Nail stem cell and its unique role in digit bone homeostasis and regeneration

The nail grows continuously throughout life in both mice and humans, and nail growth has been implicated in homeostasis and regeneration of the underlying digit bone. However, whether or not these associations are causally related is under debate, mainly due to the unclear location of nail stem cells (NSCs) and their differentiation mechanism. By genetic lineage tracing in adult mice, we identified NSCs at the proximal end of the nail epithelium. Microarray analyses revealed that Wnt signaling is suppressed in NSCs compared to their progeny, distal matrix cells. Removal of β-catenin, a mediator of Wnt signaling, in epithelial cells did not preclude the maintenance and proliferation of NSCs but inhibited their differentiation into distal matrix cells. This led to the regression of not only the nail but also the underlying digit bone. Characterization of the bone defects revealed active bone resorption, which is suppressed by Wnt activation in osteoblast and osteoclast precursors. In addition, we found that Wntless (Wls) expression, essential for Wnt ligand secretion, was lacking in the β-catenin deficient nail epithelium. Genetic deletion of Wls in the nail epithelium led to the down-regulation of Wnt activation in osteoblast and osteoclast precursors, and subsequently led to regression of the underlying digit bone. Furthermore, we found that epithelium specific β-catenin deficient mice fail to regrow the nail and regenerate the digit including the digit bone upon digit tip amputation unlike control mice. Amputations proximal to the Wnt-active nail progenitors result in the failure to regenerate the digit in control mice. Nevertheless, forced Wnt activation by β-catenin stabilization in the NSC region induced nail regrowth and digit regeneration. Taken together, these data clearly demonstrated the causal relationships between nail growth and maintenance as well as regeneration of digit bone and show that epithelial Wnt/β-catenin signaling is a key mediator for these interactions. Our findings suggest that NSCs can be a novel therapeutic target not only for nail disorders and associated digit bone but also for digit amputation.