Hair Follicle Stem Cells Provide a Functional Niche for Melanocyte Stem Cells

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IN MOST STEM cell systems, the organization of the stem cell niche is still largely unknown. Melanocyte stem cells (MelSC) and hair follicle stem cells (HFSC), which are originally derived from a completely different developmental origin, are located in the bulge area of mammalian hair follicles. While our previous studies indicated that the niche plays a dominant role in MelSC fate determination[1], the underlying mechanisms and the identity of niche cells for MelSCs are still unclear.

Our recent study published in *Cell Stem Cell* revealed that HFSCs provide a functional niche for MelSCs through transforming growth factor β (TGF- β) signaling to prevent premature hair graying[2]. To explore the roles of HFSCs as niche cells, we have focused on Collagen XVII (Col17a1/BP180/BPAG2), a hemidesmosomal transmembrane collagen and transforming growth factor β 1/2 (TGF-β1/2), both of which are preferentially highly expressed by HFSCs.

First, to examine the possible involvement of these two molecules in MelSC maintenance, we analyzed deficient mice of Col17a1 gene and Tgfbr2 gene. Tgfbr2 null mice show progressive hair graying but not hair loss[3], while Col17a1 deficient mice show premature hair loss as well as premature hair graying[2] (Fig.1).

Analysis of HFSCs and MelSCs of the Col17a1 null mice showed that Col17a1 is critical for maintenance not only of HFSCs but also of MelSCs, which do not express Col17a1 but directly adhere to HFSCs, through maintaining their quiescence and immaturity[2] (Fig.2). This potentially explains the mechanism underlying hair loss in human COL17A1 deficiency. Interestingly, Col17a1 deficient mice show defective TGF-β production by HFSCs[2]. TGF-β signaling is activated in MelSCs when they reenter the quiescent non-cycling state during hair cycles[3]. Therefore, we analyzed MelSCs in conditional Tgfbr2 deficient mice which lack TGF-β type II receptor specifically in the melanocyte lineage and found that Tgfbr2 is essential for the maintenance of MelSC immaturity and quiescence to prevent hair graying[2,3]. These data indicate that HFSC-derived TGF-β is a critical niche factor that regulates MelSC immaturity and quiescence.

Finally, forced expression of COL17A1 in basal keratinocytes, including HFSCs, in Col17a1 null mice rescues MelSCs from premature differentiation and restores TGF-β signaling, demonstrating that HFSCs function as a critical regulatory component of the MelSC niche through TGF-β signaling (Fig.3).

The interactions between different lineages of stem cells turned out to be crucial for cyclic regenerative growth of pigmented hair. This points to a complex but efficient crosstalk in stem cell niches. The maintenance of somatic stem cell populations by another type of somatic stem cells in a coherent cell mass might be a recurring strategy for somatic stem cell maintenance.

References

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Fig.1: Hair graying and hair loss found in a Col17a1-deficient mouse.

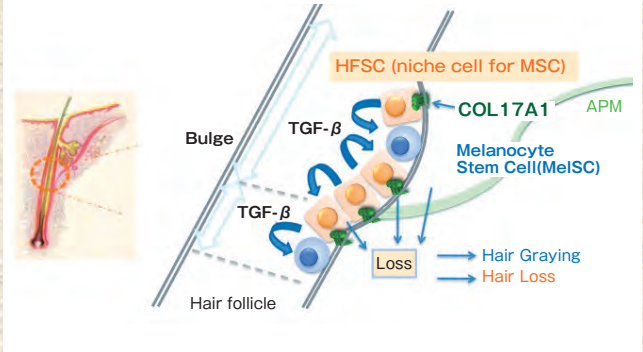

Fig.2: Mechanisms of stem cell maintenance in the hair follicle niche.

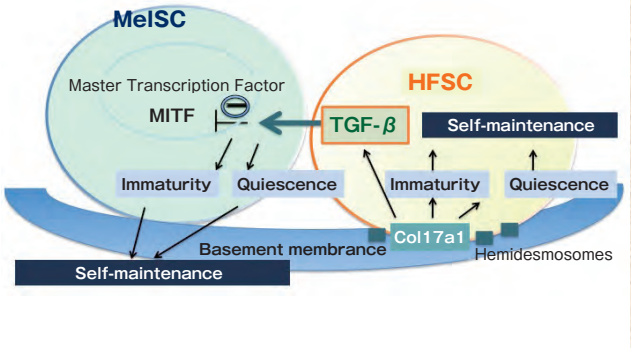

Fig.3: Stem cell regulation by stem cells in the hair follicle niche.