Form 3

Abstract of Thesis

Name （SAHA MITHUN KUMAR）	
Title	**Tissue and stage-specific role of *Gata3* in embryonic craniofacial development** **(鼻中隔の発生過程におけるGata3の組織特異的な役割の探索)**

Abstract of Thesis

【Introduction】 Embryonic development of a head comprises several distinct cellular processes such as outgrowth of facial prominences. Among these congenital craniofacial defects, orofacial clefts are relatively well studied, from their cellular and molecular etiology to clinical outcomes. On the other hand, the developmental process of primary palate including nasal septum and impact of its defects at a clinical level is largely elusive. In our previous study, we discovered eliminating *Rdh10,* a rate-limiting enzyme for synthesizing all-trans-retinoic acid and reduced retinoid signaling during embryonic craniofacial development results in midfacial cleft with severe nasal septum deformity and CA. Following investigation revealed *Gata3* as an intermediate molecule which elimination could result in a partially overlapped phenotype with reduced retinoid signaling like CA. CA is known to cause by failure of primitive choanae development, which occur at the lateral edge of nasal septum. These results strongly indicate that loss of retinoid and *Gata3* signaling during embryonic craniofacial development influences the development of nasal septum. *Gata3* is a transcription factor that plays multiple roles for diversified tissue development and maintenance. For these reasons, in the present

study, we utilized multiple genetic models to eliminate Gata3 from different embryonic tissue to investigate the role of *Gata3* in nasal septum and primary palate development.

【Objectives】Assessing the functions of *Gata3* during the development of the primary palate and nasal septum in mice.

【Methods】 *Gata3* mRNA and protein expression were assessed with *In situ* hybridization and immunohistochemistry. Eliminating *Gata3* during embryonic development was performed by crossing tamoxifen-inducible ubiquitous Cre (*ERT2Cre*) or neural crest cell-specific Cre (*Wnt1Cre*) mice into *Gata3* flox mice. The morphological and histological analyses were performed with fluorescent DAPI staining and histological sections. Immunohistochemistry of Ki67, SOX9, and E-cadherin was performed to assess the tissue-specific effect of *Gata3* during craniofacial development.

【Results】Strong *Gata3* mRNA expression could be detected in the frontonasal and maxillary process at E11.5 and gradually restricted its expression in the lateral edge of the nasal septum from E12.5. Section immunohistochemistry revealed that *GATA3* protein localizes in facial ectoderm and mesenchyme from E11.5 to E13.5. After eliminating *Gata3* from E9.5 using the *ERT2Cre:Gata3* mice or from neural crest cells using the *Wnt1Cre: Gata3* mice, we detected malformation of the nasal septum with down-regulation of *SOX9* and *SOX10*. Reduced cell proliferation and increased cell death could also be seen in developing nasal septum in both mutants.

【Conclusions】These findings revealed important functions of *GATA3* in controlling cellular activities throughout the nasal septum development through regulating proper cell proliferation and survival with gene expression which is important for cartilage development.

様式７

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究では転写因子である *Gata3* を頭部神経堤細胞や胎生時期特異的に除去したマウス胎児の観察を行い *Gata3* が鼻中隔の形態形成に関与している事を明らかにした。さらに組織学的な解析から発生中の鼻中隔における *Gata3* は軟骨細胞の分化や細胞増殖に関与している事を明らかにした。

本研究では *Gata3* が鼻中隔の形態形成に果たす新たな知見を見出だし HDR 症候群の病態の一端を明らかにしたものであり、博士（歯学）の学位論文として価値のあるものと認める。