DEVELOPMENT

Mechanical properties pattern the skin

Morphogens induce variations in tissue mechanics to promote feather budding

By **Samhita P. Banavar**[1] and **Celeste M. Nelson**[1,2]

As tissues develop, their growth is guided by diffusible molecules known as morphogens. In some tissues, initially uniform fields of cells become patterned over time to form spatially distinct anatomical features, such as hair follicles in the skin or villi in the intestine. This transition from anatomical uniformity to spatially patterned diversity is called symmetry breaking. Classically, symmetry breaking was thought to be initiated by spatial differences in gene expression caused by morphogens (*1*). On page 902 of this issue, Yang *et al.* (*2*) propose an alternative mechanism: spatial differences in the mechanical properties of clusters of cells, which give rise to mechanical instabilities at the "supracellular" scale. The study combines analyses of skin explants and cultured dermal cells from embryonic chicks (*Gallus gallus domesticus*) with a theoretical framework to show that patterning of the avian skin emerges from the mechanical properties of the dermal tissue, which are influenced by morphogens.

The term "morphogenesis" derives from the Greek words "morphē," meaning shape, and "genesis," meaning emergence, and is the process by which a tissue generates its form. Morphogens can provide signals that guide the gene-expression changes necessary for morphogenesis. It has largely been assumed that initiation of the changes in tissue shape at the start of morphogenesis is also due to intracellular signaling and alterations in gene expression downstream of morphogens. The emergence of these biochemical patterns would necessitate a "prepattern" in the concentration of the morphogens themselves.

The skin is a prototypic example of an organ whose underlying pattern of appendages (hair follicles in mammals or feather follicles in birds) is guided by morphogens, such as fibroblast growth factor (FGF) or bone morphogenetic protein (BMP). Feather follicles are evenly spaced in the avian skin, which is composed of three layers: the outermost epidermis, the intervening basement membrane, and the innermost dermis. Previously, the locations at which hair or feather follicles formed were thought to be determined by prepatterned spatial variations in the concentrations of morphogens within the dermis. An initially homogeneous field of morphogens can resolve itself into discrete spots of high concentration from the interplay between chemical reactions and diffusion (*3*). However, recent work has reported that follicles also form in response to physical patterns. In mammalian skin, hair follicles emerge through cell rearrangements, which give rise to stationary cores of cells surrounded by a dynamic field of motile cells that consists of two populations—one moving clockwise and one moving counterclockwise (*4*). In avian skin, feather follicles bud at the same time as patterns of gene expression appear, rather than after (*5*).

> **"...symmetry breaking that forms the pattern of feather follicles is thus a physical process..."**

Yang *et al.* demonstrate that the emergence of the bud of the follicle begins with the ruffling of the basement membrane under the epidermal layer. The dermal layer then separates into two regions of cells: a stiffer, solid-like core and a more fluid margin, the mechanical properties of which were confirmed using atomic force microscopy. Using transcriptomic and immunofluorescence analyses, the authors found that signaling downstream of FGF led to a stiffening of cells in the core. By contrast, signaling downstream of BMP led to a more fluid-like domain of tissue at the margin. After this supracellular phase separation, the basement membrane was degraded and the margin contracted, pushing the stiffer core out of the plane of the tissue and causing the feather bud to emerge. The symmetry breaking that forms the pattern of feather follicles is thus a physical process, influenced by molecular and genetic controls.

Understanding the mechanical properties of complex tissues is challenging (*6*–*8*). Yang *et al.* adopted methods from outside of developmental biology to study the extent to which the mechanical properties of dermal cell clusters might be modulated by FGF and BMP in culture. In one approach, the authors dried reconstituted dermal tissue after treating it with FGF or BMP and then mapped the patterns of cracks to infer whether the tissues became more solid (brittle) or more fluid (less brittle). In another approach, based on surface tension of coalescing droplets (*9*), aggregates of dermal cells were cultured with FGF or BMP and the extent to which they coalesced was used to infer whether the tissues became more solid-like (in which aggregates failed to merge) or more fluid-like (in which aggregates merged). These approaches need to be validated against standardized models to determine whether they might be applicable to other developing tissue systems.

Recent studies using mouse embryos hinted at mechanical underpinnings for symmetry-breaking events during branching of the pulmonary airways (*10*, *11*), condensation of digit cartilage (*12*, *13*), and the emergence of intestinal villi (*14*, *15*). Collectively, these findings suggest that the process of morphogenesis relies on spatial patterns in the physical properties (mechanical stiffness, volumetric growth, active forces) of the tissue that are determined by morphogens. The results of Yang *et al.* now indicate that spatial patterns in physical properties might also serve as the triggers that induce uniform fields of cells to begin morphogenesis in the first place.

The findings of Yang *et al.* show that morphogens can do more for tissue development than just alter gene expression; they can also, in principle, cause patterns of mechanical properties to emerge at the supracellular scale, which can initiate populations of cells to change the overall shape of their constituent tissue. Understanding how the interplay between molecular dynamics and supracellular mechanics affects the emergence of morphological patterns will become a powerful asset in studies of tissue development. ■

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REFERENCES AND NOTES

1. A. Kicheva, J. Briscoe, *Annu. Rev. Cell Dev. Biol.* **39**, 91 (2023).
2. S. Yang *et al.*, *Science* **382**, eadg5579 (2023).
3. H.-S. Jung *et al.*, *Dev. Biol.* **196**, 11 (1998).
4. M. Cetera *et al.*, *Nat. Cell Biol.* **20**, 541 (2018).
5. A. E. Shyer *et al.*, *Science* **357**, 811 (2017).
6. C. M. Nelson, *J. Cell Biol.* **216**, 29 (2017).
7. P. Roca-Cusachs *et al.*, *Nat. Cell Biol.* **19**, 742 (2017).
8. O. Campàs, *Semin. Cell Dev. Biol.* **55**, 119 (2016).
9. D. Gonzalez-Rodriguez *et al.*, *Science* **338**, 910 (2012).
10. J. P. Gleghorn *et al.*, *Dev. Dyn.* **241**, 852 (2012).
11. K. E. Peak *et al.*, *Biol. Open* **11**, bio059436 (2022).
12. C. Parada *et al.*, *Dev. Cell* **57**, 854 (2022).
13. C. I. Lorda-Diez *et al.*, *Dev. Dyn.* **251**, 105 (2022).
14. K. D. Walton *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 15817 (2012).
15. K. D. Walton *et al.*, *Development* **143**, 427 (2016).

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