Key role for transforming growth factor-β in melanocyte stem cell immaturity and quiescence

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Organization of the stem cell niche is fundamental for stem cell maintenance. We previously demonstrated that the stem cell niche plays a dominant role in stem cell fate determination in melanocyte stem cell (MSC) systems. However, the niche cells and niche-derived factors responsible for stem cell maintanence is largely unknown not only in hair follicles but also in many other stem cell systems. Melanocyte stem cells in the bulge area of hair follicles are responsible for hair pigmentation and when defective, result in hair graying. We analyzed the process of MSC entry into the quiescent state and showed that niche-derived transforming growth factor b (TGF-b) signaling plays an important role in this process. TGF-b not only induces reversible cell cycle arrest, but downregulates MITF, the master regulator of melanocyte differentiation, and its downstream melanogenic genes, *in vitro*. TGF-b signaling is activated in MSCs when they reenter the quiescent non-cycling state during hair cycles and this process is Bcl2-dependent for MSC survival in-vivo. Furthermore, targeted TGF-b type II receptor (TGFBRII) deficiency in the melanocyte lineage causes incomplete maintenance of MSC immaturity and resultant hair graying. These data demonstrate that the TGF-b signaling pathway is a key niche factor for melanocyte stem cell quiescence and immaturity.