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Current Opinion in Genetics & Development

Round and round gets you somewhere: collective cell migration and planar polarity in elongating *Drosophila* egg chambers

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Planar polarity is a developmental mechanism wherein individual cell behaviors are coordinated across a two-dimensional plane. A great deal of attention has been paid to the roles that the Frizzled/Strabismus and Fat/Dachsous signaling pathways play in this process; however, it is becoming increasingly clear that planar polarity can also be generated through alternate mechanisms. This review focuses on an unconventional form of planar polarity found within the follicular epithelium of the *Drosophila* egg chamber that helps to create the elongated shape of the egg. We highlight recent studies showing that the planar polarity in this system arises through collective migration of the follicle cells and the resulting rotational motion of the egg chamber.

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Current Opinion in Genetics & Development 2015, **32**:10–15

This review comes from a themed issue on **Developmental mechanisms, patterning and organogenesis**

Edited by **Deborah J Andrew and Deborah Yelon**

http://dx.doi.org/10.1016/j.gde.2015.01.003

Introduction

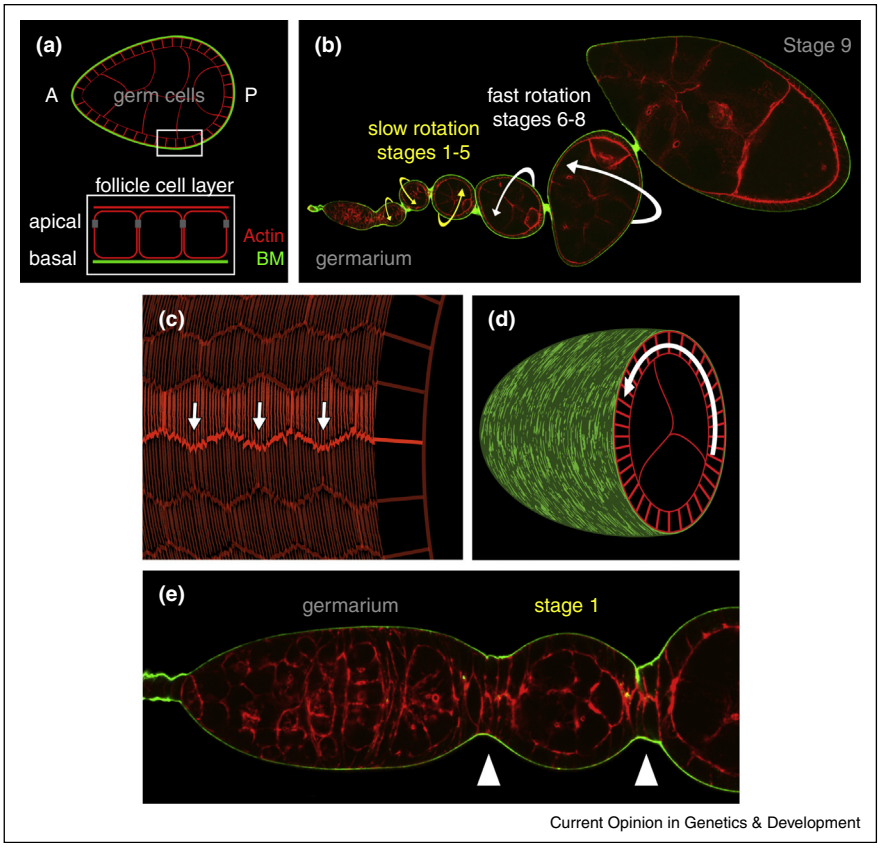
Planar polarity is a phenomenon in which cells become coordinately polarized across the plane of a tissue to provide directional information for morphogenetic events. Many examples of planar polarity rely on the highly conserved Frizzled/Strabismus and Fat/Dachsous signaling cassettes, which can function either alone or in combination to polarize a tissue [1,2]. It has long been recognized that there is a deep connection between planar polarity and large scale cellular movements [3]. For example, the Frizzled pathway directs the convergence of cells toward the midline during gastrulation in vertebrates. Recent work has also revealed that bulk cellular flows can function upstream of the Frizzled cassette to help orient the component proteins with respect to the proximal-distal axis of the *Drosophila* wing [4]. Important new insight into the relationship between planar polarity and collective cell movement has come from three tissues in *Drosophila* whose polarization is independent of the pathways described above. These include the primary embryonic epithelium and the Malpighian tubules, where unconventional forms of planar polarity direct convergent extension movements during tissue elongation [5,6]. This review focuses on a third example — the planar polarization of the follicular epithelium that helps to shape the fly egg. In particular, we discuss recent studies revealing that follicle cell planar polarity depends on a whole tissue rotation that is driven by the collective migration of these cells.

Overview of egg chamber elongation

In *Drosophila*, each egg arises from a multicellular structure in the ovary called an egg chamber (Figure 1a). The egg chamber consists of a germ cell cluster surrounded by a somatic epithelium of follicle cells. The apical epithelial surface lies against the germ cells, whereas the basal surface contacts a basement membrane extracellular matrix (ECM). Egg chambers are assembled in an ovarian region called the germarium (Figure 1b). Once a new egg chamber buds from this structure, it joins an assembly line of progressively older egg chambers that are linked together by chains of stalk cells. Each egg chamber then progresses through fourteen developmental stages that are largely classified by their morphology. Initially, the egg chamber is spherical. Between stages five and ten, however, it elongates along its anterior–posterior (AP) axis to create the elliptical shape of the egg.

Egg chamber elongation requires an unconventional form of planar polarity within the follicular epithelium. This planar polarity is most readily seen through the organization of contractile actin bundles at the basal surface (Figure 1c). The bundles are organized into a parallel array within each cell, and globally across the tissue, such that they all align perpendicular to the AP axis [7]. Interestingly, the basement membrane (BM) becomes similarly polarized, with linear fibril-like structures oriented in the same direction as the actin bundles (Figure 1d) [8••,9,10•]. Together, the actin bundles and fibrillar BM are thought to act as a 'molecular corset' that resists the expansive growth of the germ cells, thus biasing total egg chamber growth to the AP axis [7,10•]. In support of this notion, manipulations that

Figure 1



Introduction to egg chamber rotation. **(a)** Image of a developmental array of egg chambers indicating the developmental window and two phases in which rotation occurs. **(b)** Overview of egg chamber structure. **(c)** A schematic of a transverse section through an egg chamber showing that rotation occurs within the surrounding BM. **(d)** Illustrations showing the planar polarization of actin bundles and leading edge protrusions at the basal surface of the follicular epithelium during rotation. **(e)** At the time rotation begins the egg chamber is connected to the germarium at its anterior pole and to stalk cells at its posterior pole (white arrow heads). For all images, anterior is to the left.

disrupt tissue-level actin bundle alignment and/or BM structure produce rounded eggs [8••,10•,11,12,13,14••,15,16••,17,18]. Moreover, during stages nine and ten, the circumferentially organized actin bundles undergo oscillating Myosin-mediated contractions, suggestive of a more active constriction mechanism [19,20].

Egg chamber elongation also coincides with a dramatic whole tissue rotation (Figure 1b-d) [8••]. During this process, the follicle cells undergo a directed migration on the inner surface of the BM. Because the apical epithelial surface is adhered to the germ cells, this collective motion causes the entire egg chamber to rotate within the surrounding matrix. Rotation occurs perpendicular to the egg chamber's AP axis, mirroring the orientation of the molecular corset [8••]. Although this motion was originally reported to occur during stages five through eight [8••,21•], it was recently shown that rotation actually begins shortly after the egg chamber forms at stage one [16••].

This basic understanding of the mechanisms controlling egg chamber elongation now sets the stage to explore the planar polarity in this system in more detail. We will first introduce the mechanisms that promote collective follicle cell migration. Next, we discuss how follicle cell migration helps to build the molecular corset required for egg chamber elongation. Finally, we examine the follicle cells as a model for understanding how coordinated cellular movements can play an instructive role in the planar polarization of a tissue.

Collective migration of the follicle cells during egg chamber rotation

In many ways, the collective migration of the follicle cells that causes the egg chamber to rotate is similar to other forms of epithelial motility [22–25]. Each cell's basal surface has a clear front-rear axis that is oriented in the direction of tissue movement, and migration along the BM is powered through dynamic integrin-based focal adhesions [8••,16••,17•,21•]. The front-rear axis, itself, is most easily seen through the actin-rich protrusions that

extend from each cell's leading edge (Figure 1c) [16••,17•,26]. However, the trailing edge is also well defined, with two proteins required for rotation, the atypical cadherin Fat2 and the Ste20-like kinase Misshapen, specifically localizing to this site [17•,21•]. Interestingly, homologs of these proteins had previously been implicated in collective migration in other systems [27–30]. Work in the follicle cells has yielded new insight into their function showing that Fat2 helps to direct the growing ends of microtubules toward the trailing edge [21•], whereas Misshapen promotes the release of trailing edge focal adhesions to allow forward motion [17•].

There is also an important aspect of the follicle cell system that differentiates it from other well-studied forms of collective migration. Typically, collectively migrating cells move as a two-dimensional sheet across a substrate or as a cohesive cluster through a three-dimensional scaffold [25]. Under these conditions, cells at the front of the migrating unit have a free leading edge [23], and these 'leader cells' often make larger contributions to tissue motility than the cells that follow. In contrast, the follicle cells form a topologically closed epithelium around the germ cells where each cell appears to contribute equally to tissue movement [16••,17•]. In this way, the egg chamber resembles cultured cysts of mammalian epithelial cells that spontaneously rotate within three-dimensional ECMs [31–33]; however, the cellular mechanisms that power cyst rotation remain to be elucidated. The lack of a leader cell population suggests further studies of the follicle cells may reveal unique mechanisms that guide collective migration.

One important open question is how the direction of collective migration is chosen, both in terms of the rotational axis and its chirality. Rotation always occurs perpendicular to the egg chamber's AP axis. This invariant behavior may result from physical constraints imposed by cell–cell contact. During most of the rotational period, the egg chamber is fully encapsulated within its BM, and the stalks that link one egg chamber to the next bind to the outside of this matrix. In contrast, when rotation begins, the follicle cells have direct cell–cell connections with the germarium at the egg chamber's anterior pole, and with stalk cells at the posterior pole that may limit movement parallel to the AP axis (Figure 1e). The bigger mystery is how chirality is determined, as rotation can occur in either a clockwise or counterclockwise direction irrespective of the neighboring egg chamber's chirality. This variability is likely due to the closed epithelial topology, as the tissue lacks a free leading edge to provide an external polarizing cue [23]. To initiate rotation, therefore, the follicle cells must make a collective decision about which way to go. Identifying the cellular mechanisms that underlie this symmetry-breaking event will be an exciting area for future research.

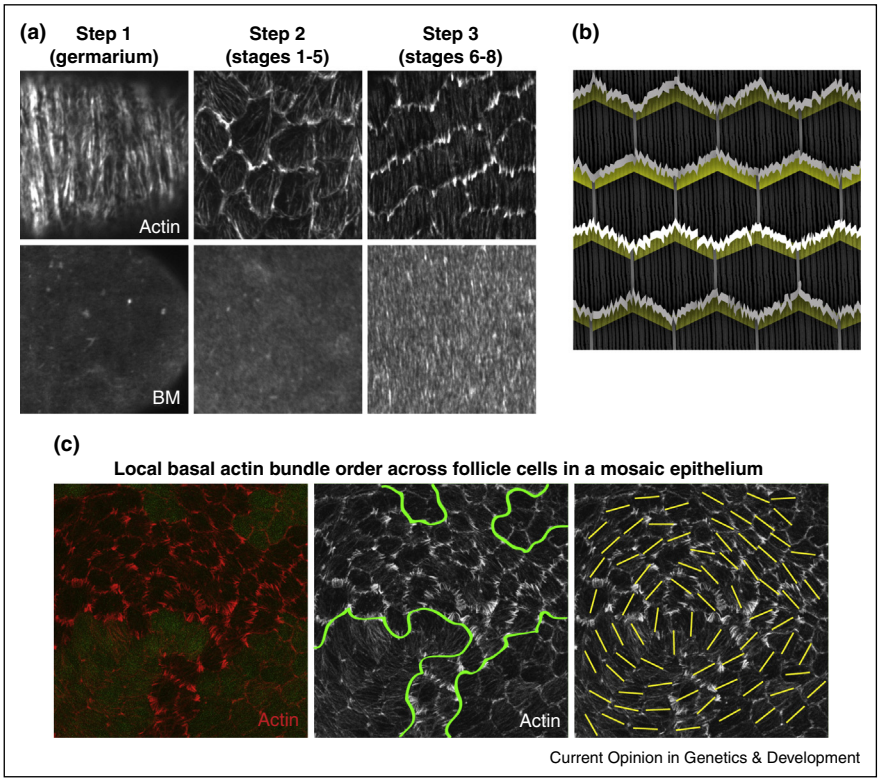
A three-step model for the formation of the molecular corset

In most examples of collective migration during development, the cells have a clear destination. In contrast, the migrating follicle cells just go round-and-round inside their BM. What does this rotational motion do? The prevailing model is that rotation builds the molecular corset for egg chamber elongation — a structure that will persist after rotation is complete [8••,16••]. It had been widely believed that rotation, tissue-level actin bundle alignment, and BM polarization all began roughly concurrently at stage five [8••,21•,34–38]. However, the discovery that rotation actually begins at stage one has revealed that the construction of the molecular corset begins much earlier than previously thought and that it occurs in three steps (Figure 2a) [16••]. During Step 1, the tissue-level alignment of the basal actin bundles is established among the follicle cell precursors within the germarium through an unknown mechanism [12]. At the start of Step 2, the egg chamber buds from the germarium and begins rotating to maintain the circumferential actin bundle pattern as the tissue grows. Evidence for this relationship comes from the observation that a rotational block causes a dramatic loss in tissue-level actin bundle alignment over time [16••]. Step 3 begins approximately 30 h later when rotation creates the system of polarized fibrils within the BM [8••,16••]. Once the BM is polarized, the global actin bundle alignment shows increased coherence, and rotation becomes dispensable for maintaining this pattern [16••]. Because the basal actin bundles are known to interact with the BM through focal adhesions [11,39], it is likely that their tissue-level organization is stabilized through direct cell-ECM communication. In support of this notion, the actin bundles lose their tissue-level alignment in the absence of the BM component Collagen IV [8••].

How the early rotation during Step 2 maintains the tissue-level actin bundle alignment inherited from the germarium is currently unknown; however, this phenomenon may ultimately be best understood in the context of individual cell motility. We envision that the basal actin bundles might show a dynamic treadmilling behavior during rotation, in which the polymerizing ends of the microfilaments are preferentially oriented toward each cell's leading edge and the depolymerizing ends to the trailing edge. Because the actin bundles are associated with the BM through focal adhesions, this orientation might also promote the formation of new adhesions at the cell's front and their subsequent disassembly at the rear. In this model, the coordinate alignment of the basal actin bundles may also reinforce unidirectional tissue movement.

In addition to the changes described above, the transition from Step 2 to Step 3 is also marked by a refinement of the follicle cells' front-rear axes and a two-fold increase in rotation rate [16••]. The leading edge protrusions, which can occupy a broad area at the front of each follicle cell

Figure 2



Planar polarity within the follicular epithelium. **(a)** The tissue-level alignment of the basal actin bundles occurs in three steps. Representative images of the basal actin bundles (rhodamine phalloidin) and BM (Collagen IV-GFP) are shown for each step. **(b)** The front-rear axes of the migrating follicle cells are also aligned across the tissue. Leading edge protrusions (white jagged lines) mark the front of each migrating follicle cell and the localization of the Fat2 and Misshapen proteins (yellow chevrons) define the rear. **(c)** Local order can exist in the follicular epithelium in the absence of global polarity. In a mosaic epithelium that is comprised of both wild-type cells and cells that lack the β-integrin subunit Myospheroid, the basal actin bundles can show a swirling pattern. Wild-type cells are marked in green in the first two panels. The orientation of the actin bundle array within each cell is indicated by the yellow lines. For all images, anterior is to the left.

during Step 2, become significantly narrowed. Moreover, it is during Step 3 that Fat2 has been reported to become clearly localized to each cell's trailing edge (Figure 2b) [14••,21•]. These differences can likely also be explained by interactions between the follicle cells and the fibrillar BM. When migratory mammalian epithelial cells are cultured on micropatterns that contain parallel microgrooves and ridges, their leading edge protrusions preferentially align with the pattern [40]. Likewise, the velocity and coherence of their movement increases [41]. Interaction with a fibrillar ECM also increases the coherence of collectively migrating prechordal plate cells in zebrafish [42]. If the BM fibrils influence the follicle cells in a similar way, the increased rotation rate may result from a positive feedback loop in which rotation first polarizes the BM, and then the polarized BM increases the migratory efficiency of the follicle cells.

Mechanisms controlling follicle cell planar polarity

In the previous section, we introduced the idea that the unconventional form of planar polarity seen in the follicular epithelium depends, in part, on egg chamber rotation. Here, we explore this relationship in more detail, and propose that there are, in fact, two levels of planar polarity in this epithelium that should both be considered in future studies.

The first evidence that the planar polarization of the basal actin bundles is a direct consequence of the epithelial rotation came through careful studies of *fat2* mosaic egg chambers [14••,43]. When *fat2* mutant cells comprise less than 60% of the epithelium, the actin bundles are still perfectly aligned across the tissue. In contrast, when *fat2* mutant cells exceed 60%, actin bundle orientation is globally perturbed. This observation contrasts with the fly wing, where even a small patch of *frizzled* mutant cells can alter the polarity of individual cells both within the clone itself and in adjacent cells [2]. It was later shown that loss of Fat2 from the entire epithelium blocks rotation [16••,18,21•]. The presence of a small *fat2* mutant clone does not block rotation, however, as the mutant cells can be carried along by their wild-type neighbors [21•]. Thus, the deciding factor between global actin

bundle alignment and global perturbation seems to be whether there are enough migratory cells in the epithelium for rotation to proceed. The bimodal nature of the actin bundle phenotype has also been noted in follicle cell mosaics for two other pro-migratory genes [16••,17•]. The model that emerges is that the planar polarization of the basal actin bundles is an all-or-none process that depends on bulk tissue movement.

Interestingly, regions of local order have been observed in egg chambers that lack tissue-level actin bundle alignment and are therefore unlikely to be rotating [8••,11,12,14••,15,44]. In these cases, the actin bundles are coordinately aligned across patches of cells, sometimes even taking the form of swirls (Figure 2c). Thus, polarity information can still propagate across clusters of follicle cells in the absence of bulk tissue movement. These planar signals could be transmitted through contact-based cell-cell signaling, or directed mechanical stresses, similar to what occurs in the fly wing [4]. It is also possible that subsets of follicle cells retain some migratory capacity, or that polarity cues are relayed from one cell to the next through structural changes in the BM. Determining how this local order emerges will require long term live imaging of epithelia lacking global polarity, and may require the identification of new molecular players. It is likely, however, that these efforts will yield new insight into how polarity cues are conveyed across the basal plane of an epithelium.

Although the basal actin bundles have traditionally been used as the primary readout for follicle cell planar polarity, we propose that the front-rear cellular axes should receive equal attention. This may seem like a subtle distinction, since the actin bundles track with the front-rear axes under normal conditions. However, recent work has revealed that this relationship is not fixed, as leading edge protrusions can extend orthogonally from the basal actin bundles even in wild-type cells [16••]. Moreover, coordinate alignment of the front-rear cellular axes is a prerequisite for the tissue motility that ultimately creates the stable actin bundle pattern. Thus, to understand how planar polarity is generated within this epithelium will likely require the simultaneous monitoring of both cellular features, particularly under conditions where rotation is impaired.

Concluding remarks

The planar polarization of tissues is a fundamental requirement for many morphogenetic processes. It is becoming increasingly clear, however, that collective cell movements can also play instructive roles in tissue polarization. In the case of the fly wing, directed cellular flows work in concert with the Frizzled/Strabismus and Fat/Dachsous signaling cassettes to promote tissue polarization [4]. Determining whether the collective migration of the follicle cells is coupled to a yet to be discovered planar signaling pathway will be an important avenue for future inquiry. Fat2 is an appealing candidate to participate in such a system, as it is the homolog of Fat; to date, however, no Fat2-interacting proteins have been identified in *Drosophila*. If a planar signaling system is operating in the follicle cells, it is only a matter of time before unbiased genetic and proteomic approaches identify the key molecular players. Alternatively, the planar polarity in the follicular epithelium may simply be an emergent property of individual cell migratory behaviors. In either case, future studies of the follicle cell system are guaranteed to uncover new guiding principles for the generation of epithelial planar polarity.

Acknowledgements

We are grateful to Robert Ho and to members of the Horne-Badovinac lab for helpful discussions and critical comments on the manuscript. This work was supported by the National Institutes of Health (NIH), in part through NIH T32 GM007183 to M.C. and by NIH R01 GM094276 to S.H-B.

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