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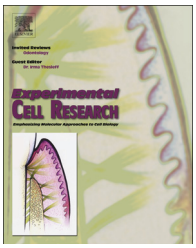

Review Article

Tooth, hair and claw: Comparing epithelial stem cell niches of ectodermal appendages

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ABSTRACT

The vertebrate ectoderm gives rise to organs that produce mineralized or keratinized substances, including teeth, hair, and claws. Most of these ectodermal derivatives grow continuously throughout the animal's life and have active pools of adult stem cells that generate all the necessary cell types. These organs provide powerful systems for understanding the mechanisms that enable stem cells to regenerate or renew ectodermally derived tissues, and remarkable progress in our understanding of these systems has been made in recent years using mouse models. We briefly compare what is known about stem cells and their niches in incisors, hair follicles, and claws, and we examine expression of *Gli1* as a potential example of a shared stem cell marker. We summarize some of the features, structures, and functions of the stem cell niches in these ectodermal derivatives; definition of the basic elements of the stem cell niches in these organs will provide guiding principles for identification and characterization of the niche in similar systems.

Contents

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Several ectodermally derived follicular structures, such as teeth, hair and nails, produce mineralized or keratinized substances that are secreted throughout the animal's life. The functions of these appendages include physical protection, camouflage, thermal insulation, feeding, and sensory perception. Comparing these three organs is useful for several reasons. First, a number of human genetic diseases, notably the ectodermal dysplasias, affect teeth, hair and nails in patients. Second, abnormalities of these organs can be readily detected because of their accessible exterior location, and this accessibility can also enable readily experimental procedures. Third, their relatively simple physiology makes these organs convenient models for deciphering the molecular underpinnings of postnatal renewal and regeneration. This is further facilitated by being able to capture all cell types, at successive stages of differentiation, in a single histological section.

Ectodermal appendages originate from an ectoderm-derived epithelium and a neural crest or mesoderm-derived mesenchyme [1–3]. Sequential epithelial–mesenchymal interactions drive development of these organs, which occurs in three phases: initiation, morphogenesis, and differentiation [4]. An epithelial thickening appears prior to an invagination into the mesenchyme. The mesenchyme then condenses into a papilla, followed by differentiation of specific epithelial and mesenchymal cell types. The morphogenesis of tooth, hair and claw utilize many of the same signaling pathways, as reviewed elsewhere [5–9], whereas differentiation of the mineralized or keratinized components is governed by organ-specific events.

The regenerative ability of tooth, hair and claw, as well as many other adult tissues, is dependent on tissue-specific stem cell (SC) populations that self-renew to maintain stable numbers and that possess the capacity to differentiate into distinct cell lineages. Adult SCs usually reside in a niche, which is a physiologically limited microenvironment whose nature and location vary, depending on the tissue [10]. Deciphering the signaling pathways that control the delicate balance between self-renewal and differentiation is fundamental for understanding how SCs are regulated in their niches.

Here, we provide an overview and comparison of the structures and signaling pathways involved in renewal and regeneration of mouse incisors, hair follicles and claws. Additionally, to illustrate potential similarities between these systems, we have compared the expression of *Gli1*, a known dental SC marker, in tooth, hair and claw.

Incisors

Teeth are used to catch and chew food and, in some species, for defense. The dentition of mammals encompasses great diversity. In contrast to humans, who replace their deciduous teeth, mice have only one set of teeth in their lifespan, consisting of four incisors and 12 molars. In some rodents, all teeth grow continuously, but in mice only the incisors grow continuously throughout the life of the animal.

The ability of the incisor to grow depends on the presence of epithelial and mesenchymal SCs that have the capacity to self-renew and differentiate into all cell types of the adult tooth (Fig. 1A). SCs located in the labial cervical loop (laCL) contribute to a population of transit-amplifying (T-A) cells that undergo several rounds of cell division before they move distally and differentiate into ameloblasts or stratum intermedium cells [11]. The ameloblasts secrete enamel matrix that mineralizes. The pre-odontoblasts, which are derived from SCs in the mesenchyme, are located adjacent to the inner dental epithelium and give rise to dentin-secreting odontoblasts that maintain contact with the basement membrane. Rodent incisors do not have a typical crown or root but rather possess a crown-like labial (near the lip) surface covered by enamel and a root-like lingual (near the tongue) surface where enamel is absent. Periodontal ligament and alveolar bone are derived from the mesenchyme and anchor the teeth to the bones in the jaw.

Slow-cycling SC populations have been identified using label retention experiments, either through injecting with BrdU or with transgenic mice harboring a tetracycline-sensitive, histone 2B(H2B)-GFP cassette under the control of a tissue specific trans-activator [11,12]. Label-retaining cells (LRCs) in the mouse incisor are found in the most proximal region of the mesenchyme and in the proximal halves of both labial and lingual cervical loops. A number of genetic markers of dental SCs have been identified in recent years using *in vivo* lineage tracing. SCs expressing *Gli1* (Fig. 2A) or *Bmi1* reside in the LRC-containing regions of both epithelium and mesenchyme, whereas *Sox2* marks SCs exclusively in the laCL [12–14]. How much the epithelial SC populations marked by these three factors overlap, or whether there exists a hierarchical relationship between them, remains to be determined. An expression of *Lgr5* is found in a number of cells in the stratum intermedium of the laCl [15,16]. In culture, these cells act like dental epithelial SCs [16]. As *Lgr5* expression does not colocalize with the slow-cycling SCs, it has been suggested that this gene marks a subpopulation of active epithelial SCs. Recently, based on *in vitro* assays and *in vivo* expression analysis, integrin α6 (CD49f) was also suggested to be a marker of epithelial SCs [14,17,18].

Several signaling pathways regulate SCs in the incisor, including the FGF, BMP/TGF-β, Notch, and Hedgehog (HH) cascades; these have been reviewed in detail elsewhere [5] and are only briefly described here. Mesenchymal FGF3 and FGF10 and epithelial FGFR1b and FGFR2b levels regulate the size and shape of the epithelial SC niche [19,20]. Follistatin (*Fst*) regulates *Fgf3* expression [19], and deletion of *Tgfbr1* (*Alk5*) in the mesenchyme leads to down-regulation of *Fgf3*, *Fgf9*, *Fgf10*, and a reduced laCL