Original

Cytokeratin 8 Promoted Sinonasal Inverted Papilloma Malignant Transformation to SNSCC

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Abstract: The sinonasal inverted papilloma is one of the more common benign tumors of the nasal cavity and sinus. It originates from the Schneiderian membrane. It has the characteristics of easy recurrence and malignant transformation. This experiment found that Cytokeratin 8 expression increased in the sinonasal inverted papilloma. To better detect the role of Cytokeratin 8 in the proliferation and deterioration of the sinonasal inverted papilloma, we divided the sinonasal inverted papilloma into NIPN, NIPAP, and NIPAH by histological. The expression of Cytokeratin 8 in the sinonasal inverted papilloma was detected by immunohistochemistry. We found that the increased expression of Cytokeratin 8 was consistent with the invasion of sinonasal squamous cell carcinoma. In vitro, it was found that after Cytokeratin 8 interference, the proliferation and invasion of head and neck squamous cells were decreased. Cytokeratin 8 played an important role of sinonasal inverted papilloma malignant transformation to sinonasal squamous cell carcinoma. Inhibition of Cytokeratin 8 could diminish the proliferation and block the invasion of head and neck squamous cells.

Key words: Sinonasal inverted papilloma, Cytokeratin 8, Proliferation, Invasion

Introduction

Sino nasal inverted papilloma (NIP) is a benign tumor that occurs in the nasal cavity and sinuses, and its pathogenesis is unclear^{1}. Reports showed that the recurrence rate of NIP was 28% to 74%, and the percentage of NIP deterioration to sinonasal squamous cell carcinoma (SNSCC) was 7% to 27% and the 5-year survival rate of afflicted patients is less than 40%^{2}. NIP recurrence and malignant transformation are due to the presence of hyperkeratosis of the squamous epithelium in the tissue^{3}. At present, the pathogenesis of NIP is still unclear. Research focuses mainly on cell cycle regulation, angiogenesis, cell proliferation, invasion and metastasis^{4,5}. Therefore, exploring the recurrence, malignant mechanisms and specific targeting of NIP molecules would be of guiding significance for the early prediction of NIP recurrence and malignant transformation. Cytokeratin (CK), one of the cytoskeletal proteins, is widely found in human epithelial tissues. The release of CK from proliferating or apoptotic cells could reflect the activity of the cells^{6}. It is important that CK8 could not be released into the normal blood circulation, whereas epithelial cells could release it^{7}. Due to the cell specificity, tissue specificity and differentiation specificity of CK8, it is often used as an epithelial cell marker protein to assist in the diagnosis of epithelial tumors^{8}. Makino detected the expression of CK8 in 210 SNSCC, of which 85 were positive for CK8. Patients with CK8-positive squamous cell carcinoma had a poor prognosis, suggesting that the progression and prognosis of CK8 and squamous cell carcinoma are closely related^{9}.

The high recurrence and malignancy rate of NIP have alerted clinicians to treat it as a precancerous lesion. Therefore, this study aimed to investigate the role of CK8 in the pathogenesis of NIP. It is intended to provide a reference for early clinical diagnosis, surgical method selection, treatment of NIP recurrence and malignant transformation.

Materials and Methods

Study design and sample

Fifty-nine patients with NIP who were admitted to the Second Affiliated Hospital of Dalian Medical University from June 2015 to March 2016 and 50 control patients (based on normal mucosa at the back of the inferior turbinate) were selected. All clinical samples were obtained through surgery after histopathological diagnosis. All patients were approved by the Ethics Committee of Dalian Medical University (No. 38 of 2016), giving informed consent. Clinical subjects were divided into three groups. The first and second groups used Real-time qPCR and Western blotting to detect the expression of CK8 in the NIP. For the third group, we selected 59 cases of NIP, 16 cases of SNSCC, and the 50-case control group was to detect the expression of CK8 in the NIP. According to the different pathological stages of NIP, we divided the NIP into those with normal active proliferation (NIPN), which pathology showed hyperplasia of the superficial epithelium with papillary hyperplasia in the stroma. NIP with active proliferation (NIPAP), which showed pathological manifestations of varus with active hyperplasia. NIP with atypical hyperplasia (NIPAH), which exhibited pathological manifestations of varus with dysplasia, inverted papilloma and active cell proliferation with chronic inflammation. The 59 cases of NIP were divided into NIPN (31 cases), NIPAP (18 cases), NIPAH (10 cases), and

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the expression of CK8 in different pathological stages and SNSCC by immunohistochemistry. Inclusion criteria were (1) NIP confirmed by pathology before or after surgery, excluding specimens containing a large amount of necrotic tissue or with a large number of infiltrated inflammatory cells, (2) Patients in the SNSCC group needing to be diagnosed as NIP before malignant transformation, (3) Patients generally in good condition undergoing routine examination and comprehensive evaluation before surgery and having absolutely no surgical contraindications, and (4) Patients confirmed to have squamous cell carcinoma and not having undergone any physical, chemical, or immunological antitumor treatment before surgery.

**Cell culture**

SCC6 cells (less malignant head and neck squamous cell) and CNE-2 cells (moderately head and neck squamous cell) purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China) which were grown in DMEM medium (Invitrogen Co. Ltd., Carlsbad, USA) supplemented with 10% FBS. The cells were maintained at 37°C under 5% CO2.

**HE staining**

The tissue was treated by conventional methods and embedded in paraffin, sliced to a thickness of 4 μm. The sections were dried at 37°C for 1 hour, hematoxylin stained sections for 5 min, eosin was stained again for 5 min. The sections were dehydrated in gradient alcohol, and the sections were added with xylene. After the sections were completely dried, they were observed under a microscope. The same experiment operator performed the pathological evaluation of the stained tissue.

**Immunohistochemistry**

Serial sections (3 μm) were prepared from paraffin-embedded tissues. The sections were fixed at 60°C for 3 h, deparaffinized in xylene and rehydrated in graded alcohol. The slides were microwaved for 20 min in citrate buffer to unmask antigens and were washed with PBS after being cooled to room temperature. Added 0.3% hydrogen peroxide solution to sections for 15 min and serum blocking solution to incubate for 1 hour, hematoxylin stained sections for 5 min, eosin was stained again for 5 min. The sections were dehydrated in gradient alcohol, and the sections were added with xylene. After the sections were completely dried, they were observed under a microscope. The same experiment operator performed the pathological evaluation of the stained tissue.

**Real-time qPCR**

We selected 59 cases of NIP and the 50-case control group was to detect the CK8 gene expression in the NIP. Isolated total RNA from paraffin blocks of tissue according to the instructions of Trizol RNA Extraction Kit (UNIQ-10, Shanghai Biotech Biotechnology Co., Ltd., Shanghai, China). Real-time qPCR reactions were performed in accordance with SYBR® Premix Ex TaqTM II (Takara Co. Ltd., Tokyo, Japan). The reaction solution was placed in the Thermal Cycler Dice® Real Time System. The PCR conditions were as follows: Stage 1, 95°C, 30 sec; Stage 2, 95°C, 5 sec; 60°C, 30 sec, 40 cycles; Stage 3, 95°C, 15 sec; 60°C, 30 sec; 95°C, 15 sec. The expression of CK8 was normalized according to that of GAPDH. We use Primer Premier (Premier Co. Ltd., Canada) to design primers. The following specific primers were designed: CK8: 5′- CACTTGGCCCATCACATCCG-3′ and 5′-TACAGTCTTTGGTGAATGCTT-3′. GAPDH: 5′-GTGAAGGTCGGAT-CAACG-3′ and 5′-TGAGGTCAATGAAGGGGTGTC-3′. Relative quantification of expression of the target gene was normalized relative to the level of GAPDH and relative to a control group (untreated cells). Differences in fold change were analyzed using the 2^(-△△Ct) method.

**Western blotting**

59 cases of NIP and the 50-case control group was to detect the CK8 expression in the NIP. Tissue were washed in PBS before incubation with Lysis Buffer (1% Triton X-100, 150 mM NaCl,10 mM Tris, pH 7.4, 1 mM EDTA, 1 mM EGTA, pH 8.0, 0.2 mM Na3VO4, 0.2 mM phenylmethylsulfonyl fluoride, and 0.5% Nonidet P-40) on ice for 15 min. The cell lysates were clarified by centrifugation at 9,000 g for 15 min, and the supernatants were collected. The protein concentration was measured with the QuantiPro BCA Assay Kit (KeyGen Biotech Co. Ltd., Shanghai, China). The membranes were incubated overnight at 4°C with specific anti- CK8, Bel-2, caspase3 (diluted 1: 500; Abcam), anti-MM2 (diluted 1: 200; Abcam), anti-MM9 (diluted 1: 200; Bios, Beijing, China), and anti-GAPDH (diluted 1: 5,000; Bioworld Co. Ltd., Minnesota, USA). Incubation with the secondary antibody lasted 1 h. The ECL luminescent solution was configured to collect the blotting results with a BIO-RAD gel imaging system, and the results were analyzed with Image Lab software.

**IRNA knockdown experiments**

For the knockdown experiments, siRNA targeted the CK8 gene (CK8-siRNA; 200 nmol/well) and a negative control siRNA were designed by GenePharma Co. Ltd., (Shanghai, China). The SCC6 cells and CNE-2 cells were transfected with the CK8-siRNA Xfect RNA Transfection Reagent (TaKaRa).

**Cell-counting Kit-8**

The 10^4 cells were seeded in 96-well plates at 100 μl per well and cultured for 24 h. 10 μl Cell-Counting Kit-8 solution was added to each well. Absorbance (OD) at 450 nm was measured. (Dujindo, Co., Ltd., kumamoto, Japan).

**Transwell invasion assay**

The inside compartment of the Transwell inserts was coated with Matrigel (BD Biosciences, Co., Ltd., New Jersey, USA) at 37°C for 3 h and then blocked with 1% PBS solution for 30 min at room temperature. The SCC6 and CNE-2 cells (10^5/well) were loaded in the upper chamber in a culture medium for 24 h. The invasion cells were photographed and counted using ImageJ (National Institutes of Health, Maryland, USA) software.
Statistical methods

One-way ANOVA were performed (SPSS 21.0 for Windows IBM Co. Ltd., New York, USA) to detect statistically significant differences. P value < 0.05 was considered statistically significant.

Results

The association of pathological staging with recurrence and malignant change

The patients were divided into a control (NC) group, NIPN group, NIPAP group, NIPAH group, and SNSCC group by H&E staining. Results are shown in Fig. 1A. NC pathology exhibited normal nasal mucosa. NIPN pathology showed hyperplasia of the superficial epithelium with papillary hyperplasia in the stroma. NIPAP showed pathological manifestations of varus with active hyperplasia. NIPAH exhibited pathological manifestations of varus with dysplasia, inverted papilloma and active cell proliferation with chronic inflammation; some cells were atypical. SNSCC displayed pathological manifestations of less cytoplasm, round nuclei, arranged in a braid or sheet.

According to the group, the postoperative recurrence and malignant transformation of the NIPN, NIPAP, and NIPAH groups were followed up for 2 years. The results showed that the recurrence rate of the NIP group was 11.54%. The recurrence rate of the NIP group was lower than that of the NIPAP and NIPAH groups (P < 0.05). However, there was no statistical difference between the NIPAP group and the NIPAH group (P > 0.05). The malignancy rate of the NIP group was lower than that of the NIPAH group, and the results were statistically different, as shown in Fig. 1B. This indicated that the more localized the keratinization or dysplasia of the squamous epithelium, the more likely would the patient’s condition be to relapse and become malignant.

Expression of CK8 in NIP

According to the experimental group, the expression of CK8 in NIP was detected by RT-qPCR and Western blotting. RT-qPCR results showed that the expression of CK8 in the NIP was higher than that in the control group, and the results were statistically different (P < 0.05), as shown in Fig. 2A. Western blotting showed CK8 expression in NIP was higher than that in the control group (P < 0.05), as shown in Fig. 2B. The results indicated that the expression of CK8 in NIP was increased.

Expression of CK8 in different pathological stages of NIP

In order to better detect the role of CK8 in the proliferation and malignant transformation of sinonasal inverted papilloma, we used immunohistochemistry to illustrate the expression in different pathological stages of NIP and SNSCC. The results showed that CK8-positive cells were located in epithelial cells, which were light brown or brown. The nonsquamous epithelial cells in the interstitial tissues were blue and no stained granules were observed in the patina. Results are shown in Fig. 3A. The area-weighted cumulative optical density (IOD/area) values of CK8 in each group of tissues were measured using ImageProPlus 6.0.

Figure 1. Recurrence and malignancy rates in the NIPN, NIPAP, and NIPAH groups. (A) H&E staining was used to identify the histological features and cell morphology of each group. Scale bar = (100 μm and 20 μm). (B and C) Patients in the NIP, NIPAP, and NIPAH groups were followed up for 2 years for the number of relapses and malignancies. (P < 0.05).
With the increase in pathological degree, the expressed color of CK8 became deeper and deeper. The different pathological stages of NIP CK8 expressed the highest intensity in the NIPAH group, but the expression of CK8 was less than in the SNSCC group. The results were statistically significant ($P < 0.05$), as shown in Fig. 3B.

CK8-siRNA inhibited the invasion of SCC6 and CNE-2 cells

After 24 h of transfection with CK8-siRNA, the SCC6 and CNE-2 cells were observed to have good staining properties under the fluorescence microscope. Both RT-qPCR and western blotting showed that CK8-siRNA was lower at the gene and protein levels than the control group, and the results were statistically significant ($P < 0.05$). As shown in Fig. 4A and B. The transwell assay results showed that CK8-siRNA reduced the invasive ability of the SCC6 and CNE-2 cells; Results are shown in Fig. 4C. Western blotting showed that the expression of the invasion markers MMP2 and MMP9 were decreased when the cells were treated by CK8-siRNA (Fig. 4D). It is suggested that CK8 played a certain role in the local abnormal keratinization of the squamous epithelium of the NIP.

**CK8-siRNA inhibited the proliferation of SCC6 and CNE-2 cells**

CCK-8 was used to detect the effect of different expression levels of CK8-siRNA on the proliferation of the SCC6 and CNE-2 cells. The results of CCK-8 showed that the proliferation of the SCC6 and CNE-2 cells were inhibited at the 24th and 48th h after inhibition of CK8, and the results were statistically significant ($P < 0.05$). The result is shown in Fig. 5A. Western blotting showed that the expression of caspase 3 and bax was increased when the cells were treated by CK8-siRNA, but the expression of Bcl-2 was decreased (Fig. 5B), indicating that CK8-siRNA promoted cell apoptosis. Ki67$^+$ cells are a proliferating, cell-associated nuclear antigen that is expressed in proliferating cells but not in resting cells. We used immunofluorescence to detect the proliferating...
Figure 4. CK8-siRNA inhibits the invasion of SCC6 and CNE-2 cells. (A and B) RT-qPCR and Western blotting were used to verify the transfection efficiency of CK-8. (C) Result of Transwell assay. Scale bar = 20 μm. (D) Result of Western blotting showed the expression of MMP2 and MMP9 (P < 0.05).

Figure 5. CK8-siRNA inhibits the proliferation of SCC6 and CNE-2 cells. (A) The results of CCK-8. (B) The result of Western blotting. (C) Immunofluorescence was used to detect the expression of Ki67 (P < 0.05). Scale bar = 20μm.
marker Ki67 cells; the result showed that CK8-siRNA significantly reduced the expression of Ki67 cells compared with the control group (Fig. 5C; \( P < 0.05 \)), indicating that inhibition of CK8 may reduce cell proliferation.

Discussion

The NIP may invade the nasal cavity and sinus. Its histological features include pseudostratified, ciliated columnar cells or respiratory epithelium, and some epithelium may be squamous. Its main manifestation is hyperplasia of the epithelium, which is inverted into the matrix, but the basal cell membrane is intact. Scholars have found that occurrence of the NIP is associated with a high expression of tumor-suppressor genes such as P53, P21, P16, and PDCD4, and an abnormal expression of cytoskeletons such as IQGAPs, FSCN1, 14-3-3 protein, and cytokeratin. It is also associated with a high expression of growth factors such as VEGFA, TGFβ1, and IGFr1, as well as viral infections such as HPV and EBV. In summary, the occurrence and development of the NIP is a multifactorial participation, multistep regulation, and a multi-stage change process, involving cell proliferation and apoptosis, new blood vessel production, and viral infection.

The histological characteristic of NIP is that it is composed of obviously hyperplastic non-keratinized squamous epithelium, which grows into the tumor stroma. Many pathological results show that the NIP cells show proliferative changes or dysplasia. Therefore, we assume that the process of NIP transition from benign to malignant is progressive and multistep. We followed NIP patients (including NIP, NIPAP, and NI-PAH patients) for 2 years who were treated with endoscopic sinus surgery. We found three patients with NIP recurrence and one with malignant transformation. Among the 18 patients in the NIPAP group, 6 had recurrence within 2 years and 1 had malignant transformation. The results showed that the recurrence rate of the NIP group was lower than that of either the NIPAP group or the NI-PAH group \( (P < 0.05) \). There was no statistical difference between the NIPAP group and the NIPAH group \( (P > 0.05) \). The malignancy rate of the NIP group was lower than either the NIPAP group or the NI-PAH group \( (P < 0.05) \). The malignancy rate of the NIPAP group was lower than that of the NIPAH group, and the results were statistically different.

Based on the above clinical evidence, we believe that the experimental group might not only be the NIP or the SNCC group, but the process of NIP to SNCC transformation should be refined. In the control, clinicians need to have a clearer understanding of what changes have occurred at what stage and cause NIP to change from benign to malignant. Therefore, combining the clinical with the pathological results, we first grouped NIP through different pathological stages. In so doing, we combined the clinical and pathological results for the first time to group NIP through different pathological stages, referring to the classification method of cervical intraepithelial neoplasia. According to the microscopic characteristics of the cells in different progressions, the NIP was broken down into three groups: NIPN appeared to be epithelial hyperplasia and mucosal epithelial proliferation, extending into the lamina propria, showing inversion growth; NIPAP is on the same basis as NIP, the number of cell layers was increased, and cell proliferation was active; NIPAH was on the same basis as NIPAP: papilloma cells proliferated actively; some cells appeared to undergo shape changes. Cytokeratin is an important part of the cytoskeleton and is the core component of the inner fiber skeleton. The expression of different cytokeratins in carcinogenesis is tissue-specific. Kim’s study showed that CK cannot be used to detect early lesions in lung cancer. Experiments have shown that CK expression was detected in the supraclavicular lymph nodes, suggesting early metastasis of the tumor.

In our experiment it was found that after Cytokeratin 8 interference, the proliferative and invasion of head and neck squamous cells were decreased. Cytokeratin 8 played an important role of sinonasal inverted papilloma malignant transformation to sinonasal squamous cell carcinoma. Inhibition of Cytokeratin 8 could diminish the proliferation and block the invasion of head and neck squamous cells. It is revealed that CK8 may be a marker of sinonasal inverted papilloma malignant transformation to SNSSC, and may become a therapeutic target for the treatment NIP. NIP manifested as squamous epithelium, metastatic epithelium and ciliated columnar epithelium, while CK8 was expressed in all monolayer, stratified, and pseudostratiﬁed epithelium. Hunain has demonstrated that abnormally high expression of CK8 promotes tumor genesis and cell migration.

In future experiments, we will further analyze the effects of regulating CK8 on cell proliferation, migration, and apoptosis. Changes in the expression of related pathway signal molecules will be analyzed, gradually revealing the causes of recurrence and malignant transformation of NIP and providing some references for the early clinical diagnosis of NIP recurrence and malignant transformation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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