REVIEW

Asymmetric cell division: from A to Z

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Cell divisions producing two daughter cells that adopt distinct fates are defined as asymmetric. In all organisms, ranging from bacteria to mammals, in which development has been studied extensively, asymmetric cell divisions generate cell diversity. Asymmetric cell divisions can be achieved by either intrinsic or extrinsic mechanisms (Fig. 1). Intrinsic mechanisms involve the preferential segregation of cell fate determinants to one of two daughter cells during mitosis. Asymmetrically segregated factors that bind cell fate determinants and orient the mitotic spindle may also be necessary to ensure the faithful segregation of determinants into only one daughter cell.

Extrinsic mechanisms involve cell-cell communication. In metazoans, a dividing cell's social context provides a wealth of positional information and opportunity for cell-cell interactions. Interactions between daughter cells or between a daughter cell and other nearby cells could specify daughter cell fate. Interaction between a progenitor cell and its environment can also influence cell polarity by directing spindle orientation and the asymmetric distribution of developmental potential to daughter cells. Recent studies have indicated that a combination of intrinsic and extrinsic mechanisms specify distinct daughter cell fates during asymmetric cell divisions.

We focus on asymmetric cell divisions that occur during the development of the *Caenorhabditis elegans* and *Drosophila* nervous systems. Although we touch upon asymmetric cell divisions in the early *C. elegans* embryo, more extensive reviews on this subject are available (Guo and Kemphues 1996a; Han 1997; Kemphues and Strome 1997; Bowerman 1998).

Asymmetric cell divisions in *Drosophila* neurogenesis

In *Drosophila*, four cells comprise the external sense (es) organ, one major type of sensory organ in the peripheral nervous system (PNS). These cells arise from a stereotyped pattern of asymmetric cell divisions of a sensory organ precursor cell (SOP) (Fig. 2; Jan and Jan 1993). Development of the PNS initiates with the restricted expression of proneural genes in a cluster of epidermal cells. The cells within these proneural clusters are com-

petent to adopt a neural fate. A single cell from each cluster is specified to become an SOP by the action of the neurogenic genes. Two of the neurogenic genes, *Notch* and *Delta*, encode transmembrane domain proteins that function as a receptor and ligand, respectively. *Notch* and *Delta* prevent neighboring cells from assuming a neural fate, a process known as lateral inhibition. This process ensures that only a single cell in each cluster adopts the SOP fate. The SOP divides asymmetrically to produce a IIa and a IIb cell. The IIa cell divides again to generate a socket cell and a hair cell—the outer support cells. The IIb cell gives rise to a sheath cell and a neuron—the inner cells (Fig. 2A). A combination of intrinsic and extrinsic mechanisms is used during these asymmetric cell divisions to generate four cells with distinct fates.

The embryonic central nervous system (CNS) develops from neuroblasts that delaminate basally from the neuroectoderm (Campos-Ortega 1993; Goodman and Doe 1993). As in the PNS, the decision whether to adopt a neuroblast versus epidermal fate involves cell-cell communication mediated by *Notch* and *Delta*. Neuroblasts then divide asymmetrically along their apical-basal axis in a stem cell-like lineage to produce a larger neuroblast and a smaller ganglion mother cell (GMC). Each GMC then divides once to produce two postmitotic neurons or glia. Asymmetric neuroblast divisions can occur normally in vitro, suggesting that the asymmetry of this division is controlled primarily by intrinsic mechanisms (Furst and Mahowald 1985; Huff et al. 1989; Luer and Technau 1992).

Numb behaves like a cell-fate determinant

In the SOP lineage, Numb is an asymmetrically distributed protein that behaves like a cell-fate determinant. *numb* encodes a membrane-associated protein that contains a phosphotyrosine binding (PTB) domain at its amino terminus. It is localized asymmetrically in a crescent to one side of the SOP during mitosis and is preferentially inherited by the IIb cell (Rhyu et al. 1994; Knoblich et al. 1995; Gho and Schweisguth 1998). Cortical crescents of Numb are also observed in both the dividing IIa and IIb cells (Fig. 2B; Wang et al. 1997; Gho and Schweisguth 1998).

Genetic analysis revealed that *numb* function specifies the fate of the SOP progeny in both the embryonic and adult PNS. Loss of *numb* function causes a symmet-

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Figure 1. Intrinsic and extrinsic mechanisms in asymmetric cell divisions. Intrinsic factors indicated in red are distributed asymmetrically in the progenitor cell and inherited by one daughter cell (Z). These factors can be cell fate determinants that specify the fate of the daughter cell that inherits them, factors that distribute cell-fate determinants, or factors that orient the spindle. Extrinsic mechanisms require cell signaling that can occur (1) between daughter cells, (2) between a daughter cell and surrounding cells, or (3) between the precursor cell and surrounding cells.

ric division of the SOP, resulting in the generation of two IIa cells (Uemura et al. 1989; Rhyu et al. 1994). In addition, transformations of hair cell to socket cell and neuron to sheath cell have been observed (Fig. 2C) (Rhyu et al. 1994; Wang et al. 1997). When *numb* is overexpressed in the SOP and its daughters, reciprocal cell-fate transformations occur (Fig. 2D) (Rhyu et al. 1994; Wang et al. 1997). Thus, *numb* acts in all three asymmetric divisions of the SOP lineage to specify the fates of the IIb cell, the hair cell, and the neuron.

Numb is also localized asymmetrically in mitotic neuroblasts of the embryonic CNS. The protein is associated with the membrane, forming a crescent on the basal side of the dividing neuroblast and is inherited by the GMC (Rhyu et al. 1994; Knoblich et al. 1995). However, the role of *numb* in CNS neuroblasts remains unclear, as the neuroblast divisions are unaffected in *numb* mutant embryos (Uemura et al. 1989; Rhyu et al. 1994; Spana et al. 1995). One explanation to account for the lack of phenotype in CNS neuroblast divisions is that *numb* has a maternal component that may provide sufficient function in the absence of zygotic *numb*. Both maternally deposited Numb protein and RNA are found in early embryos (Uemura et al. 1989). Alternatively, molecules that act redundantly with Numb could provide the essential function for these divisions in the absence of zygotic *numb*.

Although lacking an obvious function in most of the CNS, *numb* is required in the division of the MP2 precursor. Unlike the more complicated neuroblast divisions of the CNS, MP2 divides once to produce a slightly larger dorsal neuron, dMP2, and a smaller ventral neuron, vMP2 (Doe et al. 1988). During division of MP2, Numb localizes dorsally and is inherited by dMP2. Lack of *numb* function transforms dMP2 into vMP2, whereas overexpression of Numb transforms vMP2 into dMP2. In both transformations, the initial asymmetry in daughter cell size is unaffected (Spana et al. 1995). These experi-

ments demonstrated that Numb functions as a determinant to specify the fate of the daughter cell that inherits the protein.

As in the nervous system, the asymmetric segregation of Numb is also required in muscle progenitor cells for their daughter cells to adopt distinct cell fates (Uemura et al. 1989; Ruiz and Bate 1997; Carmena et al. 1998). Thus, the role of Numb in the asymmetric divisions of the SOPs, MP2 precursors, and muscle progenitor cells indicates that Numb does not specify one specific cell fate but, instead, is necessary for daughter cells derived from an asymmetric cell division to adopt distinct fates.

Two mouse Numb homologs, m-Numb and Numblake

Figure 2. Wild-type and mutant SOP lineages. Numb and Notch function in the SOP, IIa and IIb divisions. (A) Wild-type SOP lineage. (B) Wild-type SOP, IIa, and IIb divisions showing the distribution of Numb in red. (C–F) Phenotypes of *numb* and *Notch* mutant SOP, IIa, and IIb divisions, as well as the phenotypes caused by misexpression of Numb or expression of a constitutively activated form of Notch, Notch^{ACT}. (C) In strong loss-of-function *numb* mutants, the transformation of IIb into IIa precluded analysis of the IIb division. Isolation of a weaker *numb* mutation in which the SOP division is often normal, also revealed a requirement for *numb* in the IIb division. (D) The effects of overexpressing *numb* using a heat shock promoter (hs-numb) was analyzed in all three divisions by altering the timing of heat shock induction. (E) The requirement for *Notch* in the SOP lineage was analyzed using a temperature-sensitive allele. (F) Notch^{ACT} was overexpressed in the SOP lineage using the UAS–GAL4 system.

(Nbl), are expressed during mouse cortical neurogenesis (Verdi et al. 1996; Zhong et al. 1996, 1997). Both proteins are ~60% homologous to the amino-terminal half of *Drosophila* Numb, which includes the PTB domain, whereas the carboxyl termini diverge. During mammalian neurogenesis, mitotically active neuroblasts reside in a distinct region of the developing cortex called the ventricular zone. Neuroblasts can divide symmetrically to generate two neuroblasts, or asymmetrically to produce a postmitotic neuron and a neuroblast (for review, see Rakic 1988; Caviness et al. 1995; McConnell 1995). m-Numb localizes asymmetrically to the apical membrane of dividing cells in the ventricular zone and may be differentially inherited by the two daughter cells, depending on the orientation of the cleavage plane (Zhong et al. 1996). In contrast, Nbl is a cytoplasmic protein that is expressed in postmitotic neurons outside the ventricular zone (Zhong et al. 1997).

Both m-Numb and Nbl have been expressed in *Drosophila*. m-Numb localizes asymmetrically in both mitotic CNS neuroblasts and SOPs in a pattern identical to endogenous D-Numb (Zhong et al. 1996). This expression is capable of rescuing the *numb* mutant phenotype, whereas overexpression of m-Numb in the SOP results in the transformation of IIa into IIb, the D-Numb overexpression phenotype (Verdi et al. 1996; Zhong et al. 1996). As in mammalian neurons, Nbl is detected throughout the cytoplasm of *Drosophila* neuroblasts (Zhong et al. 1997). In the SOP lineage, inheritance of Nbl by both daughter cells results in the transformation of IIa into IIb. These experiments demonstrate that the cellular machinery required for Numb localization, as well as downstream effectors, is likely to be conserved between *Drosophila* and mammals.

Numb inhibits Notch

Numb specifies cell fate by inhibiting *Notch* function. Phenotypic analysis of a temperature-sensitive *Notch* mutant revealed that in addition to singling out SOPs, Notch signaling also plays a crucial role in the divisions that require *numb*. Reduction of *Notch* function during divisions in the SOP lineage results in IIa to IIb, transformations of sheath cell to neuron and socket cell to hair cell, phenotypes opposite those observed in *numb* mutants (Fig. 2E) (Hartenstein and Posakony 1990; Guo et al. 1996). Expression of an activated form of the Notch receptor results in reciprocal cell-fate transformations, similar to those observed in *numb* mutants (Fig. 2F). Loss of *Notch* function also affects the division of the MP2 precursor. Two dMP2 neurons are produced, a phenotype opposite that observed in *numb* mutant embryos (Spana and Doe 1996).

The reciprocal transformations generated by *numb* and *Notch* mutants led to the proposal that *numb* might antagonize *Notch* signaling (Posakony 1994). Genetic epistasis experiments demonstrate that *Notch* acts downstream of *numb* in both the embryonic SOP and MP2 lineages (Guo et al. 1996; Spana and Doe 1996). Therefore, the asymmetric inheritance of Numb speci-

fies cell fate by inhibiting *Notch* signaling in the daughter cell that inherits the protein.

Numb appears to inhibit *Notch* function by direct protein-protein interactions. The intracellular domain of Notch consists of a RAM23 region followed by six tandem CDC10/ankyrin repeats and a PEST sequence at the very carboxyl terminus (Yochem et al. 1988; Tamura et al. 1995). The PTB domain of Numb binds in vitro to the RAM23 region and the carboxy-terminal tail of Notch (Guo et al. 1996). Similarly, m-Numb interacts with the intracellular domain of the mammalian Notch homolog Notch1 (Zhong et al. 1996). Deletion of the PTB domain of Numb renders the protein nonfunctional. Although the deleted protein is still localized asymmetrically, it can no longer inhibit Notch function (Frise et al. 1996). Deletion of the carboxyl terminus of Numb also eliminates its ability to inhibit Notch function, although this region of the protein does not interact directly with Notch (Frise et al. 1996; Guo et al. 1996).

The genes *Suppressor of Hairless* [*Su(H)*], *Hairless*, *tramtrack*, and *sanpodo* appear to act downstream of *numb* in the SOP lineage. *Su(H)* encodes a protein similar to the mammalian RBP-J κ DNA-binding protein and functions as a transcription activator (Furukawa et al. 1992; Schweisguth and Posakony 1992; Bailey and Posakony 1995; Lecourtois and Schweisguth 1995). Like *Notch*, *Su(H)* functions during the process of lateral inhibition to select a single SOP from a proneural cluster and also specifies cell fate within the SOP lineage (Schweisguth and Posakony 1992; Schweisguth 1995). In the IIa division, loss of *Su(H)* function results in a transformation of socket cell to hair cell, a *Notch* phenotype, whereas overexpression produces two socket cells (Schweisguth and Posakony 1994). *Su(H)* protein accumulates to high levels in the socket cell, consistent with a role in specifying socket cell fate (Gho et al. 1996). Genetic epistasis experiments place *Su(H)* downstream of *numb* in the IIa division (Wang et al. 1997). Consistent with *Su(H)* acting downstream of *numb*, loss of *numb* function results in *Su(H)* expression in both IIa daughters, whereas overexpression of Numb lowers *Su(H)* levels in the daughter cell normally destined to become the socket cell (Wang et al. 1997).

Hairless encodes a novel basic protein that acts as a negative regulator of *Notch* signaling, presumably by antagonizing *Su(H)* activity (Bang and Posakony 1992; Maier et al. 1992; Bang et al. 1995). In the IIa division, *Hairless* loss- and gain-of-function mutations result in reciprocal cell-fate transformations to those observed with *Su(H)* loss- and gain-of-function mutations, respectively (Bang et al. 1991; Bang and Posakony 1992; Schweisguth and Posakony 1994). *Hairless* binds to *Su(H)*, and this interaction inhibits the DNA-binding and transcriptional activation functions of *Su(H)* (Brou et al. 1994). *Hairless*, like *Notch*, also binds to the Numb PTB domain in vitro (Wang et al. 1997).

tramtrack encodes two alternatively spliced zinc finger proteins that act as transcriptional repressors (Harrison and Travers 1990; Brown et al. 1991; Read and Manley 1992). In *tramtrack* mutants, IIa is transformed into

IIb, a phenotype opposite that produced by *numb* mutations, whereas overexpression of *tramtrack* results in a transformation of IIb to IIa (Salzberg et al. 1994; Guo et al. 1995). Genetic epistasis experiments place *tramtrack* downstream of *numb*. *Tramtrack* is expressed in all support cells of an es organ, but not in the neuron and likely functions as a transcriptional repressor of neuronal fate in the support cells. *Tramtrack* also acts as a negative regulator of neuronal differentiation in the developing eye and embryonic CNS (Xiong and Montell 1993; Giesen et al. 1997; Li et al. 1997b; Tang et al. 1997).

Mutations in *sanpodo* affect the asymmetric division of IIb (Dye et al. 1998). The sheath cell is transformed into a neuron, a phenotype also produced by loss of *Notch* function in the IIb division and opposite that observed in *numb* mutants. A low frequency of transformations of socket cell to hair cell in *sanpodo* mutants suggests that *sanpodo* also functions in the IIa division. Genetic epistasis experiments reveal that *sanpodo* functions downstream of *numb* and thus might be a novel member of the *Notch* signaling pathway. *sanpodo* encodes a homolog of tropomodulin, a vertebrate actin/tropomyosin-associated protein (Dye et al. 1998). In addition to its role in the IIb division, *sanpodo* also functions to regulate bristle length and morphology. Mutations in *chickadee*, which encodes a Profilin, and *singed*, which encodes an actin-bundling protein, result in bristle phenotypes similar to those displayed by *sanpodo* mutants (Dye et al. 1998).

Additional proteins besides *Notch* and *Hairless* interact with *Numb*. *Numb*-associated kinase (*Nak*), a putative serine/threonine kinase, was isolated in a yeast two-hybrid screen using *Numb*'s PTB domain as bait (Chien et al. 1998). Consistent with a role for *Nak* in the SOP lineage, *Nak* overexpression causes a phenotype similar to that observed in *numb* mutant embryos. Perhaps *Nak* phosphorylates *Numb* directly to inhibit *numb* activity. In a two-hybrid screen for proteins that interacted with the PTB domain of m-*Numb*, Ligand of *Numb*-protein X (*LNK*), a novel protein containing a amino-terminal RING finger domain and four PDZ domains, was isolated (Dho et al. 1998). The biological relevance of this interaction has yet to be tested.

Source of Notch ligands

The involvement of *Notch* signaling in both the SOP and MP2 lineages raises two questions. First, what is the ligand for *Notch*? To date, two *Notch* ligands, *Delta* and *Serrate*, have been identified in *Drosophila*. Second, which cells are the source of ligand? Either sister cells within the lineage or adjacent cells could supply ligand. In the MP2 lineage, the relevant ligand appears to be *Delta* (Spana and Doe 1996). Loss of *Delta* function leads to the same cell-fate transformations in the MP2 lineage as loss of *Notch* function. The source of *Delta* appears to be the adjacent mesoderm, in which the protein is expressed at high levels, and not the MP2 daughter cells,

which lack detectable *Delta* expression (Fig. 3A). Consistent with this hypothesis, division of an isolated MP2 precursor in culture results in the production of two dMP2 neurons, a phenotype produced by loss of *Notch* or *Delta* function.

Initial observations also suggested that *Delta* is the ligand for *Notch* in the SOP lineage. Altering *Delta* function at the time of SOP division using a temperature-sensitive allele results in a *Notch* phenotype (Parks and Muskavitch 1993). However, large mitotic clones generated using a null allele of *Delta* had no effect on divisions in the SOP lineage (Zeng et al. 1998). In addition, generating mosaic animals in which *Delta* function was specifically removed in the SOP lineage had no effect on the fate of the daughter cells (Zeng et al. 1998). This discrepancy can be explained if the temperature-sensitive *Delta* allele alters rather than reduces *Delta* function. Although removing *Serrate* function in the SOP lineage also had no effect on the fate of daughter cells, eliminating both *Delta* and *Serrate* function resulted in a *Notch* phenotype (Zeng et al. 1998). Thus, *Delta* and *Serrate* act as redundant *Notch* ligands. Because loss of *Delta* and *Serrate* function within the SOP lineage produced a *Notch* phenotype, *Notch* signaling occurs between SOP daughters (Fig. 3B).

Asymmetric distribution of the transcription factor Prospero

Prospero, a homeodomain protein, is also an asymmetri-

Figure 3. Inhibition of *Notch* signaling by *Numb*. *Numb* is asymmetrically inherited by one daughter cell in which it inhibits *Notch* presumably by direct protein-protein interactions. (A) In the MP2 daughter cells, *Delta* is the *Notch* ligand and the source of *Delta* is from outside the lineage. (B) In the SOP division, both *Delta* and *Serrate* are *Notch* ligands, and signaling occurs between the two daughter cells.

cally distributed factor that behaves like a cell-fate determinant in *Drosophila* (Doe et al. 1991; Vaessin et al. 1991; Hirata et al. 1995; Knoblich et al. 1995; Spana and Doe 1995). In interphase CNS neuroblasts, Prospero is detected at the apical cortex (Spana and Doe 1995). During mitosis, Prospero moves to the basal cortex, colocalizing with Numb. When the neuroblast divides, Prospero is inherited by the GMC, where it translocates to the nucleus (Fig. 4) (Hirata et al. 1995; Knoblich et al. 1995; Spana and Doe 1995). In the GMC, Prospero functions as a transcriptional activator and repressor (Doe et al. 1991; Vaessin et al. 1991). Prospero and Numb localize to the basal cortex independently; each protein localizes normally in the absence of the other (Knoblich et al. 1995; Spana and Doe 1995).

The colocalization of Numb and Prospero to the basal cortex of CNS neuroblasts during mitosis suggests that they might utilize common mechanisms for their localization. However, differences in their localization pattern are apparent. The early apical localization of Prospero in interphase neuroblasts is not observed with Numb, and this difference might reflect the function of Prospero as a transcription factor. Apical localization to the cell cortex early might prevent inappropriate nuclear translocation (Spana and Doe 1995). In addition, Numb is asymmetrically localized in the MP2 precursor, whereas Prospero is detected in the nucleus (Spana and Doe 1995). These differences suggest that Numb and Prospero may also utilize different mechanisms to achieve their localization.

Miranda localizes Prospero

The product of the *miranda* gene is necessary for the asymmetric distribution of Prospero. Miranda was originally identified in a two-hybrid screen for proteins that interacted with a region of Prospero that is required for its asymmetric localization (Hirata et al. 1995; Ikeshima et al. 1997; Shen et al. 1997). Miranda contains four predicted coiled-coil domains and two leucine zipper motifs, sequences normally involved in protein-protein interactions. At the carboxyl terminus are eight predicted protein kinase C (PKC) phosphorylation sites. Miranda colocalizes with Prospero in CNS neuroblasts (Fig. 4). At

interphase, Miranda is detected in an apical crescent. During mitosis, Miranda relocates to the basal cortex and is inherited by the GMC (Schuldt et al. 1998; Shen et al. 1998). In the GMC, Miranda disappears rapidly while Prospero translocates to the nucleus (Ikeshima et al. 1997; Shen et al. 1997, 1998; Schuldt et al. 1998). The amino terminus of Miranda is sufficient for its asymmetric localization, while a more carboxy-terminal region that is predicted to form a coiled-coil domain interacts with Prospero (Ikeshima et al. 1997; Shen et al. 1998). Miranda is also expressed in the PNS, but its role here has yet to be characterized (Ikeshima et al. 1997; Shen et al. 1997).

In *miranda* mutant embryos, Prospero is localized throughout the cytoplasm of the CNS neuroblast and is inherited by both daughter cells where it enters each nucleus (Ikeshima et al. 1997; Shen et al. 1997; Schuldt et al. 1998). These embryos display a weak *prospero* phenotype (Ikeshima et al. 1997). In wild-type embryos, Prospero activates expression of the Even-skipped protein in a subset of GMCs and neurons (Doe et al. 1991). In *miranda* mutant embryos, many of these cells fail to express Eve (Ikeshima et al. 1997). This phenotype may result from a reduction in Prospero levels in the GMC caused by the distribution of Prospero between two daughter cells. Alternatively, Miranda might have functions in the GMC distinct from its role in tethering Prospero.

The loss of detectable Miranda after cytokinesis suggests that Miranda degradation might be a prerequisite for the nuclear translocation of Prospero. Consistent with this hypothesis, Miranda contains four weakly conserved destruction boxes, a 9-amino-acid motif originally identified in A and B cyclins that is involved in their cell-cycle-dependent degradation (King et al. 1996; Shen et al. 1997). If the degradation of Miranda is necessary for the translocation of Prospero to the nucleus, then overexpression of Miranda might retain Prospero at the cortex. However, when Miranda is overexpressed, Prospero translocates to the nucleus despite high levels of Miranda at the cortex (Ikeshima et al. 1997). Analysis of a specific *miranda* mutant, *miranda*^{RR127}, suggests an alternative model. In this mutant, Prospero localizes to the basal cortex of the neuroblast and segregates to the GMC normally but then fails to translocate to the nucleus,

Figure 4. Distribution of Inscuteable, Miranda, Prospero, Staufen and *prospero* mRNA in CNS neuroblast divisions. (Adapted from Schuldt et al. 1998.)

remaining associated with the cortex. The *miranda*^{RR127} mutation causes a frameshift, replacing the carboxy-terminal 103 amino acids, which contain the consensus PKC phosphorylation sites, by 112 unrelated amino acids (Ikeshima et al. 1997). This result raises the possibility that phosphorylation might regulate the Miranda/Prospero interaction. If true, then the degradation of Miranda might be a consequence, rather than the cause, of Prospero's release from the cortex.

Miranda also interacts physically with Staufen, an RNA-binding protein involved in the localization of *oskar* and *bicoid* mRNAs during oogenesis (Ephrussi et al. 1991; Kim-Ha et al. 1991; St Johnston et al. 1991; Ferrandon et al. 1994). Staufen protein localizes in CNS neuroblasts in a pattern similar to Miranda (Fig. 4). It is concentrated apically during interphase and then relocalizes in a basal crescent during mitosis (Li et al. 1997a; Schuldt et al. 1998; Shen et al. 1998). In *miranda* mutants, Staufen is no longer localized asymmetrically in mitotic neuroblasts and is detected either in the cytoplasm or diffusely around the cell cortex (Schuldt et al. 1998; Shen et al. 1998).

The carboxyl terminus of Staufen is essential for its asymmetric localization in neuroblasts. Deletion of the last 157 amino acids of Staufen, the region that binds Miranda, eliminates both the apical and basal cortical crescents. Instead, the mutant protein is detected throughout the cytoplasm (Schuldt et al. 1998; Shen et al. 1998). The Staufen binding site in Miranda is located in a region containing one of the predicted coiled-coil domains and partially overlaps the predicted Prospero binding site (Schuldt et al. 1998).

Staufen functions during CNS neuroblast divisions to localize *prospero* RNA (Fig. 4). In most interphase neuroblasts, *prospero* RNA is localized apically in a cortical crescent. During mitosis, *prospero* RNA is observed in a basal crescent and is subsequently segregated into the GMC (Li et al. 1997a; Broadus et al. 1998). Loss of *staufen* function disrupts *prospero* RNA localization during mitosis, though not completely, indicating that additional factors may be required to tether *prospero* RNA (Li et al. 1997a; Broadus et al. 1998). As expected, because Miranda is required for the localization of Staufen, *prospero* RNA is also mislocalized in *miranda* mutants (Schuldt et al. 1998).

In vitro and in vivo binding studies demonstrate that Staufen may localize *prospero* RNA directly by interacting physically with the *prospero* 3' UTR (Li et al. 1997a; Schuldt et al. 1998). Surprisingly, no phenotype is associated with the inability to segregate *prospero* RNA to the GMC in *staufen* mutants (Broadus et al. 1998). However, under conditions in which *prospero* activity is compromised, *prospero* RNA localization is important. The inability to segregate *prospero* RNA asymmetrically enhances the weak phenotype of a partial loss-of function *prospero* mutant (Broadus et al. 1998).

Miranda also interacts with Numb. A central region of Miranda, distinct from the region that interacts with Prospero, binds to Numb in vitro (Shen et al. 1997, 1998). However, the biological relevance of this interaction is

unknown, as no defects in Numb localization in CNS neuroblasts have been observed in *miranda* mutants (Ikeshima et al. 1997; Shen et al. 1997). Possibly Miranda acts redundantly with other factors necessary for the asymmetric localization of Numb, or maternally deposited Miranda is sufficient to localize Numb.

Inscuteable coordinates asymmetry in CNS neuroblasts

The amino terminus of Miranda, which is responsible for its asymmetric localization, interacts with Inscuteable (Shen et al. 1998). The Inscuteable protein contains five ankyrin-like repeats, a polyproline region that fits the SH3 binding site consensus sequence, and a carboxyl terminus predicted to be rich in α -helices (Kraut and Campos-Ortega 1996). The modular structure of Inscuteable has led to the proposal that it functions as an adapter protein that interacts with several components, including the cytoskeleton. Miranda binds to a central region of Inscuteable containing the ankyrin-like repeats (Shen et al. 1998).

inscuteable is necessary for several events in the asymmetric divisions of CNS neuroblasts, placing it upstream of other components involved in this process. *inscuteable* is required for orienting the mitotic spindle, a prerequisite for the correct partitioning of asymmetrically localized factors to daughter cells. In *inscuteable* mutant neuroblasts, the spindle no longer aligns along the apical-basal axis but, instead, aligns randomly (Kraut et al. 1996). *inscuteable* is also required for proper localization of Numb, Miranda, Prospero, Staufen, and *prospero* RNA. In *inscuteable* mutant neuroblasts, Numb, Prospero, and Miranda either localize symmetrically at the cortex or form crescents that orient randomly relative to the spindle (Kraut et al. 1996; Shen et al. 1997). When distributed in random crescents, Numb, Miranda, and Prospero still colocalize with one another. This observation suggests that factors, in addition to Inscuteable, can contribute to the asymmetric distribution of these proteins.

Because Miranda localizes Staufen, which in turn localizes *prospero* RNA, one might have expected that Staufen and *prospero* RNA distribution in *inscuteable* mutant neuroblasts might have mirrored the pattern of Miranda mislocalization. However, in *inscuteable* mutants, the localization of Staufen and *prospero* RNA is distinct from the localization of Miranda. Neither *prospero* RNA nor Staufen have been reported to form random crescents. Instead, the percentage of interphase neuroblasts with Staufen localized in an apical crescent is reduced, and Staufen is distributed symmetrically at the cortex (Li et al. 1997a). *prospero* RNA localizes to the apical cortex normally during interphase, but its transition to the basal cortex during mitosis fails to occur in *inscuteable* mutants (Li et al. 1997a).

In addition to interacting physically with Miranda, Inscuteable also binds Staufen both in vitro and by yeast two-hybrid analysis (Li et al. 1997a; Shen et al. 1998). The carboxyl terminus of Inscuteable, containing the predicted α -helices, binds to the carboxyl terminus of

Staufen. This region of Inscuteable is distinct from the region that interacts with Miranda.

The Inscuteable protein is first detected in the stalk connecting the delaminating neuroblast with the neuro-epithelium (Kraut et al. 1996). In interphase neuroblasts, Inscuteable, like Prospero, Miranda, Staufen, and *prospero* RNA, is observed in an apical cortical crescent. During prophase when these proteins and RNA become localized to the basal cortex, Inscuteable remains apically localized until metaphase, after which point only weak diffuse staining is observed.

These observations have led to the model that Inscuteable interprets the apical-basal polarity of the neuroblast and acts to direct the formation of a protein/RNA complex on the apical side. This complex is released from Inscuteable during mitosis and translocates to the basal side (Li et al. 1997a; Schuldt et al. 1998). Alternatively, part or all of the protein/RNA complex might disassemble and reform de novo on the basal side. Inhibitor studies have shown that the asymmetric localization of Numb, Prospero, *prospero* RNA, Miranda, Staufen, and Inscuteable all depend on the actin cytoskeleton but not on microtubules (Kraut et al. 1996; Knoblich et al. 1997; Broadus et al. 1998; Shen et al. 1998). These studies suggest that the transition of proteins and RNA from the apical to basal side may involve an actin-based motor. While no myosin has been implicated in this process, the generation of cellular asymmetry in the *C. elegans* embryo requires a myosin motor. Several of the PAR proteins, which establish polarity in the early embryo, are asymmetrically localized (for review, see Guo and Kemphues 1996a; Kemphues and Strome 1997). A non-muscle myosin II heavy chain, NMY-2, interacts with PAR-1 and is necessary for the asymmetric localization of PAR-1, PAR-2, and PAR-3 (Guo and Kemphues 1996b).

Although *inscuteable* mediates several events necessary for the asymmetric divisions of neuroblasts, other unidentified factors are likely to be involved in establishing apical-basal polarity. The normal localization of *prospero* RNA apically in the absence of *inscuteable* suggests that mutant neuroblasts still retain some apical-basal polarity.

Asymmetric division of the GMCs

GMCs also display the same apical-basal polarity that is observed in neuroblasts. Inscuteable is localized in a apical crescent, whereas Numb is detected in a basal cortical crescent (Buescher et al. 1998). GMCs frequently divide asymmetrically to generate two postmitotic sibling neurons with distinct fates, as assayed by the expression of molecular markers and axonal projections. GMC4-2a, for example, divides asymmetrically to generate a larger RP2 daughter and a smaller RP2sib daughter, whereas GMC1-1a divides asymmetrically to produce aCC and pCC neurons. Because of the size difference between RP2 and RP2sib, it was possible to show that Numb is preferentially segregated to RP2 (Buescher et al. 1998). In *inscuteable* mutants, GMC4-2a divides symmetrically

to produce two equally sized daughter cells that both develop as RP2 neurons, whereas division of GMC1-1a produces two aCC neurons (Buescher et al. 1998). In the majority of mutant GMCs, Numb no longer forms a basal crescent but, instead, is distributed symmetrically around the cortex. As in neuroblast divisions, *inscuteable* is also necessary for correct spindle orientation during GMC divisions (Buescher et al. 1998).

Analysis of more severe alleles than those used in previous studies revealed a requirement for Numb in specifying sibling neuron identity. In *numb* mutants, RP2 is often transformed into RP2sib, but the two daughter cells remain unequal in size (Buescher et al. 1998; Skeath and Doe 1998). Thus, the cell that normally inherits Numb assumes the fate of its sister cell. Cell-fate transformations were also observed between additional sibling neuron pairs examined, except for aCC/pCC (Buescher et al. 1998; Skeath and Doe 1998). The aCC/pCC neurons are the first born among the pairs analyzed. Because none of the available *numb* alleles appear to be null and there is a maternal *numb* component, low levels of *numb* function may be sufficient to specify aCC/pCC fates (Buescher et al. 1998; Skeath and Doe 1998). Alternatively, the fates of aCC and pCC may be determined by another mechanism. In the grasshopper, laser ablation of either aCC or pCC immediately after birth results in the remaining cell always adopting an aCC fate (Kuwada and Goodman 1985). Thus, interactions between the two daughter cells are necessary for pCC fate in the grasshopper.

As in the asymmetric divisions of the SOPs and CNS neuroblasts, *numb* appears to function in GMC divisions by inhibiting Notch signaling. Mutations in *Notch*, *Delta*, *mastermind*, and *sanpodo* all transform RP2sib into RP2, the reciprocal transformation to that observed in *numb* mutants (Buescher et al. 1998; Schuldt and Brand 1998; Skeath and Doe 1998). Other components that participate in Notch-mediated lateral inhibition during neuroblast specification, *enhancer of split* and *neuralized*, do not function in specification of sibling neuron fate (Skeath and Doe 1998). Conversely, *sanpodo*, a gene that functions in the *Notch* pathway during asymmetric divisions in the SOP lineage and GMC divisions, does not have an earlier requirement in lateral inhibition (Dye et al. 1998).

Asymmetric cell division in the *C. elegans* nervous system

In *C. elegans*, asymmetric neuroblast divisions generate all 302 neurons of the hermaphrodite nervous system. Several genes involved in *Drosophila* asymmetric cell divisions have homologs in *C. elegans*. The *C. elegans* sequencing consortium has identified homologs for Numb and Prospero. How these genes function during nematode development has not been described, and their potential roles in asymmetric cell divisions await further analysis. Many of the genes in the *Drosophila* Notch signaling pathway have homologs in *C. elegans* (for review, see Kimble and Simpson 1997; Greenwald 1998).

However, they have not been implicated in asymmetric cell divisions during nervous system development.

Although a *miranda* homolog has not been identified in *C. elegans*, the HAM-1 protein may function as a tether for cell fate determinants. The HAM-1 protein is localized asymmetrically in a crescent at the cell periphery of many embryonic neuroblast cells (Guenther and Garriga 1996). In particular, HAM-1 is localized asymmetrically in the HSN/PHB neuroblast, which divides to generate an anterior cell that dies and a posterior neuroblast cell, the HSN/PHB precursor. This precursor divides to generate the HSN motor neuron and PHB sensory neuron (Sulston et al. 1980). HAM-1 localizes to the posterior periphery of the HSN/PHB neuroblast and is inherited by the HSN/PHB precursor. In *ham-1* mutants, the anterior daughter cell is often transformed into a second HSN/PHB precursor, resulting in duplication of HSN and PHB neurons. Thus, the fate of the daughter cell that does not inherit HAM-1 is transformed. The mutant phenotype and the protein localization led to a model in which HAM-1 tethers determinants to ensure that they are asymmetrically segregated to the HSN/PHB precursor. In the absence of HAM-1, determinants presumably are distributed symmetrically throughout the HSN/PHB neuroblast and are inherited by both daughter cells. In this model, the anterior daughter cell, which normally dies, differentiates into a second HSN/PHB precursor due to the presence of mislocalized determinants. Four additional asymmetric cell divisions are altered by *ham-1* mutations. The affected divisions occur at the same time during embryogenesis and produce one daughter that undergoes programmed cell death and either a neuron or neuronal precursor.

Although HAM-1 and Miranda are predicted to function as tethers for cell fate determinants, the proteins share no obvious sequence similarities. Miranda tethers at least two proteins, Prospero and Staufen. Confirmation of HAM-1's function as a tether awaits the identification of determinants that it binds.

Although factors directly associated with HAM-1 have

not been identified, one downstream target of HAM-1 has been characterized. HAM-1 may regulate the expression of the gene *unc-86*, which encodes a POU domain transcription factor (Finney et al. 1988). *Unc-86* is expressed in 57 of 302 neurons (Finney and Ruvkun 1990). Expression of *Unc-86*, which is necessary to distinguish daughter from mother cell fates, is detected in only one of the two daughter cells after an asymmetric neuroblast division. In the ALN/PLM neuroblast, HAM-1 is necessary for the asymmetric expression of *Unc-86*. The ALN/PLM neuroblast divides asymmetrically to generate an anterior daughter cell that dies and a posterior daughter cell that divides to produce a cell that dies and the ALN/PLM precursor. The precursor divides to produce the ALN and PLM sensory neurons. HAM-1 is distributed asymmetrically in the ALN/PLM neuroblast and is inherited by the posterior daughter cell, which expresses *Unc-86* (Finney and Ruvkun 1990; Guenther and Garriga 1996). In *ham-1* mutants, the ALN/PLM neuroblast often divides symmetrically to generate two cells that both assume the fate of the posterior daughter, resulting in a duplication of cells expressing *Unc-86* (Guenther and Garriga 1996).

Wnt signaling in *C. elegans* regulates asymmetric cell divisions

The Wnt signaling pathway regulates many key developmental processes and is conserved between *C. elegans* and mammals (for a recent review, see Cadigan and Nusse 1997). The canonical pathway is depicted in Figure 5. In *C. elegans*, LIN-44 was the first Wnt shown to orient asymmetric cell divisions. LIN-44 is expressed from a group of epithelial cells in the tip of the *C. elegans* tail and acts nonautonomously to orient the divisions of cells located more anteriorly (Herman and Horvitz 1994; Herman et al. 1995). For example, the division of the male B cell requires *lin-44* function. In wild-type males, the B cell divides asymmetrically to produce a larger anterior daughter, B.a, and a smaller posterior daughter,

Figure 5. Wnt pathway. (Left) The canonical Wnt pathway. The names of the mammalian components are given, with the *Drosophila* components in parentheses. The pathways in the middle and on the right show Wnt pathway components that have been shown to function in the asymmetric cell divisions of the *C. elegans* B and EMS cells, respectively.

B.p. The number and kinds of progeny that they generate also distinguish the two daughter cells (Sulston et al. 1980). A *lin-44* male B cell also divides asymmetrically, but the orientation of its division is reversed. The anterior daughter resembles B.p, being the smaller daughter cell and producing cells normally derived from B.p, whereas the posterior daughter looks like B.a, being larger and producing cells normally derived from B.a (Herman and Horvitz 1994).

These results have led to the hypothesis that the male B cell orients its polarity by the asymmetric signaling of LIN-44 at the posterior of the B cell membrane (Herman et al. 1995). However, two observations are difficult to reconcile with this simple model. First, LIN-44, which is expressed from a heat shock promoter, which is predicted to signal the B cell from all directions, rescues the B-cell defects (Herman et al. 1995). Thus, this result appears inconsistent with the notion that Wnt signaling at the posterior membrane of the B cell orients its polarity. One explanation offered to resolve this paradox proposes that only cells in the tail can secrete or modify LIN-44. Second, LIN-17, a Frizzled (Fz) homolog and putative LIN-44 receptor, is expressed in the B cell, but loss of *lin-17* function results in a phenotype that is different from loss of *lin-44* (Sawa et al. 1996). In *lin-17* mutants, the B cell divides symmetrically to produce two daughter cells of equivalent size that both assume the B.a fate (Sternberg and Horvitz 1988). To resolve this discrepancy, Sawa et al. (1996) have proposed that a second polarizing signal, derived from a source anterior to the B cell, also signals through LIN-17. In the absence of *lin-44* function, *lin-17* can respond to this signal whose activity is normally masked in the presence of wild-type *lin-44* function. Thus, LIN-44 and a second signal acting at opposite ends of the B cell through LIN-17 produce B cell polarity. This model predicts that animals deficient for *lin-44* and the second signal, perhaps another Wnt, would display a *lin-17* phenotype. Currently, four additional Wnt homologs have been identified in *C. elegans*.

Some questions concerning the role of Wnt signaling in asymmetric cell divisions have been addressed in studies of the asymmetric divisions of the EMS neuroblast cell. Although EMS produces no neurons, a discussion of the EMS division will clarify some of the issues concerning Wnt signaling in asymmetric cell divisions.

The first cleavage of the *C. elegans* zygote is unequal, generating a larger anterior blastomere AB and a smaller posterior blastomere P1. AB divides to produce ABa and ABp, whereas P1 divides to produce EMS and P2. EMS divides to produce a posterior daughter E, which gives rise to intestine, and an anterior daughter MS, which primarily produces pharyngeal and body wall muscle. In the four-cell embryo, interactions between EMS and P2 are required to polarize EMS. When EMS is cultured in isolation, it no longer produces intestine. Instead, both daughter cells adopt the MS fate (Goldstein 1992). When EMS is cocultured next to P2, the gut differentiation defect is rescued and the cell derived from the side of EMS contacting P2 adopts the E fate (Goldstein 1992, 1993). Thus, P2 signals EMS to divide asymmetrically.

A P2-to-EMS signal also orients the EMS mitotic spindle. In EMS, the centrosome–nuclear complex rotates 90° so the mitotic spindle is aligned roughly along the anteroposterior axis pointing toward P2 (Hyman and White 1987). When EMS is cultured in isolation, this rotation fails; coculturing EMS in contact with P2 can rescue this defect (Goldstein 1995). Although P2 can induce both E cell fate and correct spindle orientation at the same time, there is a longer window of time in which EMS is competent to respond to the signal for the induction of gut. Thus, it is unclear from these experiments whether two independent signals control EMS polarization or whether a single signal controls both aspects of EMS polarity.

Five *mom* (more of MS) genes, as well as *apr-1* and *wrm-1*, have been implicated in P2/EMS signaling (Rocheleau et al. 1997; Thorpe et al. 1997). Loss of function in these genes results in both EMS daughters adopting an MS fate, the same fate adopted by both daughters when EMS is cultured in isolation. Several of these genes have been characterized molecularly and they encode components of the Wnt signaling pathway. The *mom-1*, *mom-2*, and *mom-5* genes encode Porcupine, Wnt, and Frizzled homologs respectively, whereas *apr-1* is similar to β -catenin, and *wrm-1* encodes an APC-like gene (Rocheleau et al. 1997; Thorpe et al. 1997). Mosaic analysis revealed that *mom-1*, *mom-2*, and *mom-3* all function in P2, whereas *mom-4* is required in EMS (Thorpe et al. 1997). On the basis of its homology to Frizzled receptors, *mom-5* is also likely to function in EMS. Because only Wnt and Porcupine are known to be expressed by the signaling cell, *mom-3* may encode a novel member of the Wnt pathway.

In *C. elegans*, the function of this Wnt signaling pathway is to decrease the levels of POP-1, a LEF/TCF homolog, in the E cell. In wild-type embryos, POP-1 protein accumulates to high levels in the MS nucleus, whereas a lower level of staining is observed in the E nucleus (Lin et al. 1995). Mutations in *pop-1* cause both daughters of EMS to adopt E fates, the reciprocal transformation to that displayed by Wnt signaling mutants (Lin et al. 1995). When Wnt signaling is disrupted, POP-1 accumulates to high levels in the nuclei of both EMS daughters (Rocheleau et al. 1997; Thorpe et al. 1997). Genetic epistasis experiments confirm that *pop-1* acts downstream of the other Wnt pathway genes (Rocheleau et al. 1997; Thorpe et al. 1997). Thus, POP-1 levels are down-regulated in the E cell in response to a Wnt signal. The similarities and differences between Wnt signaling in EMS polarity and other Wnt signaling pathways have been reviewed previously (Cadigan and Nusse 1997; Han 1997).

Animals lacking *mom-1*, *mom-2*, *mom-5*, or *apr-1* function are incompletely penetrant for the transformation of E to MS (Rocheleau et al. 1997; Thorpe et al. 1997). One interpretation of this observation is that the mutants retain some function. However, the mutations in the *mom* genes have been characterized molecularly and are predicted to severely reduce, if not eliminate, gene function (Rocheleau et al. 1997; Thorpe et al. 1997). Removal of *apr-1* function in a *mom-2* or *mom-5* mutant

background results in a 100% transformation of E to MS, suggesting that the functions of *apr-1* and the *mom* genes are partially redundant. In contrast, embryos lacking *wrm-1* function are 100% penetrant for an E-to-MS transformation (Rocheleau et al. 1997). These findings led to the model that *mom-1*, *mom-2*, and *mom-5* act in a parallel pathway to *apr-1* and that these two pathways converge upon *wrm-1* (Rocheleau et al. 1997).

Like *lin-44* (Wnt) and *lin-17* (Fz), the relationship between *mom-2* (Wnt) and *mom-5* (Fz) is complicated. Whereas *mom-2* mutants are ~60% penetrant for the E-to-MS transformation, *mom-5* mutants are only ~5% penetrant, which suggests that *mom-2* may act through a second Fz receptor. Amazingly, the *mom-2*; *mom-5* double mutant phenotype resembles the less penetrant phenotype of the *mom-5* single mutant; in only 5% of the animals is there a transformation of E to MS. These observations eliminate the simple model that *mom-2* signals directly through *mom-5* to activate downstream components of the pathway. The finding that *mom-2* mutants require wild-type *mom-5* function to express their more highly penetrant phenotype suggests that *mom-2* may inhibit *mom-5*, either directly or through signaling components that act downstream of *mom-5*. Precedence for antagonistic action of different Wnt proteins exists in *Xenopus*; the ability of Wnt-1 to induce a secondary axis is suppressed by members of the Wnt-5A class (Torres et al. 1996).

Considerably less is known about the P2/EMS signal involved in the alignment of the mitotic spindle in EMS. In *mom-1*; *mom-2* double mutants the orientation of the mitotic spindle is affected in ~45% of mutant embryos, whereas *mom-1* and *mom-2* single mutants display only subtle defects (Thorpe et al. 1997). Because *mom-1* is a Porcupine homolog, it might be required for the secretion of a second Wnt involved in the process. Further investigation will be required to determine the role of the other *mom* genes, as well as *wrm-1* and *apr-1*, in spindle orientation.

One major question raised by the analysis of Wnt signaling in *C. elegans* is how does a Wnt signal polarize an individual cell? MOM-2 polarizes EMS prior to its division, ensuring that EMS divides asymmetrically. It is difficult to imagine how EMS polarity could be generated through the transcriptional regulation of downstream effectors. Consistent with this idea, inhibition of transcription does not affect spindle orientation in the early embryo (Edgar et al. 1994; Powell-Coffman et al. 1996). Although specific *mom* mutants have only subtle defects in EMS spindle orientation, mutations in several of the *mom* genes have completely penetrant defects in the alignment of the mitotic spindle in a different blastomere, ABar (Rocheleau et al. 1997; Thorpe et al. 1997). It has been proposed that Wnt signaling may influence the cytoskeleton directly, thereby directing cell polarization.

Wnt signaling in *Drosophila* tissue polarity

In *Drosophila*, a possible connection between Wnt signaling and cytoskeletal rearrangements is provided by

the analysis of tissue polarity. Tissue polarity involves the coordinate polarization of individual cells within the plane of an epithelium (for review, see Adler 1992; Gubb 1993). In the adult wing blade, for instance, a single distally pointing hair emerges from each epidermal cell. Hair formation is preceded by the accumulation of actin at the distal vertex of each epithelial cell (Wong and Adler 1993). Mutations in *fz* and *dishevelled* alter the polarity of wing hairs by affecting the subcellular location of actin accumulation (Wong and Adler 1993). Actin bundles generally form near the cell center instead of the distal vertex indicating that *fz* and *dishevelled* polarize individual cells. Whether *fz* and *dishevelled* transduce a Wnt signal is unclear, as no obvious tissue polarity phenotypes have been described for mutations in *wingless* or other components of the Wnt pathway. However, ectopic expression of *wingless* or *zeste-white 3* in the eye disrupts tissue polarity in the eye (Tomlinson et al. 1997). In addition, other genes identified that act in the generation of tissue polarity are not components of the Wnt signaling pathway (Adler et al. 1994; Krasnow et al. 1995; Eaton et al. 1996; Strutt et al. 1997; Boutros et al. 1998; Wolff and Rubin 1998).

Both *fz* and *dishevelled* are involved in the polarization of *Drosophila* adult SOPs (Gho and Schweisguth 1998). In the pupal notum, the mitotic spindles in the SOPs are aligned parallel to the anteroposterior axis, resulting in a reproducible division orientation. Mutations in *fz* or *dishevelled* randomize spindle orientation in the SOP. Numb is still associated with one end of the mitotic spindle and is preferentially inherited by one of the two daughter cells. Thus, the orientation, but not the asymmetry, of the division is affected. This phenotype differs from that produced by mutations in the *C. elegans* Fz genes *lin-17* and *mom-5*, which are necessary for precursors to divide asymmetrically to generate daughters with distinct fates. It is unclear how directly *fz* and *dishevelled* act in determining spindle orientation in the SOP. These genes could function directly in the SOP to orient its spindle. Alternatively, they could organize polarity in the surrounding epithelium, an event that would be necessary to orient the SOP spindle.

Future directions

In the past few years, rapid progress has been made in elucidating the mechanisms underlying asymmetric cell divisions. However, several outstanding questions remain to be addressed. First, how is neuroblast polarity established? For instance, there have been significant advancements in understanding how the asymmetric segregation of Numb in the *Drosophila* SOP specifies distinct cell fates. However, little is known concerning the origin of SOP polarity and hence the mechanisms that contribute to Numb's distribution. The recent finding that *fz* and *dishevelled* are involved in orienting the mitotic spindle raises the question of whether Wnt signaling may direct the asymmetric localization of intracellular molecules. Certainly, studies in *C. elegans* have demonstrated that Wnt signaling can polarize individual

cells, but as yet no asymmetrically distributed molecules have been identified in these cells.

Second, what is the role of the cell cycle in the regulation of cell polarity. In *C. elegans*, there is a limited time during the cell cycle in which EMS can respond to the signal from P2. In addition, there is a point in the cell cycle in which a signal from P2 can induce gut but no longer orient the EMS mitotic spindle. Currently, nothing is known about how the response to this Wnt signal is regulated. In *Drosophila* CNS neuroblasts, the apical-basal transition of an intracellular complex appears to be regulated by the cell cycle, but once again the mechanisms underlying this regulation are unknown.

Finally, how is the localization of intracellular complexes regulated? In *Drosophila* CNS neuroblasts, a complex of proteins and RNA moves from the apical to basal cortex during mitosis. How does this transition occur? Does it involve some form of regulated transport or does the complex diffuse and become captured on the basal side? Does this change in localization involve protein degradation and resynthesis? What is the precise role of the cytoskeleton in these changes? Answers to these questions will contribute to our understanding of how extrinsic and intrinsic mechanisms are integrated to control asymmetric cell divisions.

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Hawkins and Garriaga

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