistatic to putative null mutations in three Vul genes, *lin-2*, *lin-7*, and *lin-10* (20). Although a simple interpretation of this result is that *lin-15* acts downstream of these three Vul genes, another interpretation, which takes into account the fact that *lin-15* may act in hyp7, is that the Muv pathway is antagonistic to the Vul pathway. By this model, when the Muv pathway is defective, certain components of the Vul pathway are unnecessary.

Further investigations of the VH/SH decision will test the primary tenets of the model shown in Figure 5. Both the involvement of hyp7 in repressing the VH fate and the action of *let-23* in the vulval precursor cells to stimulate the VH fate remain speculative. Mosaic analyses and localization of the proteins involved will provide important tests for each of these hypotheses. The idea that *let-23* encodes the receptor for the anchor-cell signal stands as one of the central features of this model and the identification of this signal will be essential for understanding how vulval fates are induced.

**pal-1**

The fates of the V1–V6 cells of the male lateral hypodermis (see above) are subject to several genetic controls. In part, the decision between an anterior (seam cell) fate and a posterior (sensory ray) fate is determined by the position...
of a cell along the antero-posterior axis. The perception of this position appears to be antagonistically regulated by two genes, *lin-22* and *mab-5*, the latter of which encodes a homeodomain containing protein (14, 38). The best evidence that the decision between sensory ray and seam cell fates is also regulated by direct cell interactions comes from studies of *pal-1* mutants (for *posterior alae*) (85). In loss-of-function *pal-1* mutants, the V6 cell produces seam cells instead of rays. However, if the posterior neighbor of V6 (T) is ablated, V6 produces its normal complement of rays. To explain these results, Waring & Kenyon propose that T sends a signal to V6, causing it to produce alae instead of rays and that this signal is normally rendered ineffective, or “silenced”, by *pal-1* (85). Mosaic analysis indicates that the silencing of this signal requires wild-type *pal-1* activity within V6, but not T (84). Since *pal-1* encodes a homeodomain containing protein (84), Waring & Kenyon suggest that *pal-1* acts within V6 (or its descendants), either to prevent the expression of genes required for the transduction of a signal from T or to promote the expression of genes (e. g. *mab-5*) that are required for the production of rays. Similar signaling and silencing events may regulate the fates of other cells within the lateral hypodermis.

**Other Genetic Pathways**

We have focused above on the genetic analysis of cell interactions for which most is known both at the cellular and genetic levels. Here we mention two other pathways that may also provide insight into how signal transduction pathways regulate cell fate.

**SEX DETERMINATION** The genetic pathway controlling the sexual phenotype of the soma in *C. elegans* is one of the best understood regulatory pathways in this organism (33, 83). Essentially, a cascade of genes interprets the X/A ratio to set the activity state of a master regulator, *tra-1*. The *tra-1* gene functions cell-autonomously (36) and appears to encode a transcription factor (D. Zarkower, J. Hodgkin, personal communication). If *tra-1* is active, the soma is female; if it is inactive, the soma is male. Genetic and molecular analyses of the sex-determining genes indicate that cell interactions may be involved in the regulatory cascade. A gene mediating an early step in the pathway, *her-1*, acts nonautonomously (C. Hunter, W. B. Wood, personal communication) and encodes a small protein with an apparent signal sequence (M. Perry, W. B. Wood, personal communication). The *tra-2* gene, which is regulated by *her-1*, appears to encode a membrane protein (P. Kuwabara, J. Kimble, unpublished). Together, these data raise the intriguing possibility that *tra-1* activity depends on a signal transduction event mediated by *her-1* and *tra-2*. 
DAUER DEVELOPMENT If growth conditions are favorable, larval development consists of four stages (L1–L4). However, if overcrowded or starved, an animal will enter a facultative stage, called a dauer larva, at the second molt (reviewed in ref. 62). Environmental stimuli, received by sensory neurons in the head called amphids, are transmitted to divert development into the dauer pathway (reviewed in refs. 6, 62). The decision to develop as a dauer larva is regulated by a set of 20 daf genes that have been ordered into a pathway (6, 61, 63). Two genes that when mutant lead to constitutive dauer formation have recently been found to encode receptor protein kinases (21; D. Riddle, personal communication). The sites of action of these receptors are not known. Two reasonable possibilities are that they might be involved in transduction of environmental cues leading to dauer formation or the neural integration of this signal.

CONCLUSIONS, SPECULATIONS, AND PROSPECTS

What progress have we made over the past decade towards understanding the genetic control of cell interactions during development in *C. elegans*? In this section we present what we consider to be the most important conclusions that have emerged and discuss their implications, both for the evolution of these controls and for the direction of future investigations.

(a) Cell interactions play a significant role in regulating development in *C. elegans*. Although the first cell interactions identified in *C. elegans* were considered to be exceptions to rule by ancestry (43, 48, 80), the continued discovery of interactions, including embryonic induction (60) and control of left-right asymmetry (89), have demonstrated that this organism much like other metazoans in its reliance on cell interactions during development.

(b) The molecular controls of cell interactions in *C. elegans* are homologous to those in other metazoans, including higher vertebrates. In the past year, two genes from *C. elegans* that regulate vulval interactions, *let-23* and *let-60*, have been shown to be similar to the EGF receptor and *ras* of higher organisms (2, 27). Furthermore, vertebrate members of the LNG family were discovered during that same period (13; G. Lemke, personal communication; J. Sklar, personal communication). This similarity implies that at least some molecular mechanisms regulating cell interactions during metazoan development may have evolved in a progenitor to both nematodes and vertebrates.

The molecular similarity between nematode regulators and the vertebrate signal transduction machinery promises to be very informative. In ver-
terbrates, the developmental role of EGF and EGF receptor is not understood. Known vertebrate mutations in EGF receptor cause a gain of gene function and therefore may be misleading with regard to the normal role played by this gene during development (10). An understanding of how a protein similar to EGF receptor controls interactions in worms will provide ideas about how the EGF receptor may work in vertebrates. In addition, the functional relationship between tyrosine kinase receptors and ras has proven to be virtually intractable to date. The similarities of let-23 and let-60 to these proteins provide a genetic inroad into the problem. Furthermore, the discovery of previously undescribed proteins, such as that encoded by lin-10 (41), will certainly help to identify additional components involved in this type of transduction event.

(c) Induction and lateral signaling rely, at least in part, on the same molecular mechanism. The glp-1 and lin-12 genes are similar in structure (5, 91) and appear to be functionally interchangeable in some contexts (51, 55a, 67). Yet glp-1 primarily regulates inductive events (4, 59) and lin-12 primarily regulates lateral signaling (25, 70, 75). Furthermore, lag-1 and lag-2 mediate both inductive and lateral signaling types of interactions. Therefore this classification is likely to be artificial when viewed from the perspective of molecular mechanism.

(d) Cell interactions can be negatively regulated or "silenced". Interactions that are regulated in this manner were first detected in mutant backgrounds, e.g. pal-1(If) (85) or lin-12(0) (68). These findings suggest that the wild-type function of pal-1 and lin-12 is, at least in part, to prevent or silence a cell interaction. The extent to which the silencing of cell interactions is used for developmental regulation is not yet known.

(e) Many genes identified by their regulation of one cell interaction control other interactions as well. Such pleiotropy has important consequences for the genetic analysis of these genes. For example, the effect of glp-1 on pharyngeal induction was not appreciated until an unusual glp-1 allele was isolated in which some animals escaped the germline and hypodermal defects (59). Similarly, the role of let-23 and let-60 in cell interactions was unknown until weak alleles were isolated that had specific vulval defects (7, 18, 26). These findings underscore the necessity of analyzing weak alleles in addition to null alleles. Both kinds of mutation are informative and useful.

(f) Redundancy is not uncommon among genes controlling cell interactions. Good examples are the requirement for either lin-12 or glp-1 during embryogenesis (51) and the SynMuv genes in vulval development (19). Redundancy can make the identification of genes by mutation extremely difficult. Their discovery depends on the identification of rare double mutants (35) or dominant alleles (24, 57). Furthermore, partial redundancy can delay identification of other genes functioning in the same process.
Thus, for \(\text{lin-12}\) and \(\text{glp-1}\), finding the \(\text{lin-12 glp-1}\) double mutant phenotype allowed identification of the two \(\text{lag}\) genes, which are required for both \(\text{glp-1}\) and \(\text{lin-12}\) action (51).

(g) Regulators that are similar at the molecular level can have both overlapping and unique functions during development. For example, \(\text{glp-1}\) and \(\text{lin-12}\) are homologs that are redundant during embryogenesis (51) but have distinct roles postembryonically (4, 25, 59). The molecular basis of the separate developmental roles played by such similar genes may rely on gene-specific regulation (e. g. differences in expression) or partially divergent functions.

(h) The extracellular matrix is likely to influence genes that regulate cellular interactions. The idea that the extracellular matrix plays a critical role in controlling development is not new (see ref. 82); however, little genetic evidence has accrued to support it. The finding that mutant collagens alter the activity of \(\text{glp-1}\) provides supporting in vivo evidence and may provide a genetic model for dissecting the role of the extracellular matrix in regulatory cell interactions (55).

**CONCLUDING REMARKS**

The powerful molecular genetics of *C. elegans* coupled with the simplicity of its anatomy and development has provided a remarkable experimental accessibility for the analysis of regulatory cell interactions during development. Over the past decade it has become clear that interactions dictating development in *C. elegans* are similar both in scope and type to those analyzed in other metazoans, including both invertebrates and vertebrates. In addition, the idea is emerging that the molecular controls of nematode cell interactions are similar to those present in vertebrates. We can therefore look forward during the next decade to an increasingly productive interplay between the molecular genetic analysis of cell interactions during development and the biochemical analysis of signal transduction in vertebrate cells.

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