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学 位 論 文 要 旨

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題目: Hair-forming abilities of follicular epithelia and dermal papillae of mouse vibrissal follicles during the hair cycle

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Hair follicles periodically reproduce hair shafts with a defined length and thickness throughout the entire life of animals. This phenomenon is termed as the hair cycle which consists of the growth phase (anagen), regression phase (catagen), quiescent phase (telogen) and shedding phase (exogen). Hair cycle is driven by the autonomous and recurrent regeneration mechanisms, which is supported by the follicular epithelial stem cell system. It is known that the follicular epithelial stem cells reside in the distal permanent portion of the follicle called the bulge and their descendants actively proliferate and migrate to the hair bulbs to regenerate lower follicular epithelia and hair matrixes during anagen. While stem cells have been well investigated about their localization and regenerative ability, little is known about functional alteration of their progeny in the lower outer root sheath during hair cycles.

In this study, the author focused on the proliferative activity and hair-forming ability of the epithelial progenitor cells during hair cycles. As the progenitor cells are resource for both the regenerating follicular epithelia and hair matrixes, it is crucially important to clarify the hair-forming ability of the progenitor cells during hair cycles to understand the cellular dynamics during hair cycles and the mechanisms of hair cycle progression. In addition to the maintenance mechanisms of the stem cells, which have been studied by genes profiling using microarray and functional analyses using various knock out or knock in mice, behaviors of the progenitor cells during the hair cycle as described below are very important to comprehensively understand the mechanism of hair cycle.

We studied the hair-forming ability of epithelium and the relevant activity of dermal papilla (DP) in mouse vibrissal follicles during the hair cycle. Vibrissal follicles are useful materials for studying properties of follicular epithelial cells along the length of the follicles, since they are large enough for microdissectional analyses and microsurgical experiments to reveal the dynamic changes of cellular properties during hair cycles. The follicles were transversely cut into four pieces and each of them was associated with an isolated DP and grafted beneath the kidney capsule to induce hair formation. Various hair-cycle combinations of the fragments and DPs were examined. Hairs were generated not only in the follicle fragment containing the bulge (fragment III) but also in the fragment between the bulge and hair bulb (fragment II). The hair-forming frequencies were affected by the hair cycle stages of both the follicle fragments and DPs. Fragments III at late anagen (LA) and fragments II at catagen

frequently generated hairs when associated with early anagen (EA)-DPs, but infrequently with mid anagen (MA)-DPs. Oppositely, anagen fragments II produced hairs at a high frequency with MA-DPs and at a low frequency with EA-DPs. Hair generation in anagen fragments II is an unexpected finding because previous studies suggested that, during anagen, this region dose not contain clonogenic epithelial cells that have been believed to be crucial for hair formation. Therefore, non-clonogenic epithelial cells would be able to generate hairs as well as clonogenic ones, and they should have a latent hair-forming ability that could be more effectively awakened by MA-DP than EA-DP stimuli. Non-clonogenic epithelial cells might be a dormant phase of hair precursor cells. Proliferating follicular epithelial cells were detected in the middle and lower ORS throughout the hair cycle but scarcely at LA. These findings suggest that the hair-inductivity of DPs should be altered between EA and MA and follicular epithelial cells would change their DP stimuli-directed hair-forming ability around LA, probably linked to the proliferative activity.

The study described above showed that hair inductivity of the DPs would quantitatively change between EA and MA. Since alkaline phosphate (ALP) activity is known to relate to the hair-inductivity of the DPs, ALP activity was studied in mouse vibrissal follicles in the various hair-cycle stages. ALP activity was detected in the restricted mesenchymal and epithelial regions in mouse vibrissal follicles. Its localization and strength dramatically changed during the hair cycle. The activity in the DP was moderate in very early anagen, reached a maximal level in early anagen, decreased at the proximal region of DP after mid anagen, and was kept at a low level during catagen. The bulbar dermal sheath showed an intense ALP activity only in early anagen. Although most bulbar epithelium did not show ALP activity, germinative epidermal cells that were adjacent to the ALP-negative DP cells became ALP-positive in mid anagen and rearranged in a single layer so as to encapsulate the DP in mid catagen. During catagen, the outermost layer of bulbar epithelium became ALP-positive, which should be follicular epithelial precursors migrating from the bulge. Before the initiation of hair formation, ALP activity in the bulbar epithelium rapidly decreased and that in DP increased instead. These dynamic changes of ALP expression might be related to DP’s functions in hair induction, and also to reconstruction of the bulbar structure during the hair cycle.

In a series of the study, the author indicated the qualitative alterations of hair-forming abilities of the follicular epithelia and DPs during the hair cycle and particular changes of expression patterns of ALP activity. These detailed alterations might be difficult to be distinguished in pelage follicles because of their small size. Molecular profiles of these changes and their regulation mechanisms should be revealed further investigation, the author believe that these findings should be a new concept for understanding the control mechanisms of hair cycle.