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Review

Early inductive events in ectodermal appendage morphogenesis

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ABSTRACT

The embryonic surface ectoderm gives rise to the epidermis and ectodermal appendages including hair follicles, teeth, scales, feathers, and mammary, sweat, and salivary glands. Their early development proceeds largely the same through the induction, placode, and bud stages prior to diversification of epithelial morphogenesis which ultimately produces the wide array of mature organs. In this review we summarize the current knowledge on the molecular and cellular processes driving the shared stages of skin appendage development revealed by analysis of mouse mutants. We focus on three mammalian organs: hair follicle, tooth, and mammary gland. We reevaluate the information gained from classic epithelial–mesenchymal tissue recombination experiments in light of current molecular knowledge. We place special emphasis on the signaling pathways that mediate tissue interactions, and attempt to link the signaling outputs to changes in cellular behavior that ultimately shape the developing organ.

Contents

1. Introduction

The vertebrate ectoderm gives rise to a wonderful variety of appendages such as hair follicles, teeth, mammary and sweat glands, scales, and feathers to name a few. Despite the apparent differences in the adult form, function, and regenerative capacity, ectodermal appendages share multiple features during development. Several commonalities in the molecular regulation have been uncovered [1]. Further, the early stages of development are morphologically remarkably similar and proceed via induction, placode and bud stages followed by diverse patterns of epithelial growth (Fig. 1). They all arise from two proximate tissues: the epithelium and the mesenchyme, separated by a basement membrane. The epithelial tissue is of ectodermal origin whereas the source of the mesenchymal tissue varies [1]. Sequential and reciprocal crosstalk between the epithelium and the underlying mesenchyme is a critical and uniting theme. Its importance in all aspects of ectodermal appendage development – induction, patterning, morphogenesis, and differentiation – cannot be overemphasized.

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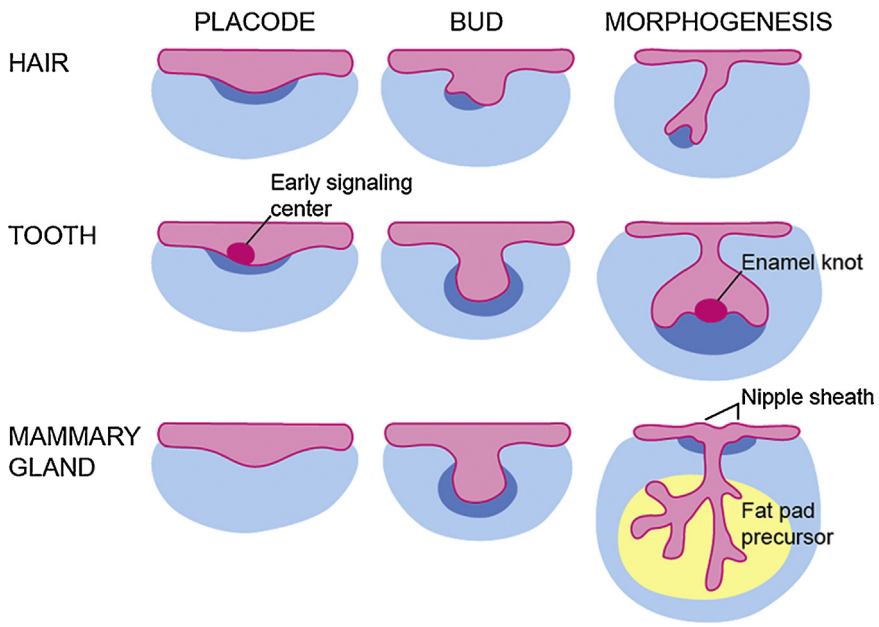

Fig. 1. Development of ectodermal appendages proceeds via shared placode and bud stages prior to diversification of epithelial morphogenesis. In teeth, the epithelial signaling centers express many of the same signaling molecules, but the relationship between the early signaling center and the enamel knot has not been clarified. Expression of many enamel knot markers is also detectable at the tip of the late bud stage tooth (not depicted in the figure). Epithelium, pink; epithelial signaling centers, purple; mesenchyme, blue; condensed mesenchyme, dark blue.

The site and timing of induction for each ectodermal appendage differ. Tooth primordia form in the oral cavity along a horseshoe-shaped region: the dental lamina that marks the future dental arch [2]. In mice, one incisor and one molar tooth rudiment, separated by a toothless diastema region, is apparent in each jaw half at embryonic (E) day E12. The development of the second and third molars differs in that they are generated from the posterior extension of the preceding molar, and thus will not be discussed further in this review. Mammary gland primordia develop along a curved line, the mammary line, that runs between the fore and hind limb on the flanks of the embryo [3]. In mice, five pairs of mammary rudiments become morphologically distinct from the surrounding epidermis between E11 and E12. Accordingly, expression of many placode markers can be detected along the mammary line between E11 and E12, but from ~E12.5 onwards they become restricted to individual mammary primordia [3]. Hair follicle development initiates somewhat later. Murine pelage hair follicles develop in three waves: the first ones, primary hair follicles, are induced at E13.5 and become morphologically pronounced during the following 24 h [4]. The second and third waves of hair placode formation occur at E16.5 and just before birth.

2. Overview of embryonic hair follicle, tooth, and mammary gland development

The first morphological sign of a forming ectodermal appendage is a local epithelial thickening, known as a placode. In all three organs, placodes appear as truly stratified structures (Fig. 2). It should be mentioned that the term placode has not been universally adopted in the field of tooth development research. Instead, stages prior to bud (E11–E12.5) have often been collectively referred to as the epithelial thickening, dental lamina, or simply initiation stage. However, gene expression pattern analyses suggest the presence of two distinct early stages: the continuous dental lamina resolves into separate tooth rudiments between E11 and E12. Many genes are initially (E11.0–E11.5) expressed along the entire dental lamina, but by E12 become evident as discrete spots that mark the epithelium of individual incisor and molar primordia (e.g. *Foxi3*, *Pitx2*) or the early signaling centers therein (e.g. *Shh*, *Bmp2*) [2,5–8] (Fig. 1). Based on morphological and molecular similarities, we regard the E12.0–E12.5 tooth stage equivalent to the placode stage in mammary glands and hair follicles.

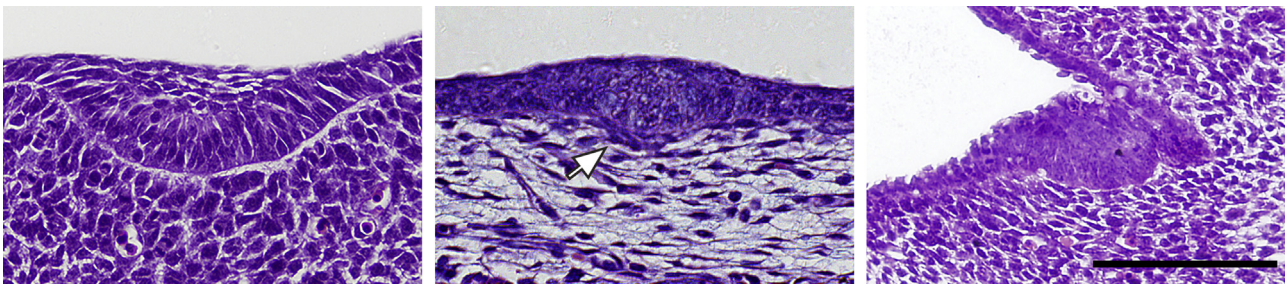

Fig. 2. Hematoxylin-eosin stained sections of a placode stage molar tooth (left), hair follicle (middle), and mammary gland (right). Scale bar, 100 μm. Arrow points to the hair follicle dermal condensate.