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Review

Genetic basis of skin appendage development

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Abstract

Morphogenesis of hair follicles, teeth, and mammary glands depends on inductive epithelial–mesenchymal interactions mediated by a conserved set of signalling molecules. The early development of different skin appendages is remarkably similar. Initiation of organogenesis is marked by the appearance of a local epithelial thickening, a placode, which subsequently invaginates to produce a bud. These early developmental stages require many of the same genes and signalling circuits and consequently alterations in them often cause similar phenotypes in several skin appendages. After the bud stage, these organs adopt diverse patterns of epithelial growth, reflected in the usage of more divergent genes in each.
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1. Introduction

Skin appendages such as teeth, hairs, feathers and a number of glands including mammary glands are all derivatives of the embryonic ectoderm. Although fully formed ectodermal organs diverge greatly in number, shape, function, and regenerative capacity the early steps in their development are remarkably similar both at the morphogenetic and molecular levels [1]. The formation of skin appendages is regulated by reciprocal and sequential interactions between the ectodermal epithelium and the mesenchyme that can originate either from the mesoderm (hair and mammary gland) or the neural crest (tooth, vibrissae, and cranial hair). The epithelial–mesenchymal crosstalk is mediated by a relatively small number of signalling pathways including the Wnt, fibroblast growth factor (Fgf), transforming growth factor β (Tgfβ), hedgehog (Hh), and

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tumour necrosis factor (Tnf) families and their downstream transcription factors that are used reiteratively during development. The functions of growth and transcription factors are widely conserved across species as well as across appendages [2,3]. This is reflected in ectodermal dysplasias (EDs), a large group of congenital hereditary disorders where the development of two or more epithelial appendages is affected [4], as well as in the phenotypes of a great number of genetically modified mice [1].

Molecular details of tooth, hair, and feather development have been better characterized than those governing development of other skin appendages but recent years have witnessed considerable progress in understanding embryonic mammogenesis as well. Much of our knowledge on the genetic control of skin appendage development is based on natural mouse mutants or genetically modified mouse models generated either by gain- or loss-of-function strategies. Functional redundancy or early lethality and/or early developmental arrest often makes it difficult to clearly discern the developmental role of a gene of interest although the latter two can nowadays usually be overcome by usage of conditional or inducible transgenic approaches. Also, comparison of the phenotypes is sometimes challenging due to different techniques, markers and developmental stages that have been used to analyze a given mouse mutant. Here I will review the current data on molecular regulation of embryonic tooth, hair, and mammary gland development in light of mouse mutants and human conditions displaying congenital skin appendage defects.

2. Overview of embryonic morphogenesis

2.1. From placode to bud

The first steps of tooth, hair and mammary gland development are highly similar (Fig. 1), and it is possible although not proven that they develop via same cellular mechanisms [1]. The onset of hair follicle development is marked by the formation of a regular array of placodes, local thickenings of the epithelium resulting from the clustering of epidermal keratinocytes in response to signals emanating from the dermis (Fig. 2) [2]. Each placode sends a message back to underlying dermis, which results in the formation of an aggregate of mesenchymal cells known as the dermal condensate. In the mouse pelage, hair placodes develop in three successive waves that are thought to give rise to different types of hairs called guard, awl/auchene and zig zag hairs, respectively [6]. The primary hair placodes are first evident in the lateral surface ectoderm at embryonic day 13.5 (E13.5) from where they spread over most of the body during the following 6–12 h, while the second and third waves are initiated around E16 and E18, respectively [6]. After placode formation, continuous conversation between the epithelium and the mesenchyme drives proliferation in both compartments accompanied by upregulation of cyclin D1 and the formation of the hair germ, or bud [7,8].

Tissue recombination experiments have indicated that, in contrast to hair follicle and mammary gland, the inductive signals for tooth development reside in the epithelium [9–11].

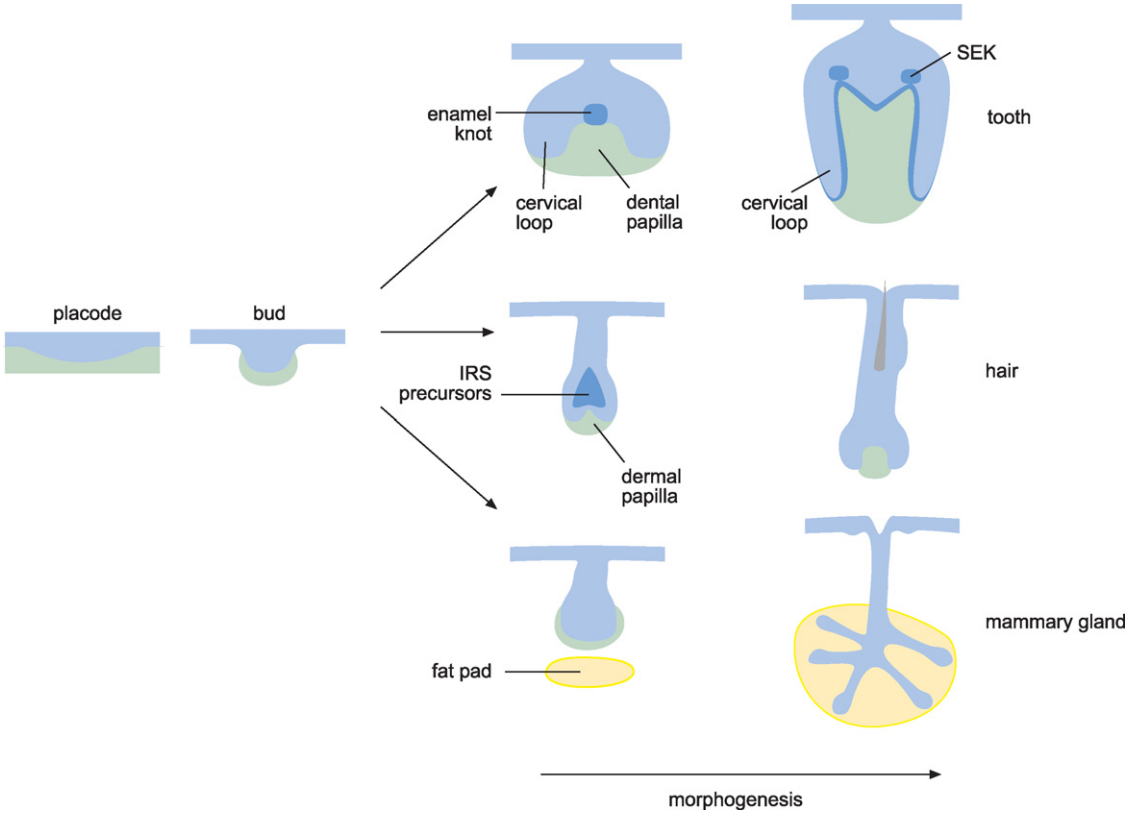

Fig. 1. Schematic view of a developing tooth, hair, and mammary gland. IRS, inner root sheath; SEK, secondary enamel knot.

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