ELT-1, a GATA-like transcription factor, is required for epidermal cell fates in *Caenorhabditis elegans* embryos

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Epidermal cells are generated during *Caenorhabditis elegans* embryogenesis by several distinct lineage patterns. These patterns are controlled by maternal genes that determine the identities of early embryonic blastomeres. We show that the embryonically expressed gene *elt-1*, which was shown previously to encode a GATA-like transcription factor, is required for the production of epidermal cells by each of these lineages. Depending on their lineage history, cells that become epidermal in wild-type embryos become either neurons or muscle cells in *elt-1* mutant embryos. The ELT-1 protein is expressed in epidermal cells and in their precursors. We propose that *elt-1* functions at an early step in the specification of epidermal cell fates.

[Key Words: *C. elegans*; hypodermal cells; cell fate specification; lineage patterns; GATA transcription factor]

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Recent studies have identified some of the maternally expressed genes that pattern the early *Caenorhabditis elegans* embryo (for review, see Kemphues and Strome 1997; Schnabel and Priess 1997). However, there is very little molecular information about the embryonically expressed genes that presumably are regulated by these maternal genes and that lead to tissue-specific differentiation. In the present study, we provide evidence that the embryonically expressed gene *elt-1* functions in the specification of a major tissue in *C. elegans*, the epidermis.

The epidermis consists of a simple layer of cells, one cell thick. The apical surface of each cell is encircled by an adherens junction, so that adjacent cells are linked together; the basal surface overlies a basement membrane. Historically, nematode epidermal cells have been called hypodermal cells because an extracellular cuticle covers the apical surface of these cells. In *C. elegans*, hypodermal cells arise from several different branches of the embryonic lineage. Both blastomeres, AB and P₁, of the two-cell-stage embryo produce several hypodermal cells. The lineage patterns by which AB and P₁ produce hypodermal cells, however, are very different. Whereas most of the nonhypodermal descendants of AB become neurons or pharyngeal cells, most of the nonhypodermal descendants of P₁ become intestinal cells or body-wall muscle cells.

Genetic and experimental studies have shown that the early molecular events that lead to hypodermal specification of P₁ descendants are different from the events that specify hypodermis from AB. The maternally expressed gene *pal-1* is required for P₁ to produce hypodermal cells as well as other cell types (Hunter and Kenyon 1996). In contrast, *pal-1*(+) is not required for AB descendants to produce hypodermal cells. *pal-1* encodes a transcription factor with sequence similarity to *Drosophila* CAUDAL (Waring and Kenyon 1991), and the PAL-1 protein is present in the nuclei of P₁ descendants, but not AB descendants (Hunter and Kenyon 1996).

The hypodermal fates of AB descendants are determined by a combination of cell-cell interactions (Priess et al. 1987; Gendreau et al. 1994; Hutter and Schnabel 1994; Mango et al. 1994; Mello et al. 1994; Hutter and Schnabel 1995). During the two-cell stage of embryogenesis, the P₁ blastomere appears to influence the development of the AB blastomere such that AB acquires the ability to produce both hypodermal and neuronal cell types (Hutter and Schnabel 1995). In the next few cell divisions, two additional cell-cell interactions determine which specific AB descendants will produce predominantly neurons and which will produce predominantly hypodermal cells. These latter two interactions are both mediated by maternal expression of the *glp-1* gene (Priess and Thomson 1987; Hutter and Schnabel 1994; Mello et al. 1994; Moskowitz et al. 1994). The GLP-1 protein is a transmembrane receptor similar to *Drosophila* NOTCH and *C. elegans* LIN-12 (Yochem and Greenwald 1989). GLP-1 is expressed in AB and its daughters, but not in P₁ or in P₁ daughters (Evans et al.

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1994). Thus, the production of hypodermal cells by AB and P_1 is influenced initially by distinct genetic pathways involving GLP-1 and PAL-1, respectively.

Maternally expressed genes like *glp-1* and *pal-1* define identities of early embryonic blastomeres; they initiate the complex patterns of cell division and differentiation that distinguish the blastomeres. These maternal genes must directly or indirectly activate new transcription, leading to blastomere-specific expression of the embryonic genome. In this report we show that mutations in the *elt-1* gene, which was shown previously to encode a GATA-like transcription factor of unknown function (Spieth et al. 1991), is required for the embryo to produce hypodermal cells. We find that the ELT-1 protein is expressed in the early embryo in both AB and P_1 -derived hypodermal precursors. We show that cells that produce hypodermis in wild-type embryos produce nonhypodermal cell types in *elt-1* mutant embryos, and that the specific fates of these transformed cells depend on whether they are descendants of AB or P_1 . Thus, *elt-1* identifies a point of convergence between the initially distinct pathways AB and P_1 use to produce hypodermal cells.

Background

C. elegans embryogenesis begins with a period of rapid cell proliferation. Near the end of this period, cells on the dorsal and dorsal-lateral surfaces of the embryo become visibly different from all other cells (Fig. 1A). The dorsal cells cease division, flatten and spread, and become linked through adherens junctions (Fig. 1B). These cells differentiate as hypodermal cells. Cells on the ventral surface of the embryo undergo one to three additional divisions; almost all of these cells differentiate as neurons or neuronal support cells (Fig. 1A). The hypodermal cells spread ventrally (Fig. 1C) and anteriorly until they enclose the embryo, thus forming a continuous epithelial surface called the hypodermis.

Two basic types of hypodermal cells, major and minor, have been described (Gendreau et al. 1994). The major and minor classes were used originally to distinguish between AB-derived descendants. All P_1 -derived hypodermal cells, however, have characteristics of the major class, and, in this paper, are included in the major class. There are 71 major hypodermal cells; these are large cells that are born at the 9th round of embryonic cleavage and that cover most of the body surface. There are 11 minor hypodermal cells; these are relatively small cells that are born at the 10th round of cleavage and that form specialized syncytia at the head and tail. Analysis of the *C. elegans* cell lineage has shown that major hypodermal cells originate from four blastomeres in the 12-cell stage embryo (Fig. 1D; Sulston et al. 1983). The AB-derived descendants are ABarp, ABpla, and ABpra; the P_1 -derived descendant is C. Each of these blastomeres undergoes an additional five rounds of cell division before generating major hypodermal cells.

Figure 1. Positions and origins of the major hypodermal cells. (A) Scanning electron micrograph of the lateral surface of an embryo about 270 min postfertilization. The large rectangular cells on the dorsal (top) and dorsolateral surfaces are major hypodermal cells. The arrow points to the leading edge of one of several cells in the ventralmost row of hypodermal cells; these cells are in the process of spreading ventrally. The arrowhead indicates the anterior-most cell in the row of lateral, or seam, hypodermal cells. Surface cells anterior (left) and ventral (below) of the hypodermal cells are predominantly neuronal precursors that will be covered as the hypodermal cells spread across and enclose the embryo. (B) Immunofluorescence micrograph of an embryo stained with mAb MH27 to visualize adherens junctions. The age, orientation, and labeling of the embryo is the same as in A. Note that adherens junctions are present only at points of contact between hypodermal cells. (C) Embryo at 310 min postfertilization after the hypodermal cells have enclosed the ventral, but not anterior, body surface. The labeling and orientation of the embryo are as in A. (D) Diagram of a 12-cell stage embryo indicating the four hypodermal precursors described in this paper; each of these blastomeres produces large numbers of hypodermal cells in addition to other cell types (Sulston et al. 1983). Embryos are ~45 μ m in length.

Results

Isolation of *elt-1* mutations

In screens for recessive, embryonic-lethal mutations affecting tissue development, we found three mutants,

zu180, *zu220*, and *zu228*, that appeared by light microscopy to have no hypodermal cells but more neurons than wild-type embryos. Genetic analysis showed that all three mutants are defective in the same gene (see Materials and Methods). The *zu180* mutation was mapped to chromosome IV between *fem-3* and *daf-14* (Fig. 2). Cosmids covering this region were obtained from the *C. elegans* Genome Project and were tested for their ability to rescue the *zu180* lethality (see Materials and Methods). We found that each of the overlapping cosmids W03E7, T01G2, and T12F9 has rescuing activity. Analysis of the rescuing DNA fragments showed that each contains a gene called *elt-1*. Because no mutations in *elt-1* had been described previously, we tested whether the *zu180* embryonic phenotype could be phenocopied by injection of antisense *elt-1* RNA into the gonads of wild-type hermaphrodites (Guo and Kemphues 1995). The injected hermaphrodites produced inviable embryos that appeared identical to *zu180* mutants (see below), indicating that *zu180* was likely to be a mutation in the *elt-1* gene.

elt-1 was identified initially by its similarity to genes that encode GATA-like, zinc-finger transcription factors (Spieth et al. 1991). This family of transcription factors has been implicated in the specification of tissue type in vertebrates (Orkin 1992). The predicted ELT-1 protein contains two possible zinc finger domains and is 60% identical in these domains to vertebrate GATA factors, such as GATA-1, 2, and 3 from mouse. We sequenced the *elt-1* gene from the *zu180* strain and found that it contains a stop codon that would truncate the predicted ELT-1 protein after the first finger domain, confirming that *zu180* is a mutation in *elt-1*.

elt-1 mutants lack hypodermal cells

Homozygous *elt-1* mutants do not undergo body morphogenesis (Fig. 3, cf. D with C), a process that normally

requires hypodermal cell function (Sulston et al. 1983; Priess and Hirsh 1986). Major hypodermal cells can be identified on the surface of a wild-type embryo by their large, flat nuclei and prominent nucleoli (Fig. 3C,E). An *elt-1* mutant contains few, if any, candidates for being hypodermal cells by these morphological criteria. Instead, the surface of an *elt-1* mutant is covered with numerous cells that, by light microscopy, resemble neurons (Fig. 3D,F). Internal tissues in an *elt-1* mutant, such as the pharynx and intestine, appear to contain the normal numbers and types of cells (Fig. 3, cf. B with A). Other cell types such as neurons, muscle cells, (see below) and germ cells (data not shown) also are present in an *elt-1* mutant. Therefore, mutations in the *elt-1* appear to cause a loss of hypodermal cells, but do not affect the ability of the embryo to produce several other tissue types.

We examined *elt-1* mutant embryos with molecular markers to confirm the absence of hypodermal cells. In wild-type embryos, adherens junctions surround the apical margins of hypodermal cells, intestinal cells, and some pharyngeal cells; these adherens junctions can be visualized by staining with the antibody MH27 (Priess and Hirsh 1986; Waterson 1988). Wild-type and *elt-1* mutant embryos appear to have identical pharyngeal and intestinal MH27 staining patterns (Fig. 3, cf. G with H). However, whereas wild-type embryos have ~60 hypodermal cells that stain with MH27 (Fig. 3I), *elt-1* mutant embryos contain few or no cells with a hypodermal-like staining pattern (Fig. 3J). In *elt-1* mutants, the few non-pharyngeal or nonintestinal cells that show MH27 staining are small cells of undetermined identity (see Discussion). For a second hypodermal marker, we used the *lacZ* fusion construct *wIs1* that is expressed in wild-type embryos in the lateral group of major hypodermal cells; these 20 cells are called seam cells (Gendreau et al. 1994; see Materials and Methods). We found that *elt-1* mutants

Figure 2. Molecular cloning of *elt-1*. The *zu180* mutation maps near the *elt-1* gene on chromosome IV and is complemented by the chromosomal deficiencies eDf18 and mDf7, but not by eDf19. *zu180* mutants were rescued with the cosmids W03E7, T01G2, T12F9, and the phage BL#YH9; all of which contain *elt-1*. Rescue was not obtained with W05D7 that does not contain the *elt-1* gene. The *elt-1* gene is oriented 5' to 3'; exons are boxed; regions encoding zinc-finger domains are shaded. *zu180* is a nonsense mutation in tryptophan 283. Map of *elt-1* is from Spieth et al. [1991].

Figure 3. Comparison of wild-type embryos (left) with *elt-1* mutant embryos (right). (A–F) Nomarski photomicrographs taken at focal planes through the interior (A,B), and at the surface (C,D) of each embryo. Arrows in A and B indicate the base-membrane that surrounds the pharynx. (E,F) High magnification views of the surfaces of embryos shown in C and D, respectively. Hypodermal cells have large nuclei with clear nucleoplasm and prominent nucleoli; several hypodermal nuclei are indicated in E (arrows). Neurons are small cells that have processes and granular nucleoplasm; cells with neuronal morphology are indicated in F (arrows). (G–J) Immunofluorescence micrographs showing adherens junctions in the interiors (G,H) and surfaces (I,J) of fixed embryos after staining with mAb MH27. (G,H) Long arrows point to adherens junctions in the corpus of the pharynx (Albertson and Thomson 1976); short arrows point to adherens junctions in the intestine. Cell margins of the individual major hypodermal cells are apparent at the surface of the wild-type embryo (I); a hypodermal cell is indicated by the asterisk. Dots along the dorsal perimeter of the embryo in G correspond to optical cross-sections through the adherens junctions of the hypodermal cells. In the *elt-1* embryo (J), no major hypodermal cells are visible; however, a few small cells show MH27 staining. The wild-type embryo shown in A and C was allowed to develop for 7 hr at 22°C, at which time the surface is covered by major hypodermal cells that are differentiated. The *elt-1* embryo in B and D developed for 12 hr to allow the surface cells to finish division and differentiation. Embryos shown in G–J were each allowed to develop for 6 hr.

carrying this marker do not have detectable *lacZ* expression (data not shown). Thus, we conclude that *elt-1* mutants have a defect in either the differentiation or specification of hypodermal cells.

elt-1 mutant embryos appear by light microscopy to contain more neurons than are visible in wild-type embryos. To extend this observation, we stained *elt-1* mutants with the neuron-specific antibody anti-UNC-33; this antibody stains the cytoplasm of apparently all classes of neuronal cells (J. Shaw, pers. comm.). Although we could not accurately count the numerous cells stained with anti-UNC-33 in whole-mount preparations, the *elt-1* embryos (Fig. 4B) appear to have many more positively stained cells than do wild-type embryos (Fig. 4A). This result, combined with the lack of hypodermal markers in *elt-1* mutants, suggests that loss of *elt-1* activity may cause a transformation of some hypodermal precursors into neuronal precursors.

ABa-derived hypodermal precursors become neuronal precursors in elt-1 embryos

Twelve of the 20 seam hypodermal cells are produced by an AB descendant called ABarp (Sulston et al. 1983; Fig. 1). Because these hypodermal cells are not detectable by seam cell-specific *lacZ* expression in *elt-1* mutants, we examined the development of the ABarp blastomere by light microscopy and video recording. Results of this lineage analysis indicate that the cell division pattern of ABarp in *elt-1* mutants is different from the wild-type pattern (Fig. 5A). The first difference we observe between the wild-type and *elt-1* lineage patterns occurs ~220 min postfertilization. In wild-type embryos, four ABarp descendants undergo unequal divisions in which the large

Figure 4. Neurons in wild-type (left) and *elt-1* mutant embryos (right). (A,B) Immunofluorescence micrographs of wild-type and *elt-1* mutant embryos that developed for 6 hr at 22°C before fixation and staining with the neuronal marker anti-UNC-33. (C,D) Expression of the neuronal marker H2O-GFP in wild-type (C) and *elt-1* mutant (D) embryos in which the only blastomeres allowed to develop were ABarp and ABalp (see Materials and Methods).

Figure 5. Lineage differences between wild-type and *elt-1* mutant embryos. Examples are given of three representative lineages, ABarp, ABpla, and Cpa in wild-type and *elt-1* embryos. The horizontal lines on the lineage diagrams indicate cell divisions and the vertical axes represent time between divisions. Time 0 is at fertilization. Cell divisions observed in *elt-1* embryos that are not present in wild-type embryos are indicated by arrows. Note that divisions that are unequal in wild type, as indicated by < or > signs, are equal (=) in *elt-1*. These data are a summary from six *elt-1* embryos. Not all cells could be followed in each embryo; all lineage data presented here were observed in at least two embryos. (S) Neuronal support cell; (H) hypodermal cell; (N) neuron; (X) cell death; (?) undetermined. Data for wild-type lineages taken from Sulston et al. (1983).

220 min begin to flatten and spread, differentiating as hypodermal cells; these cells do not divide again during embryogenesis (Fig. 5A). In *elt-1* mutants, these ABarp descendants remain rounded instead of flattening, and undergo at least one additional division, producing cells with a neuronal morphology (Fig. 5A; additional divisions indicated by arrow). The extra cell divisions in *elt-1* mutants occur at a time when several blastomeres in wild-type embryos are dividing to produce neurons (Sulston et al. 1983). The abnormal ABarp lineage in *elt-1* mutants, however, is not identical in detail to the lineage pattern of any wild-type blastomere.

To determine whether the additional descendants of ABarp were becoming neurons in *elt-1* mutants, we asked if these descendants express the neuronal marker H2O-GFP. This marker consists of a neuronal-specific promoter fused to a gene encoding the green fluorescent protein (GFP) with a nuclear localization signal; wild-type nematodes carrying the H2O-GFP transgene show fluorescence in most neurons (T. Ishihara and I. Katsura, pers. comm.; see Materials and Methods). We examined the expression of H2O-GFP in operated embryos in which all blastomeres except ABarp and ABalp were killed with a laser microbeam. In wild-type development, cell-cell interactions cause ABalp to adopt a different fate from that of ABarp (Hutter and Schnabel 1994; Mello et al. 1994). Our ablation strategy, however, prevents these interactions such that both ABalp and ABarp adopt the fate of ABarp. We found that the laser-operated wild-type embryos produce many hypodermal cells as expected, and only about seven H2O-GFP-positive neurons. In contrast, operated *elt-1* mutants produce an average of 28 H2O-GFP-positive neurons, and no cells resembling hypodermal cells (Fig. 4C,D; Table 1). Thus, we conclude that *elt-1* function is necessary for the wild-type development of ABa-derived hypodermal cells and that loss of *elt-1* activity leads to this blastomere producing neurons instead of hypodermal cells.

daughter becomes a hypodermal cell and the small daughter becomes either a neuroblast or a neuronal support cell (Sulston et al. 1983). In *elt-1* mutants, these four ABarp descendants divide equally.

In a wild-type embryo, 22 of the ABarp descendants at

ABp-derived hypodermal precursors are transformed in elt-1 mutants

The ABp-derived blastomeres ABpra and ABpla produce a total of 36 major hypodermal cells in wild-type em-

Table 1. Number of neurons produced by isolated blastomeres

Blastomeres	Wild type	<i>elt-1(zu180)</i>
ABarp and ABalp	7 ± 2 (<i>n</i> = 48)	28 ± 7 (<i>n</i> = 17)
C	0 ± 0 (<i>n</i> = 15)	0 ± 0 (<i>n</i> = 11)

Blastomeres were isolated, allowed to develop, and examined for H2O-GFP expression. Details of blastomeres isolation are in Materials and Methods.

bryos. We examined the development of these blastomeres in *elt-1* mutants and found that they have abnormal patterns of cell division, similar to that of ABarp, the ABa-derived blastomere (Fig. 5, cf. B to A). ABp descendants that become hypodermal cells in wild-type embryos undergo an extra division in *elt-1* mutants, and the cells produced by these extra divisions do not resemble hypodermal cells. We isolated the ABp blastomere by laser-ablation experiments (see Materials and Methods) and examined the amount of neuronal tissue produced by H2O-GFP expression. In contrast to ABa, ABp does not appear to produce extra neurons in the *elt-1* mutant. In similar experiments we tested whether ABp produces muscle cells instead of hypodermal cells in *elt-1* mutants by use of the muscle-specific marker *hlh-1*-GFP (K. Dej, S. Xug, and A. Fire, pers. comm.), and found that ABp does not produce extra muscle cells. We conclude that *elt-1* is required for the specification of major hypodermal cells from the ABp blastomere. In *elt-1* mutants, however, ABa and ABp descendants have different transformations in cell fate.

C-derived hypodermal precursors become muscle precursors in *elt-1* mutants

In wild-type development, the C blastomere produces 13 major hypodermal cells and 32 muscle cells (Sulston et al. 1983). Two C granddaughters, Cpa and Caa, almost exclusively produce hypodermal cells, whereas the other two granddaughters, Cpp and Cap, produce only muscle cells. We examined the lineage of C in *elt-1* mutants and found that both Cpa and Caa descendants undergo an additional round of division, producing cells that do not resemble hypodermal cells in morphology (Fig. 5C shows the lineage of Cpa in both wild-type and *elt-1* mutant embryos). To test whether the abnormal Cpa and Caa descendants are becoming neurons, we examined the expression pattern of the neuronal marker H2O-GFP in laser-operated embryos in which only the C blastomere was allowed to develop. In an operated wild-type embryo, the C blastomere produces numerous hypodermal cells, but no H2O-GFP-positive cells (Table 1). We found that the C blastomere in an operated *elt-1* embryo does not appear to produce hypodermal cells but also does not produce H2O-GFP-positive cells (Table 1). These results suggest that C does not produce extra neurons in *elt-1* mutants.

To test the possibility that the abnormal Cpa and Caa descendants become muscle cells instead of hypodermal cells, we examined the expression of the muscle marker

hlh-1-GFP in *elt-1* mutants. To examine the development of only Cpa and Caa, we killed all other blastomeres with a laser microbeam. Cpa and Caa blastomeres from wild-type embryos (*n* = 19) produce hypodermal cells but do not produce muscle cells, as expected. In contrast, when either Cpa or Caa is isolated in *elt-1* mutants (*n* = 3 and 5, respectively), each blastomere produces an average of 13 muscle cells. Thus, C, ABa, and ABp blastomeres all require *elt-1* to produce hypodermal cells. In the absence of *elt-1* function, however, C produces muscle cells instead of hypodermal cells while ABa produces neurons.

Cell fate transformations in elt-1 mutants are affected by lineage-specific factors

Why do C-derived hypodermal precursors become muscle precursors in *elt-1* mutants while the ABa and ABp-derived precursors adopt nonmuscle fates? The C-derived precursors in *elt-1* mutants could respond to muscle-determining factors that are normally suppressed by *elt-1*(+) activity. These could be position-specific extrinsic factors (Schnabel 1995), or lineage-specific intrinsic factors (Hunter and Kenyon 1996). To ask whether the posterior positions of C-derived precursors affect their pattern of development in *elt-1* mutants, we constructed and examined *mex-3;elt-1* double mutants. In *mex-3* mutants, the lineage-specific transcription factor PAL-1 is misexpressed in AB descendants, causing these anterior blastomeres to adopt C-like fates and produce hypodermal cells and muscle cells (Fig. 6C; Draper et al. 1996; Hunter and Kenyon 1996). If the transformed fates of hypodermal cells in the *elt-1* mutant are caused by position-specific factors, many of these anterior blastomeres in *mex-3;elt-1* mutants would produce neurons, as do ABa descendants in *elt-1* mutants. If the transformed fate depends on lineage-specific factors, however, these anterior blastomeres would be expected to produce muscle cells, as do C descendants in *elt-1* mutants. We found that the anterior region of the *mex-3;elt-1* double mutant lacks hypodermal cells, and instead consists almost entirely of muscle cells (Fig. 6E) with very few neurons (Fig. 6F).

ELT-1 is expressed in hypodermal cells and their precursors

To determine when and where the ELT-1 protein is expressed, antibodies were generated against two regions outside the zinc finger domains of ELT-1 (see Materials and Methods). Antisera against both regions of ELT-1 give identical staining patterns. This pattern is not detected in wild-type embryos stained with preimmune sera, or in *elt-1(zu180)* mutants stained with anti-ELT-1 sera (see Materials and Methods). The 71 major hypodermal cells are born ~260 min postfertilization (about the 365-cell stage); these cells are readily identified in embryos stained for adherens junctions (Fig. 7B). At this stage, ELT-1 is detected in the nuclei of all 71 major hypodermal cells, and is not detected in any other cell type (Fig. 7A,B). Two categories of cells that do not stain

Figure 6. Immunofluorescence micrographs of body-wall muscle cells (*left*) and neurons (*right*) in wild-type (*A,B*), *mex-3* (*C,D*), and *mex-3;elt-1* (*E,F*) embryos. Embryos 6 hr after fertilization at 22°C were fixed and stained with mAb 5.6 to visualize body-wall muscle cells and with anti-UNC-33 to visualize neurons. *mex-3* embryos generate more muscle cells (*C*), but produce less neurons (*D*), than do wild-type embryos (*A* and *B*, respectively). *mex-3;elt-1* embryos produce even more muscle cells than *mex-3* single mutants (cf. *E* with *C*) and only a few neurons (*F*). Arrows point to individual neurons; a neuron has cytoplasmic staining surrounding the nonstaining nucleus.

for ELT-1 should be noted. First, ELT-1 is not detected in the nuclei of minor hypodermal precursors, and is not detected in the nuclei of their descendants later in embryogenesis. Second, ELT-1 is not detected in the nuclei of the nonhypodermal sisters of major hypodermal cells. As the embryo undergoes morphogenesis, ELT-1 levels appear to decrease in the dorsal and ventral hypodermal nuclei but persist at relatively high levels in the lateral, or seam, nuclei (Fig. 7C,E,G); ELT-1 can be detected in these hypodermal seam nuclei throughout the remainder of embryogenesis (data not shown).

The ELT-1 protein first is detected at ~100 min post-fertilization at the 28-cell stage of embryogenesis. ELT-1 is detected in the nuclei of all four C granddaughters but is not detected in any other nuclei (data not shown). Thus, at the 28-cell stage, ELT-1 is present in the two C granddaughters that produce hypodermal cells as well as the two granddaughters that produce only muscle cells. In subsequent stages, ELT-1 can no longer be detected in the C-derived muscle precursors, but is detected in the C-derived hypodermal precursors. In the 44-cell embryo, ELT-1 is detected in the C-derived hypodermal precursors

and in a subset of the 32 AB descendants (Fig. 8A). The developmental time at which staining first is detected for each hypodermal lineage is indicated by an asterisk beside the wild-type lineages in Figure 5. Because there is natural variability in the position of cells at the 44-cell stage (Schnabel et al. 1997) and because additional variability is introduced by our fixation technique, we have not yet been able to identify all of the AB descendants at this stage with certainty. However, the positions and number of cells that express ELT-1 at this stage correlate well with the positions and number of hypodermal precursors present at this stage (Table 2; Sulston et al. 1983). ELT-1 is expressed in the AB descendants through the successive rounds of cell division until

Figure 7. Expression pattern of the ELT-1 protein midway through embryonic development. Immunofluorescence micrographs of wild-type embryos stained with anti-ELT-1 sera (*left*), and with mAb MH27 (*right*) to outline major hypodermal cells. (*A,B*) Dorsal view of an embryo ~260 min postfertilization. The major hypodermal cells have just been born, and the majority of these cells reside on the dorsal surface. ELT-1 is present in the nuclei of all major hypodermal cells at this stage. Note the absence of ELT-1 staining in the anterior neuronal precursors (cf. 1A). The short arrows point to the nucleus of a seam cell in *A–H*. (*C,D*) Dorsal view of an embryo ~300 min postfertilization. A hypodermal cell in the dorsal row is indicated by the long arrow in *D*. ELT-1 staining is strongest in the seam cell nuclei. (*E,F*) Lateral view of an embryo at a similar stage to that shown in *C* and *D*. The ventral row of hypodermal cells have very faint nuclear staining. (*G,H*) Lateral view of an embryo ~400 min postfertilization.

Figure 8. Expression pattern of the ELT-1 protein at the 51-cell stage. Dorsal/lateral view of a wild-type embryo stained with anti-ELT-1 (A) and with DAPI (B) to visualize nuclei. Dorsal/lateral, but not ventral, nuclei show high levels of ELT-1.

the terminal division of the hypodermal cells (Fig. 7A). Thus, ELT-1 is expressed in blastomeres that generate major hypodermal cells and in the major hypodermal cells.

Discussion

elt-1 functions in the specification of the hypodermal cell fate

In this study we have shown that the *elt-1* gene, which encodes a GATA-like transcription factor, is essential for the development of major hypodermal cells in the *C. elegans* embryo. *elt-1* mutants lack cells with morphological and molecular characteristics of major hypodermal cells: In *elt-1* mutant embryos, no cells resembling major hypodermal cells are visible by light microscopy, or are detected with antibodies that recognize the adherens junctions of hypodermal cells. *elt-1* mutants also fail to express a marker specific for seam cells, the lateral group of major hypodermal cells. Other cell types, such as pharyngeal, intestinal, neuronal, and muscle cells are present in *elt-1* mutants, indicating that *elt-1* mutations do not affect the development of most other tissues.

elt-1 may not be required for the development of the minor hypodermal cells that normally form the specialized hypodermis at the termini of the body. *elt-1* mutants contain a few small cells of undetermined identity that are surrounded by adherens junctions. These cells may be minor hypodermal cells, but alternatively could be neuronal support cells that contain adherens junctions and that normally link to the hypodermis. ELT-1 protein is not detected in minor hypodermal cells or their precursors in wild-type embryos, consistent with the hypothesis that *elt-1* activity is not required for the development of these cells.

In principle, genes required for hypodermal development could function at one of several distinct steps in embryogenesis. Such genes could function at the beginning of embryogenesis to determine the identity of early blastomeres that ultimately produce hypodermal cells, they could function later in development to specify the hypodermal cell fate, or they could be required simply to maintain the differentiated state of hypodermal cells. Several maternally expressed genes have been described in *C. elegans* that function in specifying the identity of early blastomeres (Priess 1994). Mutations in these genes often cause the affected blastomere to adopt a pattern of

cleavage and differentiation similar, or identical, to that of a blastomere located elsewhere in the embryo. For example, mutations in the gene *glp-1* can cause ABp to adopt a pattern of development characteristic of ABa (Hutter and Schnabel 1994; Mango et al. 1994; Mello et al. 1994; Moskowitz et al. 1994). In *elt-1* mutant embryos, the ABap, ABpla, and ABpra blastomeres have abnormal lineages; however, these lineage patterns are not identical to any wild-type lineage pattern. Although these blastomeres fail to generate hypodermal cells, other cell types normally generated by these blastomeres are present in *elt-1* embryos. In normal embryogenesis, ABap, ABpla, and ABpra blastomeres produce major hypodermal cells and are the only blastomeres that produce the four specialized touch neurons. In *elt-1* mutant embryos, these four touch neurons are present (B. Page, unpubl.), indicating that *elt-1* is required for only a subset of the cell types generated by these blastomeres.

We propose that *elt-1* activity is required for the specification, rather than for the differentiation or maintenance, of major hypodermal cells. In contrast, the gene *lin-26*, which also is required for hypodermal development in *C. elegans* embryos, appears to function after the hypodermal cell fate is specified. Cells with several characteristic features of hypodermal cells are produced in *lin-26* mutant embryos, however, these cells appear to degenerate (Labouesse et al. 1994). We have shown that mutations in *elt-1* cause precursors that normally produce hypodermal cells to produce neurons or muscle cells instead. This result suggests that in wild-type embryogenesis these precursors are not irrevocably committed to the hypodermal fate prior to *elt-1* function. Thus, *elt-1* likely functions at a time when blastomeres are pluripotent, as expected for a gene involved in specifying cell fate. Molecular studies support the hypothesis that *elt-1* functions upstream of *lin-26*. Chromosomal deficiencies of the *elt-1* region have been shown to prevent the wild-type expression pattern of the LIN-26 protein (Chanal and Labouesse 1997), as do mutations in *elt-1* itself (B.P. unpubl.).

When does *elt-1* function to specify the hypodermal cell fate? The ELT-1 protein is detected in differentiated hypodermal cells as well as in precursors of hypodermal cells. We have evidence that in some hypodermal lineages *elt-1*(+) functions before the birth of the hypodermal cell. In wild-type embryos, these lineages generate hypodermal cells by an unequal cell division; the large daughter differentiates as a hypodermal cell and the

Table 2. Number of ELT-1-positive cells compared with the number of major hypodermal precursors

Approximate developmental time (min)	Total number of cells	ELT-1-positive cells	Hypodermal precursors
100	51 ± 5	18 ± 4 (n = 6)	14
170	85 ± 8	22 ± 5 (n = 9)	23

Developmental time after fertilization at 20°C. The number of hypodermal precursors is predicted from the wild-type lineage (Sulston et al. 1983).

small daughter adopts a nonhypodermal cell fate. In *elt-1* mutants, these divisions produce daughters of equal size, indicating that *elt-1* functions at or prior to these divisions. Thus, *elt-1* may function within a few cell divisions before the hypodermal cells are born.

Patterns of cell differentiation in elt-1 mutants

We propose that ABa, ABp, and C descendants adopt different nonhypodermal fates in *elt-1* mutants because these blastomeres normally generate hypodermal cells by distinct genetic pathways. We have shown that in *elt-1* mutants, the C blastomere generates muscle cells instead of hypodermal cells, whereas the ABa blastomere generates neurons instead of hypodermal cells. These results indicate that hypodermal specification in the C lineage normally may involve a choice between hypodermal and muscle cell fates, whereas hypodermal specification in the ABa lineage may involve a choice between hypodermal and neuronal cell fates.

The maternally expressed gene *pal-1* appears to promote both hypodermal and muscle fates in C descendants (Hunter and Kenyon 1996). The PAL-1 protein, a transcription factor related to *Drosophila* CAUDAL, is expressed in C descendants, but not AB descendants. If PAL-1 is expressed inappropriately in AB descendants, as is the case in *mex-3* mutants, AB descendants adopt a cell fate similar to C and produce muscle cells and hypodermal cells (Draper et al. 1996). We have shown here that AB produces muscle cells instead of hypodermal cells in *mex-3;elt-1* double mutants, as does the C blastomere in *elt-1* mutants.

At present, we do not know what cell type the ABp blastomere generates instead of hypodermal cells in *elt-1* mutants. These nonhypodermal cells, however, do not appear to be muscle cells or neurons. Why is the cell fate transformation of ABp descendants different from that of ABa in *elt-1* mutants? ABp undergoes a GLP-1/APX-1 mediated cell interaction that ABa does not; this interaction results in ABp undergoing a pattern of development that differs from ABa (Mango et al. 1994; Mello et al. 1994). In *glp-1;elt-1* mutants, we find that ABp produces excess neurons instead of hypodermal cells, a cell fate transformation similar to ABa in *elt-1* single mutants (B. Page, unpubl.). Mutations in *glp-1* and *mex-3* have no effect on the positions of early embryonic blastomeres. Thus, the different transformations in cell fate seen in *elt-1* mutants are a consequence of the different pathways used to establish the identities of the early blastomeres.

Control of elt-1 expression

ELT-1 protein is detected in the nuclei of a contiguous group of ABa, ABp, and C descendants on the dorsal surface of early embryos. The similar positions of the cells that express ELT-1 suggest the possibility that simple positional cues could contribute to *elt-1* expression. Our current understanding of cell type specification in *C. elegans*, however, suggests that lineage-specific mechanisms could also determine gene expression patterns. For

example, the homeobox gene *mab-5* normally is expressed in a simple pattern in the posterior of the embryo (Costa et al. 1988). Yet, even if cells that normally express *mab-5* are mispositioned to the anterior of the embryo, these cells still express *mab-5* (Cowing and Kenyon 1996). Little is known at present about how complex, lineage-specific patterns of expression are achieved in the *C. elegans* embryo. Promoter analysis of the muscle-specific *hlh-1* gene, which is expressed in multiple lineages, suggests that distinct *cis*-acting promoter elements can activate *hlh-1* expression in a lineage-dependent manner (Krause et al. 1994). It will be of interest to determine whether the expression of the *elt-1* gene is regulated similarly by separate, lineage-specific elements. For example, *elt-1* expression in the C, but not ABa or ABp, lineage might be directly regulated by PAL-1, since expression of PAL-1 appears to precede and overlap with that of ELT-1 in C descendants.

Part of the simple pattern of ELT-1 expression on the dorsal surface of the embryo requires the loss of ELT-1 expression in cells that leave the dorsal surface during development. We have observed that all four granddaughters of the C blastomere initially express ELT-1. ELT-1 expression is maintained in the descendants of the two C granddaughters that are hypodermal precursors; these descendants remain on the dorsal surface of the embryo. In contrast, the two C granddaughters that are muscle precursors produce descendants that leave the surface and that lose ELT-1 expression. It should be possible to test in future experiments whether loss of *elt-1* expression is a prerequisite for these C descendants to become internalized and to differentiate as muscle.

Although the early embryonic development of *C. elegans* and *Drosophila* seems very different at the cellular level, there is evidence of some common molecular features. The posterior-specific PAL-1 protein is closely related to the posterior-specific CAUDAL protein in *Drosophila* (Waring and Kenyon 1991; Hunter and Kenyon 1996). Similarly, the VAB-7 protein, which is required for proper embryonic patterning in some lineages in *C. elegans* is related to the pair-rule EVE protein in *Drosophila* (Ahringer 1996). In this respect, it is intriguing that the *elt-1* gene of *C. elegans* and the *pannier* gene of *Drosophila* encode similar GATA-like transcription factors (Romain et al. 1993). Wild-type *Drosophila* embryos express high levels of the *pannier* mRNA in the dorsal ectodermal cells (Winick et al. 1993). Severe mutations in *pannier* cause embryonic lethality, and the arrested embryos appear to lack epidermal cells. It is thus possible that *pannier* and *elt-1* have evolutionarily related functions in epidermal tissue specification. It will be interesting to determine whether other components of the pathways leading to hypodermal/epidermal specification are similar in the two organisms.

Materials and methods

Strains and alleles

The Bristol strain N2 was used as the standard wild-type strain. The genetic markers and deficiencies used in this paper are

listed by chromosome as follows: linkage group I (LGI): *bli-3(e767)*, *ced-1(e1735)*, *egl-30(ad805)*, *mex-3(zu166)*. LGIV: *daf-14(m77)*, *dpy-13(e184)*, *dpy-20(e1282)*, *emb-11(g4)*, *fem-3(e1996)*, *let-51(s41)*, *let-55(s45)*, *let-657(s1254)*, *unc-24(e138)*, *unc-43(e408)*, *eDf18*, *eDf19*, *mDf7*, *nT1*. LGX: *lin-2(e1309)*. *mex-3(zu166)* was provided by B. Draper (this laboratory). The strain JR126 contains a seam-cell specific *lacZ* fusion expression construct that is integrated into the genome (Gendreau et al. 1994); this strain was provided by J. Rothman (University of California, Santa Barbara). The H2O–GFP neuronal marker used in this study was designed and integrated into the genome by T. Ishihara and I. Katsura (National Institute of Genetics, Mishima, Japan). All other mutant strains listed were obtained or are available from the *C. elegans* Genetic Stock Center. The basic methods for worm culture and genetics were performed as described by Brenner (1974).

Isolation of *elt-1* alleles

The *elt-1(zu180)*, *(zu220)*, and *(zu228)* mutations were isolated independently in screens for nonconditional embryonic-lethal mutations. *lin-2* mutant larvae were used as the starting strain for mutagenesis as described previously (Priess et al. 1987), except that F₁ animals were scored for dead eggs instead of F₂ animals. Larvae were placed on microscope slides and viewed by Nomarski optics to score tissue differentiation in the inviable embryos.

Genetic analysis

elt-1(zu180) was positioned on chromosome IV by standard linkage tests (Brenner 1974). *zu220* and *zu228* were shown to be alleles of *elt-1* by complementation tests. *elt-1(zu180)* was mapped to the right arm of chromosome IV between *fem-3* and *daf-14* by standard three- or four-factor analysis. The mapping data are available from the *C. elegans* stock center.

Cloning of *elt-1*

The genomic DNA between *fem-3* and *daf-14* has been cloned and ordered into overlapping sets of cosmids and yeast artificial chromosomes (Coulson et al. 1986; 1988). Tom Barnes generously sent us a collection of strains carrying extrachromosomal arrays that were generated by coinjection of cosmids in the *fem-3 daf-14* region. These arrays were crossed into the strain *elt-1(zu180)unc-43(e408)/unc-24(e138)dpy-20(e1282)*. One set of arrays rescued the embryonic lethal phenotype of *elt-1(zu180)*. This array was generated by the injection of the following collection of cosmids: F13C8, C48A2, R05H9, C33A12, T01G2, T12H5, F38E11, F56H11, and T05A1. We microinjected these cosmids individually into the gonads of *elt-1(zu180)unc-43(e408)/unc-24(e138)dpy-20(e1282)* hermaphrodites using the procedures of Mello et al. (1991).

ELT-1 immunostaining

Rabbit polyclonal antibodies were raised against two different ELT-1-specific peptides: (ELT-1C) ELDQSGVWGMKNTQP-MLMTPT and (ELT-1D) SNFYFNSIEDQLEYKTC. Embryos were fixed and stained as described previously (Lin et al. 1995). Antisera against both peptides give identical staining patterns. To examine the staining pattern in *elt-1(zu180)* mutants, embryos of various stages were stained with anti-ELT-1. The hypodermal cells stained by anti-ELT-1 in wild-type embryos are absent in terminal stage *elt-1* embryos. Thus, we examined early embryos (100–200 cells) for ELT-1 staining prior to hypo-

dermal cell differentiation. Only 4% of embryos isolated from N2 hermaphrodites lacked anti-ELT-1 staining ($n = 71$). In contrast, 23% of embryos from *elt-1(zu180)* heterozygous hermaphrodites, lacked anti-ELT-1 staining ($n = 112$). The 23% of embryos not stained with anti-ELT-1 correlates with the 25% expected to be *elt-1(zu180)* homozygotes.

Analysis of embryos

A Zeiss Axioplan microscope equipped with DIC (Nomarski) optics and epifluorescence was used for microscopy. Embryos were prepared for light microscopy following the method of Sulston et al. (1983). Embryos were processed for fluorescence microscopy as described in Bowerman et al. (1992, 1993). Photographs were taken with Kodak Technical Pan film and developed in Kodak HC110 developer. Laser ablation experiments were performed at 22°C with a VSL-337 laser attached to a Zeiss Axioscope microscope as described in Avery and Horvitz (1989). The procedure for isolating ABap and ABal was as follows: at the 4-cell stage, blastomeres ABp, EMS, and P₂ were killed with a laser microbeam. Subsequently, ABa underwent a left/right division and these descendants, ABal and ABar, divided anterior/posterior. The two anterior granddaughters of ABa then were killed with a laser microbeam. The blastomere C was isolated by killing ABa, ABp, and EMS at the 4-cell stage. After P₂ divided into C and P₃, P₃ was killed. In all of these experiments, the nonablated blastomeres were allowed to develop for 20 hr at 15°C, and the number of cells expressing the H2O–GFP marker was determined by use of epifluorescence. Lineage analysis was performed with the four-dimensional system described in Draper et al. (1996).

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ELT-1, a GATA-like transcription factor, is required for epidermal cell fates in *Caenorhabditis elegans* embryos.

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