**Moving forward to build a hair follicle: mechanisms of hair follicle development unravel**

**Hair growth is regulated by a small cluster of hair-specific fibroblast cells, the dermal papilla. But exactly how the dermal papilla forms has remained elusive until now. The current study reveals the molecular regulation of this process and supports a role for cellular migration in formation of the dermal papilla.**

* Otto Mäkelä, PhD student at Institute of Biotechnology, University of Helsinki, Helsinki, Finland
* Leah Biggs, Post-doctoral researcher at Institute of Biotechnology, University of Helsinki, Helsinki, Finland

Hair is an essential part our identity and plays an integral part in many cultures. It is produced by specialised units of the skin called hair follicles all of which develop during gestation.

Throughout our lifetime, our hair follicles go through cycles of growth and rest to produce hair shafts. This is regulated by a specialized cluster of cells known as the dermal papilla. If the dermal papilla is lost, for example as the result of a skin injury, hair does not regrow in this location. Further, the dermal papilla can be transplanted to another location in the skin and produce a new hair follicle. Because of this, the dermal papilla has been extensively studied to develop regenerative therapies for hair loss. Currently the biggest obstacle of these therapies is that when dermal papilla cells are expanded in culture they lose their potential to produce new follicles. To advance these therapies, it is key to understand how the dermal papilla cells develop.

The hair follicle develops at specific spots from two different compartments of the embryonic skin, the outer surface epithelium and the underlying layer called the mesenchyme. These compartments communicate via signalling molecules to instruct cells in both tissues to undergo differentiation into hair follicle-forming cells. At the site of the developing follicle, the fibroblasts in the mesenchyme alter their gene expression and cluster to form the dermal condensate, which is the precursor to dermal papilla. A signalling molecule emanating from the epithelium, Fibroblast growth factor 20 (Fgf20) is needed for dermal condensate formation. However, it remained unknown how fibroblasts form the dermal condensate and further, what Fgf20 instructs the fibroblasts to do. In our study, we aimed to identify the cellular behaviour that results in formation of the dermal condensate, and secondly, to understand the role of Fgf20 signalling in this process.

We used hair follicles of the mouse back skin as a model because techniques to culture intact mouse skin and its cells exist, as well as tools to detect specific cell populations. We tested the hypothesis that the dermal condensate forms through local cell proliferation. To this end, we used a genetic cell cycle reporter to label individual cells according to the phase of their cell cycle with fluorescent tags. With high-resolution microscopy we observed that, compared to other fibroblasts, dermal condensate cells proliferated less and progressively stop dividing almost completely. Given that the dermal condensate cells stop proliferating at an early time point, we hypothesized that cellular migration drives dermal condensate formation. To test this, we used a high-resolution microscope to image live skin to follow movement of fibroblasts labelled with fluorescent tags and observed that they indeed migrated to form the dermal condensate.

We were further interested to know the cellular behaviours that Fgf20 alters. To study cell migration, we cultured embryonic skin fibroblasts and observed that addition of Fgf20 increased migration of these cells, suggesting that Fgf20 signal could instruct the cells to move in the developing skins too. Moreover, we wanted to identify the genes that are regulated by Fgf20. To study this, we treated intact skin mesenchyme with Fgf20 and analysed changes in gene expression by a technique called RNA sequencing. We observed that Fgf20 can induce expression of a subset of the genes expressed specifically in the dermal condensates suggesting that additional factors are required to instruct the cells to become dermal papilla cells.

In this study our goal was to investigate the cellular behaviour that leads to formation of the dermal condensate and to examine how cells respond to Fgf20 signal during this process. We discovered that the dermal condensate is formed by directed movement of the mesenchymal fibroblasts and that Fgf20 signal instructs the fibroblasts to move. Interestingly, we also observed that condensate-forming fibroblasts stop dividing. Although the significance of this phenomenon is not yet understood, this might explain why attempts to expand dermal papilla cells in culture have thus far proven futile. Past research efforts have focused on expansion of existing dermal papilla cells isolated from hair follicles but perhaps a better strategy could be to first expand fibroblasts in culture and then use signalling molecules to instruct them to become dermal papilla cells. Our study also shows that while Fgf20 can instruct fibroblast behaviour observed in dermal condensate formation, it is not sufficient to induce all changes observed. This study suggests that the signalling molecule cocktail required to make fibroblasts into dermal papilla cells contains several factors, the combination of which is still elusive.