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Review Article

Rho GTPases in ameloblast differentiation

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Summary During tooth development, ameloblasts differentiate from inner enamel epithelial cells to enamel-forming cells by modulating the signal pathways mediating epithelial—mesenchymal interaction and a cell-autonomous gene network. The differentiation process of epithelial cells is characterized by marked changes in their morphology and polarity, accompanied by dynamic cytoskeletal reorganization and changes in cell—cell and cell—matrix adhesion over time. Functional ameloblasts are tall, columnar, polarized cells that synthesize and secrete enamel-specific proteins. After deposition of the full thickness of enamel matrix, ameloblasts become smaller and regulate enamel maturation. Recent significant advances in the fields of molecular biology and genetics have improved our understanding of the regulatory mechanism of the ameloblast cell life cycle, mediated by the Rho family of small GTPases. They act as intracellular molecular switch that transduce signals from extracellular stimuli to the actin cytoskeleton and the nucleus. In our review, we summarize studies that provide current evidence for Rho GTPases and their involvement in ameloblast differentiation. In addition to the Rho GTPases themselves, their downstream effectors and upstream regulators have also been implicated in ameloblast differentiation.

Contents

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1. Introduction

Development of teeth as epithelial appendages is a complex process regulated by inductive interaction between the epithelium and the underlying mesenchymal cells. The earliest event of tooth development is the thickening of the epithelium (the primary dental lamina), followed by condensation of the mesenchymal cells [1,2]. The development of the tooth crown advances through various stages defined by the morphology of the epithelium (bud, cap, and bell) and is followed by the formation of the root. The transition from the bud to the cap stage is a critical step in tooth morphogenesis. Signals from the enamel knot, an early epithelial signaling center, regulate growth and determine the site of epithelial folds that correspond directly with the cusp pattern of the mature tooth [3]. During the cap and bell stages, the size and shape of the tooth crown become apparent by the differentiation of cells into ameloblasts and odontoblasts that secrete the mineralizing matrices of the enamel and dentin, respectively. In the bell stage, the dental epithelium (enamel organ) segregates into four distinct cell types: inner enamel epithelial cells (IEEs), outer dental epithelial cells (OEEs), stratum intermedium (SI), and stellate reticulum (SR). The IEEs eventually differentiate into ameloblasts [4]. In the subsequent transitional stage from crown to root formation, the central core of the epithelium (SI and SR) disappears, leaving only a double layer of IEEs and OEEs called Hertwig's epithelial root sheath (HERS). It directs root growth and gives rise to a fenestrated network of epithelial cells which covers the root, known as the epithelial cell rests of Malassesz (ERM) [4].

The differentiation of epithelial cells into functional ameloblasts comprises several steps of morphological and functional changes. In the proliferation stage, the low columnar IEEs actively proliferate to form the basic shape of the tooth. Then, in differentiation stage, IEEs grow into columnar cells (preameloblasts) with more protein synthesizing organelles. The distal ends of the preameloblasts are flat, and the enamel matrix secreted is called rodless enamel matrix. In the secretory stage, the cells (secretory ameloblasts) lengthen, polarize, and form conical projections called Tome's process and deposit enamel in the form of rods. In transitional stage, when enamel reaches its full thickness, the height of ameloblasts decrease and protein synthesizing organelles are drastically reduced (transitional stage ameloblasts). The number of the ameloblasts is reduced by apoptosis in this stage. In the maturation stage, the ameloblasts modulate and transport specific ions necessary for the simultaneous deposition of minerals, and at the same time they also degrade enamel proteins and resorb the degraded proteins and water. The ameloblasts initiate a series of repetitive morphological change at the enamel surface, in which tight junction and deep membrane infoldings periodically appear (ruffle-ended ameloblasts [RA]), then disappear for short intervals (smooth ended ameloblasts [SA]) from distal end of the cells. In the regressive stage, the ameloblasts (reduced enamel epithelium) lose their differentiation and become short cuboidal cell, which is indistinguishable from other layers of the enamel organ. Reduced enamel epithelium remains on the surface of formed enamel until the tooth erupts. After crown morphogenesis, the boundary where IEEs and OEEs meet, referred to as the cervical loop, ceases to differentiate into ameloblasts and forms HERS with OEEs to induce root formation [4–7].

Amelogenesis is a complicated process, as described above, and for the last several decades, various animal and human studies have used molecular genetics to identify a number of signaling molecules and gene networks that act at specific stages of the ameloblast life cycle and regulate its patterning and differentiation processes. Rho GTPases, including RhoA, Rac1, and Cdc42, have been identified as the regulatory mechanism for cellular events such as migration, polarization, cytokinesis, cell–cell adhesion, cell cycle, and gene expression in many cell types [8–10]. Until recently, Rho GTPases were believed to be involved primarily in the regulation of cytoskeletal organization in response to extracellular molecules. However, recent studies have demonstrated that they play crucial roles in many cellular events such as transcriptional activation, cell proliferation, cell polarity, cell–cell adhesion, membrane trafficking, muscle contraction, ion channel activity, endothelial permeability, reactive oxygen species production, phospholipid metabolism, and embryonic development [9,11]. Further, they are involved in osteoclastogenesis as well as in hematopoiesis and hemopathies [12,13]. Recently, evidence has emerged showing the involvement of Rho signaling in tooth development [14–24]. In this article, we summarize some interesting recent findings that provide molecular insights into how signaling by Rho GTPases results in tooth development, focusing on ameloblast differentiation in particular.