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L.D. Hurst *is in the Department of Biology and Biochemistry, University of Bath, Claverton Down, Bath, UK BA2 7AY.*
H. Ellegren *is in the Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Box 597, S-751 24 Uppsala, Sweden.*

Frizzled signaling and the developmental control of cell polarity

JOSHUA M. SHULMAN (jms78@hermes.cam.ac.uk)
NORBERT PERRIMON (perrimon@rascal.med.harvard.edu)
JEFFREY D. AXELROD (jaxelrod@cmgm.stanford.edu)

Within the last three years, Frizzled receptors have risen from obscurity to celebrity status owing to their functional identification as receptors for the ubiquitous family of secreted WNT signaling factors. However, the founding member of the Frizzled family, Drosophila Frizzled (FZ), was cloned almost a decade ago because of its role in regulating cell polarity within the plane of an epithelium. In this review, we consider the role of FZ in this intriguing context. We discuss recent progress towards elucidating mechanisms for the intracellular specification of planar polarity, and further review evidence for models of global polarity regulation at the tissue level. The data suggest that a genetic 'cassette', encoding a set of core signaling components, could pattern hair, bristle and ommatidial planar polarity in Drosophila, and that additional tissue-specific factors might explain the diversity of signal responses. Recently described examples from the nematode and frog suggest that the developmental control of cell polarity by FZ receptors might represent a functionally conserved signaling mechanism.

The acquisition of cell polarity is among the earliest steps during the development of multicellular eukaryotic organisms. As embryonic cells are incorporated into the blastoderm epithelia they begin to display the hallmark characteristics of apical–basal polarity, and during successive stages of development, cell polarity continues to play a significant role, influencing patterns of cell division, shape change and movement. Therefore, developmental biologists have actively sought to elucidate the genetic programs that regulate the specification and maintenance of cell polarity. Whereas much work has addressed the determination of apical–basal polarity in epithelia, relatively little is known about the specification of polarity orthogonal to the apical–basal axis, known as planar polarity, or tissue polarity. Nevertheless, planar polarity is integral to the function of many tissue-systems, ranging from the specialized hair cells of the vertebrate ear to the dynamic cilia of the tracheal and reproductive tract epithelia[1].

Here, we review recent progress in elucidating mechanisms of planar polarity specification, with special attention to the role played by the Frizzled (FZ) family of serpentine membrane receptors and its downstream signal transducers. Because the role of FZ signaling in regulating cell polarity has been studied first and most thoroughly in *Drosophila*, we have concentrated on this system. In light of previous excellent reviews[1–4], our discussion is focused on the most recent developments and emphasizes the remaining conceptual hurdles for a coherent model of polarity signaling.

Drosophila FZ was first identified many years ago for its role in regulating planar polarity[5]. Subsequently, a large number of FZ homologs, including *Drosophila* FZ2, have been found in numerous organisms, where they have been proposed to function as cognate receptors for WNT signaling molecules[6,7]. WNTs, of which murine INT1 and *Drosophila* Wingless (WG) are the founding family members, are secreted glycoproteins that regulate cell proliferation and differentiation in a wide range of developmental contexts. While the ligand for FZ during

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planar polarity specification remains unknown, its strong homology to other FZ receptors suggests that another *Drosophila* WNT could fulfill this role. Parallel studies of WNT signaling and the FZ polarity pathway have indicated that divergent signaling mechanisms are involved (Fig. 1). Whereas the WG and FZ signaling pathways both require the function of Dishevelled (DSH), they demonstrate differential requirements for more downstream factors[8,9]. In WG signaling, DSH antagonizes the serine-threonine kinase Zeste-white3/ GSK3β, leading to the intracellular accumulation of Armadillo /β-catenin and the modulation of target gene expression via the Pangolin (PAN)/LEF1 transcription factor[10]. By contrast, during FZ signaling, DSH might regulate small GTPases such as RHOA, as well as a number of additional pathway- and tissue-specific factors[8,9,11].

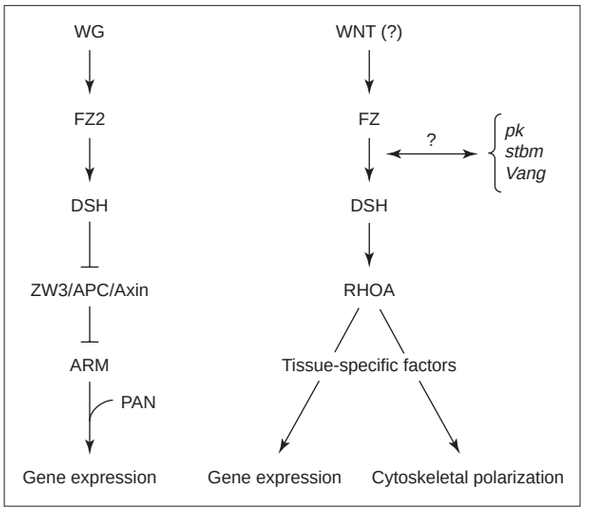

FIGURE 1. The WG and FZ signal transduction pathways. Although DSH is required for signal transduction in both contexts, distinct downstream pathways are activated. *pk*, *stbm* and *Vang* are required for hair, bristle and ommatidial planar polarity specification, but have not yet been shown to be components of the FZ pathway and might, therefore, have a direct or indirect role in FZ signal transduction. We speculate that the small GTPase RHOA could initiate a branched signal with nuclear and cytoskeletal targets.

The genetic programming of planar polarity in *Drosophila*

Drosophila is ideally suited for the genetic analysis of planar polarity specification because the adult exoskeleton is covered with easily scored, parallel arrays of cuticular structures that are polarized with respect to the body or limb axes (Fig. 2). On the thorax and abdomen, hairs and bristles project posteriorly, and on the wings and legs, these structures point distally. Planar polarity is also apparent in the eye, where each ommatidium possesses an intrinsic polarity owing to the invariant arrangement and rotation of the constituent photoreceptor cluster relative to the dorsal-ventral midline. Using a number of approaches, investigators have identified several 'tissue polarity genes' required for the specification of planar polarity in *Drosophila*. Table 1 lists these genes, the tissues in which they function and the identity of the encoded protein, if known. In only a few instances has the molecular characterization of these genes yielded clues to their function. Despite the dramatic differences in the morphogenesis of hairs, bristles and ommatidia, mutations in a subset of these genes, including *fz*, *dsh*, *prickle* (*pk*), *RhoA*, *strabismus* (*stbm*) and *Van Gogh* (*Vang*), disrupt the polarity of all three structures (Fig. 2). Throughout this review, we will refer to these genes as the 'core' group, since they might function as a conserved signaling cassette for the specification of planar polarity (Fig. 1); however, at present, there is still no direct evidence that *pk*, *stbm* or *Vang* are components of the FZ signaling pathway. In the remainder of this section, we review the development of hair, bristle and ommatidial planar polarity, and describe the phenotypic consequences of mutations in the tissue polarity genes.

Each cell of the developing wing epithelium normally produces a single, distally directed hair (trichome) (Figs 2, 3). This planar polarity arises from the polarized assembly of a single actin bundle 'pre-hair' to the distal vertex of each hexagonal wing cell[12]. Mutations in the core polarity genes (at least those that have been examined) abolish this aspect of subcellular asymmetry, resulting in prehair formation at the center of each cell, and deflecting hairs from their wild-type distal polarity. Mutations in the tissue-specific genes, *inturned* (*in*), *fuzzy* (*fy*) and *multiple wing hairs* (*mwh*), cause polarity disruptions and the production of extra hairs, suggesting they might normally function to inhibit hair initiation and/or outgrowth. The similar phenotypes produced by a dominant-negative form of Rac1, as well as a *RhoA* mutant, implicate these small GTPases in the pathway as well[11,13,14]. Genetic epistasis studies suggest that the core polarity genes *fz* and *dsh* function sequentially and upstream of *in*, *fy* and *mwh*, and that this pathway coordinately functions to derepress hair outgrowth at the distal vertex of each wing cell[12,15].

By contrast with wing hairs, very little is known about the determinants of bristle planar polarity. Polarized arrays of bristles are found at the wing margin, along the length of each leg and over the thoracic surface, and mutations in the tissue-polarity genes can disrupt bristle polarity at all of these loci (Fig. 2). Each bristle is the ultimate product of a single sensory organ precursor cell (pI), which gives rise to a four-cell cluster including a shaft, socket, sheath and neuron (Fig. 3)[16]. A recent report suggests that FZ signaling might regulate the pattern of asymmetric cell division that generates this cluster[17]. Whereas, on the dorsal thorax of wild-type flies, the division of pI is invariably parallel to the anterior–posterior axis, mutations in *fz* and *dsh* randomize the orientation of the pI mitotic spindle and cleavage plane. Interestingly, however, the asymmetric partitioning of Numb protein and the orientations of subsequent divisions are unaffected in these mutants, suggesting that additional, FZ-independent, pathways contribute to bristle polarity. In addition, it remains unclear to what extent the oriented pI mitotic division is linked to the ultimate polarity of the sensory bristle produced.

Each *Drosophila* eye is an exquisitely ordered hexagonal array comprised of hundreds of photoreceptor clusters, termed ommatidia. During the development of the eye imaginal disc, a wave of differentiation called the morphogenetic furrow sweeps from posterior

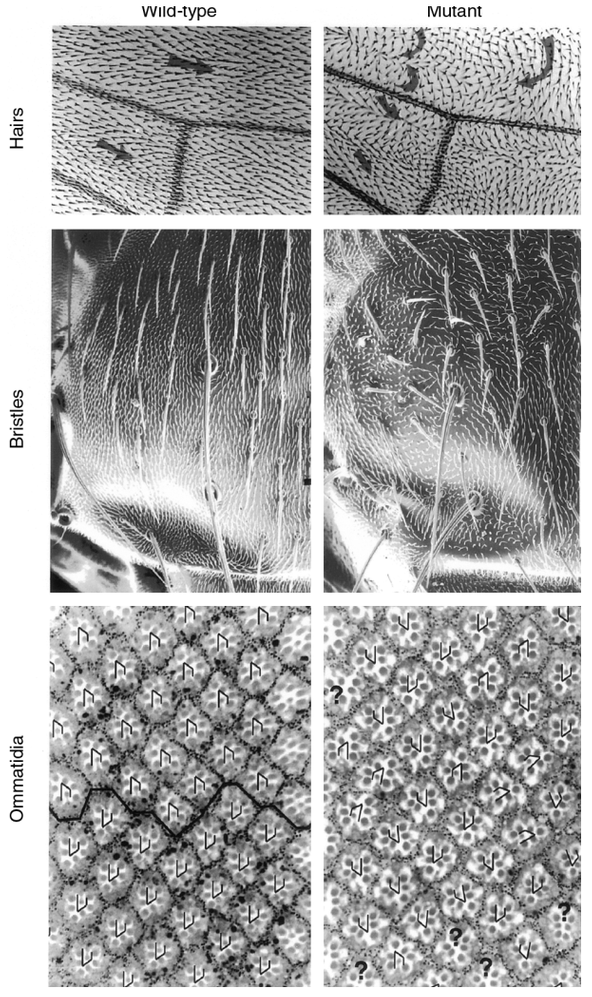

FIGURE 2. Wild-type and mutant planar polarity phenotypes. Hair polarity is shown in wild-type and *dsh*^{1} wings; anterior is up and distal is to the right. Bristle polarity is shown for a wild-type and *dsh*^{1} thorax; posterior is down. Examples of ommatidial polarity are taken from wild-type and *pk* flies (images kindly provided by D. Gubb). The eye equator is highlighted in wild type, but is obscured in the mutant. Ommatidial orientations are drawn in for clarity in both panels.

to anterior, recruiting the eight photoreceptors into individual ommatidial units[18]. The topography of furrow initiation and progression, which is coordinately controlled by WG, Hedgehog and Decapentaplegic/TGF-β signaling factors, ensures the precise stacking of maturing ommatidia and might define the position of the eye 'equator' at the dorsal–ventral midline[4]. Posterior to the furrow, each ommatidium rotates 90° towards the equator and acquires chirality, such that the dorsal and ventral eye hemispheres ultimately contain ommatidial forms that are reflected across an equatorial axis of mirror symmetry (Figs 2, 3). Mutations in the core group of tissue-polarity genes, *fz*, *dsh*, *pk*, *stbm* and *RhoA*, induce ommatidial chirality reversals, misrotated clusters, and defects in photoreceptor fate specification and positioning[11,19,20]. Such phenotypes suggest that these genes function in a pathway that specifies ommatidial polarity. In direct analogy to the wing, it has been proposed that this core polarity pathway regulates more downstream, tissue-specific factors, such as Nemo and Roulette, which have been implicated in the control of ommatidial cluster rotation[21].

FZ signaling and global polarity control

While phenotypic and epistasis analysis have helped define a genetic pathway for polarity specification, they have not addressed the intriguing problem of global regulation at the whole-tissue level. In which cells is tissue-polarity gene function absolutely required? From where does the cue for polarity originate? How is the signal propagated from one cell to the next? Much of the most exciting recent work aims to answer these questions through the use of genetic mosaic experiments.

Eleven years ago, the startling discovery was made that mitotic clones of *fz* mutant tissue in the wing show a non-autonomous effect, such that hair polarity is disrupted distal to, but not proximal to the clone[22]. Whereas most *fz* alleles, including nulls, demonstrate this non-autonomy, four independently isolated missense alleles at the identical residue behave cell-autonomously[23]. More recently, a distal to proximal gradient of FZ overexpression was induced via a heat-shock responsive transgene by dripping hot wax over the distal tip of pupal wing discs[24]. This 'waxing' protocol induced dramatic reversals in wing hair polarity, suggesting that planar polarity points from high to low levels of FZ signaling (presumably proximal to distal in the wild-type case). By contrast with *fz*, genes proposed to function downstream, such as *dsh*, *in* and *fy*, show solely cell-autonomous effects in mutant clones, consistent with their proposed role in intracellular signal transduction[25–29]. Significantly, mutant clones of *zw3* and *arm* do not disrupt planar polarity in the wing, suggesting that FZ uses a signal transduction mechanism that is distinct from the WG pathway (Fig. 1)[8].

Cumulatively, these studies support at least two potential models for the global control of FZ signaling in the wing[24]. One possibility is that the signal is serially regenerated in a wave that propagates along the proximal–distal axis. In such a scenario, the existence of cell-autonomous and non-autonomous *fz* alleles might suggest that distinct pathways downstream of FZ mediate cell polarization and intercellular signal relay, respectively[15]. In an alternative model, the FZ ligand might diffuse out from a localized source and act over long distances as part of a morphogen gradient. The picture has become still further confused with the identification of a class of genes, including *pk*, *Vang* and *dachsous* (*ds*), that might influence the directionality of FZ signal propagation or interpretation. Whereas a *ds* mutant background can enhance the distal non-autonomy of *fz* clones[30], a dominant allele of *pk* converts the direction of *fz* non-autonomy to proximal (P.N. Adler, pers. commun.). It is also remarkable that mutant clones of *Vang* have an effect completely opposite to that of *fz*, disrupting hair polarity proximal, but not distal to the clone[56]. If these genes regulate signal propagation, they might participate in either the serial regeneration of FZ ligand or the control of ligand diffusion. It is also possible, however, that these genes might have a more downstream role in signal interpretation, perhaps by specifying the orientation of cell polarization.

TABLE 1. The tissue-polarity genes

Gene (abbreviation)	Affected tissues: Hairs	Bristles	Ommatidia	Protein identity	Refs
frizzled (*fz*)	X	X	X	Seven-transmembrane protein; putative receptor for wnt signaling factors	5
dishevelled (*dsh*)	X	X	X	Novel, predominantly cytoplasmic protein with three conserved domains: DIX (axin-like), PDZ (protein interaction), and DEP (implicated in G-protein regulation)	28, 29
RhoA	X	?	X	Small RAS-like GTPase	11
strabismus (*stbm*)	X	X	X	Putative transmembrane protein with PDZ binding domain	20
Van Gogh (Vang)	X	X	X	Unknown	56
prickle (*pk*)	X	X	X	Novel LIM-domain-containing protein (two isoforms, PK and SPLE produced from alternatively spliced RNAS)	a
dachsous (*ds*)	X	?	?	Cadherin-like protein	30, 55
inturned (*in*)	X	X	–	Novel, putative transmembrane protein	26
fuzzy (*fy*)	X	X	–	Novel protein with four putative transmembrane domains	27
multiple wing hairs (*mwh*)	X	–	–	Unknown	
nemo (*nmo*)	–	–	X	Serine/threonine kinase; human homolog localizes to the nucleus	21, 45
roulette (*rlt*)	–	–	X	Unknown	21

[a]D. Gubb, pers. commun.

In a manner analagous to that seen in the wing, *fz* mutant clones in the eye cause non-autonomous ommatidial polarity disruptions that are biased towards the polar side of the clone (opposite to the equator)[19]. These studies also demonstrate a preferential requirement for *fz* in the R3 and R4 photoreceptors, such that the cell with greater FZ activity will adopt the R3 cell fate and asymmetric positioning anterior to R4. Cumulatively, these data are consistent with a model whereby an equatorial signal activates FZ leading to: (1) the correct specification of R3 versus R4 cell fate; (2) the correct choice of rotational direction; and (3) the execution of a 90° turn. As in the wing, mutant clones of genes that are proposed to act downstream of *fz*, such as *dsh* (but see below), *stbm*, *RhoA* and *nemo*, show cell-autonomous effects in the eye[11,19–21]. It is important to note, however, that whereas FZ signaling conveys polarity information along the equatorial–polar axis, the ultimate chirality of ommatidia also requires the passage of the morphogenetic furrow, which contributes vectorial information along the anterior–posterior axis[31–33]. This dual requirement for directional signals along the equatorial–polar and anterior posterior axes has been referred to in the literature as the two-vector, or cruciform planar polarity model[33,34].

By contrast with the wing polarity system, where WG appears to play no role, gain-of-function or loss-of-function in WG signaling components can influence ommatidial polarity[34]. Mutant clones of *arrow*, *zw3*, *arm* and *dsh* (in rare cases) were shown to disrupt ommatidial polarity non-autonomously, with a bias towards the equatorial side of the clone, opposite to what is seen for *fz*. These data have been interpreted to suggest that eye planar polarity is specified via two sequential signaling cascades. WG first signals in the polar to equatorial direction, inducing the expression of a graded secondary signal, Factor X, which subsequently activates the FZ pathway in the equatorial to polar orientation[34]. Consistent with this scenario, *wg* is expressed at the two poles of the eye disc, from where it might diffuse inwards to pattern the dorsal–ventral axis[33,35–37]. In future work, it will be important to determine whether the effects of WG signaling perturbations on ommatidial polarity can be explained entirely by disruptions in equator specification and the topography of morphogenetic furrow progression. Furthermore, since the WG and FZ signaling pathways share certain components, such as *dsh*, it is possible that experimental perturbations of one pathway might cross-activate or suppress signaling by the other. Indeed, ectopic expression of *wg* during polarity specification in the wing might be able to titrate DSH activity from the FZ pathway[8].

In strong analogy to the role proposed for WG in the eye, two recent reports investigating abdominal patterning similarly implicate the Hedgehog (HH) signaling pathway with the induction of a secondary, polarizing signal (again, Factor X)[38,39]. As described above for the thorax, the *Drosophila* abdomen is similarly decorated with arrays of hairs and bristles that project towards the posterior. Whereas HH acts as a gradient morphogen to directly pattern positional identity in the anterior of each abdominal segment, HH signaling only indirectly influences planar polarity, most probably via a secondary signaling event. Although tissue polarity mutants do show abdominal phenotypes[25], it remains to be determined whether the FZ pathway responds to Factor X in this context. Nevertheless, if this hypothesis proves true, the *Drosophila* eye and abdomen might exemplify a novel developmental paradigm for linking the patterning of positional information (via WG or HH, respectively), to the control of planar polarity by FZ.

Because the ligand for FZ remains unknown, experiments have only indirectly addressed the question of how the signal propagates from cell to cell, and over what distance it might act. However, given the likelihood that

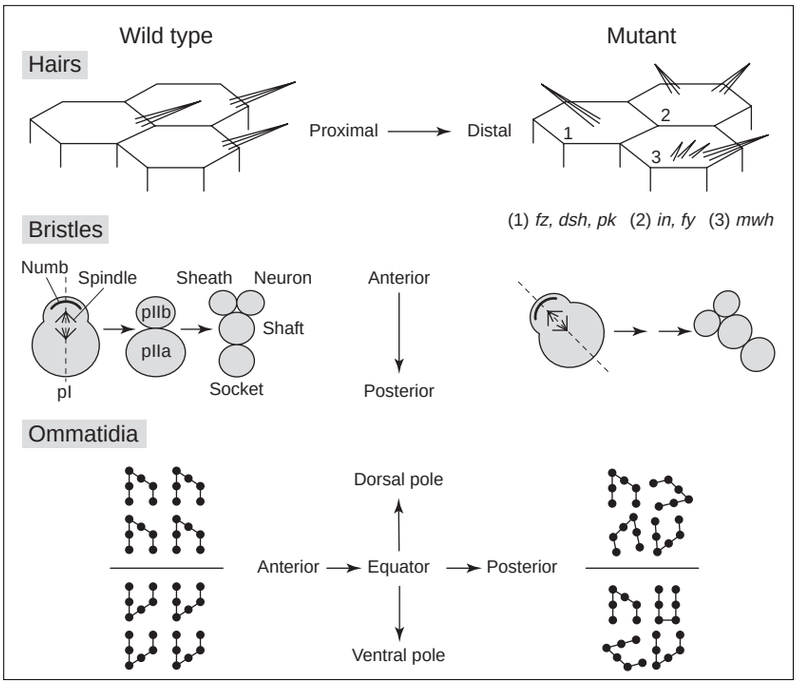

FIGURE 3. Drawings of wild-type and mutant planar polarity specification in three tissues. In wings, hair growth is restricted to the distal vertex of each hexagonal wing cell. In *fz*, *dsh* or *pk* mutants, mispolarized hairs elongate from the center of each cell, whereas *in*, *fy* and *mwh* mutants grow ectopic, mispolarized hairs that are restricted to the cell periphery. A thoracic bristle is the product of a stereotyped sequence of asymmetric cell divisions. Mutations in *fz* or *dsh* randomize the orientation of the pI mitotic spindle, which is aligned parallel to the anterior–posterior axis in wild type, but do not disrupt the asymmetric segregation of Numb protein or the orientations of subsequent divisions. Ommatidia adopt one of two chiral forms that are selectively found in the dorsal or ventral eye hemispheres. In *fz*, *dsh*, *pk*, *stbm* or *RhoA* mutants, some ommatidia are misrotated or show chirality reversals. Defects in photoreceptor cell fate specification can generate ommatidia that vary from the wild-type, hexagonal shape, and might be achiral.

the ligand is a WNT protein, it is tempting to extrapolate from the lessons of the WG signaling paradigm. Several studies have indicated that WG is likely to behave as a morphogen in a variety of contexts, perhaps supporting the hypothesis that a gradient of diffusing ligand underlies planar polarity specification[40,41]. Furthermore, it has recently been demonstrated that WG upregulates the expression of its own receptor, DFz2, which in turn modulates WG diffusion[42]. If this relationship also holds true for FZ and its ligand, the non-autonomous polarity disruptions caused by *fz* mutant clones might arise from discontinuities in the slope of a diffusing signal gradient. While the mechanism for WNT diffusion remains unknown, studies of mutant forms of WG are consistent with the hypothesis that its movement might be regulated by a transcytosis mechanism[43,44]. The answer to whether these mechanisms of signal propagation are conserved for the planar polarity ligand ultimately awaits its identification.

Remaining hurdles for a model of polarity signaling

Tissue specificity

How can a common set of signaling molecules function in a variety of cell types to generate an array of distinct outputs? Explaining signaling specificity continues to be a major challenge, and the case of *Drosophila* planar polarity poses an especially difficult problem. A successful polarity signaling model must account for at least two properties. First, the unit of polarity, and therefore the nature of the signal responder, is distinct in each tissue. Whereas in the wing, a single cell responds to polarizing cues in order to correctly orient a hair, the polarity of thoracic bristles and eye ommatidia involves higher-order, multi-cell clusters. Second, and equally perplexing, the ultimate cellular response to the planar polarity signal is uniquely tissue-specific. In order to specify the polarity of hairs, bristles and ommatidia, FZ signaling must apparently be able to regulate a wide range of cellular processes, including actin polymerization, mitotic spindle orientation, photoreceptor differentiation and ommatidial rotation. One solution to this dilemma is that tissue-specific factors lie downstream of a 'core' FZ signaling pathway and are responsible for mediating the distinct signal responses. The genes *in* and *fy* are specifically required for the morphogenesis of hair and bristle polarity, and *mwh* is exclusively required for wing hair polarity. Analogously, *nemo* and *roulette* selectively function in eye ommatidial rotation[21]. Nevertheless, whereas *in* and *fy* encode novel, putative integral membrane proteins[26,27], Nemo is a nuclear kinase[21,45], making it more difficult to envision how a common signaling pathway might impinge upon such distinct target molecules.

Pathway redundancy

Mysteriously, null mutations in the tissue polarity genes do not result in random polarity patterns. Instead, mutations cause distinctly aberrant, but reproducible polarity phenotypes. In a *fz* or *dsh* mutant wing, for example, selected regions exhibit intricate polarity patterns in which adjacent cells project hairs in different directions. By contrast, in other regions, cells possess a common but aberrant, non-distal hair polarity. Significantly, the spatial organization of these defects is not random, but instead creates highly reproducible patterns for all wings of a given null mutant genotype. This peculiar feature of the phenotypes suggests that, while tissue polarity gene products are required for the correct implementation of polarity, a partially redundant system might still convey some directional information in their absence. One possible scenario is that the cytoskeletal polarity of each epithelial cell is somehow linked to that of adjacent cells, perhaps via adherens junctions. Alternatively, the apparent redundancy in planar polarity specification might be explained by mechanical constraints imposed by the geometry of the

developing imaginal epithelia and its constituent cells[4]. Either of these scenarios would predict that, in the absence of FZ signaling, epithelial cells obey a default prepattern for planar polarity.

However, prepatterning by redundant mechanisms can still not adequately explain why the null mutant phenotype of each tissue polarity gene is distinct[25]. If each of the gene products functioned in a linear pathway to specify planar polarity, we might predict that removal of any individual component would block signal transduction, resulting in a uniform phenotypic response. Instead, the defective polarity pattern of *fz*, *dsh* or *pk* null mutants is as unique as a 'finger print', instantly betraying their genotype to the experienced examiner. This observation, in addition to the lack of definitive epistasis amongst the genes, might indicate that some of the factors function in a multi-protein complex as opposed to occupying discrete molecular niches on a sequential assembly line.

Destination unknown

A key goal for understanding planar polarity specification in *Drosophila* is to identify the ultimate molecular targets of FZ signaling. Nevertheless, it has been difficult thus far to determine whether FZ signaling impinges directly on the cytoskeleton, the nucleus, or perhaps even diverges in both directions during the specification of planar polarity. Recent experiments using depolymerizing drugs have demonstrated that the actin and microtubule cytoskeletons are both required for asymmetric prehair initiation and subsequent hair outgrowth[46]. Similarly, regulating the orientation of the mitotic spindle and cleavage plane during bristle morphogenesis presumably involves cytoskeletal control. Therefore, the specification of hair and bristle polarity might be mediated by a common cytoskeletal regulatory molecule. RHOA, a small GTPase that is known to directly influence cytoskeletal dynamics and has been implicated downstream of FZ, is obviously a prime candidate[11,47]. Recently, we have demonstrated that the FZ receptor can recruit DSH to the cell membrane, and that the *dsh[1]* allele, which specifically abolishes DSH activity in polarity signaling (but not in WG signaling), encodes a missense mutation in the C-terminal DEP domain[8,9]. Because DEP domains have been described in several proteins that regulate small GTPases[48], it is tempting to speculate that physiological FZ signaling might promote asymmetric recruitment of DSH to the membrane, where it might activate small GTPases such as RHOA, leading directly to a polarized cytoskeletal response. It will be interesting to determine whether any of the recently identified RHO effectors with proposed roles in cytoskeletal control participate in this pathway[47,49].

However, RHO GTPases are also known to be potent activators of the JNK and MAP kinase signaling cascades that each converge on the cell nucleus[49], raising the possibility that activation of RHOA could alter programs of gene transcription. More recently, mutant alleles of JNK pathway components were shown to influence ommatidial planar polarity in a sensitized genetic background, and more directly, DSH expression could induce phosphorylation of the transcription factor, JUN, in a cell-culture system[9,11]. Although it is possible that a cytoskeletal response might be a secondary, indirect consequence of changes in gene transcription, it is difficult to imagine how FZ signaling could convey the directional information necessary to polarize cells solely by activating a nuclear pathway. Therefore, it is perhaps most plausible to postulate that FZ signaling bifurcates downstream of RHOA, and that independent signal branches induce cytoskeletal vs nuclear responses (Fig. 1). Such a model raises the intriguing possibility that the diversity of cellular responses to FZ signaling might reflect differences in the relative strengths of distinct RHO-dependent pathways that impinge on the cytoskeleton or nucleus.

Lessons from worms and frogs

To what extent can we find evidence for a FZ-based polarity signaling system in other organisms? In the nematode, *Caenorhabditis elegans*, genes encoding members of a WNT signaling pathway are required for the specification of endodermal (E) cell fate in one descendent of the EMS blastomere[50,51]. WNT activity is also required for the rotation of the EMS and other mitotic spindles, resulting in polarized cell divisions. Whereas induction of the E cell fate was found to require the homologs of WG, FZ, ARM and Pangolin/Lef1, only the WG and FZ homologs were necessary for EMS spindle polarization. These results suggest a divergence in the nematode WNT signaling pathway, downstream of FZ but upstream of ARM, with at least one branch of the pathway controlling cell-polarization events. It will be interesting to determine if the molecular basis of this pathway divergence is analagous to the case in *Drosophila*, and whether the control of EMS spindle orientation is mechanistically similar to the proposed role for FZ signaling in polarizing bristle precursor cell divisions[17].

Emerging data from studies of the frog, *Xenopus laevis*, reveal further evidence for divergent WNT pathways. Whereas XWnt1 induces embryonic axis duplication by activating a WG-like signaling pathway, XWnt5a fails to induce axis duplication but, rather, alters morphogenetic movements during gastrulation[52]. Interestingly, a heterologous FZ, human Fz5, can serve as an 'adaptor' that binds XWnt5a but retains the specificity to activate the XWnt1 signaling pathway, thus allowing XWnt5a to induce axis duplication[53]. Therefore, in *Xenopus*, while one FZ pathway appears to be similar to the WG pathway and impinges on the nucleus to modulate gene expression, we speculate that the other might resemble the FZ-mediated polarity signal, either in transduction mechanism, polarizing function, or both. Lastly, murine WNTs have been divided into multiple classes based on their abilities to induce transformation of cultured cells[54]. While little is known about the signaling mechanisms used by these WNTs, one explanation for their differing transforming efficiencies might be the existence of divergent signaling pathways, one or more of which could control cell polarity.

Concluding remarks

Genetic investigation into the mechanisms of planar polarity specification in *Drosophila* has generated substantial recent progress. Cumulatively, the data suggest that the FZ receptor and a cassette of core signaling molecules collaborate with tissue-specific factors to pattern planar polarity in multiple tissues. Nevertheless, many

questions still remain, especially regarding how intracellular signal specificity is maintained and the nature of global signaling control. While recent work in the nematode and frog is tantalizing, much work lies ahead to determine whether the control of cell polarity by FZ receptors is conserved. However, judging by the remarkable conservation of WNT and other signal transduction pathways, we anticipate finding numerous roles for FZ signaling in planar polarity control in higher organisms.

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Note added in proof

It has recently been demostrated that *Van Gogh* and *stabismus* are allelic[56].

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J.M. Shulman *is in the Wellcome/CRC Institute, Tennis Court Road, Cambridge, UK CB2 1QR.*
N. Perrimon *is in the Howard Hughes Medical Institute, Department of Genetics, Harvard Medical School, 200 Longwood Avenue, Boston, MA 02115, USA.*
J.D. Axelrod *is in the Department of Pathology, R226A, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA.*