DEVELOPMENTAL BIOLOGY

The mechanics of positioning skin follicles

A process of mechanochemical pattern formation places feathers in the avian skin

By **Stephan W. Grill**[1,2]

The hair that covers our body is placed in an ordered manner. What determines where exactly a hair grows from our skin? On page 811 of this issue, Shyer and colleagues (*1*) reveal the mechanism by which skin follicles, the specific structures that produce hairs in mammals and feathers in birds, obtain a regular pattern in their distribution across the skin.

So how is this periodic array in follicle spacing obtained? The genome does not directly encode the exact location of every follicle in embryonic chicken skin but instead specifies a mechanism that determines a typical distance between two neighboring follicles (*2*, *3*). Follicles then arrange themselves so as to meet this distance requirement through a process of self-organization. For a long time, this distance rule was thought to be generated entirely by molecular signals and cues (*4*). Following the ideas of Turing (*5*), it is possible to specify such a distance in embryonic chick skin by combining a mechanism of local positive feedback for generating a follicle (referred to as local activation) via secretion of the signaling protein bone morphogenetic protein 7 (BMP7), with a mechanism for inhibiting the generation of follicles nearby (termed global inhibition). BMP2 prevents the formation of follicles, and so BMP7 and BMP2 could compete in a manner that generates this distance rule (*4*). Shyer *et al*. now show that this picture has to be refined, revealing instead that this distance rule for follicle placement occurs through a process that is more mechanical in nature.

The first evidence Shyer *et al*. provide that follicle placement is due to mechanical events is that there appear to be no molecular signals that precede follicle positioning. Instead, the nuclear translocation of β-catenin, an early marker of follicle cell fate, accompanies rather than precedes the earliest visible changes to the skin. More importantly, degrading β-catenin via a pharmacological perturbation does not affect these early changes in skin follicle patterning, indicating that another mechanism is involved.

What is it then that determines where follicles arise? An important clue came from the observation that the skin is slightly bent or domed around future follicles. This is interesting because the developing skin consists of two cellular layers: an epithelial layer that forms the epidermis, which sits

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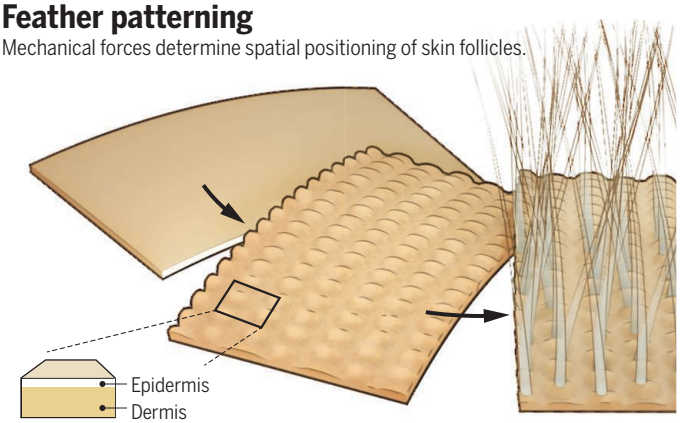
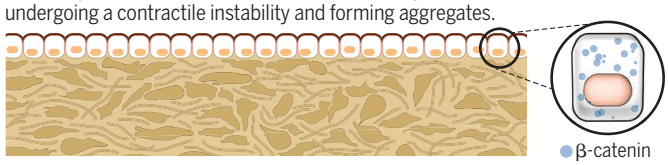
Feather positioning depends on mechanical and chemical stimuli. Feathers of a gold-laced orpington chicken are shown.

Feather patterning

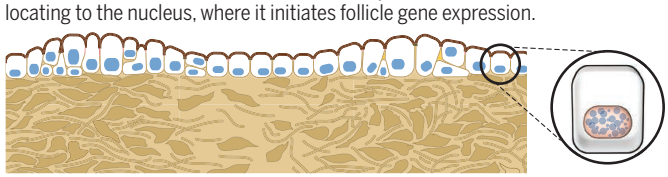
Mechanical forces determine spatial positioning of skin follicles.



1 Follicle placement in the avian skin occurs first by the **dermis** undergoing a contractile instability and forming aggregates.



2 Second, the **epidermis** becomes compressed by the dermis contraction, which is mechanotransduced as β-catenin translocating to the nucleus, where it initiates follicle gene expression.



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on top of a layer of mesenchymal cells (the dermis). One way to generate a bent shape in this doublet of layers is by one of these layers mechanically contracting, with the other layer remaining relaxed. And indeed, the authors carefully isolated the two layers and showed that the dermis (and not the epidermis) contracts, causing the overall bent shape.

The authors hypothesized that this active contraction of the dermis itself provides a mechanism for pattern formation. How could this be? There is much evidence from theoretical work (*6*, *7*) that a contracting layer can cross a so-called "instability threshold" and "pull itself apart". With enough contraction, the state of homogeneous distribution of cells within the layer is no longer favored. The system will instead adopt a nonhomogeneous configuration of cells, forming regions where there are cell aggregates, surrounded by regions where there are fewer cells (see the figure). So, the idea is that the dermis, when contracting uniformly, automatically forms an ordered array of aggregates or bumps (looking much like the goose bumps in your skin when you are cold). The distance rule between aggregates is determined by the amount of contraction (where more contraction gives rise to larger spacing) and the amount of resistance to contraction (provided by the effective stiffness of the layer doublet, with more resistance leading to shorter spacing).

To show that this mechanism is at work, the authors performed a series of experiments in which they isolate pieces of chick skin (which on their own rapidly contract when isolated, and during this rapid contraction form a cell aggregation pattern that resembles that of follicles) and attach the isolated dermis to a substrate layer of varying stiffness. Remarkably, the authors could control the spacing of the cell aggregates in the dermis in a manner that is consistent with the distance rule. This amounts to a clear demonstration that the positions of cell aggregates during skin follicle formation arise through the dermis contracting and undergoing a mechanical instability.

How does this mechanical mechanism induce the gene expression changes required for follicle formation? Here, Shyer *et al.* focus on the epidermis, arguing that the resultant aggregation of cells in the underlying dermis would lead to compressive stresses in the epithelial cells above (see the figure). Similar to how neighboring tissue responds to the pressure of growing tumors (*8*), the authors observe that mechanically compressed epithelial cells respond through β-catenin translocation to the nucleus. Importantly, the downstream gene expression program associated with new follicle generation (this involves the BMPs) is activated only in those situations in which the skin isolate is allowed to contract and β-catenin translocates to the nucleus.

Shyer *et al.* have perhaps provided one of the clearest examples of pattern formation in tissues through a combination of mechanical and regulatory chemical processes. Given that animal morphogenesis involves mechanical stresses and growth, we would not be surprised if many morphogenetic processes rely on similar types of mechano-chemical pattern formation processes (*9*). ■

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