tides (*54*). PAR-1 phosphorylation can create a binding site for 14-3-3, suggesting that PAR-1 substrates become bound to 14-3-3 after phosphorylation (*19*). *14-3-3* mutants in *Drosophila* have polarity defects identical to those seen in *par-1* mutants, consistent with the idea that 14-3-3 binding is essential for PAR-1 signal transduction (*19*). Remarkably, one of the *C. elegans 14-3-3* homologs is encoded by *par-5* (*9*), and PAR-5 protein binds to PAR-1 in a yeast two-hybrid assay (*19*). PAR-5, however, is unlikely to function only with PAR-1 in *C. elegans*, because it is required for the initial establishment of PAR domains, a process that is independent of PAR-1 (*9*, *30*). 14-3-3 proteins have been implicated in many cellular processes (*54*), including actin dynamics (*55*), and could potentially act multiple times in the PAR hierarchy. The identification of 14-3-3 proteins as potential mediators of PAR-1 function may facilitate the identification of PAR-1 substrates.

Conclusions

Three main themes emerge from a comparison of PAR functions in *Drosophila* and *C. elegans* eggs. First, PAR proteins act together to convert a transient polarity cue into a stably polarized axis. Second, of all the PARs, PAR-1 appears most directly involved in converting cortical polarity into cytoplasmic asymmetry. Last, PAR-1 orchestrates cytoplasmic asymmetries by impinging on diverse cellular functions, including microtubule dynamics, protein degradation, and, likely, many others. Thus, the secret to the *par* genes' remarkable adaptation to different cell types may lie in their ability to regulate a number of basic cellular processes. Although much has been learned, a complete picture awaits the identification of the essential cell machineries that interact with the PARs. As E. B. Wilson predicted, the key to this problem also lies in the cell biology of the egg.

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REVIEW

Shaping the Vertebrate Body Plan by Polarized Embryonic Cell Movements

Ray Keller

Polarized cell movements shape the major features of the vertebrate body plan during development. The head-to-tail body axis of vertebrates is elongated in embryonic stages by "convergent extension" tissue movements. During these movements cells intercalate between one another transverse to the elongating body axis to form a narrower, longer array. Recent discoveries show that these polarized cell movements are controlled by homologs of genes that control the polarity of epithelial cells in the developing wing and eye of the fruit fly, *Drosophila*.

How the body plan is shaped from a cohesive aggregate of individual cells during embryogenesis is an enduring mystery. A major breakthrough is the recent discovery that homologs of genes controlling the polarity of hairs on the epidermal cells of *Drosophila* (fruit fly) wings also control the polarized cell motility underlying the morphogenic movements that shape the vertebrate body plan. These movements, known as "convergence and extension" or "convergent extension," narrow (converge) the mediolateral aspect and elongate (extend) the anterior-posterior aspect of the vertebrate embryo and thereby establish its morphological and func-

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tional polarity, with a head on one end and a tail on the other (*1*). Convergent extension was first studied during amphibian gastrulation when the presumptive notochordal and the somitic tissues, which will form the vertebral column, turn inside the blastopore. As they do so, these tissues also converge mediolaterally and extend anterior-posteriorly, a process that elongates the body axis during neurulation and into the tadpole stage (Fig. 1A). Meanwhile, the overlying neural tissue, which will form the spinal cord and hindbrain, converges and extends coordinately with the underlying mesoderm (*1*, *2*) (Fig. 1A; movie S1). Convergence of these tissues squeezes the blastoporal lips together, thereby closing the blastopore; simultaneously, the extension elongates the anterior-posterior body axis (Fig. 1A, movie S1). Convergent extension literally pushes the head away from the tail and organizes the elongated structures of the trunk, including the hindbrain-spinal cord, the vertebral column, and its supporting musculature. Convergent extension elongates the body axis from its initial "egg shape" in all chordate species examined (*1*), including sea squirts (ascidians) (*3*), teleost (bony) fish (*4*), amphibians (*1*), birds (*5–7*), and mammals (*8*), and it has roles in many other morphogenic processes (*1*).

Cell Intercalation as a Shaping Force

The forces for convergent extension are generated within the tissues by polarized cell motility that drives organized patterns of cell intercalation. Presumptive notochordal, somitic, and neural tissues that converge and extend in the embryo also do so when explanted in a culture dish (*9*, *10*), which shows that these movements are independent of other tissues, independent of an external substrate, and driven by internal forces (Fig. 1B; movie S2). The mesodermal tissues stiffen 3 to 4 fold during convergent extension (*11*) to form a self-supporting beam that serves as the "skeleton" of the embryo and dominates its shape (*12*). But these tissues are also self-deforming and generate pushing forces of about 0.5 micronewton as they extend (*1*, *11*). These mechanical properties allow the converging and extending tissues to "push the outside of the envelope," and to extend the anterior-posterior axis beyond the spherical geometry imposed by the initial shape of the egg.

Tracing cells in amphibian embryos shows that convergent extension is driven by cell movements that are polarized in an unexpected way; the cells move transverse to the axis of extension. The tissue first thins and extends as the cells intercalate radially, or normal to the plane of the tissue (*10*, *13*, *14*) (Fig. 2A). Then the tissue converges and extends as the cells intercalate mediolaterally to form a narrower but longer array (*15–17*) (Fig. 2A). Cell intercalation is a subtle but powerful mechanism; locally, cells move only short distances as they wedge between one another, but the collective effect of this behavior is rapid change in tissue shape (movie S3). Converging tissues consist of a single layered epithelium and several tiers of deep mesenchymal cells (Fig. 2A). The deep cells generate forces for convergent extension, whereas the epithelial cells undergo passive intercalation and convergent extension (*10*, *17*, *18*). Convergent extension by cell intercalation is a common if not universal mechanism of shaping large features of metazoan embryos (Fig. 2B). It occurs during gastrulation and axis elongation of ascidians (*3*), teleost fish [(*4*, *19*) movie S4], birds (*5–7*), and mammals (*8*), and during *Drosophila* germ band extension (*20*) and echinoderm gut elongation (*21*), to name several examples.

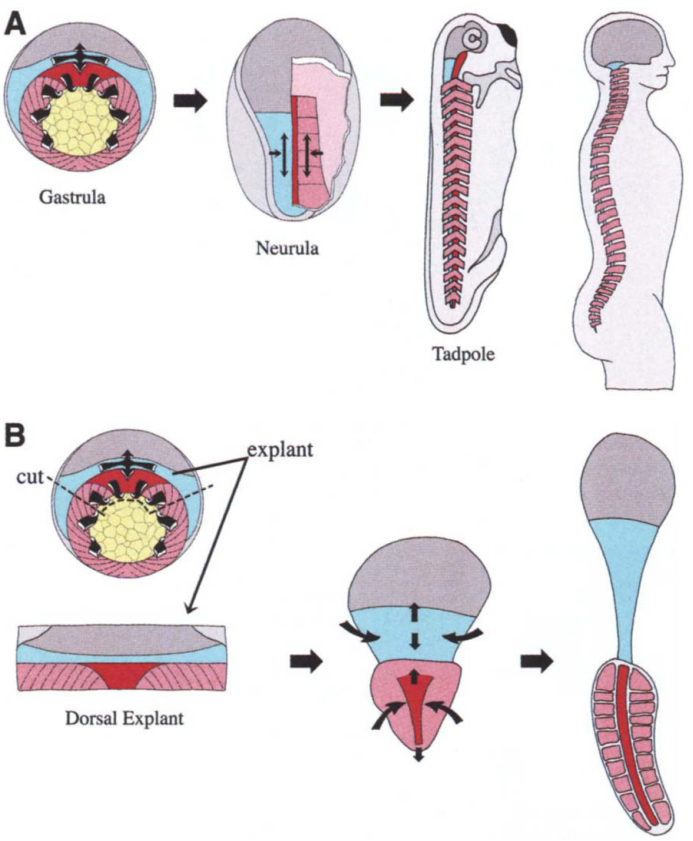

Fig. 1. Convergent extension movements elongate the anterior-posterior axis of the vertebrate body plan. The notochordal (red) and somitic (pink) tissues turn inside and converge (narrow) and extend (lengthens) in the gastrula and neurula stages of the frog embryo (**A**). The overlying presumptive hindbrain and spinal cord (blue) tissues converge and extend coordinately but on the outside of the embryo. These movements push the head away from the tail and elongate the body axis of the tadpole. Similar movements elongate the body axis of mammals. (**B**) Cultured explants of the same tissues also converge and extend, showing that convergent extension movements are driven by internal forces.

Mediolateral Intercalation Is Driven by Polarized Protrusive Activity

Time-lapse recordings show that mediolateral intercalation of mesodermal cells is driven by mediolaterally polarized protrusive activity. Before mediolateral intercalation, protrusive activity occurs in all directions, but when intercalation begins, cells form medially and laterally directed lamelliform protrusions that appear to attach to and crawl on adjacent cells. As a result of this traction, the cells elongate in the mediolateral axis and intercalate along this axis to form a narrower, longer array (*17*, *22*, *23*) (Fig. 3A, movie S5). Intercalating cells remain attached to one another at their elongated, anterior and posterior surfaces by short, dynamic filiform protrusions (movie S6). Neural cells can intercalate using bipolar protrusive activity, or they can be secondarily induced by midline-generated signals to intercalate using a monopolar, medially directed protrusive activity (*1*, *18*). We proposed a cell traction–cell substrate model that relates both the monopolar and bipolar protrusive activity to cell intercalation (*1*); only the latter will be discussed here. In this model, cells use one another as "movable substrates." The medial and lateral lamellipodia (Fig. 3, B and C) exert traction on the elongate anterior and posterior surfaces of the adjacent cells, thereby pulling the cells between one another mediolaterally. Cells adhere by numerous, filiform protrusions and contact points on their anterior and posterior surfaces (Fig. 3, B and D). But these are made and broken rapidly (movie S6), which provides local, transient openings that allows the cells to intercalate, but taken collectively, they provide the stiffness and resistance to compression necessary for the tissues to push. Substantial evidence supports this model (*1*). Notably, disrupting this polarized protrusive activity in frog embryos blocks cell intercalation

and convergent extension (*24*). The mediolateral elongation and alignment aspects of this mechanism are also shown by the intercalating cells of the teleost fish, and these features are disrupted in mutants deficient in cell intercalation and extension (*4*, *25–27*). The morphology of intercalating cells in bird and mammalian (*5*, *6*, *8*) embryos is consistent with intercalation by polarized motility. Ascidian notochord cells intercalate using transversely polarized basolateral protrusions (*3*), suggesting that cell intercalation by this type of polarized protrusive activity spans the chordate phylum.

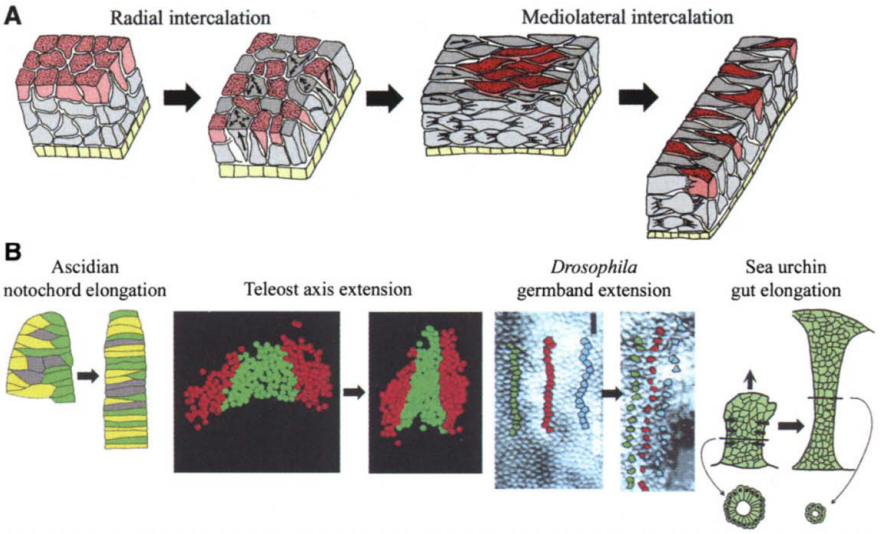

Fig. 2. (**A**) Tracings of labeled cells in frog and fish embryos (*1*, *4*) show that convergent extension occurs by two processes. Cells first intercalate between one another perpendicular to the plane of the tissue to form a thinner but longer tissue (radial intercalation). Then they intercalate between one another mediolaterally within the plane of the tissue to form a narrower, longer tissue (mediolateral intercalation). (**B**) Convergent extension by cell intercalation is a universal, body-shaping process in embryos. It occurs during axis elongation in the ascidian (*3*), a nonvertebrate chordate, and in the zebrafish [courtesy of R. Adams, C. Kimmel, N. Glickman], and during extension of the germband (body axis) of the *Drosophila* (*20*) and extension of the gut in the echinoderm embryos (*21*). The axes of extension are vertical.

The Mechanism of Polarization

The polarity of cells within the plane of the epithelium of *Drosophila* is regulated by the planar cell polarity (PCP) pathway (*28*, *29*). This pathway controls the polarity of the single hair on each epidermal cell of the fly wing and the polarity of ommatidia in the compound eye. In *Drosophila*, the pathway includes the principal components *frizzled* (*fz*), which encodes a serpentine, seven-pass transmembrane receptor, *dishevelled* (*dsh*), which encodes a cytoplasmic signaling protein, *Strabismus* (*stbm*) or *van Gogh* (*Vang*), which encodes a probable membrane protein, *flamingo* (*fmi*), a serpentine membrane protein with cadherin-like domains, and *prickle* (*pk*). These and other components are thought to assemble an asymmetric signaling complex that imparts both cell and tissue planar polarity, although the mechanisms involved are not yet resolved (*28*, *29*). These findings have inspired experiments demonstrating that a similar pathway regulates the polarity underlying the planar (mediolateral) cell intercalation in chordates (Fig. 4).

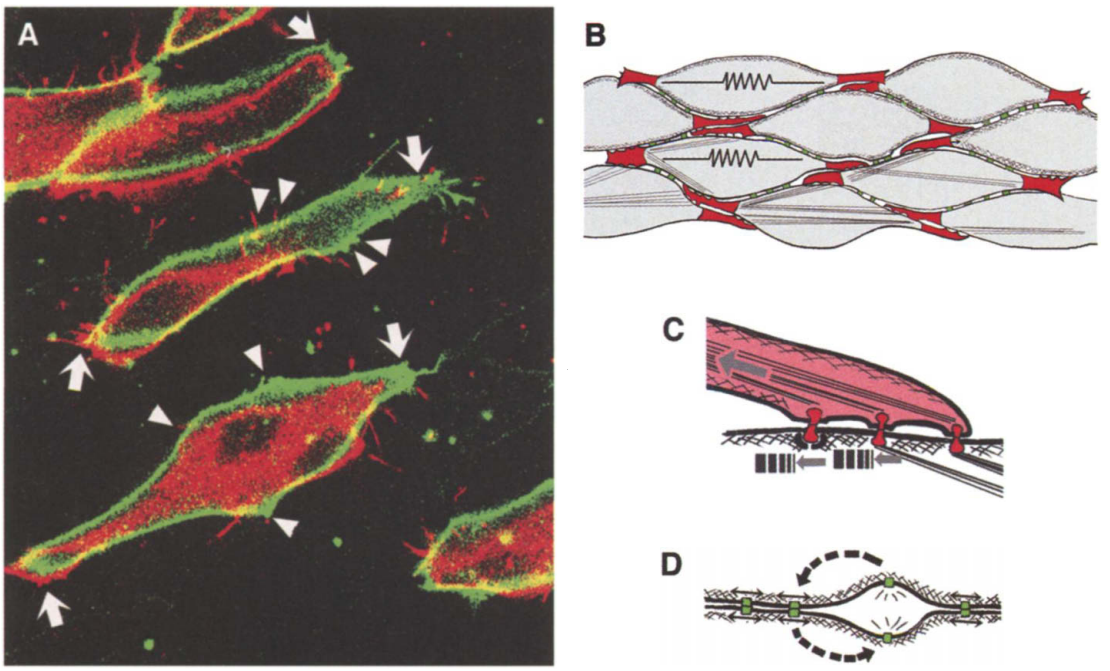

Fig. 3. An image from a fluorescence confocal movie (courtesy of L. Davidson). (**A**) Intercalating frog mesodermal cells are visualized at two levels: the surface of the explant (red image) and 5 μm deep in the tissue (green image). The cell membranes are labeled with GAP-43 green fluorescent protein (GFP), and labeled cells are tightly packed among unlabeled cells (dark areas). The labeled cells are elongated mediolaterally and are polarized by lamellipodia at their medial and lateral ends (arrows) and by short filiform contacts on their anterior and posteriorsurfaces (pointers). (**B**) A model shows how this polarized protrusive activity is thought to produce cell intercalation (*1*). The large medial and lateral protrusions, called tractive protrusions (red) are thought to exert traction on the surfaces of adjacent cells, which develops tension, elongating the cells, and pulling them between one another. (**C**) They are anchored to adjacent cells and do not slip when tension is applied by the cytoskeleton. Adhesions along the elongate anterior and posterior sides, called stiffening adhesions (green), hold the cells together to form a stiff tissue that can push, but they also slide in the plane of the membrane and turnover rapidly (**D**), which allows cell intercalation.

Dishevelled is a multifunctional protein that regulates cell polarity though the noncanonical PCP pathway but also regulates cell fate through the canonical Wnt/β catenin pathway. Mutant forms of Dishevelled, similar to ones that disrupt the noncanonical PCP pathway but not the canonical Wnt/β catenin, tissue fate pathway of *Drosophila*, also disrupt convergent extension but not tissue fate in *Xenopus* (*24*, *30*). Inhibitory forms of Dishevelled stimulate formation of more but less stable and randomly oriented protrusions, whereas overexpression of wild-type Dishevelled does not af-

fect stability of protrusion but randomizes their orientation (*24*). In both cases the normal mediolateral polarization, elongation, and alignment is lost and convergent extension fails.

In *Xenopus* and the zebrafish, *Wnt* 11, a ligand of *Frizzled* is necessary for convergent extension. Wt11 is expressed in the extending mesoderm of *Xenopus*, and expression of a dominant inhibitory form inhibits convergent extension but does not affect tissue fate (*31*). This inhibition is rescued by a form of Dishevelled that functions in the noncanonical PCP pathway but not in canonical Wnt/β-catenin pathway. Loss of function alleles of the gene *silberblick*, which encodes zebrafish Wnt 11, inhibits cell intercalation and tissue extension in the zebrafish (*32*). This inhibition is rescued by expression of wild-type Wnt 11, or a form of Dishevelled active in the PCP pathway but not by a form active in the canonical Wnt/β catenin pathway. Wnt5a also inhibits convergent extension when overexpressed in frog embryos (*33*), as do mutants of *pipetail*, the zebrafish Wnt5a (*34*). These experiments implicate Wnt 11 and 5a in the regulation of cell intercalation during convergent extension (Fig. 4).

In frog embryos, Frizzled 7, a Wnt receptor, is expressed in converging, extending tissues, and its overexpression, or expression of a secreted, inhibitory form, appears to block these movements (*35*, *36*). Inhibiting expression of Frizzled 7 protein also causes defects in gastrulation, but these are due to failure of mesodermal and overlying tissues to separate, rather than to direct effects on convergent extension (*37*). Frizzled receptors can also signal through the Wnt/Ca^{++} pathway, which involves cytoplasmic, trimeric G proteins, Ca^{++}, and protein kinase C, and is independent of Dishevelled (*38*) (Fig. 4). The tissue separation defect is rescued by expression of downstream components of the Wnt/Ca^{++} pathway but not by ones in the noncanonical PCP or canonical Wnt/β catenin pathways. This suggests that the Wnt/Ca^{++} pathway regulates tissue separation (*37*) rather than or in addition to direct effects on convergent extension.

Strabismus (*van Gogh*) encodes a putative membrane protein and shares with *Frizzled* a directional, domineering, cell nonautonomous effect on epithelial cell polarity in *Drosophila*. Nearby normal cells point toward clones of *Fz* cells and away from clones of *Strabismus* cells in the *Drosophila* wing, implying that these genes are involved in a local signaling (*28*, *39*). Strabismus is also required for polarized cell intercalation and convergent extension in frogs and zebrafish (*40*–*43*), probably through interaction with Dishevelled (*40*). As is the case with several components of the PCP pathway in *Drosophila* (*28*), both overexpression and inhibition of Strabismus suppress polarized cell motility in frogs but no domineering, cell nonautonomous effect was seen (*42*). *Strabismus* also functions in mammalian convergent extension. A homolog of *Strabismus*, *L-tap* (for loop tail–associated protein), is the probable cause of the Loop-tail mutant phenotype in the mouse, which includes shortened anterior-posterior axes and neural tube closure defects (*44*). Failure of neural fold fusion may represent a primary defect in the folds or a secondary one resulting from failure of convergence. Inhibiting frog convergent extension results in neural folds that are too far apart to meet, and they never fuse for this reason, rather than defects in the folds (*45*). This suggests that failure of convergent extension may indirectly cause neural tube defects. In mammals and birds, convergent extension involves not only mediolateral intercalation but also cell division that is preferentially oriented along the axis of extension (*6*–*9*, *46*). This raises the possibility that Strabismus, and the PCP pathway, may polarize or orient cell division as well as cell intercalation in amniote convergent extension.

Studies in *Xenopus* embryos and cultured cells show that Wnt/Frizzled signaling activates the cytoskeletal regulator Rho through activation of Dishevelled, and a direct interaction of Dishevelled with Daam1 (Dishevelled-associated activator of morphogenesis) (*47*) (Fig. 4). Daam1 binds to Dishevelled by its carboxy end and to Rho by its amino end. Daam1 contains formin homology domains, which mediate protein-protein interactions and may assemble protein complexes of Dishevelled, Rho, and other signaling molecules (*47*) (Fig. 4). These results link Wnt/Frizzled signaling during convergent extension to the Rho family of small guanosine triphosphatases (GTPases), including Rac, Rho, and Cdc42, which regulate the cytoskeleton, cell polarity, and protrusive activity (*48*, *49*).

Rho mediates formation of stress fibers, which are contractile microfilament bundles spanning the cell, and focal adhesions, the attachments of stress fibers to the substrate. Cdc42 mediates cell polarity and formation of filipodia, thin protrusions that mediate cell motility and contact interactions. Rac mediates formation of lamellipodia, which are flattened protrusions important in many forms of cell motility (*48*). Localized activity of these GTPases could regulate the elongate morphology, the mediolateral lamellipodia, and the filiform contacts on the elongate anterior-posterior surfaces of intercalating cells (Fig. 3), but no such localized activity has been reported. Rho activates Rho kinase (ROCK or ROK), which mediates contraction of stress fibers (*50*, *51*). In the zebrafish, dominant-negative Rho kinase (Rok2) disrupts mediolateral elongation, alignment, and intercalation of cells and also inhibits extension (*27*). A Wnt/Fz-stimulated Rho/Rok cascade during convergent extension might generate mediolateral contractile elements and thereby facilitate shortening and development of traction by the lamellipodia. Tension along the elongated anterior and posterior cell surfaces would also inhibit lamellipodia there (*52*) and thereby enhance polarity (Fig. 4).

Rac activity would be expected where the large lamellipodia appear, although there is no evidence for this in embryos. In culture, cyclical stretching (tensioning) of vascular smooth muscle cells on elastic,

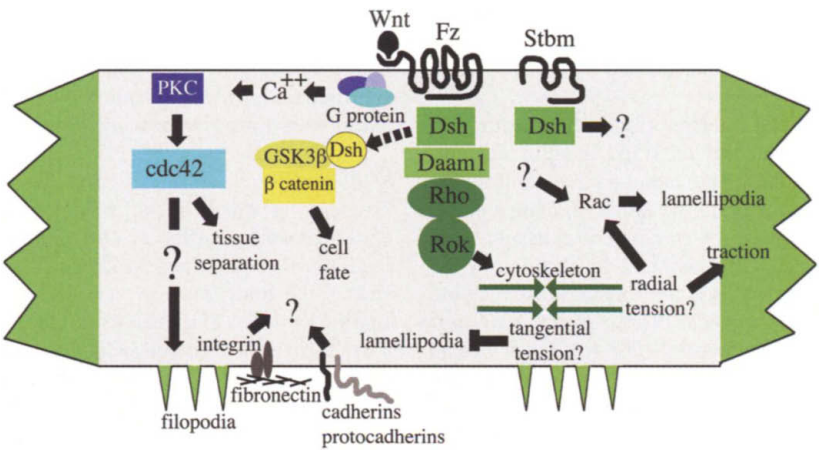

Fig. 4. Principal participants in the planar cell polarity (PCP) signal transduction pathway (green) and downstream effectors thought to be involved in polarizing intercalating cells during convergent extension. Also shown are the Wnt/Ca^{++} pathway (blue), and the canonical Wnt/β catenin (yellow) pathway. Dsh (Dishevelled), Daam1 (Dishevelled associated activator of morphogenesis), Fz (Frizzled), PKC (protein kinase C), and Stbm (Strabismus).

matrix-coated silicone membranes polarizes protrusive activity (*53*). Radial tension activates Rac and stimulates lamellipodia preferentially at the anchored, narrow ends of the stretched cells, whereas tangential tension on their elongated sides is thought to inhibit lamellipodia (*53*). In frog embryos, the elongate, intercalating cells are under tension parallel to their long axes (*1*), raising the possibility that a similar tension-mediated feedback might enhance polarization by stimulating lamellipodial traction at the ends and suppressing lamellipodia at the sides (Fig. 4).

A role for Cdc42 is suggested by the fact that inhibition of convergent extension by overexpression of Frizzled 7 is rescued by a dominant-negative Cdc42, and inhibition by a secreted, inhibitory form of Frizzled 7 is rescued by a constitutively active form of Cdc42 in frogs (*36*). Perhaps Cdc42 regulates the anterior and posterior filipodial activity, but there is no evidence for this. The function of Cdc42 in convergent extension (*54*), as well as in tissue separation (*37*), is regulated by the Wnt/Ca^{++} pathway.

Cell-cell interaction with fibronectin matrix, mediated by the $\alpha5\beta1$ integrin receptor, is essential for the radial intercalation movements underlying the initial thinning and extension phase of convergent extension (*55*) (Fig. 2A). The membrane localization of Dishevelled that is characteristic of its function in the *Drosophila* PCP pathway (*28*) also occurs in vertebrates (*24*, *40*), but it occurs during radial intercalation and is dependent on integrin-fibronectin interactions (*55*). This raises the possibility that PCP-mediated, mediolateral intercalation is also dependent on integrin-fibronectin interactions. Decrease in activity of the calcium-dependent cell adhesion molecule, C-cadherin, may also be necessary for convergent extension (*56*) and paraxial and axial protocadherins may have adhesive or signaling functions in convergent extension (*57*). Possible roles for these molecules include transient regulation of adhesion, which may allow the tissue to deform itself by cell rearrangement and yet form a stiff beam that is capable of pushing. Localization of specific cell adhesion molecules, or their activity, to the lamellipodia and filipodia, could also contribute to polarization.

Differences in Polarizing Mechanisms

Understanding the differences between planar epithelial cell polarity in *Drosophila* and planar mesenchymal cell polarity in vertebrate convergent extension would illuminate the mechanism of both. In *Drosophila*, the PCP pathway polarizes surface epithelial cells, whereas in the frog it polarizes the deep mesenchymal cells (*1*, *24*), and the same appears true in zebrafish (*4*, *25–27*). In *Drosophila*, polarity is expressed as a stable cytoskeletal structure, a hair, bristle, or arrangement of ommatidial cells, rather than the reiterated pattern of protrusive activity of intercalating cells. *Drosophila* cells are monopolar, whereas intercalating mesodermal cells are bipolar and neural cells are only secondarily monopolar. In *Drosophila*, polarity is reflected in an asymmetric localization of PCP pathway components, with Dishevelled and Frizzled predominating distally and Prickle predominating proximally (*28*, *29*). No polarized localization has been reported in intercalating cells. The domineering, cell nonautonomous effects of Frizzled and Strabismus (*39*) have not been seen in vertebrate convergent extension. Resolving the significance of these cell biological differences would provide new insights.

Conclusion

Elements of the PCP pathway controlling epithelial cell polarity in *Drosophila* also regulate the polarized cell motility that shapes the body plan in vertebrates. This finding provides and genetic and molecular basis for a polarized cell behavior underlying development of polarity at the level of the organism and thereby advances our understanding of the genetic encoding of three-dimensional form. Many exciting challenges remain. Only some of the players in this and other relevant pathways have been identified and characterized, and only some of these have been discussed here. The cell biological mechanisms of how these players interact to build a form-generating machine are yet to be resolved.

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Movies S1 to S6