

Arl4c is involved in tooth germ development through osteoblastic/ameloblastic differentiation

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論 文 名 : Arl4c is involved in tooth germ development through
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(低分子量タンパク質 Arl4c は骨芽細胞/エナメル芽細胞分化を介して歯
胚の発生を制御する)

区 分 : 甲

論 文 内 容 の 要 旨

Murine tooth germ development proceeds in continuous sequential steps with reciprocal interactions between the odontogenic epithelium and the adjacent mesenchyme, and several growth factor signaling pathways and their activation are required for tooth germ development. The expression of ADP-ribosylation factor (Arf)-like 4c (Arl4c) has been shown to induce cell proliferation, and is thereby involved in epithelial morphogenesis and tumorigenesis. In contrast, the other functions of Arl4c (in addition to cellular growth) are largely unknown. Although we recently demonstrated the involvement of the upregulated expression of Arl4c in the proliferation of ameloblastomas, which have the same origin as odontogenic epithelium, its effect on tooth germ development remains unclear. In the present study, single-cell RNA sequencing (scRNA-seq) analysis revealed that the expression of Arl4c, among 17 members of the Arf-family, was specifically detected in odontogenic epithelial cells, such as those of the stratum intermedium, stellate reticulum and outer enamel epithelium, of postnatal day 1 (P1) mouse molars. scRNA-seq analysis also demonstrated the higher expression of Arl4c in non-ameloblast and inner enamel epithelium, which include immature cells, of P7 mouse incisors. In the mouse tooth germ rudiment culture, treatment with SecinH3 (an inhibitor of the ARNO/Arf6 pathway) reduced the size, width and cusp height of the tooth germ and the thickness of the eosinophilic layer, which would involve the synthesis of dentin and enamel matrix organization. In addition, loss-of-function experiments using siRNAs and shRNA revealed that the expression of Arl4c was involved in cell proliferation and osteoblastic cytodifferentiation in odontogenic epithelial cells. Finally, RNA-seq analysis with a gene set enrichment analysis (GSEA) and Gene Ontology (GO) analysis showed that osteoblastic differentiation-related gene sets and/or GO terms were downregulated in shArl4c-expressing odontogenic epithelial cells. These results suggest that the Arl4c-ARNO/Arf6 pathway axis contributes to tooth germ development through osteoblastic/ameloblastic differentiation.

