Researchers uncover regulatory system that regulates branching patterns in lung epithelial tissue

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ERK-mediated curvature feedback regulates lung epithelial branching morphogenesis in mice. Credit: KyotoU Tobiyama / Tsuyoshi Hirashima

Branching patterns are prevalent in our natural environment and the

human body, such as in the lungs and kidneys. For example, specific genes that express growth factor proteins are known to influence the development of the lungs' complex branches. Still, until now the mechanics behind this phenomenon have remained a mystery.

Kyoto University researchers have unveiled a regulatory system linking signal, force, and shape in mouse lung structure development. The team recognized that the signal protein ERK plays an active role in causing growing lung tissue to curve. The research is published in the journal *Current Biology*.

"ERK signals the cell tissue to stretch outward to smoothen its curve," says Tsuyoshi Hirashima, formerly of KyotoU's Graduate School of Biostudies and now at the National University of Singapore's Mechanobiology Institute.

As if choreographed, a mix of chemical signals triggers the cellular mechanics of the lungs of a mouse embryo, resulting in the development of intricate branching patterns.

Mechanobiology has gained increasing attention in recent years, focusing on cell- and tissue-generated forces, intracellular signaling, and their combined interactions with geometric factors that influence morphogenesis.

"ERK's surprisingly precise signaling response to lung tissue curvature was enlightening. It suggests an elegantly more nuanced developmental orchestration than previously thought," said Hirashima.

Utilizing advanced microscopic imaging techniques, Hirashima's team observed how ERK behaves in developing lungs in real time by combining a fluorescent biosensor—for quantifying the ERK activity in living cells—with two-photon microscopy, which captures tissue cell and

molecular activities in 3D.

Results showed that ERK mediates curvature sensing and force generation in epithelial cells, causing a negative feedback loop and a repetitive branching pattern.

"We are particularly interested in exploring how disruptions in this signal-force-shape system might contribute to physiological abnormalities or diseases," says Hirashima.

These ideas may apply to the developmental processes of other organs and the formation of mouse lungs, a realization that calls for further exploration of fundamental principles.

"Ultimately, our findings offer a deeper understanding of the novel principles of biological regulatory systems, with promising applications in regenerative medicine and organoid research," concludes Hirashima.

More information: Tsuyoshi Hirashima et al, ERK-mediated curvature feedback regulates branching morphogenesis in lung epithelial tissue, *Current Biology* (2024). DOI: 10.1016/j.cub.2023.12.049

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