The transcription factor NKX2-3 mediates p21 expression and ectodysplasin-A signaling in the enamel knot for cusp formation in tooth development

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論　文　名	The transcription factor NKX2-3 mediates p21 expression and ectodysplasin-A signaling in the enamel knot for cusp formation in tooth development （ホメオボックス転写因子 NKX2-3 は p21 の発現調節および EDA シグナル経路を介して歯の咬頭形成を調節する）
論文調査委員	主　査　　九州大学　　教授　　前田　英史 副　査　　九州大学　　教授　　清島　保 副　査　　九州大学　　教授　　自見　英治郎

論　文　審　査　の　結　果　の　要　旨

During tooth development, tooth cusps are regulated by precise control of proliferation of cell clusters, termed enamel knots, that are present among dental epithelial cells. The interaction of ectodysplasin-A (EDA) with its receptor, EDAR, plays a critical role in cusp formation by these enamel knots, and mutations of these genes is a cause of ectodermal dysplasia. NKX2-3, known as a member of transcription factors of NK homeobox family, critically regulates organ development. A previous study showed that *Nkx2-3* deficiency in tooth resulted in the absence of cusp formation. However, the molecular mechanism of NKX2-3 in tooth morphogenesis remains unclear. In this study, authors examined the role of NKX2-3 in tooth development. Using gene microarray analysis in mouse embryos, *Nkx2-3* is highly expressed during tooth development and increased during the tooth morphogenesis, especially during cusp formation. In organ culture, *Nkx2-3* siRNA inhibited cusp formation, suggesting that NKX2-3 is critical for tooth morphogenesis. Cusp formation is known to be regulated by an enamel knot expressing the cyclin-dependent kinase inhibitor p21. NKX2-3 induced the expression in mRNA and protein of p21 when dental epithelial cell line, M3H1 cells were transfected with *Nkx2-3* expression vector. Furthermore, ChIP assay showed that NKX2-3 regulated transcription and expression of p21 by binding to its promoter region, resulting in alteration of cell proliferation. *Nkx2-3* was shown to be significantly induced by EDA, suggesting that *Nkx2-3* is a target transcription factor regulated by the Eda/Edar signaling pathway in the enamel knot. Moreover, NKX2-3 activated the bone morphogenetic protein (BMP) signaling pathway by up-regulating expression levels of *Bmp2* and *Bmpr2* in dental epithelium and decreased the expression of the dental epithelial stem cell marker SRY box 2 (SOX2). These results indicate that NKX2-3 plays roles during the tooth cusp formation via Eda signaling and regulating p21 expression.

The paper has included novel data clarifying the mechanism of the tooth cusp formation during dentinogenesis. Therefore, it could be recommended for a DOCTOR OF PHILOSOPHY (Dental Science) in Kyushu University.