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Control of cell polarity by noncanonical Wnt signaling in *C. elegans*

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The three Caenorhabditis elegans β-catenin each function in distinct processes: BAR-1 in canonical Wnt signaling that controls cell fates and cell migrations, HMP-2 in cell adhesion and WRM-1 in Wnt signaling pathways that function in conjunction with a mitogen-activated kinase (MAPK) pathway to control the orientations, or cell polarities, of cells that undergo asymmetric cell divisions. In addition, WRM-1 does not interact with the canonical β-catenin binding site in POP-1/Tcf. Thus, Wnt signaling through WRM-1 is noncanonical and, except for one division that might not include any of the three C. elegans β-catenin, controls cell polarity in C. elegans.

Key words: *C. elegans* / Wnt signaling / cell polarity / spindle orientation / asymmetric cell division

Introduction

In the nematode *Caenorhabditis elegans* Wnt signaling controls cell fate decisions, cell migrations and cell polarity (reviewed by Herman[1]). As in most animals, *C. elegans* has both canonical and noncanonical Wnt signaling pathways. The best-characterized canonical Wnt pathway in *C. elegans* controls the migrations of the descendants of the QL neuroblast, collectively known as the QL.d (Figure 1). Early during the first larval stage, the QL neuroblast migrates posteriorly, expresses the Hox gene *mab-5* and divides. Both daughters continue to express *mab-5* and divide to generate a total of three neurons. The anterior daughter, QL.a, continues to migrate posteriorly and generates a neuron that migrates into the tail. The posterior daughter, QL.p, stops migrating and generates two neurons. A canonical Wnt pathway that includes *egl-20/Wnt*, *mig-5/Dsh*, *sgg-1/GSK-3*, *bar-1/β*-catenin, *pry-1/Axin* and *pop-1/Tcf* control the expression of *mab-5*, which controls QL.d migration.[2–7]

Canonical Wnt signaling pathways are also involved in controlling the fates of the P12 ectoblasts and the vulval precursor cells (VPCs). In both of these cell fate decisions Wnt signals function with a Ras pathway by controlling the expression of a Hox gene: *egl-5* in the case of P12 cell fate[8] and *lin-39* in the case of VPC cell fate.[9] Furthermore, in both cases Wnt signaling appears to be required to make the cells competent to receive signals that are transduced through the Ras pathway.

Noncanonical Wnt pathways primarily control the orientations, or cell polarities, of certain cells that divide asymmetrically in *C. elegans*. Specifically, the polarities of the EMS blastomere, the T and B cells in the tail, and the Z1 and Z4 cells in the developing gonad. Wnt signaling also controls the rotation of the mitotic spindle that occurs during the divisions of certain embryonic blastomeres, including EMS.[10–12] An interaction of two Wnt pathways also appears to control the polarity of the V5 cell in the lateral epidermis,[13] one of which appears to involve canonical Wnt components.

What is noncanonical Wnt signaling?

In canonical Wnt signaling pathways a Wnt ligand binds to a Frizzled (Fz) receptor at the cell surface leading to signal transduction through Dishevelled (Dsh) which antagonizes the action of a complex of proteins that includes glycogen synthase kinase 3 (GSK-3), the adenomatous polyposis coli protein (APC), Axin and others that function to promote the degradation of β-catenin. This results in the stabilization of β-catenin, causing it to accumulate in the cytoplasm and the nucleus, where it interacts with Tcf

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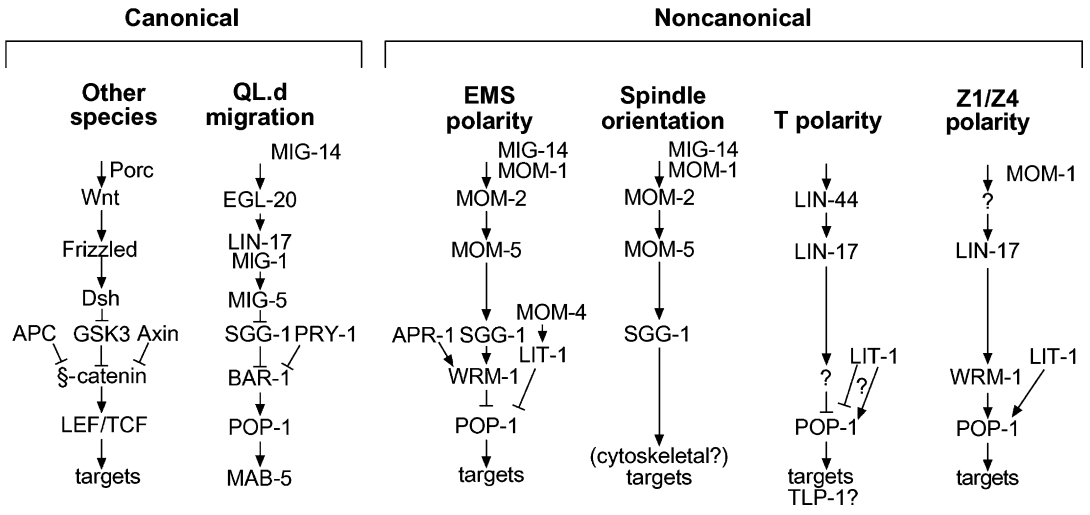

Figure 1. Representative canonical and noncanonical *C. elegans* Wnt pathways. The inferred regulatory relationships of the known genes involved in the canonical pathway that controls the migrations of the QL descendants (QL.d) and the noncanonical pathways that control EMS polarity, EMS spindle orientation, T cell polarity and Z1/Z4 cell polarity are shown. In the EMS polarity pathway APR-1 is shown influencing WRM-1 independently of SGG-1 since SGG-1 influence EMS spindle orientation whereas APR-1 does not. SGG-1 may function as a branch point for EMS polarity and spindle orientation. The symbol ''?'' indicates that unknown or multiple components function at that point in a pathway.

factors to activate target genes (Figure 1) (see reviews in References 14, 15). Wnt signaling pathways that do not include a β-catenin homolog have been termed ''noncanonical''.[16,17] *C. elegans* has three β-catenin homologs, BAR-1, WRM-1, and HMP-2. Based, in part, upon studies of the interactions between these molecules and the *C. elegans* Tcf ortholog, POP-1,[18] it appears that the functions of signaling and adhesion that are performed by a single β-catenin in *Drosophila* and two in vertebrates, have been distributed over the three β-catenin homologs in *C. elegans*.[5,19] POP-1 functions as a canonical Tcf, in that it binds to the consensus Tcf site and can complex with the *Drosophila* β-catenin, Armadillo, to activate transcription of a reporter gene containing several upstream Tcf binding sites. BAR-1 is the only *C. elegans* β-catenin that interacts strongly and directly with POP-1 in both yeast two hybrid and co-immunoprecipitation experiments and together they can activate a Tcf reporter gene.[5] Thus, BAR-1 interacts with POP-1 to function in canonical β-catenin signaling. On the other hand, WRM-1 interacts weakly with POP-1 in yeast two hybrid assays[19,20] but not in co-immunoprecipitation experiments.[5] WRM-1 also interacted weakly with a version of POP-1 in which the N-terminal consensus β-catenin binding site was deleted (ΔN-POP-1),[19] suggesting that WRM-1 and POP-1 interact differently than do BAR-1 and POP-1. Thus, WRM-1 does not appear to be a ''canonical'' β-catenin. Therefore, pathways that include WRM-1 are ''noncanonical''. In support of this, all the pathways that use WRM-1 also involve LIT-1, a nemo-like kinase that is involved in a MAPK pathway (see below). Finally, HMP-2 does not interact with POP-1 in any assay, but is the only β-catenin that interacts with HMR-1/cadherin.[5,19] Thus, *C. elegans* has distributed β-catenin functions over three proteins: BAR-1 functions in canonical Wnt signaling, WRM-1 in noncanonical signaling and HMP-2 in cell adhesion. Despite this apparent distribution of function, when overexpressed from the *bar-1* promoter, WRM-1 and HMP-2 can rescue a *bar-1* mutant. This indicates that although neither protein is normally involved in canonical Wnt signaling, when overexpressed, they can signal.[19]

EMS polarity

In the four-cell embryo, the posterior blastomere, P_2, signals anteriorly to the EMS blastomere, polarizing it and inducing it to produce endoderm. The anterior EMS daughter, MS, generates mesoderm and the posterior daughter, E, generates all the endoderm in the animal (Figure 2A). Blastomere isolation experiments demonstrated that the position of contact between EMS and P_2 established which portion of EMS

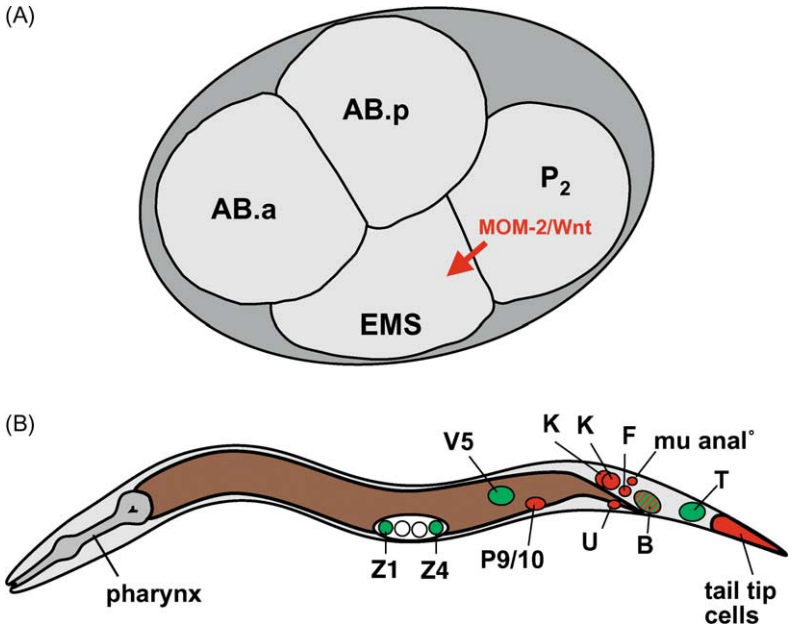

Figure 2. Positions of cells known to send or receive Wnt signals involved in cell polarity. (A) In the four-cell *C. elegans* embryo MOM-2/Wnt from the P_2 blastomere polarizes the EMS blastomere. (B) During postembryonic development LIN-44/Wnt from the tail tip epidermal cells polarize the anterior T and B cells. The P9/10, K′, K, F, U, mu anal, and B cells are the source of EGL-20/Wnt that functions as a permissive signal involved in V5 cell polarity. A Wnt signal that polarizes Z1 and Z4 has not been identified, two or more Wnt might function redundantly. Red shading indicates that a cell is a source of a Wnt signal. Green shading indicates cells whose polarities are controlled by Wnt signals. The B cell does both and is striped.

will produce endoderm.[11,21,22] Thus, the P_2-to-EMS signal is instructive. Genes defined by mutations that blocked EMS polarization and endoderm formation resulting in two MS-like cells[10,11,23] were called *mom* (for *mo*re *m*esoderm) or *lit* (for *l*oss of *in*testine). A mutation in *pop-1* (for *po*sterior *p*harynx defective) caused the opposite phenotype.[18,24] Subsequently, it was discovered that these genes encode Wnt pathway components: *mom-1/Porc*, *mom-2/Wnt*, *mom-5/Fz* and *pop-1/Tcf*. Other genes, *lit-1/NLK* and *mom-4/TAK*, encode components of a MAPK pathway.[20,25] The product encoded by *mom-3* has yet to be determined. This should be an important discovery as *mig-14* mutants, which have defects in QL.d migration and other *C. elegans* processes controlled by canonical Wnt signaling were shown to be allelic to *mom-3*; indicating that this unknown protein might function generally in Wnt signaling.[26] Isolation and recombination experiments with wild-type and mutant P_2 and EMS blastomeres demonstrated that *mom-1*, *mom-2*, and *mom-3* function in P_2 and the rest function in EMS. This makes sense for *mom-1/Porc*, *mom-2/Wnt* and *mom-5/Fz* and suggests that *mig-14/mom-3* functions in the expression or secretion of Wnt signals. Additional components including WRM-1/β-catenin, APR-1/APC, SGG-1/GSK3 and KIN-19/PP2C were identified by sequence and their functions determined by RNA-mediated interference (RNAi);[27] RNAi of each of these caused a *mom* defect. The role of Dishevelled (Dsh) in this process is not clear. The *C. elegans* genome contains three Dsh homologs and two of them, *mig-5* and *dsh-2* (C27A2.6) are enriched in oocytes, as are the other Wnt components involved in controlling EMS polarity.[28] This suggests that these two Dsh proteins may function redundantly in the control of EMS polarity.

In the absence of Wnt signals, POP-1 represses E cell fate. This occurs in the MS blastomere, where POP-1 directly represses at least one endoderm-specific gene, *end-1*, by recruiting a complex containing the histone deacetylase (HDAC) HDA-1 and UNC-37/Groucho.[29] In this sense, POP-1 represses gene expression in the absence of Wnt signals in a canonical manner. The level of POP-1 is higher in the anterior MS blastomere than it is in the posterior E blastomere.[24] In *mom* and *lit-1* mutants this distribution is disrupted and both MS and E blastomeres have high POP-1 levels.

The Wnt and MAPK pathways collaborate to lower POP-1 levels in E, allowing endoderm induction. POP-1 is repressed by MOM-2/Wnt signaling through MOM-5/Fz, perhaps a Dsh protein, LIT-1/NLK and WRM-1/β-catenin. Interestingly, this repression requires the positive action of all the genes in the pathway, which for SGG-1/GSK3 and APR-1/APC is contrary to their canonical functions. Perhaps these proteins function to target POP-1 for degradation. It is unclear how Wnt signals might activate rather than inhibit the activities of SGG-1/GSK3 and APR-1/APC in the E blastomere, however. In cultured cells, WRM-1 and LIT-1 interact and can phosphorylate POP-1. The vertebrate NLK homolog has been shown to phosphorylate TCF-4, which interferes with DNA binding by the TCF-4/β-catenin complex.[30] It is unlikely that this occurs in *C. elegans* since WRM-1 and POP-1 interact only weakly, however. In *C. elegans*, phosphorylation by the WRM-1/LIT-1 complex leads to the degradation of POP-1, lowering POP-1 levels in E. Interestingly, when POP-1 is localized to the nucleus when expressed alone in COS cells, but when coexpressed with WRM-1 and LIT-1, it becomes cytoplasmic.[20] This suggests that WRM-1 and LIT-1 might regulate POP-1 nuclear localization, which might cause a perceived lowering of POP-1 levels by dilution in the cytoplasm or alternatively, selective degradation in the cytoplasm. The fate of WRM-1 protein in these processes is also unclear, and remains a major question.

Effects of Wnt signals on the cytoskeleton

The EMS spindle is initially aligned along the left–right axis. The spindle then rotates about 90° just before EMS divides to become alighted alone the anteroposterior axis. Blastomere isolation experiments also demonstrated that signaling from P_2 is responsible for this rotation. For example, rotation does not occur if EMS is isolated away from P_2, but does occur if EMS is placed in contact with P_2. Although signaling from P_2 induces both endoderm formation and spindle orientation, these effects can be uncoupled, as EMS loses competence to respond to the spindle orientation aspect of the P_2 signal before it loses competence to endoderm induction.[31]

Mutations in *mom-1*, *mom-2*, *mom-3*, *mom-5* and *sgg-1*(*RNAi*) cause highly penetrant defects in EMS spindle orientation. Interestingly, *wrm-1*(*RNAi*) or mutations in *apr-1*, *pop-1*, *mom-4* and *lit-1* do not. This suggests that the Wnt pathway in EMS bifurcates at *sgg-1*: components upstream of *sgg-1* affect EMS polarity and spindle orientation, whereas downstream components do not (Figure 1).[12] It is possible that this Wnt pathway directly influences the cytoskeleton as the EMS mitotic spindle rotations occur very quickly after P_2 signals and can occur in the absence of transcription.[32] There is some evidence in other systems that Wnt signals target the axonal cytoskeleton (reviewed by Salinas[33]) and patterns of gap junctions in *Xenopus*.[34] Finally, other asymmetric cell divisions whose orientations are controlled by Wnt signals in *C. elegans* produce daughters of different sizes. To achieve this, the position of the mitotic spindle must be shifted toward one pole of the dividing cell. It will be interesting to see whether Wnt signaling directly affects the shifting of this spindle as well.

T cell polarity

Wnt signaling also influences the polarity of asymmetric cell divisions during *C. elegans* postembryonic development. These include the T, B and V5 cells that are oriented to the anteroposterior axis as well as the Z1 and Z4 cells that are oriented along a proximal–distal axis. TL and TR, known collectively as the T cells, lie in the tail on each side of the animal (Figure 2B). In both sexes, the anterior daughter, T.a, generates primarily epidermal cells and the posterior daughter, T.p, generates primarily neural cells (Figure 3A). The B cell divides only in males to generate epidermal and neural cells involved in copulation. The first B cell division produces a large anterior daughter, B.a, and a smaller posterior daughter B.p (Figure 3A). Certain divisions within the T cell lineage also generate daughters of different sizes. Mutations in *lin-44/Wnt* cause the polarities of the T and B cells to be reversed, including the size differences of the daughters of the B and T cell descendants.[35,36] Mutations in *lin-17/Fz* cause a loss of polarity in these same cells; both T cells daughters make epidermal cell fates both B cells daughters are of equal size.[37,38] Size differences of the daughters of the B and T cell descendants are observable immediately after division in both wild-type and *lin-44* animals, indicating that cell polarity is determined before division, rather than by cell signaling after division. *lin-44* is expressed in the tail tip cells and its function is required in these cells for proper T cell polarity.[36] Although both *lin-17* and *lin-44* affect T and B cell polarities, the difference in phenotype for a putative receptor–ligand pair is curious. One possibility is that there is an anterior signal that orients these cells in the absence of *lin-44*;[38] there is yet no evidence of such

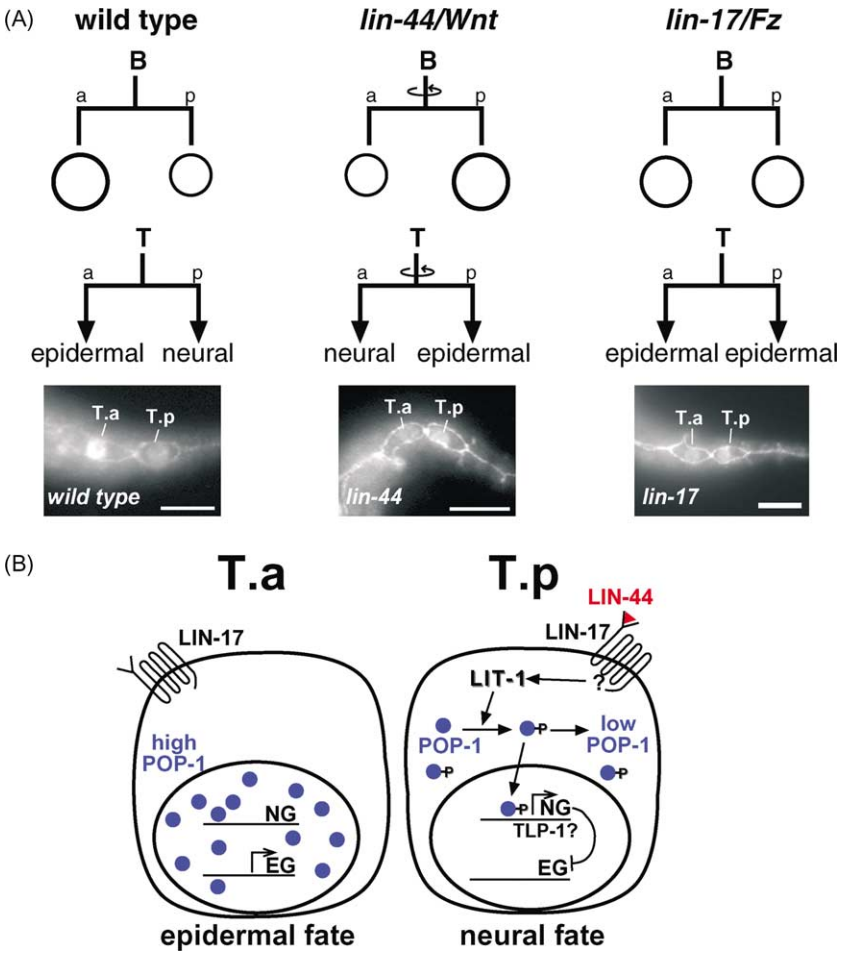

Figure 3. Control of B and T cell polarities. (A) Schematic B (top) and T (middle) cell lineages in wild-type, *lin-44/Wnt* and *lin-17/Fz* animals. Anterior (a)-to-posterior (p) division planes are indicated. (Bottom) In wild-type animals the epidermal T.a cell fate is correlated with a high level of POP-1/Tcf, whereas the neural T.p cell fate is correlated with a lower level. The levels of POP-1 in T.a and T.p are reversed in *lin-44* animals and are equal and high in *lin-17* animals. Bars: 10 μm. (B) A model for T cell polarity. LIN-44/Wnt (triangle) binds to LIN-17/Fz on the posterior surface of the T cell before division, but is shown binding to T.p for simplicity. Transduction through unknown factors (?) leads to the activation of LIT-1/NLK, which functions to phosphorylate POP-1 (circles), perhaps in combination with a n unknown factor which might function like WRM-1 in EMS polarity. Some of the modified POP-1 is degraded which lowers POP-1 levels and the remaining modified POP-1 might activate neural-specific gene (NG) expression, one of which could repress epidermal-specific genes (EG) in T.p. *tlp-1* might be a target gene activated in T.p. T.a expresses the default epidermal cell fate, perhaps through the constitutive expression of epidermal-specific genes. Without modification/phosphorylation, the high levels of POP-1 in T.a might be nonfunctional. Modified from Reference 6.

a signal, however. Although *egl-20/Wnt* is expressed in a good position to be the anterior signal, it is not (Figure 2B) (M.H. unpublished).

As is observed in the control of EMS polarity, both LIT-1/NLK and POP-1/Tcf are also involved in the control of T cell polarity. The level of POP-1 is higher in the anterior T.a cell and lower in the posterior T.p cell, as has been observed for many asymmetric cell divisions in *C. elegans* (Figure 3A).[6,24] The levels of POP-1 are reversed in *lin-44/Wnt* mutants, T.a is low and T.p is high; and in *lin-17/Fz* mutants it is high in both daughters. Thus, a high level of POP-1 appears to correlate with epidermal cell fate. However, both *pop-1*(*RNAi*) or expression of ΔN-POP-1 (which functions in a dominant-negative fashion) causes a loss of asymmetry and, like *lin-17* mutants, epidermal cell

fates. *lit-1* mutants also cause a similar loss of asymmetry. WRM-1, does not appear to be involved, however; nor do any of the *C. elegans* β-catenin homologs. This is a major difference between T and EMS polarity control. A model proposed to explain these observations contains two basic ideas (Figure 3B): (1) POP-1 levels *per se* are not necessarily responsible for the difference in cell fates, since both high POP-1 levels and the absence of POP-1 are associated with the same epidermal cell fate. (2) A directional Wnt signal through LIN-17 and LIT-1 functions to modify POP-1 to convert it into an activator of neural-specific genes. This might occur by phosphorylation of POP-1 leading to its degradation, lowering POP-1 levels, but not to zero. The remaining modified POP-1 might function to activate neural-specific genes in T.p. In the anterior T.a cell, POP-1 levels remain high, but unmodified POP-1 is unable to activate neural-specific genes and epidermal-specific genes are constitutively expressed. Thus, the high POP-1 level in T.a might be nonfunctional.[6] The C2H2 zinc finger protein TLP-1 is asymmetrically expressed in T.p. This expression is reversed or lost in *lin-44* and *lin-17* mutants, respectively; suggesting that *tlp-1* might be a target of the Wnt pathway in the T cell.[39]

V5 polarity

The polarity of the V5 cell in the posterior lateral epidermis is controlled by *egl-20/Wnt*. The V5 cell generates cuticular and sensory structures in both sexes. The anterior daughter (V5.a) fuses with the epidermal syncytium, called hyp7, that covers most of the animal. The posterior daughter (V5.p) generates sensory structures and epidermal cells. The polarity of the V5 divisions is reversed in approximately 50% of *egl-20* mutants.[13] Like *lin-44/Wnt*, *egl-20* is expressed posterior of the cells whose polarity it controls.[40] In addition, *egl-20* expressed from a heat-shock promoter can rescue the V5 polarity defects of *egl-20* mutants. Surprisingly, *egl-20* expressed from a pharynx-specific promoter (at the anterior end of the animal) can also rescue the V5 polarity defects of *egl-20* mutants (Figure 2B). Thus, EGL-20 appears to be a permissive rather than an instructive signal for V5 polarity.[13] A lateral signal from cells posterior and adjacent to V5, that requires *lin-17* and *pry-1/Axin*, appears to be responsible for the V5 polarity reversals in *egl-20* mutants. Whangbo *et al.* hypothesized that EGL-20 functions to override the lateral signal. Thus, Wnt pathways may interact to control V5 polarity.

Proximal–distal polarity of the somatic gonad precursors

Wnt signaling controls the asymmetric cell divisions of the Z1 and Z4 cells that generate the somatic gonad tissue. These asymmetric cell divisions and the resulting tissue that is generated are oriented along the proximal–distal axis of the gonad. The gonad primordium lies in the center of the animal and contains four cells: Z1 and Z4 on each end, and Z2 and Z3, which generate the germline cells, in the center (Figure 2B). The hermaphrodite gonad develops an anterior and a posterior arm, each of which has its own proximal–distal axis, and develops into an ovo-testes (reviewed by Hubbard and Greenstein[41]). The proximal–distal axes are set by the divisions of Z1 and Z4 in which distal cell fates lie at the ends of the primordium and proximal fates lie in the center. The male gonad, which at first is symmetric, later becomes asymmetric by migrations and rearrangements of somatic gonad cells.

Mutations in *lin-17/Fz* also cause a loss of asymmetry of the Z1 and Z4 divisions (Figure 4).[37] In the gonad, this defect is called Sys (for *s*ymmetric *s*isters) and results in a recognizable gonad abnormality upon which a genetic screen for additional genes involved was based. One of the genes isolated by this screen (*sys-2*) was *pop-1/Tcf*.[42] It is not known whether POP-1 levels are correlated with different proximal and distal cell fates, as POP-1 antibodies do not stain the gonads of L1 animals. The Wnt pathway that controls Z1 and Z4 polarity also includes *mom-1/Porc*, *lit-1/NLK* and *wrm-1/β*-catenin. Surprisingly, mutation or interference with each of the *C. elegans* Wnts did not cause a Sys defect, thus the Wnt ligand involved in this asymmetric division remains unidentified. It is possible that two or more of the five *C. elegans* Wnts function redundantly to control Z1 and Z4 polarities (Figure 4).

The observation that interference with *lit-1*, *wrm-1*, or *pop-1* all produce the same Sys defect is similar to the situation in the T cell (although *wrm-1* does not appear to be involved in the T cell) but contrasts the situation in EMS where *pop-1* causes a defects opposite to that of *lit-1* and *wrm-1*. Two models for how LIT-1 and WRM-1 could function to positively regulate POP-1 in the Z1 and Z4 divisions have been proposed.[42] One model proposes that WRM-1 and POP-1 interact in a somewhat canonical β-catenin/Tcf relationship to activate gene expression that leads to different proximal–distal cell fates. However, since WRM-1 binds only weakly to POP-1, this interaction would have to be stabilized by LIT-1, which does bind to POP-1. The other model is

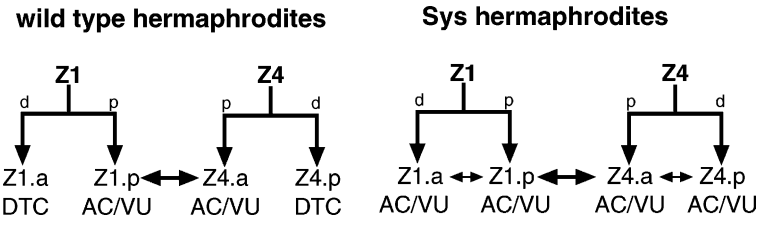

Figure 4. Schematic Z1 and Z4 cell lineages in wild-type and *sys*(*pop-1*) mutants. In wild-type hermaphrodites Z1.a and Z4.p generate distal tip cells (DTCs), whereas Z1.p and Z4.a generate AC/VU cells, with lateral signaling (arrows) leading to the formation of one anchor cell (AC) and one ventral uterine precursor (VU). In Sys hermaphrodites all four Z1/Z4 daughters generate AC/VU cells. Proximal (p)-to-distal (d) division planes are indicted. Modified from Reference 42.

similar to the T cell polarity model, in which WRM-1 and LIT-1 function to modify POP-1, leading to the activation of gene expression. It is not clear whether WRM-1 and LIT-1 might function to lower POP-1 levels as is proposed for the posterior T cell daughter, however.

Summary and remaining questions

In *C. elegans*, noncanonical Wnt pathways control the polarities of the EMS, T, Z1 and Z4 cells. These noncanonical Wnt pathways differ from those involved in planar cell polarity in *Drosophila* (Strutt, Axelrod, this issue) and convergent extension during gastrulation in vertebrates (Kühl, Wilson, this issue); although in each case, the pathways control similar processes of orientations of cells to the body axis of the animal. While there are similarities in each of these *C. elegans* pathways, such as the involvement of POP-1/Tcf and LIT-1/NLK, each pathway also has its quirks. For example, in EMS polarity POP-1 is negatively regulated by unknown mechanisms and the positive role for APR-1/APC and SGG-1/GSK-3, as well as the fate of WRM-1/β-catenin, remain as major questions. It is also curious that WRM-1 functions in EMS and Z1/Z4 cell polarity, but might not function in T cell polarity; although this negative RNAi result that will have to be confirmed when a *wrm-1* mutant becomes available. In fact, the unorthodox model for the control of T cell polarity that employs a positive role for a modified form POP-1/Tcf without a β-catenin has not been rigorously tested. Finally, although both EMS and Z1/Z4 pathways involve LIT-1 and WRM-1, the pathways must differ as POP-1 is repressed by the EMS pathway but activated by the Z1/Z4 pathway.

It is also intriguing that for EMS, T and V5 cell polarities, the source of the polarizing Wnt is posterior to the affected cells. Although EGL-20/Wnt, functions as a permissive signal in V5 polarity, MOM-2/Wnt functions as an instructive signal for EMS polarity and LIN-44/Wnt might also be instructive for T cell polarity, the significance, if any, of the posterior localization of the signals is not known. The source of the polarizing Wnt for Z1/Z4 cell polarities is unknown; it may involve two or more Wnts and could be instructive or permissive. If it is an instructive signal, it might emanate from the center of the animal since it controls a proximal–distal polarity rather than an anterior–posterior polarity.

It is also unknown how Wnt signaling could directly interact with the cytoskeleton to cause EMS spindle rotation. If it does, it will be interesting to learn whether the mechanism is related to that involved with the shifting of the position of the mitotic spindle in Wnt-controlled asymmetric cell divisions that generate daughters of different size, such as the B cell.

Lastly, the establishment of the complete set of components involved in each noncanonical Wnt pathway is needed in order to investigate the similarities and differences in the noncanonical Wnt pathways that control the various cell polarities in *C. elegans*.

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References

1. Herman MA (2002) Wnt signaling in *C. elegans*, in Wnt signalling in development (Kühl M, ed.). Landes Biosciences, Georgetown, TX, in press

2. Guo C (1995) *mig-5*, a gene that controls cell fate determination and cell migration in *C. elegans*, is a member of the Dsh family, Ph.D. in Biology. Johns Hopkins University, Baltimore, MD
3. Harris J, Honigberg L, Robinson N, Kenyon C (1996) Neuronal cell migration in *C. elegans*: regulation of Hox gene expression and cell position. Development 122:3117–3131
4. Maloof JN, Whangbo J, Harris JM, Jongeward GD, Kenyon C (1999) A Wnt signaling pathway controls Hox gene expression and neuroblast migration in *C. elegans*. Development 126:37–49
5. Korswagen HC, Herman MA, Clevers HC (2000) Distinct beta-catenin mediate adhesion and signalling functions in *C. elegans*. Nature 406:527–532
6. Herman M (2001) *C. elegans* POP-1/TCF functions in a canonical Wnt pathway that controls cell migration and in a non-canonical Wnt pathway that controls cell polarity. Development 128:581–590
7. Korswagen HC, Coudreeuse DYM, Betist M, van de Water S, Clevers HC (2002) The Axin-like protein PRY-1 is a negative regulator of a canonical Wnt pathway in *C. elegans*. Genes Dev 16:1291–1302
8. Jiang LI, Sternberg PW (1998) Interactions of EGF, Wnt and HOM-C genes specify the P12 neuroectoblast fate in *C. elegans*. Development 125:2337–2347
9. Eisenmann DM, Maloof JN, Simske JS, Kenyon C, Kim SK (1998) The beta-catenin homolog BAR-1 and LET-60 Ras coordinately regulate the Hox gene *lin-39* during *Caenorhabditis elegans* vulval development. Development 125:3667–3680
10. Rocheleau CE, Downs WD, Lin R, Wittmann C, Bei Y, Cha YH, Ali M, Priess JR, Mello CC (1997) Wnt signaling and an APC-related gene specify endoderm in early *C. elegans* embryos. Cell 90:707–716
11. Thorpe CJ, Schlesinger A, Carter JC, Bowerman B (1997) Wnt signaling polarizes an early *C. elegans* blastomere to distinguish endoderm from mesoderm. Cell 90:695–705
12. Schlesinger A, Shelton CA, Maloof JN, Meneghini M, Bowerman B (1999) Wnt pathway components orient a mitotic spindle in the early *Caenorhabditis elegans* embryo without requiring gene transcription in the responding cell. Genes Dev 13:2028–2038
13. Whangbo J, Harris J, Kenyon C (2000) Multiple levels of regulation specify the polarity of an asymmetric cell division in *C. elegans*. Development 127:4587–4598
14. Cadigan KM, Nusse R (1997) *Wnt* signaling: a common theme in animal development. Genes Dev 11:3286–3305
15. Wodarz A, Nusse R (1998) Mechanisms of Wnt signaling in development. Annu Rev Cell Dev Biol 14:59–88
16. Kühl M, Geis K, Sheldahl LC, Pukrop T, Moon RT, Wedlich D (2001) Antagonistic regulation of convergent extension movements in *Xenopus* by Wnt/beta-catenin and Wnt/Ca(2+) signaling. Mech Dev 106:61–76
17. Wallingford JB, Ewald AJ, Harland RM, Fraser SE (2001) Calcium signaling during convergent extension in *Xenopus*. Curr Biol 11:652–661
18. Lin R, Thompson S, Priess JR (1995) *pop-1* encodes an HMG box protein required for the specification of a mesoderm precursor in early *C. elegans* embryos. Cell 83:599–609
19. Natarajan L, Witwer NE, Eisenmann DM (2001) The divergent. Genetics *Caenorhabditis elegans* beta-catenin proteins BAR-1, WRM-1 and HMP-2 make distinct protein interactions but retain functional redundancy *in vivo* 159:159–172
20. Rocheleau CE, Yasuda J, Shin TH, Lin R, Sawa H, Okano H, Priess JR, Davis RJ, Mello CC (1999) WRM-1 activates the LIT-1 protein kinase to transduce anterior/posterior polarity signals in *C. elegans*. Cell 97:717–726
21. Goldstein B (1992) Induction of gut in *Caenorhabditis elegans* embryos. Nature 357:255–257
22. Goldstein B (1993) Establishment of gut fate in the E lineage of *C. elegans*: the roles of lineage-dependent mechanisms and cell interactions. Development 118:1267–1277
23. Kaletta T, Schnabel H, Schnabel R (1997) Binary specification of the embryonic lineage in *Caenorhabditis elegans*. Nature 390:294–298
24. Lin R, Hill RJ, Priess JR (1998) POP-1 and anterior–posterior fate decisions in *C. elegans* embryos. Cell 92:229–239
25. Meneghini MD, Ishitani T, Carter JC, Hisamoto N, Ninomiya-Tsuji J, Thorpe CJ, Hamill DR, Matsumoto K, Bowerman B (1999) MAP kinase and Wnt pathways converge to downregulate an HMG-domain repressor in *Caenorhabditis elegans*. Nature 399:793–797
26. Eisenmann DM, Kim SK (2000) Protruding vulva mutants identify novel loci and Wnt signaling factors that function during *Caenorhabditis elegans* vulva development. Genetics 156:1097–1116
27. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature 391:806–811
28. Jiang M, Ryu J, Kiraly M, Duke K, Reinke V, Kim SK (2001) Genome-wide analysis of developmental and sex-regulated gene expression profiles in *Caenorhabditis elegans*. Proc Natl Acad Sci USA 98:218–223
29. Calvo D *et al.* (2001) A POP-1 repressor complex restricts inappropriate cell type-specific gene transcription during *Caenorhabditis elegans* embryogenesis. EMBO J 20:7197–7208
30. Ishitani T *et al.* (1999) The TAK1–NLK–MAPK-related pathway antagonizes signalling between beta-catenin and transcription factor TCF. Nature 399:798–802
31. Goldstein B (1995) Cell contacts orient some cell division axes in the *Caenorhabditis elegans* embryo. J Cell Biol 129:1071–1080
32. Thorpe CJ, Schlesinger A, Bowerman B (2000) Wnt signalling in *Caenorhabditis elegans*: regulating repressors and polarizing the cytoskeleton. Trends Cell Biol 10:10–17
33. Salinas PC (1999) Wnt factors in axonal remodelling and synaptogenesis. Biochem Soc Symp 65:101–109
34. Krufka A, Johnson RG, Wylie CC, Heasman J (1998) Evidence that dorsal–ventral differences in gap junctional communication in the early *Xenopus* embryo are generated by beta-catenin independent of cell adhesion effects. Dev Biol 200: 92–102
35. Herman MA, Horvitz HR (1994) The *Caenorhabditis elegans* gene *lin-44* controls the polarity of asymmetric cell divisions. Development 120:1035–1047
36. Herman MA, Vassilieva LL, Horvitz HR, Shaw JE, Herman RK (1995) The *C. elegans* gene *lin-44*, which controls the polarity of certain asymmetric cell divisions, encodes a Wnt protein and acts cell nonautonomously. Cell 83:101–110
37. Sternberg PW, Horvitz HR (1988) *lin-17* mutations of *Caenorhabditis elegans* disrupt certain asymmetric cell divisions. Dev Biol 130:67–73
38. Sawa H, Lobel L, Horvitz HR (1996) The *Caenorhabditis elegans* gene *lin-17*, which is required for certain asymmetric cell divisions, encodes a putative seven-transmembrane protein similar to the *Drosophila frizzled* protein. Genes Dev 10:2189–2197

39. Zhao X, Yang Y, Fitch DHA, Herman MA (2002) TLP-1 is an asymmetric cell fate determinant that responds to Wnt signals and controls male tail tip morphogenesis in *C. elegans*. Development 129:1497–1508
40. Whangbo J, Kenyon C (1999) A Wnt signaling system that specifies two patterns of cell migration in *C. elegans*. Mol Cell 4:851–858
41. Hubbard EJ, Greenstein D (2000) The *Caenorhabditis elegans* gonad: a test tube for cell and developmental biology. Dev Dyn 218:2–22
42. Siegfried KR, Kimble J (2002) POP-1 controls axis formations during early gonadogenesis in *C. elegans*. Development 129:443–453