The force and effect of cell proliferation

Pedro Campinho and Carl-Philipp Heisenberg*

IST Austria, Klosterneuburg, Austria.

*Correspondence to: heisenberg@ist.ac.at

The EMBO Journal (2013) 32, 2783–2784. doi:10.1038/emboj.2013.225; Published online 4 October 2013

The spatiotemporal control of cell divisions is a key factor in epithelial morphogenesis and patterning. Mao *et al* (2013) now describe how differential rates of proliferation within the *Drosophila* wing disc epithelium give rise to anisotropic tissue tension in peripheral/proximal regions of the disc. Such global tissue tension anisotropy in turn determines the orientation of cell divisions by controlling epithelial cell elongation.

Oriented cell divisions play important roles in the establishment of the animal body plan by both influencing tissue morphogenesis and generating cellular diversity. Generally, the direction of the cell division plane is determined by the orientation of the mitotic spindle prior to cytokinesis. The observation that the mitotic spindle in most animal cell types aligns with the cell's longest axis has led to the formulation of the 'long-axis-rule', postulating that cell shape anisotropy is the main determinant of spindle orientation (Minc *et al*, 2011). However, cell shape anisotropy is unlikely to be the only determinant since many cell types round up during mitosis, thereby losing their shape anisotropy and others do not follow the long-axis-rule at all. In such cases, division orientation is determined by the polarizing activity of biochemical signals originating from the environment (reviewed in Morin and Bellaïche, 2011). In addition, externally applied forces have also been suggested to

control division orientation of single cells in culture independently from their effect on cell shape (Fink *et al*, 2011).

Epithelial growth implies that cells divide parallel to the tissue plane with both daughter cells remaining integrated within the tissue. Although it has been recognized that defects in apico-basal polarity lead to spindle misalignment and disruption of epithelial architecture, the molecular mechanisms underlying this regulation are still unknown. Recent work in the *Drosophila* wing disc epithelium uncovered that the junctional proteins Scribbled and Discs large 1 (Dlg1) are required for proper spindle alignment parallel to the tissue plane (Nakajima *et al*, 2013). Similarly, in the *Drosophila* follicular epithelium, spindle orientation is dependent on the lateral localization of Dlg1, independently of its role in apico-basal polarity (Bergstrahl *et al*, 2013). While such mechanisms ensure that cells divide parallel to the epithelial plane, other mechanisms must still be present to determine the orientation of the mitotic spindle within this plane.

In the *Drosophila* wing disc epithelium, symmetric cell divisions preferentially align with the proximal-distal (PD) axis, thus elongating the organ along this axis (Baena-López *et al*, 2005). This preferential cell division orientation is determined by the Fat-Dachsous pathway, which promotes

Figure 1 Differential rates of cell division between distal (green) and proximal (red) regions of the *Drosophila* wing disc epithelium (1) give rise to global patterns of tension anisotropy within the tissue (2). This tension anisotropy promotes cell elongation along the main axis of tension, thereby controlling the orientation of cell division via cell shape anisotropies in proximal regions of the wing disc (3); D, distal; P, proximal.

accumulation of the atypical myosin Dachs at PD cellular junctions. The polarized activity of Dachs in turn drives cell elongation along the PD axis, leading to a preferential orientation of the mitotic spindle along this axis (Mao *et al*, 2011). In this issue of *The EMBO Journal*, Mao *et al* (2013) report that while mitotic cells located in central regions of the wing disc indeed elongate and divide along the PD axis, cells located in the periphery (proximal edge) elongate and divide orthogonally to the PD axis (Figure 1). These results suggested some type of global planar tissue polarization in proximal regions of the wing disc overriding the local effects of Dachs on spindle orientation. By using laser ablation to reveal tissue tension, the authors showed that in peripheral/proximal regions of the wing disc, junctions oriented orthogonal to the PD axis (PD junctions) are under higher tension than junctions oriented along this axis (lateral junctions; Figure 1). This led them to hypothesize that anisotropic tissue tension might control division orientation of proximal wing cells. Through a combination of elegant genetic experiments and theoretical modelling, the authors then demonstrated that this global tension anisotropy in the proximal wing disc arises from higher cell division rates observed in central versus proximal regions of the wing disc. Furthermore, this apparent tension anisotropy causes concentric elongation of proximal wing disc cells orienting their mitotic spindle orthogonal to the PD axis (Figure 1).

References

- Baena-López LA, Baonza A, García-Bellido A (2005) The orientation of cell divisions determines the shape of *Drosophila* organs. *Curr Biol* **15**: 1640–1644
- Bergstrahl DT, Lovegrove HE, Johnston DS (2013) Discs large links spindle orientation to apical-basal polarity in *Drosophila* epithelia. *Curr Biol* **23**: 1707–1712
- Fink J, Carpi N, Betz T, Bétard A, Chebah M, Azioune A, Bornens M, Sykes C, Fetler L, Cuvelier D, Piel M (2011) External forces control mitotic spindle positioning. *Nat Cell Biol* **13**: 771–778
- Mao Y, Tournier AL, Bates PA, Gale JE, Tapon N, Thompson BJ (2011) Planar polarization of the atypical myosin Dachs orients cell divisions in *Drosophila*. *Gene Dev* **25**: 131–136
- Mao Y, Tournier AL, Hoppe A, Kerster L, Thompson BJ, Tapon N (2013) Differential proliferation rates generate patterns of mechanical tension that orient tissue growth. *EMBO J* **32**: 2790–2803
- Minc N, Burgess D, Chang F (2011) Influence of cell geometry on division-plane positioning. *Cell* **144**: 414–426
- Morin X, Bellaïche Y (2011) Mitotic spindle orientation in asymmetric and symmetric cell divisions during animal development. *Dev Cell* **21**: 102–119
- Nakajima Y-I, Meyer EJ, Kroesen A, McKinney SA, Gibson MC (2013) Epithelial junctions maintain tissue architecture by directing planar spindle orientation. *Nature* **500**: 359–362

Collectively, these results demonstrate that differential proliferation rates within a tissue can generate global tension anisotropies, which promote cell shape changes that again influence cell division orientation. Further dissection of the mechanisms by which tissue tension controls cell division orientation will clarify if anisotropic tension controls division orientation solely through cell elongation, or if additional mechanosensing mechanisms exist that more directly convey tissue tension information to the mitotic spindle. It might also be worth exploring whether cell divisions along the main axis of tension within the wing disc affect global tension anisotropy, and whether the formation of anisotropic tension around areas of cell proliferation affects the rate of cell division therein. Such interplay between tissue tension anisotropy and cell division orientation/rate will likely be critical for maintaining physiological degrees of tissue tension and growth.

In general, the work by Mao *et al* (2013) provides compelling evidence for a functional link between tissue tension and cell division orientation in a physiological relevant context, paving the way for future studies addressing the reciprocal relationship between these two aspects in tissue morphogenesis.

Conflict of interest

The authors declare that they have no conflict of interest.