

# The Impact of the Notch1 on the Migratory Capacity and the Expression of E-Cadherin and CyclinD1 in Ameloblastoma Cells

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#### Thesis

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#### Abstract

**Objective:** This study aimed to explore the impact of the Notch signalling pathway on the migratory capacity of AM cells and the expression profiles of E-cadherin and cyclinD1 protein.

Study Design: Experimental study.

**Place and Duration of the Study:** Inner Mongolia Key Laboratory of Oral Craniomaxillofacial Diseases Research, Affiliated Hospital of Chifeng University, from June to October 2023.

**Methods:** In vitro cultures of AM cells and dental follicle (DF) cells were established. Transwell assays were conducted to assess cell migration and invasion, while Western blot analysis was employed to evaluate the protein expression levels of Notch1, E-cadherin, and cyclinD1. The inhibition of the Notch signalling pathway was achieved using FLI-06, allowing for comparative analysis of the migration and invasion abilities of AM and DF cells, alongside the expression levels of E-cadherin and cyclinD1 proteins in AM cells.

**Results:** AM cells exhibited significantly enhanced migration capacity compared to DF cells (P<0.05). The expression levels of Notch1 and cyclinD1 were notably elevated in AM cells, whereas E-cadherin expression was markedly reduced (P<0.05). Following FLI-06 treatment, the migration capability of AM cells decreased significantly compared to the control group (P<0.05). Additionally, there was a significant reduction in the expression levels of cyclinD1 and Notch1 in AM cells, coupled with an increase in E-cadherin expression (P<0.05).

**Conclusion:** The findings suggest the involvement of the Notch signaling pathway in AM cell migration, potentially mediated through alterations in E-cadherin and cyclinD1 protein expression.

Keywords: Notch1; Ameloblastoma; Migration; E-cadherin; CyclinD1



#### **Abbreviations**

AM: Ameloblastoma; DF: Dental Follicle; PMSF: PhenylMethylSulfonyl Fluoride; DMSO: DiMethyl SulfOxide; CDKs: Cyclin-Dependent Kinases.

#### Introduction

Ameloblastoma (AM), characterized by its benign nature yet aggressive behaviour, presents a formidable clinical challenge in the field of oncology [1,2]. Despite advancements in surgical techniques, the high recurrence rates and associated morbidities underscore the urgency for novel treatment modalities. The conventional approach to treating AM, predominantly through complete osteotomy, while effective in tumor removal, often results in significant aesthetic and functional impairments [3,4]. Facial deformities and jaw defects post-surgery not only impact the patient's quality of life but also necessitate complex reconstructive procedures. Moreover, the propensity of AM for local recurrence and potential malignant transformation further complicates treatment strategies, necessitating a paradigm shift towards targeted therapies.

In recent years, the field of oncology has witnessed a surge in targeted therapies tailored to specific molecular pathways implicated in tumorigenesis. For AM, targeting key signaling pathways such as the Wnt/ $\beta$ -catenin pathway, which plays a crucial role in AM pathogenesis, holds immense promise [5-8]. By inhibiting aberrant signaling cascades driving tumor growth, targeted therapies offer a more precise and effective alternative to traditional treatment modalities.

Studies have shown that various proteins in the body are involved in the metastasis of tumor cells. For example, reduced cell adhesion is associated with E-cadherin, while cell proliferation is linked to cyclinD [9,10]. The Notch signaling pathway is a key pathway that regulates cell proliferation, differentiation, and apoptosis, playing a crucial role in development and tissue regeneration.

Recent research has indicated that the Notch signaling pathway is activated in AM cells and contributes to the development of the tumor [11,12]. It has been suggested that Notch signaling may influence the migration and invasion of AM cells and impact the expression of E-cadherin and cyclinD1 [13,14]. However, the precise mechanism remains unclear.

FLI-06 is a novel inhibitor that targets the Notch signaling pathway. Even at low doses, FLI-06 effectively inhibits Notch signaling and can serve as a blocker in relevant studies [15].

In this study, we treated cultured AM cells with the Notch signaling inhibitor FLI-06 to investigate its effects on cell

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migration, E-cadherin expression, and cyclinD1 expression. Understanding the role of the Notch signaling pathway in AM progression could provide new insights into targeted therapies for this condition. By inhibiting Notch1 with FLI-06, we may be able to modulate cell migration and expression of key proteins involved in tumor growth. Further research in this area could lead to the development of more effective treatments for AM with fewer side effects.

#### Methodology

This study was approved by the Ethics Committee of the Mongolian National University of Medical Sciences (2023/3-04). In vitro cultures of human-derived ameloblastoma (AM) cells and human-derived dental follicle (DF) cells were established. Transwell assays were conducted to assess cell migration and invasion, while Western blot analysis was employed to evaluate the protein expression levels of Notch1, E-cadherin, and cyclinD1. The inhibition of the Notch signalling pathway was achieved using FLI-06, allowing for comparative analysis of the migration and invasion abilities of AM and DF cells, alongside the expression levels of E-cadherin and cyclinD1 proteins in AM cells.

The FLI-06 protein quantitative reagent was procured from Sigma Company in the United States, Matrigel matrix adhesive was obtained from BD Company in the United States, DMEM medium and fetal bovine serum were acquired from GIBCO Company in the United States, and the Transwell lab was sourced from Costar Company in the United States. Western blot reagents were purchased from Millipore, Germany. The ECL chemiluminescence kit was bought from Millipore Company, trypsin from Invitrogen Company, Mouse anti-human Notch/E-cadherin from AMcam Company, Rabbit Anti-human cyclinD1 from Cell Signaling Corporation, the CO2 constant temperature incubator and enzyme labeling instrument from Thermo Corporation, Germany, the inverted microscope from Life Corporation, USA, and the gel imager from Bio-Rad Corporation, USA.

Ameloblastoma (AM) and dental follicle (DF) cells were cultured in DMEM medium supplemented with 10% fetal bovine serum in a CO2 incubator set at 37°C. Upon reaching the logarithmic growth phase, the cells were enzymatically dissociated using pancreatic enzymes and harvested for subsequent analysis (fourth generation).

For the assessment of cell migration ability, Transwell chambers were employed. Specifically, Matrigel was excluded for migration assays and included for invasion assays. Cells in logarithmic growth were enzymatically detached with pancreatic enzymes, suspended in serum-free medium, and enumerated under a high-power microscope. Subsequently, a 100  $\mu$ L inoculum of cell suspension was added to the upper

chamber of the Transwell apparatus, while 600  $\mu$ L of DMEM medium (with 10% fetal bovine serum) was placed in the lower chamber. Following a 24-hour incubation period in a CO2 incubator, the media in both the Transwell chamber and the accompanying 24-well plate were aspirated and rinsed with PBS. The specimens were fixed with anhydrous ethanol at room temperature for 30 minutes, stained with 0.1% crystal violet, and rinsed with water after 10 minutes. Migration and invasion of AM and DF cells were observed under an inverted microscope (×200) in 8 randomly selected fields. Each experimental group was subjected to three independent replicates.

Cells in the logarithmic phase of growth were harvested from the pancreas following enzymatic treatment. A total of 150  $\mu$ L of protein lysate containing phenylmethylsulfonyl fluoride (PMSF) was added, and the mixture was vortexed to ensure homogeneity before being subjected to low-temperature lysis for 30 minutes.

The cell lysate was then centrifuged at 12,000 rpm in a cold centrifuge for 10 minutes to obtain the supernatant. The total protein concentration was quantified using a BCA protein assay kit. Subsequently, the proteins in the cell supernatant were separated via 5% SDS-PAGE. After transferring to a polyvinylidene difluoride (PVDF) membrane, the membrane was washed with TBST buffer for 10 minutes, repeated three times.

A blocking solution containing 5% BSA was applied, and the membrane was incubated at room temperature for 1 hour. Following this, a diluted primary antibody (1:1000) was added and incubated overnight at 4°C. After washing three times with TBST for 10 minutes each, a secondary antibody diluted at 1:500 was added, and the membrane was incubated at room temperature for 1 hour. The membrane was then washed again with TBST for 10 minutes, repeated three times. The proteins were visualized using a hypersensitive ECL luminescence kit, and imaging was performed with a gel documentation system. Protein expression levels were quantified using ImageJ software. Each experiment was conducted independently in triplicate for each group.

FLI-06 was solubilized in dimethyl sulfoxide (DMSO) to form a 10 mM/L stock solution, which was then cryopreserved at -70°C. Prior to the commencement of the experiment, the stock solution of FLI-06 was further diluted to a concentration of 10  $\mu$ M/L, while the control group remained untreated with FLI-06. The methodology for assessing cell migration and invasion followed the procedures outlined in the Cell Migration Test. The levels of Notch signaling pathway-associated proteins (Notch1, E-cadherin, and cyclinD1) were evaluated using Western blot analysis. Each experimental condition was independently replicated thrice.

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Statistical analysis was conducted using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA) for data entry and statistical analysis in this study. Measurement data were presented as  $\bar{x} \pm s$ , and the difference between the two groups was analyzed using LSD-t test, with  $\alpha$ =0.05 as the significance level.

#### **Results**

## Comparison of Migration and Invasion Ability of AM and DF Cells

The number of migration and invasion of the two kinds of cells was analyzed by LSD-t test, and the differences were statistically significant P<0.05. The results are shown in Table 1.

Cells	Migration	Invasion
AM	147.40 ± 26.01	139.00 ± 26.11
DF	88.40 ± 10.70	80.40 ± 3.36
Т	5.06	5.27
Р	0.01	0.01

Table 1: Migration and invasion ability of AM and DF cells.

## Expression of Notch Signaling Pathway in AM and DF Cells

Compared with DF cells, the expression levels of Notch1 protein and cyclinD1 protein in AM cells were significantly increased, while the expression level of E-cadherin was significantly decreased (P<0.05). The results are shown in Table 2.

Cells	Notch1	E-Cadherin	CyclinD1	
AM	1.44	0.87	0.39	
DF	0.41	1.23	0.19	
t	24.35	11.43	14.24	
Р	0	0.01	0.01	

**Table 2:** Expression of Notch signalling pathway relatedproteins in AM and DF cells.

#### Changes of Migration and Invasion Ability of AM Cells after Treatment with FLI-06

After Notch signaling pathway was blocked by FLI-06, the migration and invasion ability of AM cells was weaker than that of control group, and the differences were statistically significant (P < 0.05). The results are shown in Table 3 and Figure 1.

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AM	Control group	FLI-06 Treatment Group	Т	Р
Migration	148.27 ± 28.16	$40.40 \pm 9.69$	7.22	0
Invasion	137.20 ± 25.55	34.60 ± 6.95	8.21	0

 Table 3: Migration and invasion ability of AM cells after FLI-06 treatment.



**Figure 1:** Number of AM cells invasion after FLI-06 treatment. (A) Number of AM cells invasion in control group. (B) Number of AM cells invasion in the FLI-06 treatment group. (C) AM cells invasion number comparison.

#### Expression Changes of Notch Signalling Pathway Related Proteins after FLI-06 Treatment

After AM was treated with FLI-06, the expression

levels of Notch1 protein and cyclinD1 protein in AM cells were significantly decreased, while the expression level of E-cadherin was increased (P<0.05), as shown in Table 4 and Figure 2.

АМ	Notch1	E-Cadherin	CyclinD1
Control group	1.44	0.87	0.39
FLI-06 treatment group	0.69	1.44	0.18
Т	21.36	27.95	36.37
Р	0	0	0

**Table 4:** Expression of Notch signaling pathway related proteins after FLI-06 treatment.

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**Figure 2:** Expression changes of Notch1, cyclinD1 and E-cadherin proteins in AM cells treated with FLI-06 for 48h. (A) Western blot detection of the expressions of Notch1, cyclinD1 and E-cadherin proteins (1, Blank. 2, FLI-06 10µmoL/L). (B) Gray ratio of Notch1 parameter before and after FLI-06 treatment. (C) The gray ratio of the parameters in cyclinD1 before and after FLI-06 treatment. (D) Gray ratio of E-cadherin parameter before and after FLI-06 treatment. Treatment at a concentration of 10µmol/L.

#### Discussion

Tumorigenesis is a complex process influenced by various factors, among which the Notch signaling pathway emerges as a key regulator in the differentiation and function of ameloblasts [11,12,16,17]. Notch1, in particular, has been spotlighted for its indispensability in tooth morphogenesis and the determination of ameloblast fate [18,19].

Previous studies have underscored the significance of Notch signaling in various developmental processes, including tooth development. Notch receptors, particularly Notch1, 3, and 4, alongside their cognate ligands, Jagged1 and Delta1, have been identified within the ameloblastic niche, implicating their involvement in regulating cellular behaviors [11,12,20]. Of note is the heightened expression of Notch4, hinting at its potential role in dictating ameloblast functionality.

In this study, the Transwell chamber assay was employed to assess the migratory and invasive properties of AM cells in comparison to DF cells, serving as a reference population. The experimental findings revealed a marked disparity in the migratory and invasive potentials between AM and DF cells, with AM cells exhibiting significantly higher mobility and invasiveness. Upon treatment with FLI-06 to inhibit Notch signaling, a noteworthy reduction in the migration and invasion abilities of AM cells was observed, indicating the pivotal role of Notch signaling in orchestrating these cellular behaviors. These results underscore the functional relevance of the Notch pathway in regulating ameloblast migration and invasion, suggesting its potential as a therapeutic target for interventions aimed at modulating dental tissue remodelling and regeneration processes.

CyclinD1, a key player in the Notch signaling pathway, serves as a crucial regulator of the cell cycle by interacting with cyclin-dependent kinases (CDKs) and modulating the progression of various tumors [21-25]. This study employed Western blot analysis to scrutinize the expression profiles of Notch1, E-cadherin, and cyclinD1 in AM cells juxtaposed with dental follicle (DF) cells. The results delineated substantially elevated levels of Notch1 and cyclinD1 expression in AM cells in contrast to DF cells, while E-cadherin expression exhibited a marked diminution. Significantly, treatment with FLI-06, a potent inhibitor of the Notch signaling pathway, elicited a reduction in Notch1 and cyclinD1 expression levels in AM cells concomitant with a surge in E-cadherin expression. These findings underscore the pivotal involvement of Notch signaling pathway-associated proteins in the migration and invasion of AM cells, underscoring their potential as therapeutic targets.

The upregulation of Notch1 and cyclinD1 in AM cells signifies their pivotal roles in driving tumorigenesis and supports the notion that targeting these proteins could impede cancer cell proliferation and metastasis [26]. The inverse relationship between E-cadherin expression and tumor development further underscores the significance of cell adhesion molecules in tumor progression [27-30]. The findings of this study elucidate the intricate interplay between Notch signaling components, cell cycle regulators, and cell adhesion molecules in orchestrating the migratory and invasive capacities of AM cells.

Furthermore, Studies have demonstrated that Notch1 may exhibit cross-regulatory interactions with the Wnt/ $\beta$ -catenin signaling pathway. Reduced expression of E-cadherin results in the dissociation of  $\beta$ -catenin from the cell membrane, enabling its translocation into the nucleus and subsequent activation of Cyclin D1 transcription. Notch1 may indirectly potentiate the  $\beta$ -catenin signaling by suppressing E-cadherin expression, thereby upregulating Cyclin D1 levels [12]. The positive correlation between Notch1 and cyclinD1 expression and the migratory and invasive capabilities of AM cells, coupled with the negative correlation between E-cadherin expression and these phenotypes, highlights the intricate regulatory network governing tumor progression

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in AM. These results not only deepen our understanding of the molecular mechanisms underpinning AM pathogenesis but also present a promising avenue for targeted therapy by modulating the Notch signaling pathway to impede tumor progression.

In conclusion, the findings of this study elucidate the critical role of the Notch signaling pathway in driving the migration and invasion of AM cells by modulating the expression of E-cadherin and cyclinD1. These insights not only shed light on the underlying molecular mechanisms of AM progression but also hold significant implications for the development of targeted therapies aimed at disrupting Notch signaling components to curb tumor growth and metastasis. By unraveling the intricate interplay between Notch1, E-cadherin, and cyclinD1, this study paves the way for novel therapeutic strategies in the management of AM and potentially other malignancies characterized by dysregulated Notch signaling. However, this study still has limitations. If Notch1 siRNA/Crispr is employed as the foundation, the knockout validation confirms that the observed effect of FLI-06 occurs via the Notch1 pathway. The experimental outcomes related to Notch1 are anticipated to improve. We plan to carry out further investigations in the future.

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#### **Competing Interests**

The authors declare no competing interests.

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