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치의공학과

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## Nfic-결손 생쥐에서 상아모세포의 분화 이상

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**지도교수 박 주 철**

이 논문을 치의공학 박사학위 신청 논문으로
제출함.

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**조선대학교 대학원**

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# 오현주의 박사학위 논문을 인준함

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2006년 12월 일

# 조선대학교 대학원

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# ABSTRACT

## Aberrant Odontoblast Differentiation in *Nfic*-deficient Mice

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It was reported that *Nfic*-deficient mice exhibit agenesis of molar roots and severe incisor defects. In this study, histological and immunohistochemical studies were carried out to investigate the mechanism(s) responsible for abnormal root formation in *Nfic*-deficient mice. *Nfic*-deficient mice showed aberrant odontoblast differentiation and consequently abnormal dentin formation, while other tissues/organs in the body including ameloblasts of the enamel organ appeared to be unaffected and normal. One of the most striking changes observed in these aberrant odontoblasts was the absence of intercellular junctions between them, resulting in dissociation of the cells and loss of their cellular polarity and organization. Surprisingly, these cells became trapped in dentin-like mineralized tissue and thus their overall morphology resembled osteoblasts and osteocytes. There was also an increased apoptotic activity in *Nfic*-deficient mice. These findings strongly suggested that NFI-C plays a key role in odontoblast differentiation and survival in a cell type-specific manner.

Key words: NFI-C, Dentin, Odontoblast, Disruption, Root formation

# I. Introduction

The phylogenetically conserved nuclear factor I (NFI) gene family encodes site-specific transcription factors essential for the development of a number of organ systems. There are four *Nfi* genes in mammals (*Nfia*, *Nfib*, *Nfic*, and *Nfix*) and single *Nfi* genes in *Drosophila melanogaster*, *Caenorhabditis elegans*, *Anopheles* spp., and other simple animals (Gronostajski, 2000; Mukhopadhyay *et al.*, 2001; Barchurski *et al.*, 2003). It was reported that *Nfia*-deficient mice exhibit agenesis of the corpus callosum and other forebrain defects (das Neves *et al.*, 1999; Shu *et al.*, 2003), whereas *Nfib*-deficient mice possess unique defects in lung maturation and forebrain defect (Steele-Perkins *et al.*, 2005). Recently, it was also found that *Nfic*-deficient mice show agenesis of molar roots and severe incisor defects (Steele-Perkins *et al.*, 2003).

In the present study, we investigated the possible role of NFI-C in odontoblast differentiation and root dentin formation using the innovative and invaluable *Nfic* knockout mice model with the following specific aims. First, we attempted to understand if odontoblasts change their morphology into osteoblast- and osteocyte-like cells in *Nfic*-deficient mice. Second, we examined whether disruption of the *Nfic* gene interferes with the formation of intercellular junctions, leading to dissociation of

odontoblasts. Third, we investigated if disruption of the *Nfic* gene causes apoptosis of odontoblasts. The findings from these studies helped us to better understand the possible mechanism for the formation of aberrant odontoblast differentiation and abnormal dentin formation in *Nfic*-deficient mice.

# II. Materials & Methods

### Tissue Preparation for Light and Electron Microscopy

Postnatal mice were anesthetized with isoflurance and cardiac-perfused with using 2.5% glutaraldehyde in 0.1 mol/L cacodylate buffer, pH 7.4. The mandibules were dissected out, demineralized in EDTA, postfixed in 1% osmium tetroxide and processed for embedding in Epon mixture (Polyscience, Washington, PA). For transmission electron microscopic observation, thin sections were cut on an ultramicrotome, stained with uranyl acetate and lead citrate, examined, and photographed using a transmission electron microscope (JEOL 1200 EXII, Japan).

### Immunohistochemistry

Mice were cardiac-perfused with 4% paraformaldehyde-phosphate-buffered saline (PBS), and heads were removed, decalcified in formaldehyde-formic acid at 4℃ overnight, and processed for embedding in paraffin. Four-μm thick sections were cut and stained with hematoxylin and eosin (H-E). For immunohistochemical studies, sections were incubated with 1% BSA in PBS for 30 min, and rabbit anti-ZO-1 (Zymed, South San Francisco, CA) or rabbit anti-occludin(Zymed, South San Francisco, CA) diluted 1:100 in PBS for 1 hr. They were then incubated for 1 hr at

room temperature with secondary antibody and reacted with the avidine-biotin-peroxidase complex (Vector, Burlingame, CA) in PBS for 1 hr. After color development with 0.05% DAB (3,3'-diaminobenzidine tetrahydrochloride Sigma-Aldrich, Germany), they were counterstained with hematoxylin.

**TUNEL POD Staining**

Apoptoic cells were identified using a terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling kit (In Situ Cell Death Detection Kit, POD) according to the procedures of the manufacture's directions (Roche Biochemicals, Germany). Endogenous peroxidase was blocked for 10 min by incubation in 3% $H_2O_2$ prior to enzymatic labeling. During the TUNEL procedure, sections were washed in PBS. The substrate color reaction was achieved by incubation with DAB after enzymatic labeling. Sections were counter-stained with methyl green.

# III. Results and Discussion

**Morphological Change of Odontoblasts into Osteoblast- and Osteocyte-like Cells in *Nfic*-deficient Mice**

Careful morphological analysis of the mandibular incisors of *Nfic*-deficient mice revealed that the inner enamel epithelium underwent normal differentiation into ameloblasts that form normal enamel. This finding strongly suggests that NFI-C may not play any significant role in ameloblast differentiation and enamel formation. On the other hand, dentin formed in *Nfic*-deficient mice was very different compared to normal. Interestingly, the overall morphology of dentin and its associated aberrant odontoblasts in *Nfic*-deficient mice shares morphological similarities to osteodentin that is formed as a result of dental caries. A cross-section of an incisor from a wild-type mouse showed a circular dentin and odontoblasts that line the inner surface of the dentin (Fig. 1A). The pulp chamber was filled with pulp fibroblasts. However, an incisor from mutant mice showed a horseshoe-like shape as a result of a lack of dentin formation (Fig. 1B). Abnormal dentin was thick and contained numerous cells. In longitudinal sections of wild-type and mutant incisors, both demonstrated normal neural crest-derived ectomesenchymal (NCEM) cells. In a wild-type incisor, they differentiate into preodontoblasts and odontoblasts that were elongated, highly polarized

and well organized as a sheet of cells. However, those in a mutant incisor failed to differentiate into normal odontoblasts (Fig. 1C, 1D). These aberrant odontoblasts were round in shape, and lost their polarity and organization as a sheet of cells (Fig. 2A). Many of them were trapped in an osteodentin-like mineralized tissue, and therefore, resembled osteocytes. Electron microscopic analysis of aberrant odontoblasts revealed the absence of an intercellular junctional complex also known as the terminal webs between them (Fig. 2B). Interestingly, *Nfic*-deficient mice also showed no or short and abnormal roots, but normal crowns with normal dentin and enamel formation (Steele-Perkins et al., 2003). The reason why *Nfic*-deficient mice have normal odontoblast differentiation during crown dentin formation, but aberrant odontoblast differentiation during root dentin formation remains unknown. We speculate that the unique role of the *Nfic* gene specifically in later (postnatal) stages of tooth development maybe responsible for the aberrant odontoblast differentiation and dentin formation. This speculation is based on the fact that the crown is formed during embryonic stage, while the rootis formed postnatally. The other reason may be due to the presence of enamel knots during crown formation, but not during root formation, as they have an important function as the information center for crown formation (Thesleff *et al.,* 1997). Also, it is of interest to note that additional cell types such as stellate reticulum and stratum intermedium in the enamel organ participate in

formation of the crown, while only the Hertwig's epithelial root sheath cells are involved in root odontoblast differentiation during root formation (Spouge, 1980; Zeichner-David *et al.,* 2003). These additional cell types, particularly enamel knots may secrete factors that help aberrant odontoblasts to differentiate into normal odontoblasts during crown formation in the *Nfic*-deficient mice.

As indicated earlier, aberrant odontoblasts in *Nfic*-deficient mice resemble osteoblasts and osteocytes in morphology. On the basis of these morphological observations, it is tempting to speculate that disruption of the *Nfic* gene may cause the phenotypic change of odontoblasts into osteoblasts or osteocytes. In order to test this, both *in vitro* and *in vivo* analysis are currently under investigation. It is predicted that aberrant odontoblasts from the *Nfic*-deficient mice may express predominantly bone sialoprotein, an osteoblast marker protein, rather than dentin sialophosphoprotein, the odontoblasts/dentin marker protein (Butler, 1998), if the disruption of the *Nfic* gene causes a phenotypic change of odontoblast into osteoblasts.

**Dissociation of Odontoblast by Interfering with the Formation of Intercellular Junctions**

To examine if disruption of the *Nfic* gene interferes with the formation of intercellular junctions and thus dissociates odontoblasts, both electron microscopic and immunohistochemical studies were performed. Electron microscopic analysis showed

that normal odontoblasts have intercellular junctional complex, also known as the terminal webs, at the apical end of odontoblast cell body, while aberrant odontoblasts did not (Fig. 2B). In order to confirm the electron microscopic findings, we investigated the immunohistochemical localization of two major structural proteins of the junctional complexes such as ZO-1 and occludin in *Nfic*-deficient mice. Immunoreactivity for ZO-1 was strong at the distal and proximal junctional complexes of ameloblasts in both wild-type and mutant mice. Odontoblasts of wild-type mice showed weak and punctuate ZO-1 expression at the apical region, while aberrant odontoblasts from *Nfic*-deficient mice showed no ZO-1 expression (Fig. 3A, B). Occludin immunoreactivity was observed at the junctional complexes between odontoblasts from wild-type mice, but not in aberrant odontoblasts from *Nfic*-deficient mice (Fig. 3C, D).

Unlike osteocytes and chondrocytes, normal odontoblasts are always located on the pulpal surface of the dentin without being trapped in dentin (Linde and Goldberg, 1993). As preodontoblast differentiate into odontoblasts, they are joined and attached together at their apical end by well-developed terminal webs of cytoskeletal actins, tight and adherens junctions (Sasaki and Garant, 1996). This junctional complex is responsible for alignment of odontoblast as a single layer of cells functioning as a unit and preventing their entrapment in the predentin (Avery, 2001). Therefore, these

junctional complexes appear to play a crucial role in the formation and maintenance of smooth-surfaced predentin and dentin (Arana-Chavez and Katchburian, 1997).

In relation to tight junctions, ZO-1 is a peripheral 225-kDa membrane protein present at the cytoplasmic surface of tight junctions (Joao and Arana-Chavez, 2003). ZO-1 is a key junctional protein that binds to claudins, occludin, ZO-2, ZO-3, and actin (Joao and Arana-Chavez, 2004). The present study showed that ZO-1 and occludinwere barely detected in aberrant odontoblasts from *Nfic*-deficient mice, whereas they were clearly detected in normal odontoblasts of wild-type mice. It suggests that disruption of the *Nfic* gene might cause dissociation of odontoblasts by interfering with the formation of intercellular junctions that contribute to aberrant odontoblast differentiation and abnormal dentin formation.

**Apoptosis of Odontoblasts in *Nfic* –deficient Mice**

Agenesis of roots in *Nfic*-deficient mice may be associated with the death of odontoblasts during root formation. To test this model, we performed TUNEL POD staining for the detection of apoptotic cells. No TUNEL-positive odontoblasts were observed in incisors from wild-type mice (Fig. 4A). However, apoptotic cells in *Nfic*-deficient mice were evident in a sub-odontoblastic region, and more prominent in the area where abnormal preodontoblasts are located during root formation (Fig. 4B).

An electron micrograph also showed apoptotic abnormal odontoblasts of a mandibular P-18 inncisor from *Nfic*-deficient mice (Fig. 5).

Apoptosis, as an evolutionally conserved phenomenon of programmed cell destruction, involves in a variety of physiological processes from embryogenesis to everyday homeostasis maintenance (Wyllie *et al.,* 1984). Balanced cell proliferation and death are involved in the morphogenetic events leading to final tooth formation, and the specific temporospatial distribution of apoptosis suggests its important roles in odontogenesis (Matalova *et al.,* 2004). During tooth formation these signals control key processes involved in odontogenesis-cell proliferation, migration, adhesion, and cell death. In developing teeth, apoptosis occurs during all stages: early tooth morphogenesis (Sigemura *et al.,* 1999), amelogenesis (Bronkers *et al.,* 2000), dentinogenesis (Vermelin *et al.,* 1996), and tooth eruption (Ten Cate and Anderson, 1986). Hence, apoptosis seems to have a crucial role in morphogenetic processes during tooth development. However, the causes and signaling pathways leading to the apoptosis of dental tissue cells are far from understood. A wide range of factors, including withdrawal of growth factors, chemical agents and genetic factors are believed to be responsible for apoptosis. Indeed, several growth factors including bone morphogenetic proteins have been implicated in apoptosis of the enamel knot in the early stages of tooth development (Vaahtokari *et al.,* 1996).

In this study, TUNEL-positive cells were observed more frequently in *Nfic*-deficient mice compared to wild-type mice This finding suggests that odontoblast apoptosis is induced by disruption of the *Nfic* gene may result in a decrease inthe number of odontoblasts and consequently agenesis of roots in *Nfic*-deficient mice. This functional uniqueness of NFI-C partially explains why there are increased apoptotic odontoblasts in *Nfic*-deficient mice. However, the mechanism by which disruption of the *Nfic* geneinduces odontoblast apoptosis in a cell-specific manner remains unknown. This is under investigation using the *Nfic*-deficient mice that offers an invaluable and unique experimental animal model. Further, it is anticipated that this will allow us to determine the apparent central role of NFI-C in odontoblast differentiation and dentin formation particularly in postnatal tooth development.

Finally, the findings of this study will help us to better understand the mechanism responsible for aberrant odontoblast differentiation and osteodentin formation during dentin repair. In addition, the *Nfic* -/- phenotype also resembles some of hereditary dental disorders such as dentinogenesis imperfecta II (Takagi and Sasaki, 1988). Thus, it will be of great interest to know if disruption of the *Nfic* gene is associated with these hereditary disorders. Also, this information may have a potential value in bioengineering of natural roots *in vitro* that could replace metallic dental implants.

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## Figure legends

Figure 1. Light micrographs showing cross-sections of incisors from wild-type and *Nfic*-deficient mice (P-10). (A) A normal incisor shows a circular dentin (d) and odontoblasts (O) that line the inner surface of the dentin. (B) A mutant incisor shows an open area (arrowheads) as a result of failure of dentin formation by abnormal odontoblasts. Note thick osteodentin that contains numerous trapped cells (arrows). (C) Abnormal odontoblasts of a mutant P-10 incisor are embedded in osteodentin (arrows). (D) Abnormal odontoblasts (arrows) of a mutant P-18 molar show short and round shape. H-E staining. e; enamel, d; dentin, P; pulp. Scale bars = 200μm.

Figure 2. Electron micrographs showing abnormal odontoblasts in a mandibular incisor from *Nfic*-deficient mice (P-18). (A) Abnormal odontoblasts are round in shape and lost their polarity and organization as a sheet of cells. Scale bar = 3μm. (B) Odontoblasts are embedded in osteodentin (od). Neither intercellular junctions nor terminal webs are observed. Scale Bar = 1μm.

Figure 3. Immunohistochemical localization of ZO-1 (A, B) and occludin (C, D) in ameloblasts and odontoblasts from wild-type and *Nfic*-deficient mice(P-18). (A) A

normal molarlines positively reactive forZO-1 at the proximal and distal ends of ameloblasts (Am). Weak immunoreactivity of ZO-1 is also observed in the odontoblasts (arrowheads). (B) A mutant molar showslabeling for ZO-1 at the proximal and distal ends of ameloblasts (Am). Staining for ZO-1 is not observed in odontoblasts of a mutant molar. (C) A normal incisor shows labeling for occludin at the proximal end (arrows) of ameloblasts (Am) and also in odontoblasts (O).(D) A mutant incisor shows immunolabeling for occludin at the proximal (arrows) and distal (arrowheads) ends of ameloblasts. However, staining for occludin is not observed in the abnormal odontoblasts. e; enamel, d; dentin, od; osteodentin, P; pulp. Scale bars = 200μm.

Figure 4. Tunnel POD staining of incisors from wild-type and *Nfic*-deficient mice (P-10). (A) There areno TUNEL-positive cells in odontoblasts (O) of normal mice. However, apoptotic cells are evident in a sub-odontoblastic region, and aremore numerous in differentiating abnormal preodontoblasts (arrows) of the root-forming region than in the crown region of the pulp of *Nfic*-deficient mice. Am ameloblast, od; osteodentin, P; pulp. Scale bars = 200μm.

Figure 5. Electron micrographs showing apoptotic abnormal odontoblasts of a mandibular P-18 inncisor from *Nfic*-deficient mice (×3,000).

## Figures

Fig. 1

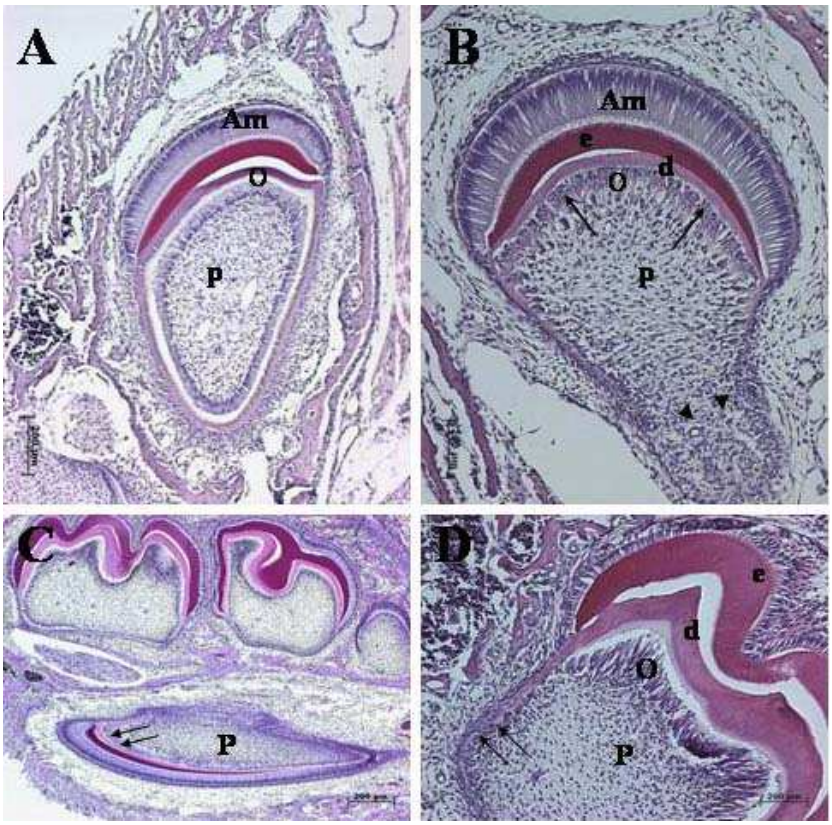


Fig. 2

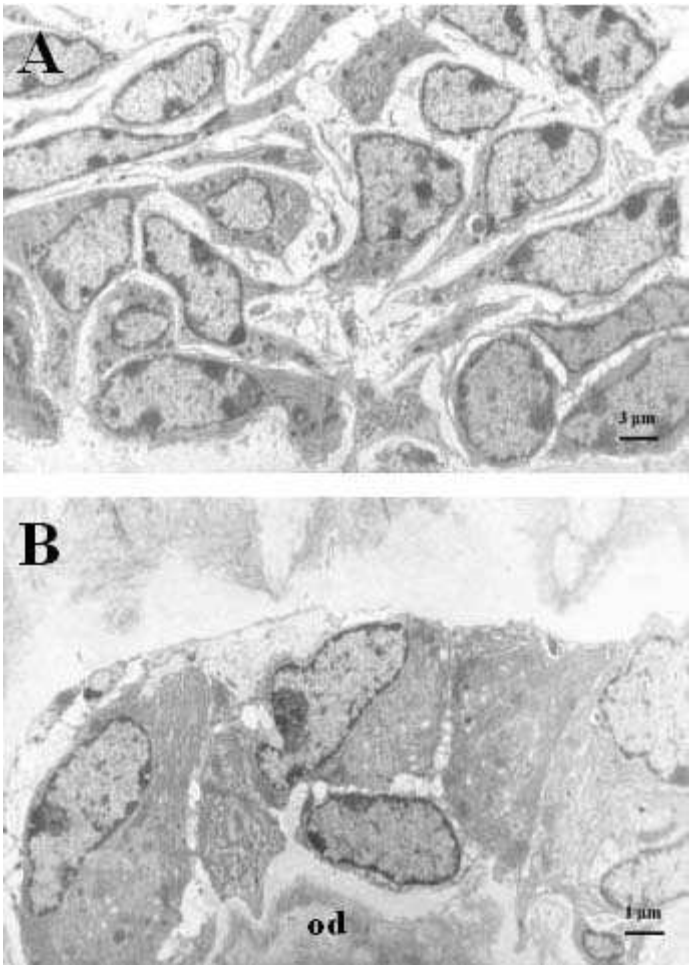


Fig. 3

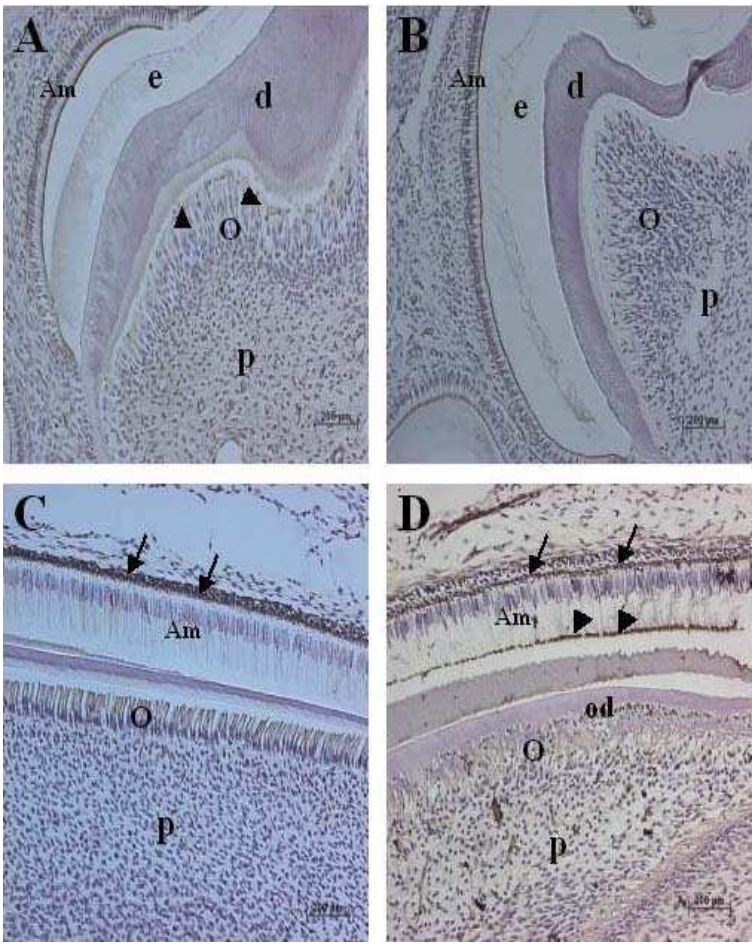


Fig. 4

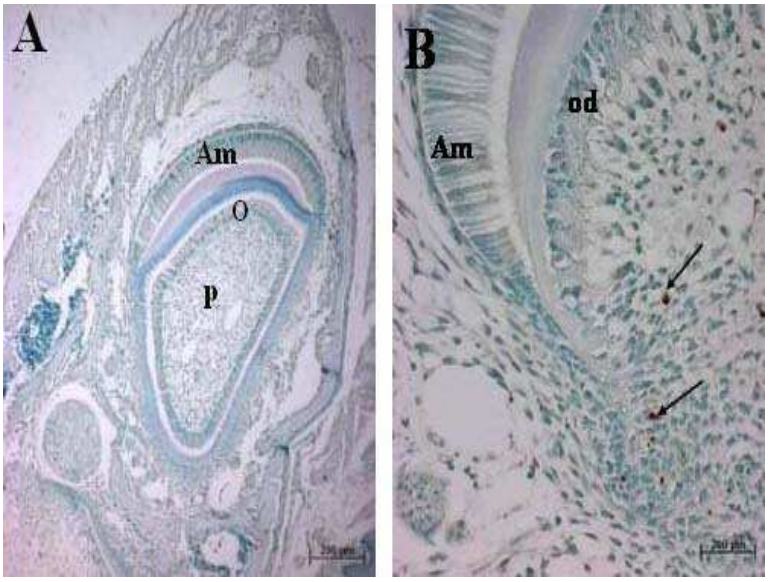
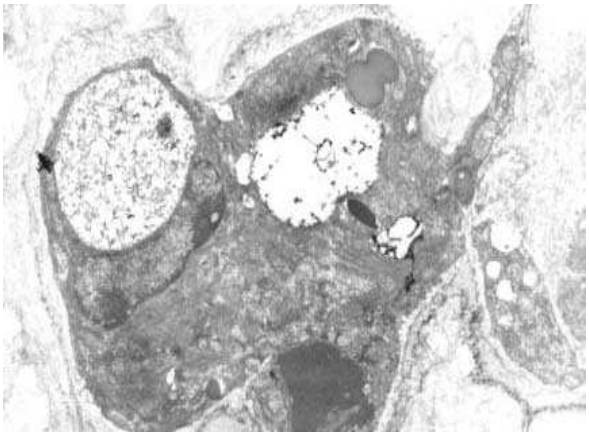



Fig. 5



# Abstract in Korean

## Nfic-결손 생쥐에서 상아모세포의 분화 이상

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최근의 연구에 의하면 *Nfic*가 결손 되면 구치의 발생이 잘 이루어지지 않고 심각한 절치의 변형이 나타나는 것으로 알려지고 있다. *Nfic*의 결손은 상아모세포의 분화 이상을 일으켜서 결과적으로 비정상적인 상아질 형성을 유도하나, 법랑모세포를 포함하는 신체의 다른 세포들의 이상은 유발하지 않는다.

이 연구는 *Nfic*-결손 생쥐에서 비정상적인 치근이 형성되는 기전을 알아보고자 하였다.

생후 10일과 18일의 정상과 *Nfic*-결손 생쥐들에서 상•하악골을 적출한 후 2.5% glutaraldehyde에 고정 한 후 통법에 따라 파라핀에 포매하여 광학현미경 표본을 제작하였고, 1% $OsO_4$에 고정한 후 epon에 포매하여 전자현미경 표본을 제작하였다. 정상과 *Nfic*-결손 생쥐들의 상아모세포의 형태학적 특징을 광학현미경과 전자현미경으로 관찰 하였고, 세포사이의 치밀결합의 주요 성분인 ZO-1과 Occludin 항체를 이용하여 정상과 *Nfic*-결손 생쥐들의 상아모세포의 세포간 결합장치의 변화를 관찰 하였다. 또한, TUNEL POD 염색을 통하여 정상과 *Nfic*-결손 생쥐들의 상아모세포의 사멸을 관찰 하였다.

*Nfic*-결손 생쥐에서 나타나는 형태학적으로 가장 특징적인 상아모세포의 분화

이상 현상은 변이된 상아모세포들의 세포사이 결합장치가 결핍되어, 결과적으로 세포들이 서로 분리되고 극성을 상실하게 되고 조직화된 구조를 이루지 못하게 된다는 것이다. 이러한 변이된 상아모세포들은 상아질과 유사한 석회화 조직에 함입되어 골모세포나 골세포와 유사한 특징을 나타내게 된다. 또한, *Nfic*-결손 생쥐의 치수에서는 사멸된 세포들이 다수 관찰되었다.

이 결과는 NFI-C가 세포특이적으로 상아모세포의 분화와 생존에 중요한 역할을 함을 시사한다.

# 저작물 이용 허락서

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| | 영문 :Aberrant odontoblast differentiation in *Nfic*-deficient mice | | | | |

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집·형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

**동의여부 : 동의( V ) 반대( )**

2007년 2월 일

저작자: 오 현 주 (서명 또는 인)

## 조선대학교 총장 귀하