



Title	Role of TMEM2-Mediated Hyaluronic Acid Catabolism in Normal Palatal Development
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論文内容の要旨

氏 名 (シヤマ ヒシヤマ)	
論文題名	Role of TMEM2-Mediated Hyaluronic Acid Catabolism in Normal Palatal Development (口蓋発生過程におけるヒアルロン酸分解酵素TMEM2の役割の解明)
論文内容の要旨 Introduction Cleft lip and/or palate (CL/P) is one of the most common congenital anomalies affecting the craniofacial region and is associated with feeding, speech, and hearing impairments that profoundly affect quality of life. Proper palatal development is a multistep embryonic process in which bilateral palatal shelves derived from the maxillary prominences grow, elevate, contact, and fuse at the midline. Because the palatal mesenchyme is largely derived from cranial neural crest cells (NCCs), disturbances in NCC migration, proliferation, or differentiation readily result in cleft palate. These morphogenetic events depend on dynamic remodeling of the extracellular matrix (ECM), which requires a coordinated balance between anabolic and catabolic regulation. Among ECM components, hyaluronan (HA) plays a particularly critical role during palatogenesis, its rapid extracellular turnover is thought to provide the flexibility required for tissue expansion and morphogenesis. While the role of HA anabolism has been investigated using HA synthase-deficient mouse models, the developmental significance of HA catabolism during palatogenesis remains poorly understood. We recently identified transmembrane protein 2 (TMEM2) as a functional extracellular hyaluronidase during embryogenesis; however, <i>Wnt1</i>-Cre-mediated deletion of <i>Tmem2</i> results in mid-gestational lethality, preventing analysis of palatal development. Aims This study aimed to clarify the essential role of TMEM2-mediated extracellular hyaluronan degradation in neural crest-derived palatal mesenchyme during the elevation-to-fusion stages of mouse palatogenesis, overcoming the early lethality of <i>Wnt1</i>-Cre-driven mutants by employing a later-acting <i>Sox10</i>-Cre driver. Methods: Neural crest-specific <i>Tmem2</i> conditional knockout mice (<i>Tmem2^{fl/fl}</i>; <i>Sox10</i>-Cre) were generated, and embryonic palatal development was examined by morphological, histological, immunofluorescence, and transcriptomic analyses. Cell proliferation, apoptosis, neural crest cell distribution, vascular organization, tissue hypoxia, and HA localization were quantitatively assessed in serial coronal sections. RNA sequencing followed by STRING and gene set enrichment analyses was used to identify molecular pathways altered by <i>Tmem2</i> deficiency. Results: <i>Tmem2^{fl/fl}</i>; <i>Sox10</i>-Cre embryos exhibited a fully penetrant cleft palate characterized by normal shelf elevation but severely impaired horizontal outgrowth and fusion. Palatal mesenchyme displayed showed reduced cell proliferation and increased apoptosis, as indicated by decreased Ki-67 and increased TUNEL staining. RNA-seq analysis revealed upregulation of hypoxia-related pathways and strong suppression of cell-cycle and DNA replication programs. Consistently, HIF-1α-positive and pimonidazole-labeled hypoxic cells were significantly increased in mutant palatal shelves. HA staining demonstrated diffuse HA accumulation accompanied by disorganization of neural crest-derived mesenchymal cells. Furthermore, CD31 and NG2 immunofluorescence revealed abnormal vascular patterning and reduced pericyte association, indicating impaired vascular maturation. Conclusions:	

TMEM2-dependent hyaluronan degradation is essential for proper extracellular matrix remodeling and coordinated migration, survival, and differentiation of neural crest–derived mesenchymal cells during palatogenesis. Loss of TMEM2 causes excessive HA accumulation, disrupts neural crest cell organization and vascular maturation, and leads to local hypoxia, reduced proliferation, and increased apoptosis, ultimately resulting in cleft palate formation. These findings define TMEM2 as a key regulator linking HA turnover to neural crest cell dynamics and vascular development in palatal morphogenesis.

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 本研究は、口蓋発生過程における細胞外ヒアルロン酸（HA）分解酵素 Transmembrane protein 2（TMEM2）の役割について検討した。 その結果、<i>Tmem2</i> 欠損によって口蓋突起の成長が障害され、口蓋裂が生じることが明らかになった。さらに、口蓋突起内には HA が異常に蓄積し、細胞増殖の低下及び細胞死の増加を伴うことが示された。加えて、神経堤由来細胞の局在異常を背景とした口蓋突起における血管形成および血管成熟の異常が認められ、これにより組織の低酸素状態が引き起こされることも明らかになった。 以上の結果から、TMEM2 を介した HA 代謝制御が口蓋形成に必須であることが示された。本研究は、口蓋形成における HA 分解と血管形成・低酸素環境との関連を示す新たな病態メカニズムを明らかにし、口唇口蓋裂をはじめとする先天異常の病態理解に重要な知見を提供するものである。よって、本論文は博士（歯学）の学位論文として十分に価値のあるものと認められる。			