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Correlation between IL-17A expression in nasopharyngeal carcinoma tissues and cells and pathogenesis of NPC in endemic areas

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Abstract

Objective We investigated the correlation between the expression of IL-17A in nasopharyngeal carcinoma tissues and cells and the occurrence and development of NPC was also investigated.

Methods Forty-five NPC biopsy specimens from January 2014 to January 2016 were selected. Forty-five NPC tissue specimens and 45 chronic nasopharyngitis tissue samples were detected by immunohistochemistry. Statistical methods were used to analyze the correlation between IL-17A expression and the clinicopathological variables of NPC. The NPC patients were followed up. The levels of IL-17A mRNA in 40 NPC tissue specimens and 45 chronic nasopharyngitis tissue samples were detected by real-time PCR. IL-17A expression in 15 NPC tissue specimens and chronic nasopharyngitis tissue samples was further detected by Western blotting assays.

Results IL-17A expression in NPC tissues was significantly higher than that of chronic nasopharyngitis tissues ($P < 0.05$). IL-17A was expressed in the nucleus and cytoplasm of both NPC tissues and chronic nasopharyngitis tissues. Stage III + IV NPC, tumor volume ≥ 50 mm, and hepatic envelope invasion and cervical lymph node metastasis were associated with significantly higher IL-17A levels versus stage I + II NPC, tumor size < 50 mm, no membrane invasion and lack of cervical lymph node metastasis ($P < 0.05$). IL-17A was statistically associated with tissue differentiation, serum EBV-lgA levels, and EBV infection. IL-17A-positive patients had significantly longer median survival versus IL-17A-negative patients (21.0 vs. 13.0 months, log-rank test: $P < 0.05$). Furthermore, 65% (26/40) of NPC tissue samples had significantly higher IL-17A mRNA levels than chronic nasopharyngitis ($P < 0.05$). IL-17A expression was significantly higher in NPC ≥ 50 mm, stage III + IV NPC and NPC with cervical lymph node invasion than its corresponding chronic nasopharyngitis tissue.

Conclusion IL-17A may be involved in the regulation of various malignant biological behaviors of NPC, which is closely related to the occurrence and development of NPC.

Keywords IL-17A · Nasopharyngeal carcinoma · NPC · Mechanism

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Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors of the head and neck. In recent years, its incidence has been increasing [1, 2]. Its pathogenesis is complex and may be related to EBV infection, environmental, regional, and genetic factors, and chronic inflammatory stimuli [3, 4]. As an important proinflammatory cytokine, IL-17A is elevated in many human tumors and is associated with the malignant biological behavior of tumors [5, 6]. IL-17A stimulation increased the proliferation of human NPC cells in vitro [7]. Exogenous IL-17A promoted cell migration and invasion significantly in both NPC-039 and CNE-2Z cell lines. In addition, the expression of matrix metalloproteinase-2 (MMP-2)/-9 and vimentin could be elevated by IL-17A stimulation; meanwhile, the expression of E-cadherin was decreased [8]. However, the regulation of IL-17A in NPC is currently unclear. In this study, immunohistochemistry, real-time PCR and Western blot assays were used to detect IL-17A mRNA and protein levels in NPC tissues and chronic nasopharyngitis tissues, and their relationship with clinicopathologic variables and patient prognosis was analyzed, and the role of IL-17A in the development of NPC was explored.

Data and methods

Clinical data

NPC tissue and chronic nasopharyngitis tissue biopsy samples were collected at our hospital from January 2014 to January 2016. The resected specimens were confirmed as NPC by independent pathologists, and had complete clinical records and follow-up data. The male-to-female ratio was 4:1; the patients were between 32 and 68 years old, with a median age of 47 years and a mean age of 48.33 ± 10.55 years. The differentiation of NPC cells was classified into grade I (highly differentiated), grade II (medium differentiation), and grade III (low differentiation) according to the Edmondson classification. Clinical staging was done using the UICC TNM staging criteria. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Medical College of Xi'an Jiaotong University. It conformed to the principles of medical ethics and written informed consent was obtained from each participant.

Methods

H&E staining

All tissue specimens were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin (H&E) staining and immunohistochemical staining were performed after 5 μm section was dewaxed. Citric acid buffer was boiled and repaired; diaminobenzidine (DAB) staining and hematoxylin re-staining were performed.

Immunohistochemical staining

Phosphate buffer solution (PBS) was used as a negative control instead of primary antibody. Positive cervical cancer staining samples were used as positive controls to evaluate the expression of p57. Positive expression of p57 was indicated by the distribution of brown and yellow granules in the nucleus. Samples whose percentage of positive cells was $\leq 5\%$ were considered negative, 6–25% weakly positive, 26–50% moderately positive, and $> 50\%$ strongly positive. Weak–strong positive expression was considered as a positive expression.

Real-time PCR

Cells were seeded in 96-well plates overnight, and the Ct values of p57 mRNA and GAPDH mRNA of each sample were measured by ABI prime 7000 SDS software (the number of cycles experienced when the fluorescence signal in each reaction tube reached the set threshold), while $\triangle$Ct1 and ΔCt2 of adjacent tissues of each sample were expressed semi-quantitatively. When the expression of the target gene was compared with that in the adjacent tissues, $\triangle\triangle$Ct = the target gene ΔCt1 in the cancer tissue − the gene $\triangle$Ct2 in the paracancerous tissue. When the amplification efficiency of the target gene was close to that of the internal reference gene, $2-\Delta\Delta$Ct indicated the relative expression of the target gene in the test sample relative to that in the reference sample.

Western blot analysis

Cells were lysed for 30 min and the cellular lysate was centrifuged for 5 min at 4 °C for 12,000 r/min. Equivalent supernatant (protein) was mixed with SDS loading buffer and heated in a boiling water bath at 100 °C, for 5 min to fully denaturate the protein. Then, 1 μL was taken for protein quantification. Cells were treated with protein lysate and protein samples were collected. The protein samples were quantified by BCA method. SDS-PAGE electrophoresis was carried out with 50 μg protein per well. After electrophoresis, proteins were transferred to PVDF membrane, and the transfer membrane was sealed with 1% BSA. Thereafter, 1:1000 rabbit anti-actin (1:1000, Neomarker, CA, USA), IL-17A (1:1000, Cell Signaling Technology) and CDK2 (1:1000, Cell Signaling Technology) polyclonal antibodies were added and placed overnight in the refrigerator at 4 °C. After washing with TBST three times, 1:5000 labeled anti-rabbit secondary antibody was

added, incubated for 1 h at room temperature, and washed three times in TBS. Then, the protein bands were visualized by ECL chemiluminescence. The gray ratio of the target bands to that of the internal reference bands was the relative expression of the target proteins (Table 1).

Statistical analysis

Data were analyzed by SPSS 20.0 statistical analysis software (IBM, USA); measurement data were expressed as mean ± standard deviation, and comparison between groups was done using one-way ANOVA or repeated measures of variance analysis. The LSD *t* test was used for comparison between the two groups; count data were expressed as percentage (%), and comparison between groups was performed using χ^2. $P < 0.05$ indicated statistically significant difference.

Results

Expression of IL-17A in NPC and chronic nasopharyngitis tissues and its clinicopathological significance

Expression of IL-17A in NPC and chronic nasopharyngitis tissues

To clarify the expression of IL-17A in NPC tissue samples, 45 NPC tissue samples and 45 chronic nasopharyngitis tissue samples were detected by immunohistochemistry. As shown in Fig. 1, IL-17A was strongly positive in NPC tissues and showed brownish yellow coarse particles. In chronic nasopharyngitis tissues, the IL-17A-positive cells were lightly colored, small in number, and arranged in different orders and disordered. The expression of IL-17A was found in the nuclei and cytoplasm of NPC tissues and chronic nasopharyngitis tissues, suggesting that IL-17A can be expressed in both nucleus and cytoplasm in inflammatory nasopharyngeal cells and some NPC cells.

Table 1 Comparison of IL-17A expression in NPC tissues and chronic nasopharyngitis

Grouping	Positive	Negative
NPC organization	18	27
Chronic nasopharyngitis	32	13
χ^2 value	8.820	
P value	0.003	

Relationship between IL-17A and clinicopathologic variables of NPC patients

To further clarify the role of IL-17A in the development of NPC, a statistical analysis of the correlation between IL-17A expression and various clinicopathologic variables of NPC patients was performed. The results showed (Table 2) that stage III + IV NPC, NPC ≥ 50 mm, and NPC with hepatic envelope invasion and cervical lymphatic metastasis had significantly higher IL-17A scores versus stage I + II NPC, NPC < 50 mm, no hepatic envelope invasion and lacking cervical lymphatic metastasis ($P < 0.05$). However, IL-17A expression was statistically associated with tissue differentiation, serum EBV-lgA levels, and EBV infection ($P > 0.05$).

Relationship between IL-17A protein and prognosis of NPC patients

To elucidate the relationship between IL-17A and prognosis of NPC patients, we followed up all NPC patients. The follow-up was performed until December 2017, and survival was calculated from the first postoperative day to death or the date of the last follow-up. We censored patients who were lost to follow-up or whose cause of death was not due to NPC. Univariate analysis using the Kaplan–Meier method showed that the median survival of IL-17A-positive patients was 21.0 months versus 13.0 months for IL-17A-negative patients. Log-rank test showed significant difference between the two groups ($P < 0.05$) (Fig. 2), indicating that IL-17A was one of the important factors affecting the prognosis of NPC patients (median survival: half of the survival period, that was, when the cumulative survival rate was 0.5, the corresponding survival time, indicating that only 50% of individuals can live this time).

IL-17A mRNA levels in NPC and chronic nasopharyngitis tissues

In this study, the levels of IL-17A mRNA in 40 NPC tissue samples and 40 chronic nasopharyngitis tissue samples were further tested by real-time PCR. Based on the levels of GAPDH mRNA transcripts, $2-\Delta\Delta Ct$ analysis showed that the level of IL-17A mRNA transcripts in NPC tissues was significantly lower than that in chronic nasopharyngitis tissues, and the difference was statistically significant ($P < 0.01$) (Fig. 3). In 40 NPC samples and 40 chronic nasopharyngeal tissue samples, 65% (26/40) of NPC tissue samples had higher IL-17A mRNA levels than chronic nasopharyngitis, and the difference was statistically significant ($P < 0.05$).

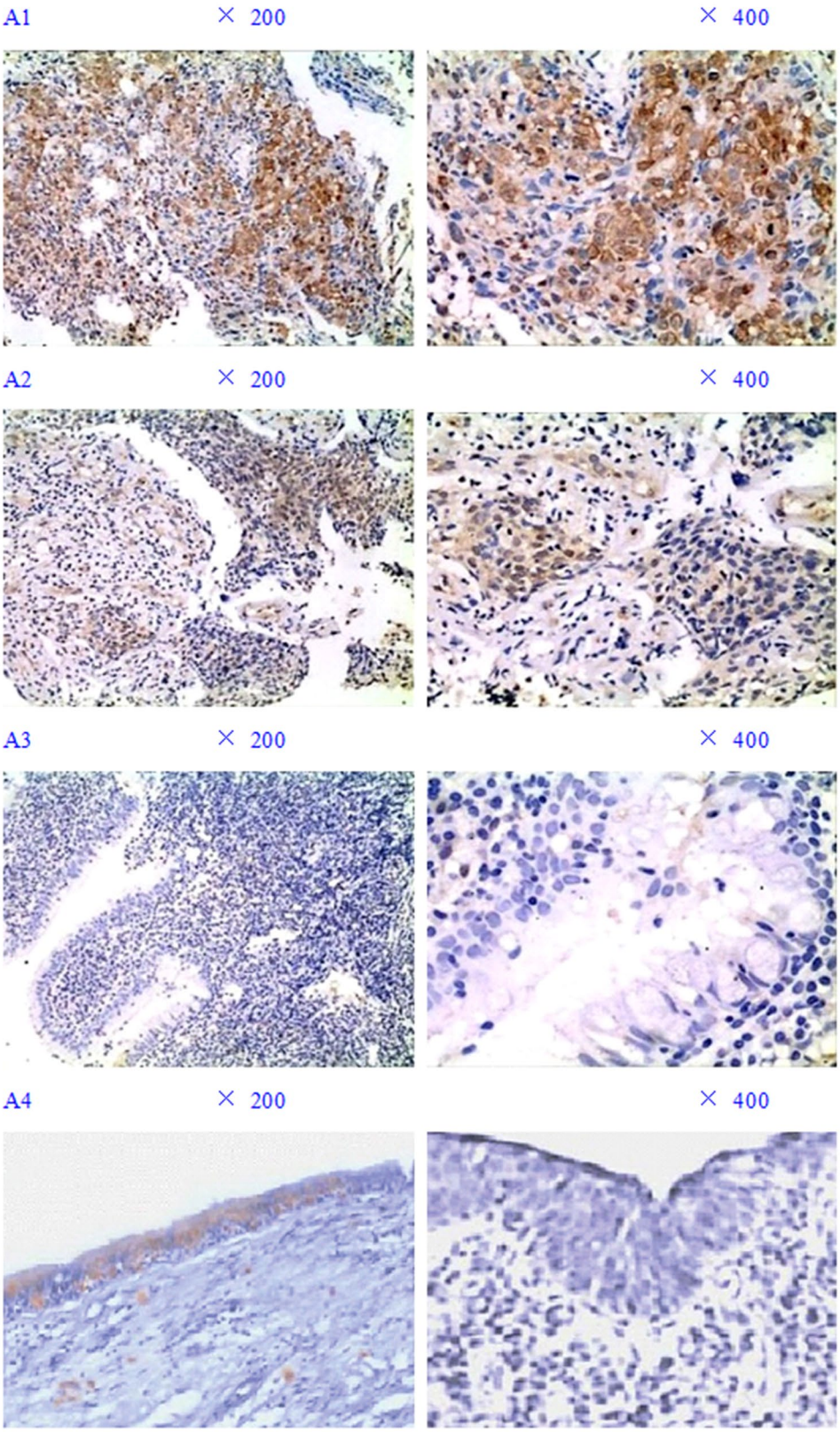

Fig. 1 Expression of IL-17A in NPC tissues and chronic nasopharyngitis tissues (×200, ×400; *A1* strong positive expression of IL-17A in NPC tissues, *A4* positive expression of IL-17A in NPC tissues, *A3* weak positive expression of IL-17A in NPC tissues, *A2* negative expression of IL-17A in chronic nasopharyngitis)

Table 2 Relationship between IL-17A protein expression and clinicopathological factors of NPC ($\bar{x} \pm s$)

Clinicopathological factors	Number of cases	IL-17A protein expression	*P*
Tumor size			0.001*
< 50 mm	18	5.51 ± 1.56	
≥ 50 mm	27	3.79 ± 1.66	
Degree of tissue differentiation			0.278
Level I + II	36	4.63 ± 1.93	
Class III	9	3.89 ± 1.12	
TNM staging			0.000**
Phase I + II	12	6.50 ± 1.31	
Phase III + IV	33	3.74 ± 1.35	
Hepatic envelope invasion and extrahepatic metastasis			0.001*
Have	24	3.65 ± 1.59	
No	21	5.43 ± 1.60	
EBV-lgA level			0.058
< 400 μg/L	21	5.05 ± 1.64	
≥ 400 μg/L	24	4.02 ± 1.85	
EBV			0.169
Positive	42	4.58 ± 1.78	
Negative	3	3.08 ± 2.01	

*$P < 0.05$, **$P < 0.01$

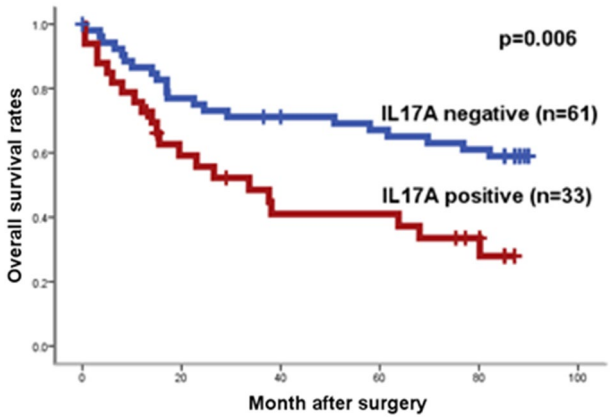

Fig. 2 Survival curves of the IL-17A positive group and IL-17A negative groups

Western blot analysis of IL-17A expression in NPC and chronic nasopharyngitis tissues

IL-17A protein expression in 15 NPC tissue samples and 15 chronic nasopharyngitis tissue samples was further examined in this study. To avoid the difference in protein content between tissues, the IL-17A protein of each tissue with the gray level of its corresponding internal reference protein β-actin was compared, and the ratio of IL-17A/β-actin was applied as the relative IL-17A protein expression. The results showed that

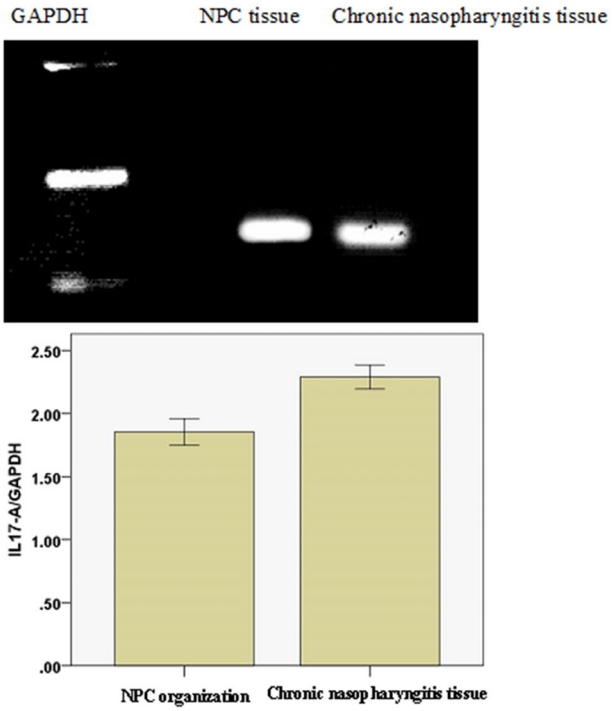

Fig. 3 Real-time PCR for relative quantification of IL-17A mRNA transcripts in NPC tissues and chronic nasopharyngitis tissues

the expression of IL-17A/β-actin in 80% (12/15) NPC tissue samples was significantly higher than that in the corresponding chronic nasopharyngitis tissues ($P < 0.01$) (Fig. 4). Western blotting results confirmed that IL-17A expression was significantly higher in NPC tissues ≥ 50 mm, stage III + IV NPC and NPC with cervical lymph node invasion compared with the chronic nasopharyngitis tissue samples (Fig. 5).

Calculation of blood plasma EBV-DNA content

Plasma EBV-DNA copy number $C = Q \times (\text{VDNA/VPCR}) \times (1/\text{Vext})$. C was the plasma concentration of EBV-DNA to be tested (copies/mL). Q represents the original DNA copy number detected by computer after PCR amplification; VDNA represents the volume of DNA diluent extracted. VPCR was the DNA volume used for PCR amplification. Vext represents the volume of plasma used to extract DNA. The detection limit was 100 copies/mL, which was positive.

Discussion

Increased expression of IL-17A mRNA and protein in NPC tissues and its possible mechanism

Early- and intermediate-stage NPC generally carries a good prognosis, but for patients with recurrent or metastatic

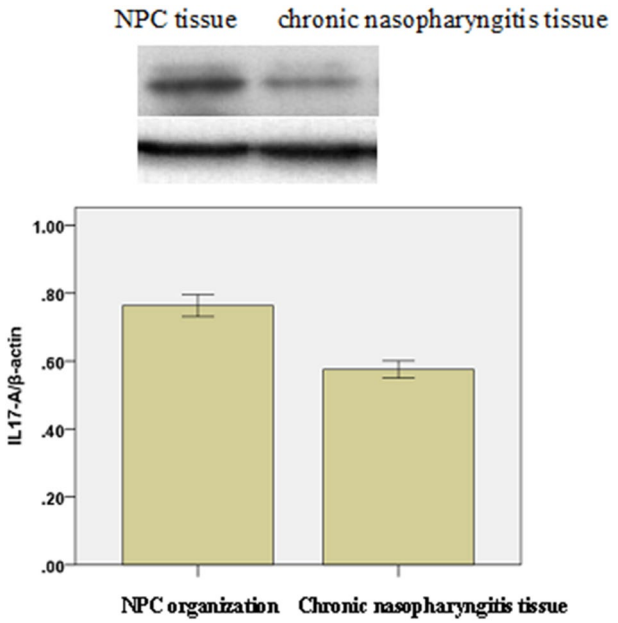

Fig. 4 Western blot analysis of IL-17A expression in NPC tissues and chronic nasopharyngitis tissues (**$P < 0.01$)

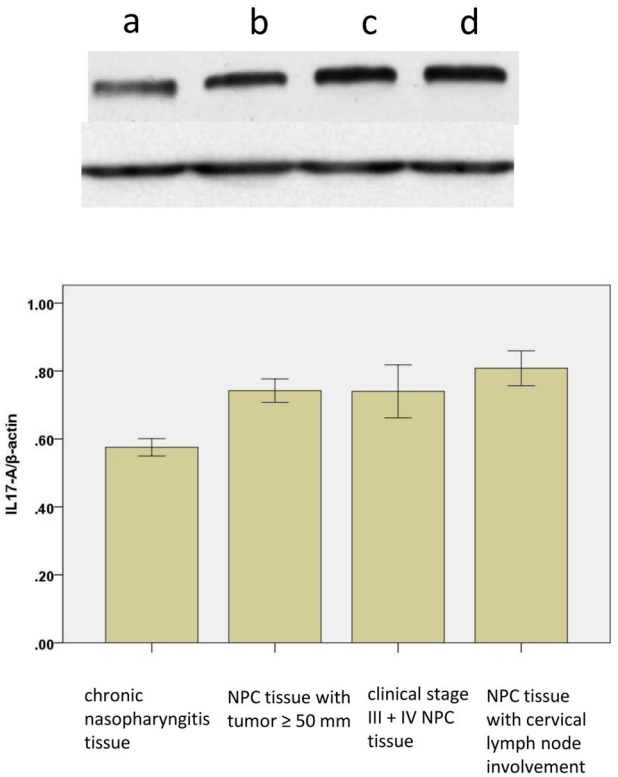

Fig. 5 Western blot analysis of the relationship between IL-17A and clinicopathologic variables of NPC patients. **a** Chronic nasopharyngitis tissue, **b** NPC ≥ 50 mm, **c** clinical stage III + IV NPC, and **d** NPC with cervical lymph node involvement

disease, options are limited [9–11]. In this study, the levels of IL-17A mRNA and protein were detected by real-time PCR, immunohistochemistry and Western blotting assays. The results showed that IL-17A mRNA expression in NPC tissues was significantly lower than that in adjacent liver tissues. It is indicated that the *p57* gene is down-regulated during the transcriptional phase during the development and progression of NPC. Substantial literature supports that p57 rarely underwent gene mutations during the development and progression of tumors, mainly due to regulation of transcription levels and modification of translation levels [12, 13]. The regulation of p57 transcription levels is mainly involved in *p57* imprinting and heterozygous deletion, promoter methylation and acetylation, and microRNAs cleavage of p57 mRNA [14, 15]. In addition, some upstream signaling molecules such as TGF-β can also regulate the transcription of *p57*, which in turn affects the expression of p57. Heterozygous deletion, promoter methylation, and regulation of p57 mRNA by microRNAs in HCC tissues were shown to be involved in the development of NPC [16, 17]. Our study further found that the expression of p57 protein in NPC tissues was also significantly lower than that in adjacent liver tissues, and Western blot results showed that the decrease of p57 protein level was more obvious than the decrease of mRNA levels. These results suggested that the down-regulation of p57 expression was accompanied by post-translational modification and degradation in addition to the down-regulation of the level of mRNA. The post-translational regulation of p57 levels is primarily involved in phosphorylation and ubiquitination degradation [18]. A variety of ubiquitin ligands are involved in the regulation of p57 protein degradation. Among them, SKP2/CSK1 degraded p57 protein, enhanced the sensitivity of NPC in nude mice, and was associated with poor prognosis in NPC patients [19]. In addition, studies found that the expression of p57 was decreased in prostate cancer, and the formation of prostatic epithelial tumor-like tissue and neoplasms was further found in the prostate of p57 knockout mice, suggesting that down-regulation of p57 may be the initiating factor of tumorigenesis [20]. The results of this study showed that IL-17A expression in NPC was higher than that in adjacent liver tissues at both the mRNA and protein levels. It was concluded that although regulated by many factors, the upregulation of IL-17A may be the key factor affecting the occurrence and development of NPC.

Relationship between IL-17A and NPC clinicopathologic variables and prognosis

To further clarify the role of IL-17A in the development of NPC, a statistical analysis of the relationship between IL-17A expression and clinicopathologic variables and prognosis of NPC was performed. The results are shown in Table 3. In stage III + IV NPC and NPC ≥ 50 mm, the protein score of

Table 3 Comparison of EBV-DNA levels in NPC tissues and chronic nasopharyngitis

Grouping	Positive	Negative
NPC organization	22	23
Chronic nasopharyngitis	35	10
χ^2 value	7.520	
P value	0.005	

IL-17A was significantly higher in NPC with nasopharyngeal capsule invasion and cervical lymph node metastasis than that of stage I + II NPC, NPC < 50 mm and no nasopharyngeal capsule invasion and lack of cervical lymph node metastasis ($P < 0.05$). In addition, we followed up all NPC patients and found that the median survival of the IL-17A positive group was significantly lower than that of the IL-17A negative group. These results suggested that IL-17A played a role in oncogenesis and development of NPC, and its elevation may promote the evolution of NPC, which is consistent with the role of IL-17A in other tumors [21]. As an important cytokine, the correlation between IL-17A overexpression and tumor size can be explained by its positive regulation of the cell cycle to promote cell proliferation. It has been found that in a variety of human tumors including cervical cancer, kidney cancer, gastric cancer, breast cancer and lung cancer, elevated IL-17A expression was associated with tumor cell proliferation. More importantly, we first found that IL-17A expression was elevated in NPC tissues with extranasal pharyngeal invasion and lymph node metastasis, suggesting that IL-17A may be involved in the invasion and metastasis of NPC [22]. Foreign scholars found that IL-17A overexpression in cervical cancer, lung cancer, and urinary tract tumors was associated with invasive phenotypes and lymph node metastasis, which is consistent with our findings. In addition, the loss and down-regulation of IL-17A expression were more pronounced in stage III + IV NPC patients and in NPC patients with a poor prognosis, suggesting that IL-17A may be closely related to disease progression and outcome in NPC patients, which was reported in oral squamous cell carcinoma, laryngeal cancer, ovarian cancer and breast cancer [23]. In conclusion, IL-17A plays an important role in many human tumors, including NPC. As a key positive regulator in the development of NPC, IL-17A may be involved in the invasion and metastasis of tumors as well as malignant transformation and proliferation of tumors, thus affecting the prognosis of cancer patients.

Advantages of real-time PCR for detecting IL-17A mRNA levels

Real-time PCR is real-time fluorescent quantitative PCR. Its working principle is to indirectly reflect the increase of DNA quantity by adding fluorescent groups in the reaction system and increasing the fluorescent signal proportionally, so as to monitor the amplified products of real-time PCR. Compared with ordinary PCR, real-time PCR has the characteristics of accurately determining the initial template copy number, wide dynamic range and high sensitivity [24]. The results can be used for qualitative purposes as well as for quantification. This experimental method greatly saves experiment time and improves experiment efficiency. In addition, the reaction and detection of real-time PCR are carried out in the reaction tube, so the probability of sample contamination is greatly reduced, and the experimental operation after amplification is not required [25]. SYBR green fluorescent dye used in this study can be specifically incorporated into DNA double strands, emit fluorescent signals, and monitor the amplification of any dsDNA sequence. No probe design was required, and the detection method was simpler. The analysis of the results of real-time PCR can be divided into two categories: absolute and relative quantification. Absolute quantification is a comparative analysis of the Ct value of a sample and a standard curve, and the result is the amount of nucleic acid per unit mass of the sample. The relative quantitative analysis results are the relative ratios of target genes in a considerable amount of test and control groups. This experimental study used a relative quantification method, because we were more concerned with differences in the expression level of IL-17A in NPC tissues relative to paracancerous liver tissues. In addition, in this experiment, the housekeeping gene *GAPDH* was used as an internal standard to correct the interference factors in the existing reaction system, so the results were more reliable and accurate. In addition, P300/CBP histone acetyltransferase (HAT), one of the important macromolecular proteins in P300/CBP is highly homologous; although encoded by different genes, their amino acid sequence and function are similar, and the two proteins belong to the same family and are often written as P300/CBP. P300/CBP is involved in the activation of many transcription factors, and it also has acetyltransferase activity, which can acetylate four core histones and many transcription factors. P300 binds to the Il-17 promoter region and induces Il-17A, thereby regulating the occurrence and development of laryngeal cancer [7, 26].

In summary, IL-17A may be involved in the regulation of multiple malignant biological behaviors of NPC, which is closely related to the oncogenesis and development of NPC. Because of the occult position of NPC, patients often have no symptoms, which easily causes misdiagnosis or missed diagnosis; 70% of NPC patients are diagnosed in the mid- and late stages. In recent years, comprehensive individualized treatment for advanced NPC patients has become an important means to improve local control rate and survival rate. However, the toxicity of conventional radiotherapy and chemotherapy is relatively high, and some patients cannot

tolerate it, and some patients are resistant to platinum-based chemotherapy. More and more molecular targeted drugs have been used in combined radiotherapy of NPC, which can specifically block the signal transduction pathway that plays a key role in the growth of tumor cells. While killing tumor cells, it can reduce the impact on normal cells, with fewer side effects and better safety. It can effectively improve the survival rate and quality of life of the patients. Based on the results of this study, we speculate that inhibiting IL-17A or its receptors may be a key potential strategy for the treatment of NPC patients.

Compliance with ethical standards

Conflict of interest The authors declare there is no conflict of interest related to this study.

Research involving human participants and/or animals The study protocol was approved by the Ethics Committee of Renmin Hospital, Hubei University of Medicine.

Informed consent Informed consent was obtained from all the study subjects before enrollment.

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