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Review

Regulatory roles of microRNAs in human dental tissues

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ABSTRACT

MicroRNAs (miRNAs) are a class of small, non-coding RNAs that provide an efficient pathway for regulation of gene expression at a post-transcriptional level. Tooth development is regulated by a complex network of cell-cell signaling during all steps of organogenesis. Most of the congenital dental defects in humans are caused by mutations in genes involved in developmental regulatory networks. Whereas the developmental morphological stages of the tooth development already are thoroughly documented, the implicated genetic network is still under investigation. The involvement of miRNAs in the regulation of tooth genetic network was suggested for the first time in 2008. MiRNAs regulate tooth morphogenesis by fine-tuning the signaling networks. Unique groups of miRNAs are expressed in dental epithelium compared with mesenchyme, as well as in molars compared with incisors. The present review focuses on the current state of knowledge on the expression and function of miRNAs in human dental tissues, including teeth and the surrounding structures. Herein, we show that miRNAs exhibit specific roles in human dental tissues and are involved in gingival and periodontal disease, tooth movement and eruption, dental pulp physiology including repair and regeneration, differentiation of dental cells, and enamel mineralization. In light of similarities between the tooth development and other organs originating from the epithelium, further understanding of miRNAs` function in dental tissues may have wide biological relevance.

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Abbreviations: miRNA, microRNA; DFCs, dental follicle cells; CCD, cleidocracial dysplasia; SATB2, special AT-rich sequence-binding protein 2; ECM, extracellular matrix; SCAPs, stem cells from apical papilla; DSPP, dentin sialophosphoprotein; PDL, periodontal ligament; DPCs, dental pulp cells; VEGF, vascular endothelial growth factor.

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1. Introduction

1.1. Genetic basis of tooth development

Tooth formation, odontogenesis, is regulated by a complex network of cell-cell signaling during all steps of development and is initiated from two tissue components: the epithelium and the underlying ectomesenchyme (Fig. 1) (Jussila & Thesleff, 2012). The transcription of >2400 genes, integrated both in terms of space and time, is required for tooth development (Landin et al., 2012). Most of these genes encode various proteins, e.g. ligands, receptors, transcription factors, co-factors, and intracellular signaling molecules. Conserved signaling pathways that control the majority of processes in embryonic development are also necessary for tooth formation (Tummers & Thesleff, 2009). It is evident that developmental regulatory genes have mainly been conserved during evolution and most of the proteins implicated in odontogenesis belong to the four conserved signal pathway families, i.e. Bmp, Fgf, Hh, and Wnt (Jussila & Thesleff, 2012; Tummers & Thesleff, 2009; Bei, 2009; Mikkola, 2007; Thesleff, 2003). The developing human tooth shares the same regulatory molecules with other ectodermal organs during the first steps of initiation and morphogenesis. However, in contrast to several other human epithelial appendages, human teeth do not exhibit regenerative capacity. During tooth formation, unique cell types, whose differentiation is closely linked with morphogenesis, form the dental hard tissues, enamel, dentin, and cementum. The precise function of several genes for the formation of dental tissues is known, as are the outcomes of their mutations on normal tooth development. It is apparent that most of the congenital dental defects in humans are caused by mutations in genes involved in developmental regulatory networks (Thesleff, 2000). Whereas the developmental morphological stages of the odontogenesis are already thoroughly documented (Thesleff & Tummers, 2008), the implicated genetic network is still under investigation.

1.2. MicroRNAs regulate gene expression

Embryonic development in vertebrates is thoroughly orchestrated and demands a precisely regulated genetic network. Today there is increasing evidence that microRNAs (miRNAs), a class of small non-protein-coding RNAs, have a considerable role in vertebrate development, as shown by the early embryonic lethality of mice with imperfections in the miRNA biogenesis pathway (Abbott et al., 2005; Bernstein et al., 2003; Liu et al., 2004). MiRNAs have emerged as essential factors in RNA interference-mediated post-transcriptional gene regulation and are considered as inevitable to normal cellular physiology (Mendell, 2005). These small powerful molecules provide an efficient pathway for regulation of gene expression at a post-transcriptional level. It has been suggested that they may regulate the expression of about 30% of

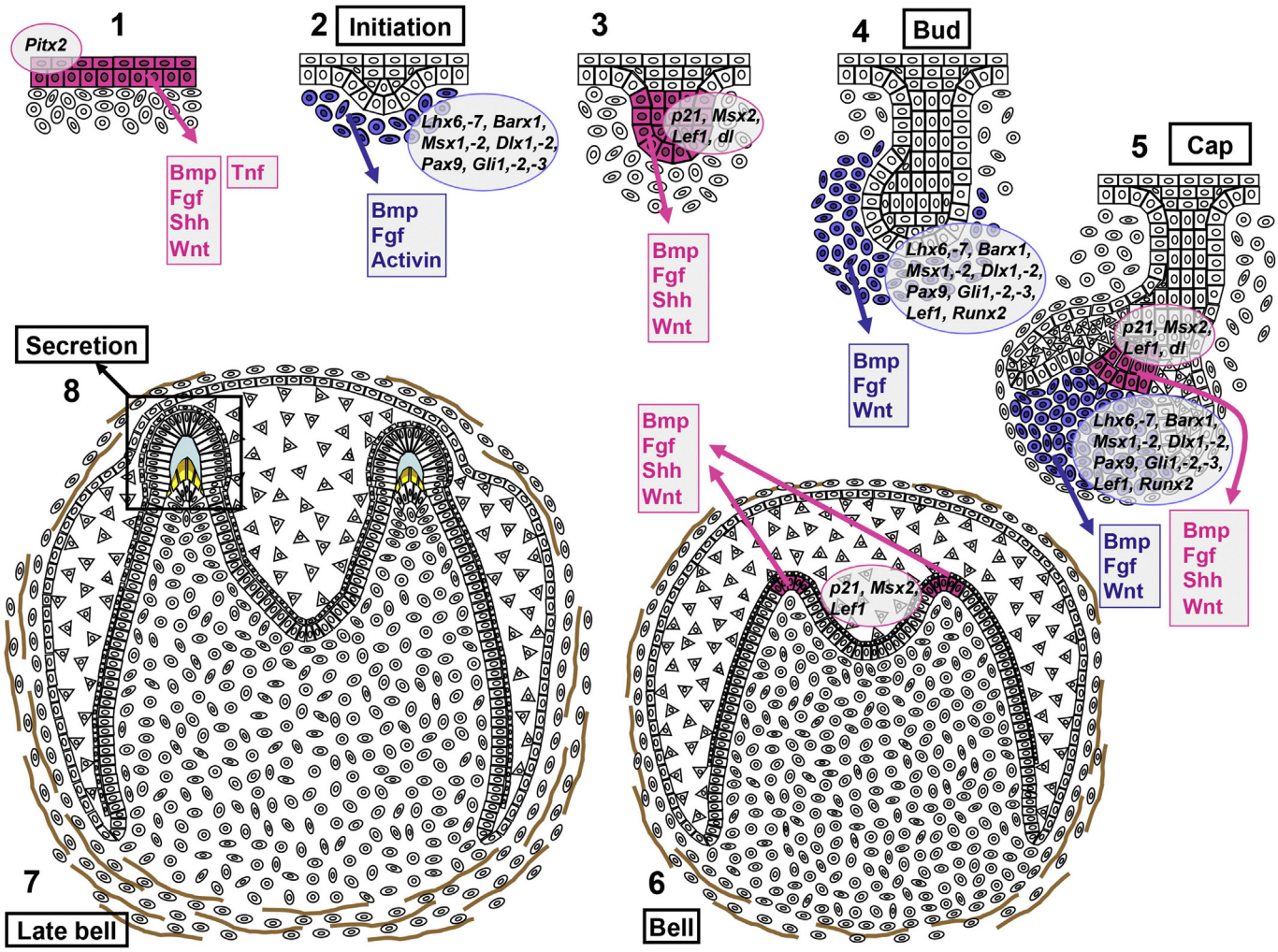

Fig. 1. Schematic presentation of tooth development. Tooth development, from initiation to secretion of the extracellular matrices of dentin and enamel, is controlled by sequential and reciprocal interactions between the dental epithelium and mesenchyme. The same signaling pathways regulate tooth development in all stages. The genes presented in the boxes are critical for normal tooth morphogenesis as shown by knockout mice studies.