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Short survey

A three-tiered mechanism for regulation of planar cell polarity

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Some epithelial cells are polarized along an axis orthogonal to their apical–basal axes. Recent studies in Drosophila lead to the view that three classes of signaling molecules govern the planar cell polarity (PCP) pathway. The first class, or module, functions across whole tissues, providing directional information to individual cells. The second module, apparently shared by all planar polarized tissues, and related to the canonical Wnt signaling pathway, interprets the directional signal to produce subcellular asymmetries. The third modules are tissue specific, acting to translate subcellular asymmetry into the appropriate morphological manifestations in the different cell types.

Key words: *Drosophila* / planar cell polarity / frizzled / fat

Introduction

Epithelia in multicellular organisms are polarized along their apical–basal axes. The development and function of some of these epithelia also requires their polarization in the plane orthogonal to the apical–basal axis, known as planar cell polarity (PCP). Overt examples of planar polarized epithelia are the cochlear hair cells of the inner ear and migrating mesodermal and neuro-ectodermal cells undergoing convergent extension during vertebrate embryogenesis (reviewed in 1). There may be many other epithelia that are polarized in this manner but which lack morphological features that allow us to assess the their polarity. The cuticle of the adult fruit fly, *Drosophila melanogaster*, has several external features that allow the polarity of the underlying epithelium to be visualized and thus studied. These include the hair and bristles that cover the body surface of the adult fly and the photoreceptors in the ommatidia of the eye. Easy assessment of PCP, coupled with the genetic and cell biological analyses possible in this system has made *Drosophila* a powerful model for studies of the processes governing PCP.

Most of the cells secreting the adult cuticle of *Drosophila* construct a trichome (also called a hair), an actin rich projection emanating from the apical surface of each cell (Figure 1A). All these hair point posteriorly on the body surface and distally on the appendages. Similarly, many body surfaces produce an array of sensory bristles that point toward the posterior of the fly (Figure 1C), or toward the distal end of appendages. The polarity of the cells underlying these tissues can be determined simply by examining these polarized structures. The epithelium giving rise to the adult eye is composed of repeating units called ommatidia. Each of the ~800 ommatidial units in each eye is made up of ~20 cells, eight of which are light-sensing photoreceptor cells. The rhabdomeres of the eight photoreceptor cells are arranged in a chiral and oriented pattern (Figure 1E). PCP in the eye can be seen by sectioning through the surface of the eye to visualize these cells.

The existence of mutant genes that affect all of these planar polarized structures suggests that the encoded proteins are required for a common polarizing mechanism that functions in these widely different tissues. Perturbation of these genes result in wing hair pointing in novel, non-random patterns, and sometimes in the production more than one hair per cell (Figure 1B). The bristles become similarly mis-oriented (Figure 1D), and ommatidial polarity is disrupted (Figure 1F). These genes encode the transmembrane proteins Frizzled (Fz),[2] Flamingo (Fmi),[3,4] Vang-gogh (Vang)[5,6] and the cytoplasmic proteins Prickle (Pk),[7] Dishevelled (Dsh)[8] and possibly Diego (Dgo).[9] Because these proteins are thought

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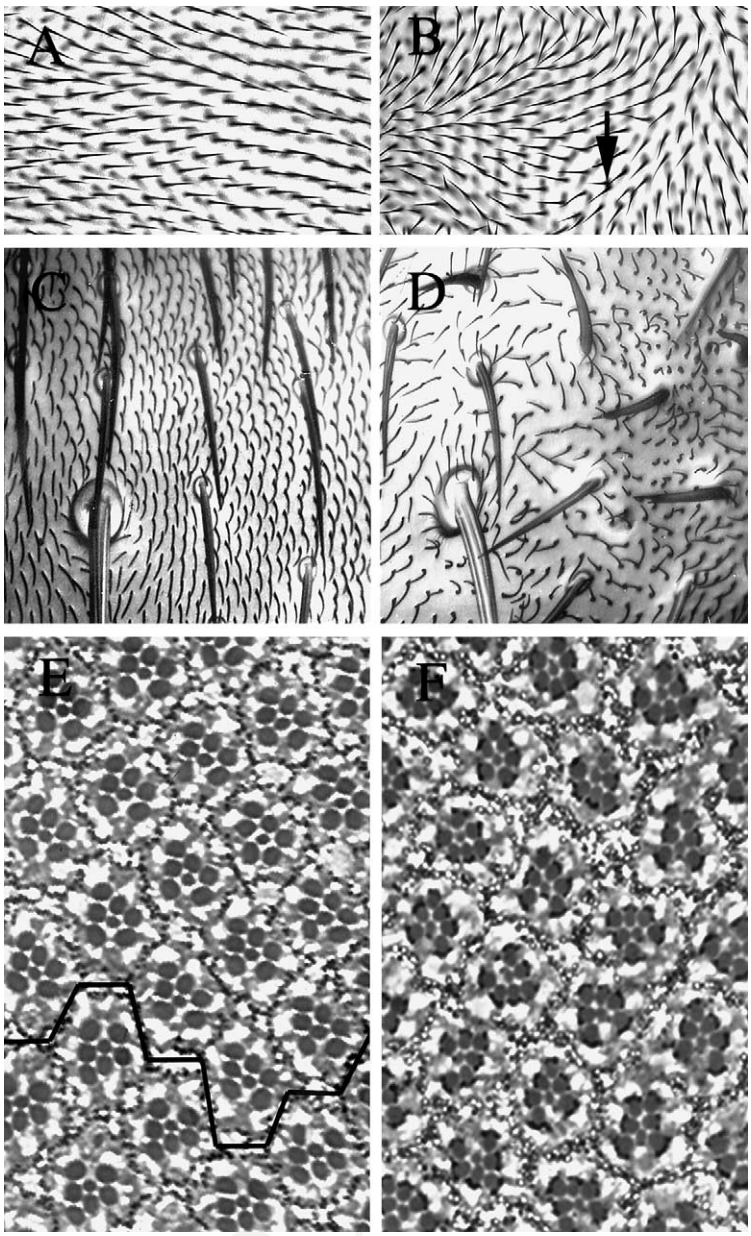

Figure 1. Wild-type polarization of *Drosophila* epithelia and the phenotypes of mutations in the PCP genes. (A) Wild-type wing cells all produce a single, distally pointing hair. (B) In a $pk^{pk\text{-}sple13}$ wing the hair adopt a novel, mutant pattern which is invariant. Some cells produce more than one hair (arrow). (C) The notum of the wild-type fly is covered with both hair and bristles that are polarized distally. (D) The notum of a fly mutant for dsh^{1} produces bristles that are oriented in a novel, mutant pattern. Note that the mutant pattern of bristles is essentially invariant. (E) In the wild-type *Drosophila* eye, the organization of rhabdomeres in the ommatidia is polarized, and exists in opposite chiral forms in the dorsal and ventral halves of the eye (the equator is indicated with a black line). (F) In a *fz* mutant eye the polarization and chirality of the ommatidia is disrupted.

to mediate a PCP function common to the polarized tissues, they have been termed the 'core' PCP genes.[10]

Genetic analyses of the core PCP genes led to the view that the PCP pathway is a linear signaling pathway from a 'receptor' of a polarity signal, Fz,[11] through a downstream, cytoplasmic transducing protein, Dsh, to tissue specific proteins.[12] However, recent studies of the subcellular localization of several PCP proteins

in the pupal wing have led to a modified view of this process. In the pupal wing, Fz and Dsh become asymmetrically localized to the distal vertex of the cell, marking the site of subsequent prehair assembly.[13,14] Fmi and Dgo also become preferentially localized to proximal–distal cell boundaries.[3,9] Indirect evidence indicates that a feedback mechanism is required for the evolution of this asymmetry.[13,14] Although only studied in detail in the pupal wing, it seems likely that the formation of asymmetrically localized complexes involving Fz and Dsh also regulates PCP signaling in other cell types. Thus, the core PCP genes may function in a feedback mechanism which generates subcellular asymmetry. This subject is reviewed in more detail in this volume.[15]

The feedback mechanism described above must depend on factors acting upstream of the core proteins to result in their asymmetric localization. Furthermore, factors acting downstream of the core proteins effect the correct cellular response in the different cell types. PCP signaling can therefore be considered as three steps (Figure 2): (1) directional extracellular signaling; (2) the formation of polarized signaling complexes; (3) the downstream translation of the molecular polarization of the cell into the morphological polarization of the adult structures. Step (2) is the subject of another work in this volume.[15] Here we will discuss steps (1) and (3).

Upstream of Fz—the search for Factor X

Because Fz proteins serve as receptors for the Wnt family of secreted glycoprotein signaling molecules,[16] it has been hypothesized that a PCP ligand might be a member of the Wnt family. It was expected that this putative ligand would provide directional information to the PCP pathway by localized secretion and diffusion to form a gradient, and in this capacity has been referred to as 'Factor X.' However, no Wnt has emerged from any study as a candidate for this role, and the nature of the global directional signal remained mysterious. However, recent work by Yang *et al.* describes a mechanism providing directional information to the PCP pathway in the fly eye,[17] and may require a reformulation of questions concerning the identity of Factor X.

About 800 photoreceptor units, or ommatidia, form the *Drosophila* compound eye. The dorsal and ventral hemispheres of the eye contain chiral ommatidial

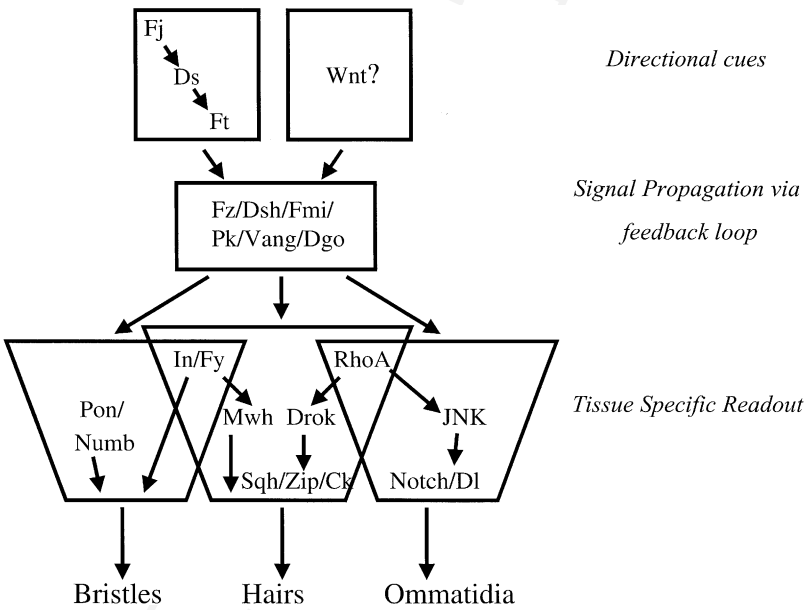

Figure 2. An overview of the three-tiered PCP signaling pathway. In the first module, graded expression of Fj and Ds signal through Ft to provide directional information across developing epithelia. It is unknown whether a Wnt is required to activate Fz. Subsequently, the 'core' polarity genes in the second module receive directional information and generate subcellular asymmetry, via a feedback loop. The third modules serve as tissue specific readouts, acting downstream of the asymmetrically assembled 'core complex' to shape the final morphology of each tissue.

units of opposite orientation, forming mirror images across the dorsal/ventral midline (or the equator) of the eye. During eye development, a wave of photoreceptor differentiation known as the morphogenetic furrow sweeps across the eye imaginal disc from the posterior to the anterior. Behind the furrow, photoreceptor cells are sequentially recruited into the nascent ommatidia in a pair-wise manner, forming ommatidial preclusters (reviewed in 18). Determination of ommatidial polarity is critically dependent on two events: the prospective R3/R4 photoreceptor cells adopt their fates, and the precluster subsequently rotates. In the wild-type precluster, the R3 precursor is located closer to the equator, and is referred to as the èquatorial cell' whereas the R4 precursor is the 'polar cell.' Once the R3/R4 cell fates in an ommatidium are determined, the precluster rotates 90°. The core PCP genes are required for cell fate determination and rotation. Mosaic analyses indicate that the cell with higher Fz activity becomes R3.[19]

What leads to the higher Fz activity in R3? Yang *et al.*[17] describe the function of three molecules working in concert, upstream of Fz, to influence PCP in the developing eye. They consist of a type II secreted/transmembrane protein, Four-jointed (Fj), and two large non-classical cadherins, Dachsous (Ds) and Fat (Ft). Previously, these three proteins were shown to affect PCP,[20,21] as well as being involved in other processes, but their mode of action was unknown. Four-jointed is required for formation of the proximal–distal axis of appendages, in addition to its role in PCP. A graded expression pattern of Fj in the eye disc led Zeidler *et al.* to postulate that it might in fact be the long-sought Factor X.[20] However, these investigators found that homozygous *fj* wings only occasionally exhibit minor polarity defects, although clones of *fj* may have much more dramatic phenotypes, depending on the position of the clones. The authors concluded that Fj must act redundantly with other unknown factors to affect PCP signaling. Both *ds* and *ft* mutant flies display phenotypes consistent with a role in cell adhesion, and mutant wings display PCP phenotypes.[21]

The expression patterns of lac-Z enhancer traps in both *ds* and *fj* in the eye disc suggest potential functions for these genes. *fj-lacZ* expression is prominent along the dorsal/ventral mid-line, and fades gradually toward the poles.[20] In contrast, *ds-lacZ* is expressed in an opposing gradient, showing highest expression at the poles, and lowest at the equator.[17] Epistasis analysis shows that *fj* works upstream of *ds*, which in turn functions upstream of *ft*. All three work upstream of *fz*. Interestingly, several arguments indicate that these proteins bias *fz* activity in favor of the equatorial cell, but are not required for *fz* activity. *fz* ommatidia frequently fail to distinguish R3 and R4, resulting in symmetric ommatidia that rotate aberrantly.[22,23] In contrast, in *fat*, *ds* and *fj* mutant ommatidia, a clear choice of R3/R4 is always made, albeit often incorrectly. Dsh and Fmi localization, which is asymmetric in wild-type but symmetric in *fz* mutants, is asymmetric in *fat*, *ds* and *fj* mutant ommatidia. Finally, the ensuing ommatidial rotation always correctly follows from the choice of R3/R4 cell fate. Thus, Fz signaling is still occurring, but the orientation is now disconnected from the global signal. These findings do not rule out a function for a Wnt as a Fz ligand during PCP signaling in the eye, but they suggest that if a Wnt is required to activate Fz, it may play a permissive role rather than providing directional information. How do *fat*, *ds* and *fj* bias Fz activity? The biochemical functions of these proteins remain to be determined.

The expression patterns of both Fj and Ds ultimately respond to a Wingless gradient in the eye disc, which promotes Ds, and inhibits Fj expression. Furthermore, the regulation of the three proteins is complex. A feedback loop apparently exists among the three. Do Wg, Ds and Fj gradients govern PCP signaling in other tissues? That remains to be seen. However, the graded expression of *fj-lacZ* in the wing, as well as the wing PCP phenotypes of all three mutants suggest that the function of these proteins may indeed be conserved in other tissues. Additional questions remain. Is a Wnt involved in activating Fz? How is the directional information conveyed by Fj/Ds/Ft translated at a cellular level? What other factors also participate in biasing Fz activity? What are the biochemical functions of these components?

Downstream of the core components: the tissue specific modules

We turn now to the question of how the asymmetrically assembled core PCP signaling complexes direct morphological consequences. In each case the polarity seen in the adult structures is the consequence of earlier events occurring during third instar or early pupal stages. In the wing, a single prehair is localized to the distal vertex, in the bristle precursor cells a specifically oriented cell division is orchestrated, and in the eye a cell fate decision has to be made prior to an elaborate cellular movement. The unique nature of these events demands that some tissue specific features are

peculiar to each one. We will discuss the three polarized structures in turn: the hair, the bristles and the ommatidia, describing the possible functions of the tissue specific PCP genes.

The hair

At around 33 h APF, the signaling complex containing Fz and Dsh is highly asymmetrically distributed to the distal boundaries of wing cells. By an unknown mechanism, this causes the accumulation of actin at the distal vertex. The actin rich prehair then forms, and is subsequently extruded from the surface of the cell (Figure 3A). Several 'tissue specific' PCP genes are required to localize the prehair and orient bristles, but are not required to generate polarity in the eye. Mutations in these genes, including *fuzzy* and *inturned*, both putative transmembrane proteins with no other recognizable protein domains[24,25] (but see 26), cause polarity defects, and many more multiple hair cells than do *fz* or *dsh*[1]. These genes are somehow involved in regulating the number of prehair initiation sites. Analysis of double mutant phenotypes implies that they act downstream of the second module,[12] but the manner in which they do so is unclear.

RhoA, a well known modulator of the cytoskeleton has been implicated in the generation of PCP.[27] *RhoA* is a small GTPase which modulates the cytoskeleton of a wide variety of cell types, from yeast to mammalian cells, effecting cell shape change, cell movement, axon outgrowth and guidance. Loss-of-function of *RhoA* produces multiple prehair initiation sites, but little or no orientation defect. Genetic interactions between *RhoA*, *fz* and *dsh* suggest *RhoA* acts downstream of Fz and Dsh. How these small GTPases are linked to Fz/Dsh activation/localization has remained unknown. However, a novel *Xenopus* Formin homology protein, Daam, was recently reported to physically interact with both Dsh and *RhoA* and mediates the formation of Wnt-induced Dsh–RhoA complexes.[28] Daam is required for correct gastrulation in *Xenopus*, a process that is thought to be mediated by a PCP-related

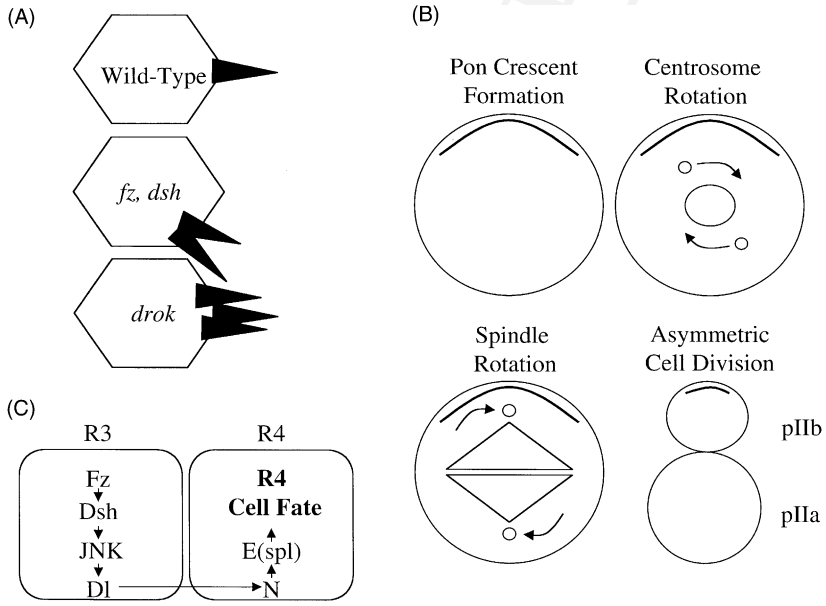

Figure 3. Molecular events underpinning PCP. (A) Wild-type pupal wing cells produce a single, distally pointing prehair at around 33 h APF. PCP mutants, such as *fz* and *dsh*[1] produce non-distally pointing prehair and sometimes produce more than one prehair. Mutant clones of *Drok* produce multiple prehair of wild-type polarity. (B) In the pI cell, a crescent of Numb and Pon forms at the anterior cortex. The centrosomes then rotate in a Fz dependent manner, as does the mitotic spindle after its formation. Finally an asymmetric cell division occurs with the Numb/Pon crescent being inherited by the anterior, pIIb daughter cell. (C) In the eye, the pre-R3 cell is closer to the equator than the pre-R4 cell. Fz becomes more strongly activated in R3, leading to the increased transcription of D1, via a JNK signaling pathway. Increased levels of D1 in the pre-R3 cell cause the activation of Notch in the pre-R4 cell which leads to the transcription of E(spl) splice variant mδ. This confers R4 fate on the polar cell and leads to appropriate rotation of the ommatidial precluster.

pathway in vertebrates. Study of Daam in *Drosophila* may therefore yield insights into linking the localized PCP signaling complexes to cytoskeletal modulators.

Whether *RhoA* induces transcription during PCP signaling in the wing is unknown. However, a downstream effector of *RhoA* that defines a novel branch of the PCP signaling hierarchy has also recently been described. *Drosophila* Rho-associated kinase (Drok) binds specifically to the constitutively active form of RhoA, and serves as an effector for RhoA signaling.[29] Rather than affecting the polarity of the wing hair, loss-of-function of *Drok* causes each cell to produce multiple hair. Consistent with this role for Drok in restricting the number of hair a cell produces, activating Drok in a dsh^1 mutant background rescues the dsh^1 multiple hair phenotype but not the dsh^1 polarity pattern. Drok has been shown to phosphorylate Spaghetti-squash (Sqh), the *Drosophila* homologue of the non-muscle myosin regulatory light chain (MRLC), and genetically interacts with Zipper (Zip, *Drosophila* myosinII) and Crinkled (Ck, *Drosophila* myosinVIIA). These unconventional myosins therefore appear to be involved in organizing f-actin at the distal vertex of pupal wing cells to regulate the number of prehair. However, the precise role for these myosins remains unknown. Intriguingly, myosin VIIA is implicated in Usher Syndrome 1B, a human inherited deafness disorder in which the stereocillia on cochlear hair cells are disorganized.[30] This and other clues suggest that these cells are organized by a system analogous to PCP signaling in *Drosophila*. This possibility is strengthened by the observation that two other genes causing Usher Syndrome encode Cadherin-like molecules, as are Ft, Ds and Fmi (reviewed in 1).

The bristles

Study of thoracic bristle polarity has focused on the polarity of the initial progenitor cell division that gives rise to all the cells constituting a single bristle. Each bristle on the *Drosophila* thorax originates from a single sensory organ precursor (SOP) cell. Each SOP divides asymmetrically into two secondary precursors, the larger, posterior pIIa cell and the smaller, anterior pIIb cell. These cells divide again, once and twice, respectively, to produce the four cells that make up the bristle, and one glial cell.[31] The polarity of the pI cell division is polarized in the plane of the epithelium along the anterior-posterior axis. In *fz*, *dsh* and *fmi* mutants, the orientation of the division is randomized.[32] The subsequent divisions of the pII cells follow from the axis of division of pI.

Numb and Partner of Numb (Pon) are involved in the asymmetric division of another sensory cell: the neuroblast, which divides asymmetrically along its apical–basal axis (reviewed in 33). Recently, the function of the proteins Numb and Pon has been studied in the pI cell division. In the wild-type pI cell, Numb and Pon accumulate at the anterior pole and are thus inherited by the anterior cell, which adopts the pIIb cell fate[34] (Figure 3B). Using time-lapse photography, Bellaiche *et al.* showed that the Numb/Pon crescent forms before mitotic spindle formation. The spindle then rotates to line up with the Pon crescent. In *fz* mutants, however, the Numb/Pon crescent, when it does form, does so with random orientation, and is only sometimes associated with a perhaps incorrectly oriented spindle pole. The PCP pathway therefore directs polarity of the bristles by directing correct spindle orientation, ensuring the unequal partitioning of the cell-fate determinants Numb and Pon. In the absence of *fz*, Pon is inherited by a single daughter cell 73% of the time.

There remain a number of puzzling questions about the polarization of the bristles. It is still unclear what directly links the PCP pathway to spindle orientation and to the movement of the cell-fate determinants to the pole of the cell. Also, the cues against which the subsequent divisions of the pIIa and pIIb cells are polarized remain unknown. The connection between the polarity of the division of the pI cell and the final polarity of the adult bristle is confusing. The polarity of the division is randomized in *fz* and *dsh* mutants, whereas phenotypically, the adult bristles have invariant patterns in these mutants. Also, the area of the mesothoracic disc in which the polarity of the pI division has been studied gives rise to the medial portion of the notum, where, in the mutants, the adult polarity of the bristles is essentially wild-type. Thus the polarity of the pI division does not directly specify the polarity of the adult bristle, implying that there must be other signaling events that lead to the alignment of the bristle to its final polarity.

The ommatidia

In the eye, the polarity of the ommatidia is determined by the cell fate decision between the prospective R3/R4 pair. Fz activity is higher in the equatorial R3 progenitor than in the polar R4 progenitor.[19] A consequence of relatively greater Fz activity in R3 is increased expression of D1 in that cell[22,23] (Figure 3C). This leads to the activation of Notch in the prospective R4 cell, and its cell fate decision requires the

expression of Enhancer-of-split genes in the R4 cell. The cause of D1 activation in R3 has been the subject of much investigation. Genetic interactions suggested that JNK pathways may act downstream of Dsh and RhoA in the eye, and Dsh can phosphorylate JNK in cultured cells.[35] However, loss-of-function analysis of members of the JNK pathway has failed to reveal PCP phenotypes, leading to the suggestion that the JNK pathway must act redundantly with other related pathways.[35,36] Clones of loss-of-function of the *Drosophila* homologue of Jun show defects in R3 specification, and gain-of-function of Jun resembles gain-of-function of Fz, so it is possible that Jun may be a transcription factor at the bottom of two or more signaling cascades that leads to increased transcription of D1 in R3.[37]

Concluding remarks

In this review, we have presented evidence suggesting a three-tiered mechanism for regulation of PCP. Future investigations will focus on understanding the mechanisms within each tier, and how they interact.

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