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Expression profile and clinical significance of IL-17B/IL-17RB in laryngeal squamous cell carcinoma

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Abstract

Interleukin-17B (IL-17B) and its receptor IL-17 receptor B (IL-17RB) are implicated in several cancers. However, data on their expression profile and clinical significance in laryngeal squamous cell carcinoma (LSCC) remain unavailable. This study aimed to explore the expression profile of IL-17B/IL-17RB in LSCC and to evaluate their predictive and prognostic value in LSCC patients. Tumor and serum samples from 30 LCSS patients and 30 controls were analyzed. Flow cytometry, enzyme-linked immunosorbent assay (ELISA), and immunohistochemistry (IHC) assessed IL-17RB expression on T helper type 2 (Th2) cells and monocytes, and IL-17B/IL-17RB in serum and tissues. Target gene expression levels at the mRNA and protein levels and their correlation with overall survival (OS) were further analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA; 519 head and neck squamous cell carcinoma [HNSCC] and 44 normal tissues) and the Human Protein Atlas (HPA; 492 RNA samples and 183 HNSCC and normal samples). Result showed weak IL-17RB expression on Th2 cells and monocytes and negative immunoreactivity of IL-17B/IL-17RB in LSCC tissues, consistent with GEPIA and HPA databases. No differences in IL-17B/IL-17RB levels in serum were found in LSCC patients compared with healthy controls. Neither IL-17B nor IL-17RB was correlated with OS. This study provides the first comprehensive evaluation of IL-17B/IL-17RB in LSCC, combining patient samples with bioinformatics datasets. Findings indicate that IL-17B and IL-17RB are not prognostic markers in LSCC, and their potential as serum markers in clinical practice is limited. Further studies are warranted to validate these negative findings and explore alternative roles of IL-17B/IL-17RB in LSCC.

Keywords: Laryngeal squamous cell carcinoma; IL-17B/IL-17RB; Head and neck squamous cell carcinoma

1. Introduction

Laryngeal squamous cell carcinoma (LSCC) is a subtype of head and neck squamous cell carcinoma (HNSCC), representing a group of solid tumors that arise from the squamous epithelium of the oral cavity, oropharynx, larynx, and hypopharynx, commonly related to alcohol consumption and smoking.[1] As the sixth most common type of cancer worldwide, HNSCC results in a death toll of about 350,000 annually, with a 5-year morbidity and mortality rate of about 40%–50%.[2] LSCC accounts for roughly 20% of all HNSCC cases, making it one of the most common malignancies within this group.[3] Evidence is rapidly converging to show that the tumor microenvironment (TME) is a key driver of HNSCC initiation and progression, fostering tumor aggressiveness, treatment resistance, and ultimately poor clinical outcome.[4] At present, in addition to the main treatment options—surgery, radiotherapy, chemotherapy, and neoadjuvant treatment—multiple therapeutic strategies have been introduced for HNSCC, especially immunotherapy approaches such as immune checkpoint blockade, antigenic vaccines, co-stimulatory agonists, adoptive T-cell infusion, oncolytic virotherapy, and epidermal growth factor receptor (EGFR)-targeted agents.[5-7] Despite these advances, late diagnosis, frequent locoregional relapse, and lymphatic spread continue to drive dismal long-term outcomes in LSCC.[5,8-10] Hence, it is important to identify new biomarkers for early detection and prognostic stratification in LSCC.

Mounting data suggest that multiple interleukins (ILs) not only drive HNSCC pathogenesis but also represent attractive therapeutic targets. One study found that the HNSCC microenvironment, particularly through IL-10, severely impairs interferon alpha (IFN-α) secretion by plasmacytoid dendritic cells (pDCs), which cannot be restored by CpG-oligonucleotides. This suggests that restoring immune function in HNSCC requires both immunostimulation with CpG motifs and inhibition of cytokine receptors like IL-10R.[11] The IL-6-induced ferroptosis resistance and the IL-6/STAT3/xCT axis driving tumor progression have been reported to play key roles during HNSCC carcinogenesis.[12] Another study demonstrated that co-targeting IL-6 and C-C motif chemokine receptor 2 (CCR2) markedly enhances natural killer (NK) cell antitumor efficacy in human papillomavirus (HPV)-negative HNSCC.[13] The distinct IL-6/STAT3 signaling axis was also found to correlate with reduced responsiveness to EGFR-tyrosine kinase inhibitors (EGFR-TKI). Pharmacologic blockade of STAT3, combined with EGFR-TKIs, achieved complete tumor eradication or durable remission of HNSCC *in vitro* and across multiple pre-clinical models.[14] A study showed that IL-12 upregulates NKG2A expression on tumor-reactive $CD8^+$ cytotoxic T lymphocytes (CTLs) in HNSCC.[15] $SPP1^+$ macrophages ($SPP1^+$ Macs) appear to amplify antitumor activity by releasing tumor necrosis factor alpha (TNF-α) and IL-1β through nuclear factor kappa B (NF-κB) signaling, which in turn induces osteopontin (OPN) production in both tumor cells and macrophages, reinforcing the cycle.[16]

The IL-17 family encompasses six ligands (IL-17A–F) that selectively engage five distinct receptors (IL-17RA–E).[17] IL-17 cytokines act as pleiotropic pro-inflammatory mediators that orchestrate host defense, drive inflammatory disorders, facilitate tissue repair, and promote cancer progression.[18,19] They function as a pivotal molecular bridge linking chronic inflammation to tumorigenesis among various inflammatory signals. During tumor initiation, IL-17 signaling acts as a direct mitogenic cue for malignant cells. Mechanistically, microbiome fluctuations modulate IL-17 release, thereby shaping tumor progression.[20] Another review offers an in-depth analysis of IL-17 signaling, covering its normal physiology and highlighting how aberrant IL-17 responses drive systemic lupus erythematosus, tumor initiation, and metastatic spread.[18] Notably, IL-17 cytokines act as double-edged swords, mounting robust antimicrobial defenses while simultaneously promoting infection-associated and autoimmune-mediated tissue damage. New approaches should selectively curb IL-17-driven tissue damage in autoimmunity and chronic inflammation while sparing its essential antimicrobial functions.[21] Among family members, IL-17A, often simply referred to as IL-17, has been the most extensively characterized for its pro-inflammatory role in autoimmune disorders.[22] IL-17 was reported to curb cholangitis and protect bile ducts from $CD8^+$ T-cell-driven damage by inducing programmed cell death-1 ligand 1 (PD-L1) expression on cholangiocytes.[23] IL-17A also promotes neutrophil influx, macrophage activation, and irreversible lung remodeling in cystic fibrosis (CF)-like lung disease, making it as a promising anti-inflammatory target for CF therapy.[24] Both IL-17A and IL-17F have been reported to serve as pivotal drivers in hidradenitis suppurativa, a neutrophilic dermatosis.[25] In allergic asthma, IL-17A was found to drive airway epithelial ferroptosis by disrupting the xCT-GSH-GPX4 axis via TNF signaling, highlighting IL-17A inhibitors as a potential therapeutic approach.[26] Furthermore, IL-17A promotes tumorigenesis across multiple malignancies, including breast, cervical, colorectal, prostate, and cutaneous cancers, by driving proliferation, immune evasion, and metastatic spread.[19]

Although most attention has been focused on IL-17A, a growing body of research indicates that the IL-17B-IL-17 receptor B (IL-17RB) ligand-receptor pair plays key roles in a broader spectrum of cancers, including gastric,

pancreatic, thyroid, lung, hepatocellular, and breast cancers.[27-31] One study revealed that the IL-17B/IL-17RB axis drives cancer stem cell (CSC) self-renewal and tumor initiation through ubiquitin-mediated degradation of beclin-1.[27] A team developed a humanized anti-IL-17RB monoclonal antibody (1B12), guided by the crystal structure of a mouse precursor (D9), that blocks the IL-17B/IL-17RB oncogenic axis and suppresses pancreatic tumor growth *in vivo*.[32] IL-17B has also been shown to suppress hepatocellular carcinoma cell proliferation via an AKT-dependent pathway that bypasses NF-κB signaling.[33] These findings highlight the potential of IL-17B/IL-17RB-targeted therapy in cancer. However, no data are currently available on the expression profile and clinical significance of IL-17B/IL-17RB in LSCC. To explore the potential diagnostic and prognostic value of IL-17B/IL-17RB in LSCC, our study, for the first time, provides a comprehensive expression profile of IL-17B/IL-17RB in LSCC, combined with bioinformatics database analysis.

2. Materials and methods

2.1. LSCC patients and data extraction

A relatively small sample size of 30 LSCC patients with histopathological diagnosis at the Department of Otolaryngology Head & Neck Surgery in Shanxi Bethune Hospital and 30 age- and sex-matched healthy subjects were enrolled. The untreated LSCC patients confirmed by pathological diagnosis with complete clinical data were included. Exclusion criteria were: (1) Combination of malignant tumors; (2) severe diseases of the liver, kidney, or hematopoietic system; (3) pregnant/lactating women; (4) incomplete clinical data. Tumor staging was assessed according to the traditional and current tumor node metastasis (TNM) staging guidelines by the American Joint Committee on Cancer/Union for International Cancer Control.[34] The demographic data, primary sites, and TNM stages were retrieved from the medical records. The residual peripheral blood and serum after clinical analysis were collected. The study was conducted following the Declaration of Helsinki and received approval from the Ethics Committee of Shanxi Bethune Hospital.

2.2. Flow cytometric analysis for IL-17RB expression on Th2 cells and monocytes

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque density centrifugation from peripheral blood of 25 LSCC patients and 27 normal healthy donors. Cryopreserved PBMCs were stained with the following fluorescence-conjugated anti-human antibody mix: APC/Cy7-conjugated anti-CD4 (AAT Bioquest, USA), APC-conjugated anti-CD14 (BioLegend, USA), FITC-conjugated anti-CD294 (BioLegend, USA), and PE-conjugated anti-IL-17RB (R&D systems, USA). T helper type 2 (Th2) cells and monocytes were defined by the cell surface markers $CD4^+$ $CD294^+$ and $CD14^+$, respectively. A total of 1×10^6 cells per sample were analyzed using a BD FACS Canto cytometer (BD Biosciences, USA) with BD FACS Diva software v8.0.2.

2.3. Immunohistochemistry (IHC) for IL-17B/IL-17RB expression in cancer and adjacent noncancerous tissues

Formalin-fixed paraffin-embedded tissue sections from LSCC patients were subjected to IHC staining using the Roche automated multi-functional tissue pathology detection system (Benchmark XT platform, Roche, Switzerland). The slides were probed with rabbit polyclonal primary antibodies targeting IL-17B (BBI-Biotech GmbH, Germany) and IL-17RB (LifeSpan BioSciences, USA). All cases were independently evaluated by two experienced pathologists, and staining was quantified using Motic Images Plus 2.0 software (Motic China Group Co., Ltd., China).

2.4. ELISA for serum concentrations of IL-17B and IL-17RB

Serum samples were obtained, snap-frozen, and stored at −80°C until analysis. Serum levels of IL-17B and IL-17RB were measured by enzyme-linked immunosorbent assay (ELISA) kit (Jiangsu Meimian Industrial Co., Ltd, China) following the manufacturer's protocols. All measurements were performed in triplicate, and concentrations were interpolated from a standard curve.

2.5. Bioinformatic analysis for survival and expression profiling at the mRNA and protein levels

The Gene Expression Profiling Interactive Analysis (GEPIA) database, a web tool for cancer and normal gene expression profiling and interactive analysis, was used to assess transcriptome-level gene expression and its correlation with overall survival (OS) in HNSCC (http://gepia2.cancer-pku.cn/).[35] A total of 519 HNSCC tissues and 44 normal tissues were analyzed in GEPIA database. Protein expression levels and IHC localization of the target genes were assessed using the Human Protein Atlas (HPA), a comprehensive database of protein spatial distribution across human tissues and cells (www.proteinatlas.org).[36] A total of 183 HNSCC and normal samples were analyzed for relative protein expression in HPA.[1,2] Gene expression and

[1] Expression of IL17B in head and neck cancer: https://www.proteinatlas.org/ENSG00000127743-IL17B/cancer/head+and+neck+cancer

[2] Expression of IL17RB in head and neck cancer: https://www.proteinatlas.org/ENSG00000056736-IL17RB/cancer/head+and+neck+cancer

survival data from 492 RNA samples were also obtained from HPA.

2.6. Statistical analysis

Non-normally distributed continuous data were reported as median (interquartile range, IQR) and analyzed using the Mann–Whitney U test. Categorical data were presented as percentages and assessed with Fisher's exact test. Spearman correlation analysis was used to analyze the correlation between expression of the two target genes and between gene expression and clinical characteristics. All statistical analyses were performed using SPSS version 19.0 (International Business Machines Corporation, USA), and $p<0.05$ was determined as statistically significant.

3. Results

3.1. Basic characteristics of the subjects

Relevant data of healthy subjects and 30 LSCC patients, including basic demographic and clinical characteristics, are summarized in Table 1. Among the patients, the median age (29 men and 1 woman) was 67 years (range, 50–84 years). The composition of age and gender was comparable between the patient group and control group ($p>0.05$). Most cancers derived from the primary site of glottis, followed by supraglottis and subglottis. Patients in the early stages (T1 + T2) were twice as many as those in the late stages (T3 + T4). More than 30% of cases had lymph node involvement, and none of the LSCC patients had distant metastasis.

Table 1. Clinical characteristics of the subjects

Characteristics	Patients (n=30)	Controls (n=30)	p-value
Age (years)	66±7	64±9	0.338
Sex (male)	29 (96.7%)	30 (100%)	0.462
Primary site			
Glottis	16 (53.33%)	N/A	N/A
Supraglottis	12 (40.00%)	N/A	N/A
Subglottis	2 (6.66%)	N/A	N/A
T grade			
T1+T2	19 (63.33%)	N/A	N/A
T3+T4	11 (36.66%)	N/A	N/A
Nodal involvement			
Yes	11 (36.66%)	N/A	N/A
No	19 (63.33%)	N/A	N/A
Metastasis			
Yes	0 (0%)	N/A	N/A
No	30 (100%)	N/A	N/A

3.2. Expression of IL-17RB on Th2 cells and monocytes in LSCC patients

The expression of IL-17RB on Th2 cells and monocytes from LSCC patients and healthy donors was assessed by flow cytometry (Figure 1). About 4.40% (IQR, 2.80–12.35) of $CD4^+CD294^+$ Th2 cells were found to express IL-17RB, whereas only 0.30% (IQR, 0.20–0.85) of $CD14^+$ monocytes expressed IL-17RB in the LSCC group. No significant difference in IL-17RB expression was observed in these two cell populations between LSCC patients and healthy subjects ($p>0.05$).

3.3. Expression of IL-17B/IL-17RB in LSCC tissues

The expression and localization of IL-17B and IL-17RB in LSCC cancer tissues and noncancerous tissues were detected by IHC (n = 19 vs. 16). Only weak immunoreactivity of IL-17RB, located in cytoplasm and membrane, was observed in cancerous tissues, which did not differ significantly from healthy controls. No immunoreactivity of IL-17B was observed in LSCC tissues (Figure 2). No further quantitative analysis was conducted because of the negative results.

3.4. Serum levels of IL-17B and IL-17RB in LSCC patients

The serum levels of IL-17B and IL-17RB were analyzed by ELISA. No significant differences in IL-17B/IL-17RB levels were found in LSCC patients compared with the control group ($p>0.05$) (Figure 3). Spearman analysis displayed that there was no correlation between serum IL-17B and IL-17RB, nor between serum IL-17B/IL-17RB and different pathological stages ($p>0.05$, data not shown).

3.5. Transcriptomic and proteomic landscapes of target genes in HNSCC

According to GEPIA database, transcriptomic and proteomic analyses showed no significant differences in IL-17B and IL-17RB mRNA expression between 519 HNSC tissues and 44 normal tissues. Expression of IL-17B and IL-17RB was not correlated with each other. Neither gene expression nor pathological stage nor OS showed significant differences between normal and HNSCC tissues (Figure 4). The same negative results of gene expression and survival analysis of IL-17B/IL-17RB in HNSCC were obtained from 492 RNA samples in HPA. IHC images showed no expression of IL-17B but weak expression of IL-17RB in squamous cell carcinoma tissues with cytoplasmic and membranous localization in HNSCC samples from HPA (data not shown). IL-17B and IL-17RB were mainly expressed in basophils according to immune cell type expression in HPA (Figure 5).

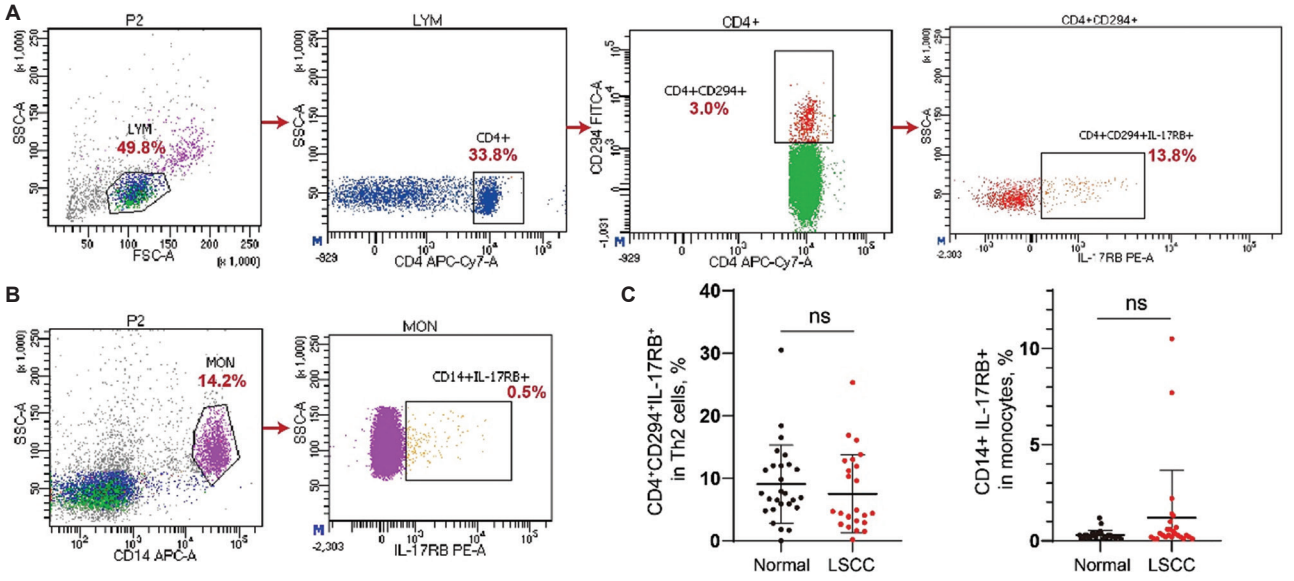

Figure 1. Frequency of IL-17RB on Th2 cells and monocytes from LSCC patients and controls analyzed by flow cytometry (n = 25 vs. 27). Representative images of IL-17RB on (A) Th2 cells (B) and monocytes. (C) No significant differences in the frequency of IL-17RB on Th2 cells and monocytes were observed between the two groups ($p > 0.05$).

Abbreviations: IL-17B: Interleukin-17B; IL-17RB: Interleukin-17 receptor B; LSCC: Laryngeal squamous cell carcinoma; LYM: Lymphocyte; MON: Monocyte; Th2: T helper Type 2.

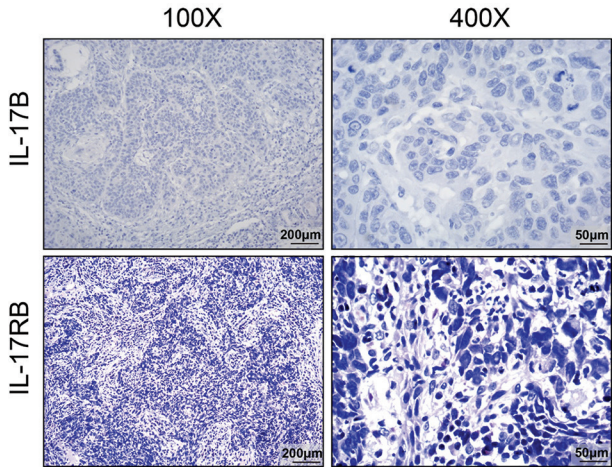

Figure 2. IL-17B and IL-17RB immunoreactivity in LSCC tissues detected by IHC

Abbreviations: IHC: Immunohistochemistry; IL-17B: Interleukin-17B; IL-17RB: Interleukin-17 receptor B; LSCC: Laryngeal squamous cell carcinoma.

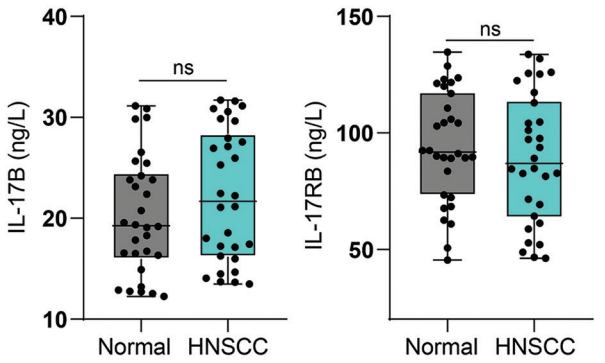

Figure 3. Serum levels of IL-17B and IL-17RB in LSCC patients and normal volunteers examined by ELISA (p>0.05)

Abbreviations: ELISA: Enzyme-linked immunosorbent assay; HNSCC: Head and neck squamous cell carcinoma; IL-17B: Interleukin-17B; IL-17RB: Interleukin-17 receptor B; LSCC: Laryngeal squamous cell carcinoma.

4. Discussion

This is the first study to explore the comprehensive expression profile and clinical significance of IL-17B and IL-17RB in LSCC, combining bioinformatic analysis. In the present study, the majority of LSCC patients enrolled were male, with only one female patient, and the average age of LSCC patients was 67 years, which is consistent with the general characteristics of HNSCC.[2] Most cancers derived from the primary site of the glottis, followed by the supraglottis and subglottis, which is also a common clinical characteristics of LSCC. More than 60% of cases were in the early stages (T1 + T2), and one-third of cases had lymph node involvement, without distant metastasis.

IL-17RB expression on immune cells was examined by flow cytometry, using cell sorting with surface markers for Th2 cells and monocytes. Compared with healthy subjects, there was no significant difference in IL-17RB expression

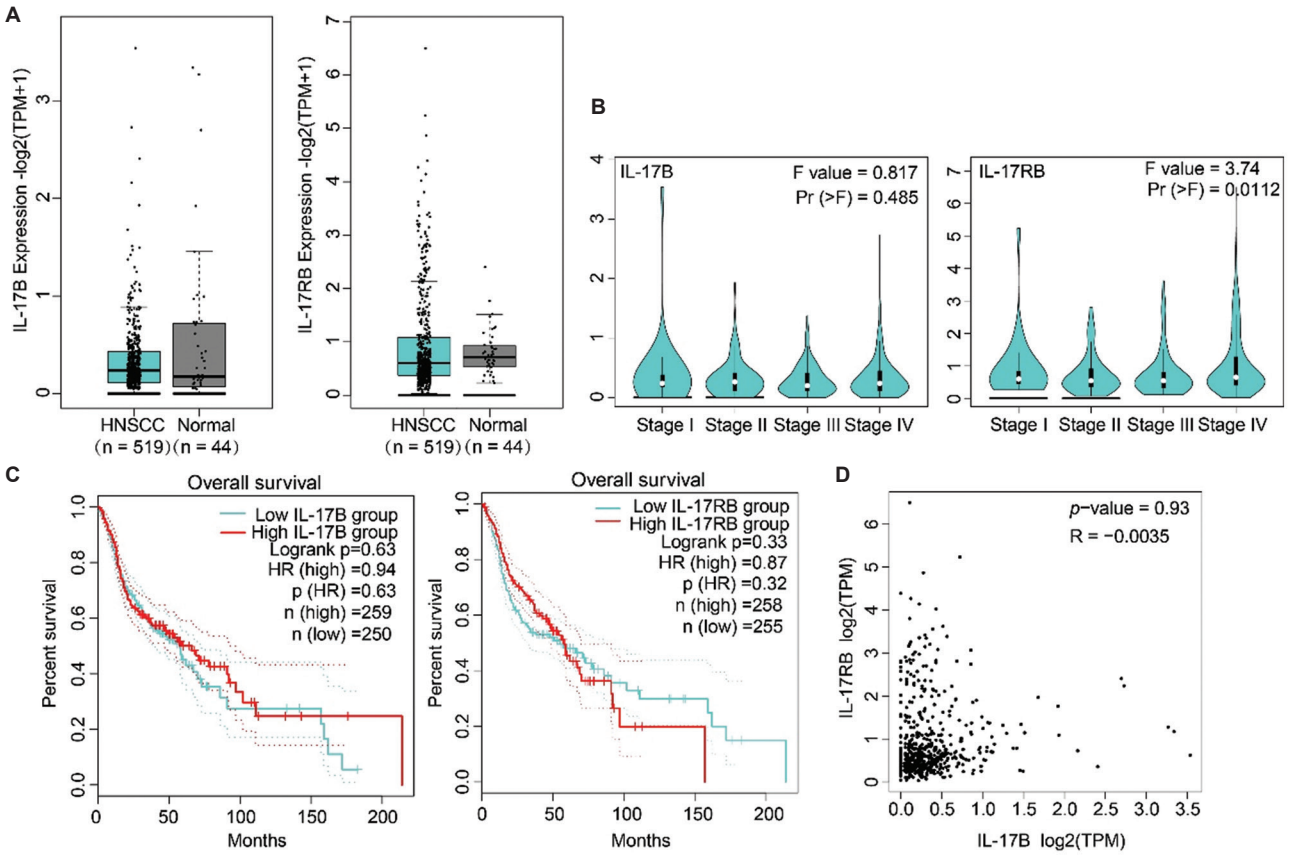

Figure 4. IL-17B/IL-17RB expression in HNSCC and normal tissues analyzed with GEPIA2. (A) Target gene expression levels. (B) Correlation of gene expression with pathological stage. (C) OS of target genes in HNSCC based on Kaplan-Meier plotter. (D) Correlation between IL-17B and IL-17RB mRNA expression level in cancer tissues.

Abbreviations: GEPIA: Gene Expression Profiling Interactive Analysis; HNSCC: Head and neck squamous cell carcinoma; IL-17B: Interleukin-17B; IL-17RB: Interleukin-17 receptor B; OS: Overall survival.

in these two cell populations in LSCC patients. The low expression of IL-17RB on $CD14^+$ monocytes was consistent with a previous report.[37] Surprisingly, according to RNA-seq data from the HPA database, IL-17B and IL-17RB were expressed on basophils in normal subjects.[36] More experiments are needed to explore IL-17RB expression on immune cells under LSCC settings.

The protein expression of IL-17B and IL-17RB in LSCC cancer tissues was revealed through IHC in our study. The IHC results showed that there was no immunoreactivity of IL-17B and weak immunoreactivity of IL-17RB located in cytoplasm and membrane in cancerous tissues, both of which showed no significant difference compared with para-cancer tissues. Consistently, IHC images from the HPA database displayed negative expression of IL-17B and weak expression of IL-17RB in similar locations across HNSC samples. Conversely, it has been reported that pancreatic tumor cells with high levels of IL-17RB also expressed its ligand, IL-17B.[38]

The detection of serum IL-17B and IL-17RB levels by ELISA displayed no significant difference between LSCC patients and healthy controls, which limited their potential as serum biomarkers for LSCC in clinical practice. Transcriptomics data extracted from GEPIA were in line with these findings. In addition, GEPIA results showed that IL-17B and IL-17RB expression were not correlated with OS in HNSC, which indicated that neither IL-17 B nor IL-17RB could be prognostic indicators in LSCC.

As cancer-related genes with low cancer specificity, the expression patterns of IL17B/IL-17RB and their roles differ in various cancers. Bie *et al.*[39] found that gastric cancer tissues exhibited markedly elevated IL-17RB levels, and this overexpression predicted worse clinical outcomes. Interestingly, IL-17B was predominantly elevated in patient's serum rather than in gastric tumor tissue.[39] Mechanistically, they found that IL-17B/IL-17RB signaling promotes gastric cancer cell growth, migration, and stem-like traits by activating the AKT/β-catenin axis.[39]

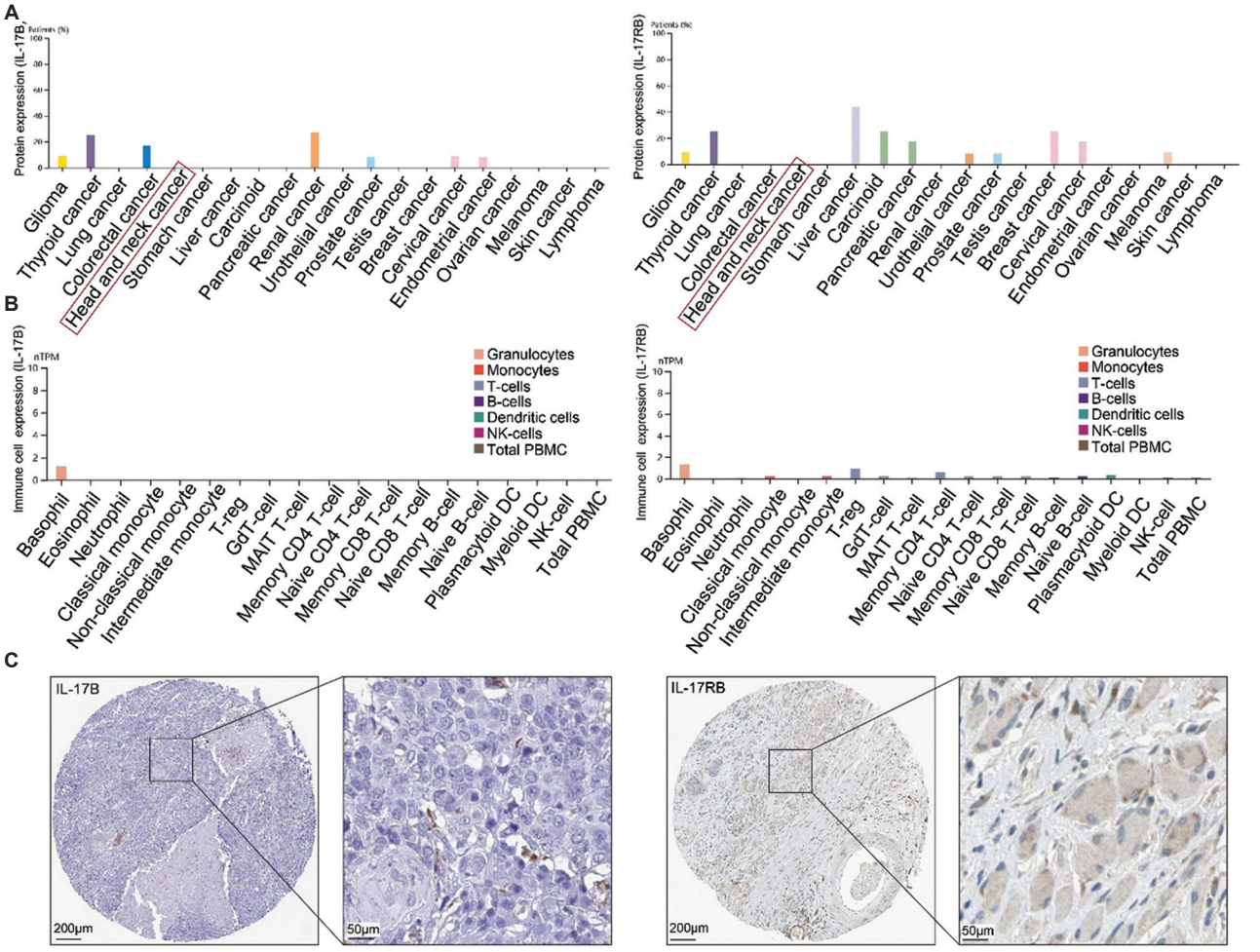

Figure 5. Proteomic analysis of IL-17B and IL-17RB in HNC based on the HPA database. (A) Negative protein expression of both genes in HNC. (B) Expression of both genes across 18 immune cell types and total PBMCs from RNA-seq data. (C) Negative expression of IL-17B and weak expression of IL-17RB located in the cytoplasm and membrane of squamous cell carcinoma tissue by IHC.

Abbreviations: HNC: Head and neck cancer; HPA: Human protein atlas; IHC: Immunohistochemistry; IL-17B: Interleukin-17B; IL-17RB: Interleukin-17 receptor B; NK-cells: Natural killer cells; OS: Overall survival; PBMCs: Peripheral blood mononuclear cells.

Another study also found that IL-17B/IL-17RB promotes the self-renewal and tumorigenesis of CSCs by inducing beclin-1 ubiquitination. Recombinant IL-17B (rIL-17B) augmented CSCs sphere formation *in vitro* and accelerated tumor growth and metastasis *in vivo*, which suggests that targeting the IL-17B/IL-17RB axis could unveil novel therapeutic avenues for cancer treatment.[27]

Another study reported that high IL-17RB expression predicts post-operative metastasis and shorter progression-free survival in pancreatic cancer. *Ex vivo* works from the same group showed that IL-17B/RB signaling, through ERK1/2, upregulates CCL20/CXCL1/IL-8/TFF1 expression, thereby driving local invasion, recruiting macrophages and endothelial cells to the primary tumor, and sustaining disseminated cancer cells in distant organs.[38] IL-17RB levels in pancreatic cancer cells and tissues positively correlated with mucin 1 (MUC1) and mucin 4 (MUC4) expression, which jointly enhanced stem-like properties and conferred chemoresistance. Moreover, IL-17RB also transcriptionally boosted MUC1 and MUC4, amplifying stem-like traits and gemcitabine resistance. Thus, IL-17RB blockade restored gemcitabine sensitivity by suppressing MUC expression in pancreatic cancer. These data establish IL-17RB as a clinically actionable target to improve pancreatic cancer therapy.[40] IL-17RB distinctly promotes tumor expansion and metastatic spread upon stimulation with IL-17B. Another study mapped the proximal signaling cascade of IL-17RB, pinpointing a possible druggable node for pancreatic cancer intervention.[30] In addition, IL-17RB expression was found to be upregulated in thyroid cancer cells and tissues. By triggering ERK1/2-dependent matrix metalloprotein-9 (MMP-9) expression, IL-17RB

accelerates thyroid cancer invasion and metastasis, making it as a promising therapeutic target.[29] In lung cancer cell lines, IL-17B–IL-17RB signaling and ERK engage in a self-reinforcing loop that amplifies invasive and migratory capacity.[31] Moreover, upregulation of Il-17RB in breast cancer cells derived from tumor-draining lymph nodes (TDLNs) contributes to higher malignancy and distant metastasis, which was mediated by TGF-β1 secreted from regulatory T cells (Tregs) in TDLNs through downstream SMAD2/3/4 signaling.[28] In colorectal cancer (CRC), decreased expression of IL-17RB was associated with disease progression. Consequently, IL-17RB emerges as a promising prognostic biomarker for CRC. Conversely, IL-17B abundance correlates positively with infiltrating $CD4^+$ T cells and mast cells, yet inversely with recurrence-free survival, indicating that IL-17B and IL-17RB influence colorectal tumorigenesis through distinct mechanistic pathways.[41]

Cytokine profiles are highly context-dependent. The negative results for L17B/IL-17RB in LSCC in our study are likely attributable to differences in tumor biology, expression levels, and cellular context compared with other cancer types. Consequently, as discussed earlier, a given cytokine may act as a tumor-promoting factor in one cancer type while remaining silent or even tumor-suppressive in another. The role and function of IL17B/IL-17RB in LSCC tumorigenesis were not further explored in the present study due to their negative expression profiles.

The present study has certain limitations. First, the modest sample size limited the broader applicability of our findings. Second, the findings should be interpreted with caution due to the selection bias in clinical studies. Third, the present study was designed with well-operated experiments combining bioinformatics, which disclosed the negative expression of IL-17B/IL-17RB in LSCC and their limited clinical significance, which is, although objective, somewhat disappointing.

In conclusion, the present study unveiled a comprehensive expression profile of IL-17B/IL-17RB in LSCC, combining bioinformatic evidence for the first time. The integration of bioinformatics with experimental data enhanced the study's overall importance. Weak expression of IL-17RB on Th2 cells and monocytes, and negative immunoreactivity of IL-17B/IL-17RB in LSCC tissue were observed, which were validated by GEPIA and HPA databases. The study demonstrated that the transcriptome and proteome expression of IL-17B/IL-17RB were not correlated with OS in LSCC. Negative results of serum level also limited the possibility of IL-17B/IL-17RB as serum-based markers for LSCC in clinical practice. Further studies to confirm the negative findings of IL-17B/IL-17RB or to explore other cytokines within the IL-17 family in the context of LSCC should be encouraged.

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Conflict of interest

The authors declare that they have no competing interest.

Author contributions

Conceptualization: Peixia Yu, Yongjin Ji
Formal analysis: Hairu Wang, Deng Liu
Investigation: Shuxin Wen, Hairu Wang, Xueting Li, Xiaohong Zhang
Methodology: Shuxin Wen, Yongjin Ji
Writing–original draft: Yongjin Ji
Writing–review & editing: Peixia Yu

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanxi Bethune Hospital (YXLL-2021-088), and written informed consent for participation was obtained from participants or their guardians.

Consent for publication

Written informed consent for publication was obtained from participants or their guardians.

Availability of data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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