Medical & healthcare, Drug discovery

Deciphering disease biology through energy metabolism: A novel approach focusing on hyaluronan

Department of Orthodontics and Dentofacial Orthopedics, Graduate School of Dentistry/Department of Orthodontics, The University of Osaka Dental Hospital

Associate Professor Toshihiro Inubushi

Researchmap https://researchmap.jp/opathone0141?lang=en

Abstract

We previously identified *Tmem2* as a novel extracellular hyaluronidase, revealing an active degradation mechanism for hyaluronan (Figure1). As hyaluronan turnover is rapid and closely linked to glycolysis, its dysregulation may contribute to disease. Notably, hyaluronan accumulates in type 2 diabetes and liver disease. This study aims to clarify how hyaluronan synthesis and degradation are altered in human diseases through metabolic changes. By identifying disease-specific abnormalities in hyaluronan regulation, we seek to develop targeted therapeutic strategies that restore balance and prevent disease progression.

Background & Results

Hyaluronan is the most abundant extracellular matrix component in the body and is characterized by its rapid turnover, with a half-life of approximately three days. Despite this, the biological rationale for its constant synthesis and degradation remains unclear. Traditionally, hyaluronan breakdown was thought to occur via passive, physical mechanisms.

We previously identified *Tmem2* as a novel extracellular hyaluronidase, establishing the presence of an active degradation system. Using conditional knockout (CKO) mice, we showed that *Tmem2* plays a central role in hyaluronan catabolism and is essential for embryonic development and tissue homeostasis. Notably, *Tmem2* deficiency led to increased apoptosis, suggesting that hyaluronan metabolism is critical for cell survival.

To explore tissue-specific functions of *Tmem2*, we generated various Cre-driver mouse models. In *Col2a1;R26-Tmem2* mice, where *Tmem2* is overexpressed in chondrocytes, osteoarthritis (OA) progression was markedly enhanced following surgical induction (Figuer2). We also found that *Tmem2* expression increases during early OA, potentially contributing to cartilage hyaluronan depletion. Based on these findings, we are now evaluating *Tmem2*-neutralizing antibodies for OA therapy.

In palatogenesis, *Tmem2* deletion via *Sox10-Cre* and *Osr2-Cre* led to complete cleft palate, with increased apoptosis, reduced proliferation, and enhanced hypoxia-related glycolytic activity in palatal tissues (Figure3). These results highlight a potential link between hyaluronan metabolism and energy regulation during craniofacial development.

Significance of the research and Future perspective

This research may lead to a new paradigm in understanding and treating hyaluronan-related diseases. We focus on cleft lip and/or palate, a common and challenging congenital disorder, aiming to develop preventive strategies through metabolic control of hyaluronan. Since abnormal hyaluronan turnover is also linked to osteoarthritis, fibrosis, aging, and cancer, our findings may have broad applications. Collaboration across disciplines and with industry could accelerate innovation and therapeutic translation.

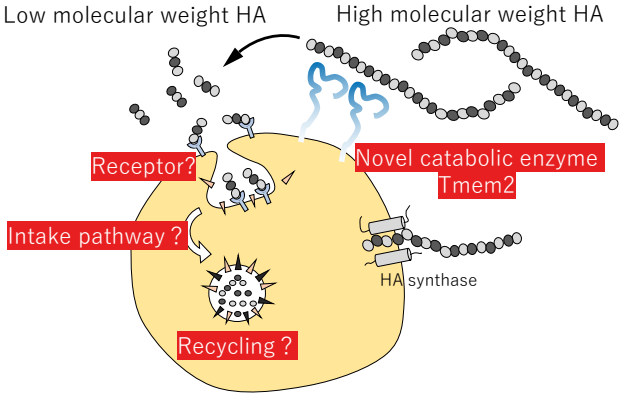


Figure1. Hyaluronic acid (HA) catabolic pathway

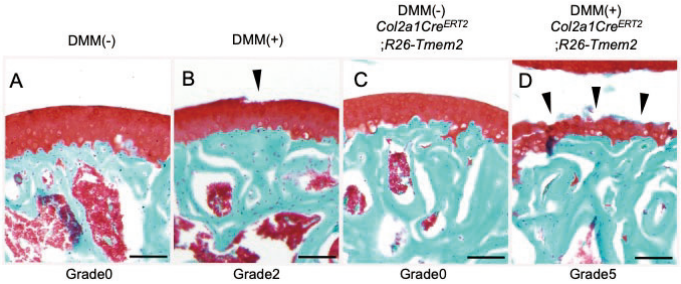
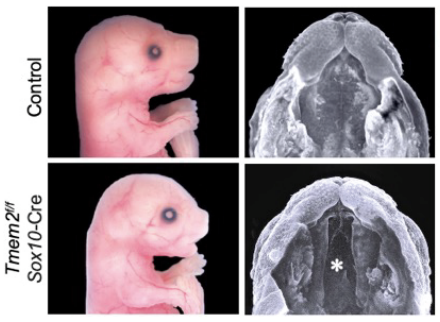


Figure 2. Safranin O staining of knee joint cartilage.(A) Control group, (B) *Tmem2*-overexpressing group, (C) control group subjected toDMM surgery, and (D) *Tmem2*-overexpressing group subjected to DMM surgery.



E16.5	Cleft
Control	0/5 (0%)
Tmem2$^{f/f}$ *Sox10*-Cre	5/5 (100%)

Figure 3. Stereomicroscopic (left) and fluorescence images ofembryos from neural crest cell-specific *Tmem2* knockout miceand control mice. An asterisk (*) indicates cleft palate.

Patent

Treatise

Inubushi, Toshihiro; Nag, Priyanka; Sasaki, Jun-Ichi et al. The significant role of glycosaminoglycans in tooth development. Glycobiology. 2024, 34(5), cwae024. doi: 10.1093/glycob/cwae024

Nag, Priyanka; Inubushi, Toshihiro; Sasaki, Jun-Ichi et al. Tmem2 deficiency leads to enamel hypoplasia and soft enamel in mouse. J Dent Res. 2023, 102(10), 1162-1171. doi: 10.1177/00220345231182355

Inubushi, Toshihiro. In vitro investigation of the effects of the hyaluronan-rich extracellular matrix on neural crest cell migration. J Vis Exp. 2023, 192, e64749. doi: 10.3791/64749

Inubushi, Toshihiro; Nakanishi, Yuichiro; Abe, Makoto et al. The cell surface hyaluronidase TMEM2 plays an essential role in mouse neural crest cell development and survival. PLoS Genetics. 2022, 18(7), e1009765. doi: 10.1371/journal.pgen.1009765

Yamamoto, Hayato; Tobisawa, Yuki; Inubushi, Toshihiro et al. A mammalian homolog of the zebrafish transmembrane protein 2 (TMEM2) is the long-sought-after cell-surface hyaluronidase. Journal of Biological Chemistry. 2017, 292(18), 7304-7313. doi: 10.1074/jbc.M116.770149

URL

Keyword hyaluronan, extracellular matrix, cleft lip and/or palate, osteoarthritis, hyaluronidase