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Epithelial histogenesis during tooth development☆

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ABSTRACT

This paper reviews the current understanding of the progressive changes mediating dental epithelial histogenesis as a basis for future collaborative studies. Tooth development involves morphogenesis, epithelial histogenesis and cell differentiation. The consecutive morphological stages of lamina, bud, cap and bell are also characterized by changes in epithelial histogenesis. Differential cell proliferation rates, apoptosis, and alterations in adhesion and shape lead to the positioning of groups of cells with different functions. During tooth histo-morphogenesis changes occur in basement membrane composition, expression of signalling molecules and the localization of cell surface components. Cell positional identity may be related to cell history. Another important parameter is cell plasticity. Independently of signalling molecules, which play a major role in inducing or modulating specific steps, cell–cell and cell–matrix interactions regulate the plasticity/rigidity of particular domains of the enamel organ. This involves specifying in space the differential growth and influences the progressive tooth morphogenesis by shaping the epithelial–mesenchymal junction. Deposition of a mineralized matrix determines the final shape of the crown. All data reviewed in this paper were investigated in the mouse.

1. Introduction

Odontogenesis involves morphogenesis, epithelial histogenesis and cell differentiation. The consecutive stages of tooth development (lamina, bud, cap and bell) refer to morphologic changes. They are also characterized by changes in epithelial histogenesis. Extensive remodelling of the epithelium results from differential cell proliferation rates, apoptosis, changes in cell adhesion and shape leading to the positioning of groups of cells with different functions. Since proliferation and apoptosis are regulated in space and time, positional information, determined by morphogenetic gradients as well as cell–cell and cell–matrix interactions, must play a critical role. Indeed, during tooth histo-morphogenesis changes occur: (1) in the

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Abbreviations: BMP, bone morphogenetic protein; BMPR, bone morphogenetic receptor; BP-230, bullous pemphigoid antigen 1; DiI, 11′-dioctadecyl-333′3′-tetramethylindocarbocyanine perchlorate; EDA, ectodysplasin; EDAR, ectodysplasin receptor; EFA, enamel free area; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IDE, inner dental epithelium; LEF-1, lymphoid enhancer binding factor 1; MSX, muscle segment homeobox; PEK, primary enamel knot; SEK, secondary enamel knot; SI, stratum intermedium; SR, stellate reticulum.

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basement membrane composition,[1,2] which involves metalloproteinases and their inhibitors[3]; (2) in the expression of signalling molecules[4]; (3) in the localization of cell surface components such as integrins,[5,6] cadherins[7,8] and receptors for signalling molecules.[9,10] Cell positional identity may be related to cell history.[11] The same concept has been used to explain the gradients of odontoblast differentiation.[12–14] These changes may occur when epithelial cells are still interacting through adherens junctions. The molecular mechanisms involved in such changes are being investigated.[15] The mesenchyme is involved in the control of epithelial histogenesis during tooth development.[16] During epithelial histogenesis as probably during earlier stages of morphogenesis, complex processes regulate the cell number[17] and positioning.[18] These include proliferation, apoptosis, and plasticity in cell–cell and cell–matrix interactions.[19] This paper reviews current understanding of the progressive changes mediating dental epithelial histogenesis.

2. Lamina stage

Early during tooth initiation, Wnt7b/Shh may intervene in the delimitation between the dental epithelium and oral ectoderm.[20–22] However, little is known about the possible role of signalling molecules in the compartmentalization of the dental epithelium during the later stages of bud to cap transition. Concerning the segmentation of the dental epithelium, which takes place at the lamina stage (Fig. 1A), 3D reconstructions allow visualization and tracing over time the formation and differential fate of the different segments, arising from the dental lamina.[23] However, the molecular regulation in space of their disappearance, mediated by apoptosis, or survival and then differential growth of these different elements is still poorly understood.[24] Different mechanisms may control the early stages of molars versus incisor development in one jaw or odontogenesis in the upper versus lower jaw.[25,26] As with these morphogenetic events, the progression of epithelial histogenesis along the mesial–distal axis is regulated through complex mechanisms as developed below and may vary depending on the cell compartment to be considered. For example, at later stage, the geometry of the histogenesis of the inner dental epithelium (IDE) is different from that of the stratum intermedium (SI).

3. Bud stage

At the bud stage (Fig. 1B), two different cell types can be distinguished in the dental epithelium: elongated cells in contact with the basement membrane and round internal cells.[27,28] It is not clear whether in vivo, cells from these two groups are really separated or may move from one to the other ''compartment''. However, experimental approaches in vitro suggested that the shape of cells, elongated or not, was determined whether they were in contact with the basement membrane or not.[16]

Depending on their position, epithelial cells at the bud stage show differential expression of γ-catenin and desmoglein,[29] as well as E- and P-cadherins.[30] Cadherins are involved in determining the cell shape by interfering with the microfilament system[31–33] and microtubule organization.[34,35] Cell interactions can influence directly or indirectly signalling pathways.[36,37] Cadherins and integrins have been suggested to intervene in mecanotransduction.[38–40] Thus, it is proposed that cells and tissues use tensegrity architecture to structure themselves.[41–43]

4. Cap stage

From the bud to cap stage (Fig. 1B and C), the dental epithelium becomes the enamel organ. The complexity of the epithelium increases during this transition and, at the cap stage, four distinct cell types form the inner and outer dental epithelium (ODE), the stellate reticulum (SR) and transiently the primary enamel knot (PEK). At the early cap stage, the IDE becomes separated from the ODE by the SR. The peridermal cells present at the lamina stage might participate in the formation of the SR.[23] The histogenesis of the IDE is accompanied by a change in the composition of the basement membrane, as illustrated by the transient disappearance of laminin-5.[1] The extracellular matrix may also influence the cell shape as well as such activities as cycling, migration and metabolism by means of integrin–cytoskeleton interactions.[44–46]

5. The primary enamel knot

The enamel knot is a complex transient structure containing cells in contact with the basement membrane, internal round cells and concentrically arranged peripheral cells. The exact relationship between these distinct cells types is not known. The cells in contact with the basement membrane probably represent the most important group. They survive and later segregate while internal cells rapidly disappear by apoptosis.[8,47–50]

The subcellular localization of β-catenin, E- and P-cadherins in the enamel organ at the cap stage was investigated using confocal microscopy.[8] At this stage, a strong staining for β-catenin was associated with the surface of IDE cells, in agreement with its role in cell adhesion. However, the intracellular staining for β-catenin was different in cells of the IDE and cells of the PEK, where it was intense.[8] These differences might reflect local changes in the canonical Wnt signalling pathway. β-catenin is a multi-functional protein involved in both cell–cell adhesion and signalling.[51,52] LEF-1 is strongly expressed in the PEK[53] where it might represent an effector of the Wnt/β-catenin signalling. Furthermore, the accumulation of β-catenin in the nucleus of PEK cells was much higher there than in any other part of the enamel organ. The simultaneous upregulation of P-cadherin suggests a relationship between cell adhesion and Wnt signalling in the PEK.[8]

It has been suggested that a precursor of the PEK might already exist at the bud stage in the first lower molar of the mouse.[54] However, this more probably corresponds to the very transitory PEK of the R2 rudiment, which is the main bud located mesially to the first molar proper.[55]