# Role of COUP-TFII in Odontoblast Differentiation

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| URL | http://hdl.handle.net/10097/00097042 |

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| 学位の種類 | ： | 博　士　（歯　学） | 学位記番号　：　歯　博　第　7　6　3　号 |
| 学位授与年月日 | ： | 平成 28 年 3 月 25 日 | 学位授与の要件　：　学位規則第 4 条第 1 項該当 |
| 研究科・専攻 | ： | 東北大学大学院歯学研究科（博士課程）歯科学専攻 | |
| 学位論文題目 | ： | Role of COUP-TFII in Odontoblast Differentiation （象牙芽細胞分化における COUP-TFII の役割） | |
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# 論文内容要旨

Purpose of this study is to identity the role of COUP-TFII in odontoblast differentiation. Results are as in the following,

The expression of COUP-TFII was increased in maxillary molar germs of rats as development of the tooth progressed, and it was also gradually increased in primary human dental pulp cells and murine dental papilla-derived cells cultured in a mineralizing medium in a time dependent manner. From the expreiments of overexpression and down-regulation of COUP-TFII expression, it was identified that COUP-TFII acts as a stimulatory factor. Mechanistically, it showed that COUP-TFII directly binds to the promoter of DSPP, an important marker of odontoblast differentiation, to enhance the transcription activity of DSPP. Through protein interaction with Msx2, the inhibitory regulator of DSPP, COUP-TFII antagonistically regulated the Msx2 effect on DSPP promoter activity. From the results, the author showed that COUP-TFII has stimulatory effect on the differentiation of odontoblast by enhancing the transcription activity of DSPP, suggesting COUP-TFII may be used as a novel target protein for dentin regeneration strategy.

This study contributed on dental field development remarkably by identifying the role and mechanism of COUP-TFII in odontoblast differentiation.

# 審 査 結 果 要 旨

This study is investigated a role of chicken ovalbumin upstream promoter transcription factor 2 (COUP-TFII) on odontoblast differentiation.

Odontoblast is originated from neural crest derived stem cell, and their differentiation is tightly regulated by interaction of mesenchymal and epithelial. Investigation of molecular mechanisms that regulated odontoblast differentiation is critical in the development of dentin regeneration therapy using mesenchymal dental stem cells. Diverse signals including bone morphogenetic proteins, fibroblast growth factors, Wnts or transcription factors Runx2, Msx-1, 2 and Dlxs are involved in these processes. However the precise mechanisms of odontoblast differentiation are still unknown.

COUP-TFII, an orphan nuclear receptor belonging to the steroidthyroid hormone receptor superfamily, plays an important role in cell fate determination of mesenchymal stem cells (MSCs). For instance, COUP-TFII stimulates differentiation of MSCs to adipocyte and chondrocyte with the increased expression of peroxisome proliferator-activated receptor-gamma (PPAR-$\gamma$) and Sox 9, while COUP-TFII inhibitsWnt signaling and Runx2 activity to interrupt myogenic and osteoblast differentiation. Since odontoblast is differentiated from MSCs, it is suggested that COUP-TFII involved in odontoblast differentiation processes. However no report was found that role of COUP-TFII in odontoblast differentiation.

In the present study, author investigated the functional role of the COUP-TFII during odontoblast differentiation processes. Expression of COUP-TFII is specifically increased during odontoblast differentiation in the bell stage of developing tooth germ, human dental pulp cell (HDPC) and murine dental papilla-derived cells (MDPC-23). Overexpression of COUP-TFII in MDPC-23 increased odontoblast differentiation, matrix mineralization and expression of odontoblast marker genes such as DSPP and DMP-1. In contrast, down-regulation of COUP-TFII suppressed differentiation of MDPC-23 into odontoblast. DSPP and DMP-1 are dentin specific non-collagenous protein, and is essential for the proper development of bone and dentin. Previous report indicated that homeodomain transcription factors including Dlxs and Msxs are involved in transcription of DSPP and DMP-1. Among these, Msx2 and Dlx5 act as a negative regulator of mineralization related genes such as DSPP. In the present study, COUP-TFII induced DSPP expression through the inhibition of Msx2 affected on DSPP transcription, indicating that COUP-TFII regulates Msx2 antagonistically. Reporter analysis and Chip assay revealed that the COUP-TFII positively regulated transcriptional activity of DSPP through the directly binding to DSPP promoter region at -333 to -328 where located COUP-TFII binding motif. These data indicated that COUP-TF-II has a stimulatory effect on the odontoblast differentiation by enhancing transcriptional activity of DSPP.

From these findings, author concluded that COUP-TFII plays an important role in the DSPP transcription and matrix mineralization of odontoblast lineage cells.This study contributes to the field of tooth development by investigating role of COUP-TFII in odontoblast differentiation.

As the manuscripts presents a very well thought out and is very well written, it is suitable for Ph.D. thesis.