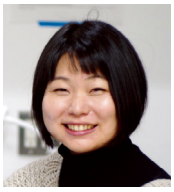
Medical & healthcare, Drug discovery

Elucidating the origins of homeostatic systems: developmental transition from morphogenesis to tissue homeostasis



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Abstract

The foundational basis of organ homeostasis, maintained by tissue stem cells, is thought to be established during fetal morphogenesis and inherited after birth; however, the underlying processes remain insufficiently understood (Fig. 1). In this study, we aim to elucidate the previously uncharacterized transition from the morphogenetic phase to the homeostatic phase in both stem cells and developing organs. By doing so, we aim to clarify the origins and generative principles of homeostatic systems and to establish a technological platform that enables the application of these insights to basic and medical research.

Background & Results

Using the hair follicle as a model, we have developed an original data-driven analytical approach and constructed a "4D lineage and transcriptome atlas" that integrates cell dynamics, lineage relationships, and state transitions during development. This analysis revealed that fetal stem cells differ markedly from adult stem cells in both properties and behavior, and that they progressively acquire stem cell identity—including self-renewal capacity and quiescence—from the morphogenetic phase to the postnatal period. Clarifying the nature of this maturation process will contribute to understanding the mechanisms by which homeostatic systems are established, as well as the principles underlying stem cell niche formation.

Furthermore, by incorporating insights into stem cell maturation into our unique ex vivo skin and hair follicle culture systems, we aim to achieve ex vivo organ maturation, which has not been realized using conventional organoid or organ culture methods. Establishing such a maturation technology is expected to advance regenerative medicine models and enhance the precision of drug screening, thereby generating broad impact across both basic and applied research.

Significance of the research and Future perspective

Proper organ function requires the coordinated spatial organization of cells and the continuous operation of tissue stem cell systems that replace cells lost through daily turnover. Although the molecular characteristics of adult tissue stem cells and their interactions with the niche have been increasingly elucidated, how these homeostatic systems arise during fetal morphogenesis and transition into the adult stem cell state remains an unresolved question.

To address this issue, we have established an original data-driven analytical platform that integrates single-cell-resolution live imaging with single-cell transcriptomics, enabling multi-dimensional analysis of hair follicle development. Recently, we expanded this framework by generating comprehensive datasets covering fetal and postnatal skin and hair follicles, including time-series single-cell transcriptomes spanning the major developmental stages and spatial transcriptomics (Xenium) across ten developmental stages. Integrated analysis of these multi-layered datasets has begun to reveal that the compartmentalization of epithelial cells and the corresponding mesenchymal domains develop in synchrony, providing insights into the epithelial–mesenchymal interactions that underpin organ formation (Fig. 2). These datasets, which capture normal development in a systematic and detailed manner, represent a valuable resource not only for accumulating fundamental knowledge but also for comparative analyses with disease models and developmental abnormalities.

Furthermore, analysis using NFATc1 reporter mice, which label the hair follicle stem cell domain from fetal to adult stages, demonstrated that fetal hair follicle stem cells contribute to the formation of the adult stem cell domain while not generating differentiated progeny, confirming that fetal and adult stem cells differ fundamentally despite sharing molecular markers. We were also able to clearly capture the stepwise acquisition of stem cell functions—including quiescence and colony-forming capacity—from embryonic stages to the postnatal period. We are currently advancing single-cell multi-omics analyses and mass spectrometry imaging to elucidate the molecular principles governing stem cell maturation.

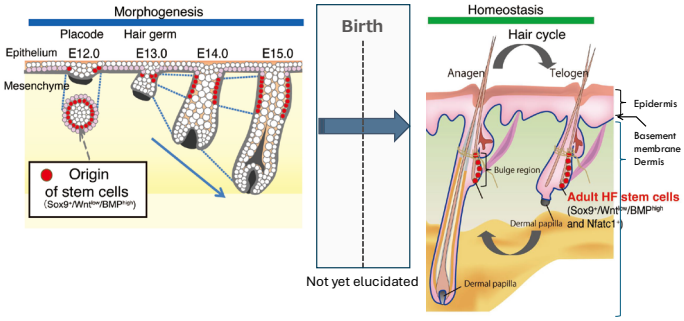

Fig.1

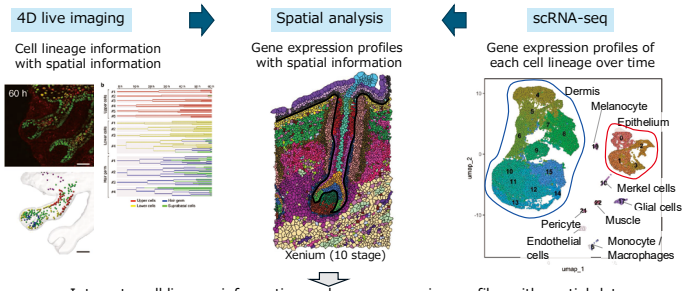

Fig.2

Patent	
Treatise	Morita, Ritsuko; Sanzen, Noriko; Sasaki, Hiroko et al. Tracing the origin of hair follicle stem cells. Nature. 2021, 594, 547–552. doi: 10.1038/s41586-021-03638-5 Morita, Ritsuko; Fujiwara, Hironobu. Tracing the developmental origin of tissue stem cells. Dev Growth Differ. 2022, 64(9), 566-576. doi: 10.1111/dgd.12816
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