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# Cell Shape in Proliferating Epithelia: A Multifaceted Problem

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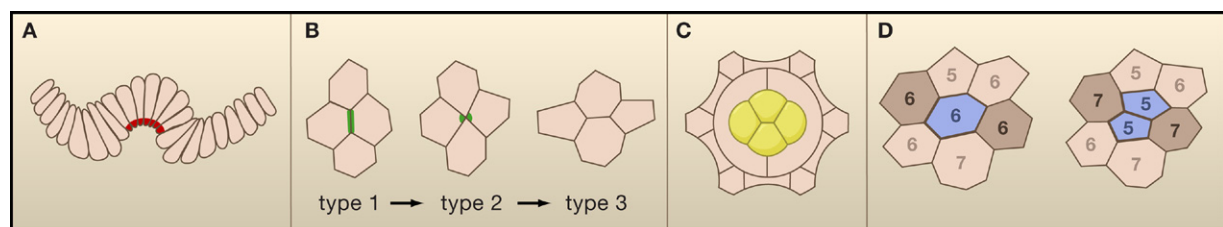
A specific and unexpected distribution pattern of polygonal cell shapes in proliferating epithelia is revealed in a recent study that combines mathematical modeling with experimental data (Gibson et al., 2006). This pattern is conserved in epithelia from diverse species, suggesting that this distribution is a fundamental property of proliferating epithelial sheets.

Modulation of cell shape is a key process that drives morphogenesis during development. For example, in the *Drosophila* embryo, constriction of the apical epithelial surface during gastrulation results in invagination (Figure 1A), whereas more complex cell shape changes give

rise to other structures such as grooves and tubes. Within the plane of an epithelial sheet, regulated cell shape—as defined by the polygonal character of the cells in two dimensions—is critical to the formation of some tissues. How these polygonal shapes form is a fascinating ques-

tion. In a recent study in *Nature*, Gibson et al. (2006) address this question in the proliferating wing-disc epithelium of *Drosophila*.

Achieving a particular polygonal cell shape is not simply a consequence of optimal cell packing (see Figure 1). In the fly embryo,



**Figure 1. Modes of Regulating Epithelial Cell Shapes**

(A) Cartoon of a transverse section through the ventral portion of a gastrulating *Drosophila* embryo. Prospective mesodermal cells within the ventral furrow constrict their apical surfaces (red), driving their shapes toward wedges and powering invagination.

(B) Cartoon of myosin II-dependent junctional reorganization in the converging and extending *Drosophila* germband embryo. Myosin II (green), localized selectively at anterior-posterior cell junctions, is required to shrink the junctions, converting type 1 to type 2 junctions. Type 2 junctions are unstable and resolve directionally toward type 3 junctions, causing an intercalation. Note that the number of sides of participating cells also changes during this event. (Modified after Bertet et al., 2004.)

(C) Schematic cross-section through a *Drosophila* retina at the level of the adherens junctions. Cone cells (yellow) are surrounded by primary pigment cells, which are in turn surrounded by other cell types. The cone cells express N-cadherin, whereas the primary pigment cells do not. Selective N-cadherin expression causes the cone cells to adopt a configuration identical to a cluster of soap bubbles, demonstrating a tendency to minimize their junctional contacts with the surrounding primary pigment cells. (Modified after Hayashi and Carthew, 2004.)

(D) Changes in polygonal sidedness during division of an epithelial cell. In this example, a six-sided cell divides to produce two five-sided daughters (blue). Two neighboring cells bounding the cleavage plane each gain a side. (Modified after Gibson et al., 2006.)

elongation and narrowing of the embryo along the anterior-posterior axis is accompanied by a transition from a relatively ordered hexagonal packing pattern to one in which this pattern is largely extinguished, suggesting that modulation of cell geometry is important for this process (Zallen and Zallen, 2004). The elongation and narrowing is driven, at least in part, by cells intercalating between their neighbors in an oriented fashion (Figure 1B). This process appears to depend on the directed reorganization of cellular junctions controlled by myosin II-dependent cytoskeletal reorganization (Bertet et al., 2004). Different forces are at work in the fly retina, which is composed of a repeating pattern of defined cell types, each of a specific polygonal shape, and each fitting into its specified position in the pattern (Hayashi and Carthew, 2004). Here, selective cell adhesion, mediated by selective expression of cadherins, together with an apparent tendency to minimize surface free energy, contributes to the shape of the cells (Figure 1C).

Theories of how polygonal cell shape in an epithelial sheet is controlled have often invoked physical-chemical properties, such as minimization of surface free energy, to explain why cell packing patterns tend toward regular hexagonal arrays and how they evolve over time (Taylor, 1976). Although some epithelia appear to approach the ideal hexagonal packing predicted by minimization of surface free energy, others, notably including those that are proliferating, contain many hexagonal cells yet are far from regular hexagonal arrays.

Gibson and colleagues (2006) considered the question of what controls the distribution of polygonal shapes in a proliferating epithelium. Using a first-order Markov model with assumptions validated by data gathered from live imaging, the authors tested the possibility that the distribution of polygonal cell shapes in proliferating epithelia is a simple and predictable consequence of the changes in cell

sidedness associated with cell divisions. They came to the remarkable conclusion that the frequency distribution of cellular polygons of a given number of sides converges to an invariant steady state, and this distribution is extraordinarily well matched by empirical data from epithelia of widely divergent species. Therefore, this steady-state distribution of polygons appears to be a fundamental property of epithelia in which cells are replicating.

Focusing on the fly wing imaginal disc—an epithelium that undergoes a massive proliferation prior to differentiation into a wing—the authors determined that daughters of replicating cells share a common, new cell border at least 94% of the time. Furthermore, although the mitotic mother cell enlarges and rounds up, it maintains its contacts with neighboring cells throughout the division. Both observations indicate that cell migration is negligible during this phase of growth. Based on these and other empirical observations, they then defined six conditions from which to construct their Markov model: (1) Cells have four or more sides; (2) cell migration or sorting is insignificant; (3) sister cells retain a shared cell junction after division (the difference between modeling 94% and 100% is subsequently shown to be very small); (4) cell cycles are asynchronous and of similar length; (5) cleavage planes intersect sides rather than vertices of a cell; and (6) existing cell junctions are randomly distributed to daughter cells, but no fewer than two segregate to each daughter. The net result for the model is that the daughter cells have fewer sides than the mother, whereas two immediate neighbors acquire an extra side in a defined way (Figure 1D).

The Markov model describes the state of the system at discrete times, as defined by the number of sides of each cell, as well as the probability of each cell transitioning from one state to another through time. Because the Markov model satisfies defined criteria (the Per-

ron-Frobenius theorem), it rapidly converges to a steady state independent of the starting conditions. The model predicts a steady-state distribution of 28.9% pentagons, 46.4% hexagons, 20.8% heptagons, 3.6% octagons, and declining fractions of cells with increasing numbers of sides. Remarkably, this distribution is almost indistinguishable from those empirically observed in the imaginal wing-disc epithelium, as well as for proliferating epithelia from *Xenopus* and hydra.

The steady-state polygon distribution can therefore be regarded as an emergent property of the process by which cells replicate; the result requires no consideration of surface free energy and only assumes that cell adhesion is stable through cell divisions. What, then, are the implications of this observation? At least two processes whose study might be informed by extension of these results come to mind: anisotropy of tissue growth from oriented cell division, and cell competition during which faster- and slower-growing cells coordinate to regulate tissue or organ size.

Through the study of clone size and shape and of oriented cell divisions, researchers have deduced that anisotropic growth of clones (progeny of an individual cell) can determine the final shape of a plant or animal organ such as a flower petal or wing (Resino et al., 2002; Rolland-Lagan et al., 2003). In turn, oriented cell division appears to regulate the shape and orientation of clone growth (Baena-Lopez et al., 2005). However, no detailed analysis of cell shapes when cleavage planes are oriented has been performed. What would be the cell geometric consequences of orienting cell divisions during replication? Orienting the cleavage plane does not violate the six preconditions of the model, but neither does the model explicitly capture orientation of polygons. Might there be a signature of cell geometries resulting from various forms of anisotropic growth that could be recognized as diagnostic of the anisotropy?

It has long been known that tissues and organs grow to a predetermined size even if a fraction of the cell population comprising them is impaired for growth or supercharged for growth. The strong competitors express higher levels of Myc (de la Cova et al., 2004) and send a signal that induces apoptosis in the neighboring, weaker competitors (Moreno et al., 2002). But what is the signal that recognizes the difference between the populations? What maintains this balance in a wild-type tissue? Gibson and colleagues (2006) show that a clone of more rapidly proliferating cells shifts to a polygon profile with a lower average number of sides. Is the correlation between reduced mean number of sides and more rapid proliferation incidental, or might the number of sides be involved in regulating a cell's competitiveness?

Finally, many postmitotic epithelia show a much more regular hexagonal packing pattern than their replicating precursors. The force driving reorganization from the distribution described by Gibson and colleagues (2006) to a more regular hexagonal array is not known. It will be important to determine whether this is a passive physical process or a genetically encoded transition.

A resurgence of mathematical modeling applied to biological problems has provided new insights into a variety of processes. Gibson and colleagues (2006) have enabled us to appreciate a pattern where none was previously apparent, and their result is elegant in its simplicity. It remains to be seen whether we can appreciate the consequences of this pattern.

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# Matrix Control of Stem Cell Fate

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**A key challenge in stem cell research is to learn how to direct the differentiation of stem cells toward specific fates. In this issue of *Cell*, Engler et al. (2006) identify a new factor regulating stem cell fate: the elasticity of the matrix microenvironment. By changing the stiffness of the substrate, human mesenchymal stem cells could be directed along neuronal, muscle, or bone lineages.**

Stem cell maintenance and differentiation are governed by unique local microenvironments (Watt and Hogan, 2000; Fuchs et al., 2004). Identifying specific cues in the microenvironments, such as secreted factors, and understanding how neighboring cells and the extracellular matrix control developmental fate will provide new tools with which to promote the differentiation of stem cells into par-

ticular cell types. Many studies have established that complex interactions between soluble and extracellular matrix molecules regulate intracellular signaling and differentiation. Although direct activation of signal transduction by matrix molecules through integrin receptors has been well-studied, the physical properties of the matrix, such as its elasticity or stiffness, are also important (Discher

et al., 2005; Vogel and Sheetz, 2006). In this issue, Engler et al. (2006) apply techniques originally used to study the effects of matrix elasticity on the morphology and growth of differentiated cells to provide a new approach to direct stem cell fate.

The importance of sensing the mechanical properties of the extracellular matrix has been established in studies with fibroblasts and tumor