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RAPID COMMUNICATION

Transcriptomic analysis identifies a pan-cancer association of IL27 expression with cancer prognosis and immune microenvironment

Nowadays great progress has been made in targeted therapy and comprehensive therapy for a few cancers. But the prognosis of the vast majority of cancer patients is still weakness. It has been proven that inflammation can affect the development and treatment of cancer. Some previous studies have suggested that inflammation-related interleukins (ILs) play a significant role in the development of some cancers.[1,2] ILs act as a considerable role in immunity,[3] and inflammation affects the development of cancer. Therefore, the expression profile of *IL* gene may also be one of the vital markers of early pathological changes, occurrence and progression of cancer.[4,5] Currently, studies on the expression of *IL27* in cancer are still extremely limited. Our work comprehensively and systematically studied the *IL27* gene expression in the generic cancer when compared with the existing *IL27* gene related research experiment. We screened out cancer species linked with poor prognosis, and explored the correlation between *IL27* gene expression and immune cell infiltration and immune microenvironment in these cancers further, providing an increasing number of the direct basis for subsequent studies. Our findings showed that IL27 can be used to assess prognosis and immune infiltration in patients with colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), skin cutaneous melanoma (SKCM) and testicular germ cell tumors (TGCT) as a biomarker.

We analyzed the *IL27* gene's differential expressions in 33 tumors and normal tissues by Genotype-Tissue Expression (GTEx) and The Cancer Genome Atlas (TCGA) data sets, and the results were further verified by Cancer Cell Line Encyclopedia (CCLE) database. Univariate Cox risk regression analysis was used for exploring the types of cancer in which *IL27* expression was linked with overall survival. Kaplan–Meier plotter and Tumor Immune Estimation Resource (TIMER) were used to study the correlation between IL27 and immune invasion of cancer cells. To analyze the relationship between *IL27* gene expression and immune neoantigen, tumor mutation burden (TMB), microsatellite instability (MSI), DNA repair pathway mismatch repair (MMRs) and DNA methylation, we used the Spearman rank correlation coefficient. Gene Set Enrichment Analysis (GSEA) was used to analyze signaling pathways which were related to *IL27* gene expression. Finally, in order to further compare the expression difference of *IL27* gene in tumor tissues of patients with stage I and III, we used the result of immunohistochemistry (IHC) in Human Protein Atlas (HPA) database to verify the differences.

GTEx information set investigation demonstrated that *IL27* gene might have been hardly communicated over bone marrow and other 31 tissues, but was most expressed in liver (Fig. S1A). From the CCLE database analysis testified among 21 tumor cell lines, *IL27* gene expression was lowest in thyroid glands and highest in biliary tract (Fig. S1B). The expression differences of *IL27* in various tissues were compared and analyzed according to the sequencing data of cancer and para-cancer tissues in TCGA. The results are shown in Figure S1C. Using gene expression profile data, we analyzed the expression and prognosis of *IL27* gene in 33 tumors from TCGA database in this study. In many cancers, *IL27* is differentially expressed between cancerous and normal tissues. Compared with the corresponding normal tissues, *IL27* gene has a much lower expression in adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), HNSC, kidney renal clear cell carcinoma (KIRC), lung squamous cell carcinoma (LUSC), rectum adenocarcinoma (READ), uterine corpus endometrial

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carcinoma (UCEC) and so on. *IL27* gene was highly expressed in COAD, esophageal carcinoma (ESCA), GBM, kidney chromophobe (KICH), lung adenocarcinoma (LUAD), prostate adenocarcinoma (PRAD), SKCM, TGCT and so on (Fig. S1D). Genes linked with these traits have been linked to cancer in previous experiments. Using the results of the forest diagram of "disease free intervention"(Fig. S1E), "disease-specific survival"(Fig. S1F), "overall survival rate"(Fig. S1G), "process free intervention"(Fig. S1H), *IL27* gene interpretation and OS related tumor sorts were screened for further contemplate. In these databases, we found that low *IL27* expression may be a risk factor for poor prognosis in patients with CESC, liver hepatocellular carcinoma (LIHC), and SKCM. In addition, high expression of *IL27* may be a risk factor for poor prognosis in PATIENTS with ACC, KIRC, brain lower grade glioma (LGG), pancreatic adenocarcinoma (PAAD), TGCT, thymoma (THYM) and Uveal Melanoma (UVM) (Fig. 1A—J; Fig. S2). This indicates that the expression of *IL27* can be used as a prognostic indicator of tumors.

Through public database TIMER analysis, we discovered that the *IL27* gene interpretation assumed a part in the safe invasion of LIHC, THYM, CESC, COAD, GBM, HNSC, KIRC, kidney renal papillary cell carcinoma (KIRP), SKCM, and TGCT (Fig. 1K—T).

What's more, improvement has been made that an ever increasing lumber of reports show that tumor resistant microenvironment assumes a specific part previously, tumor genesis. To further evaluate the role of *IL27* in the tumor immune microenvironment, we evaluated resistant scores for each growth sort, and our results showed that the *IL27* expression of in the ESTIMATE immune score might have been fundamentally connected with acute myeloid leukemia (LAML) ($P = 0$), TGCT ($P = 0$) (Fig. S3A—C), and the *IL27* expression of in the stromal score might have been fundamentally connected with LGG, SKCM, and BLCA (Fig. S3C). Our findings suggested that there are common immune checkpoints in CESC, HNSC, KIRC, LUAD, ovarian serous cystadenocarcinoma (OV), sarcoma (SARC), TGCT, UCEC and so forth (LAG3, ICOS, CD28, CD80, PDCD1, CD27, CD40, TIGIT, CD86, and TNFRSF9), and the expression of *IL27* gene was highly correlated with these immune checkpoints ($r > 0$, $^{***}P < 0.001$) (Fig. 1U). These correlations may be the underlying mechanisms in which *IL27* gene regulates the functions of *T* and B cells in CESC, HNSC, KIRC, LUAD, OV, SKCM, TGCT and so on.

We independently counted the number of neoantigens previously, in each tumor sample, and the effects demonstrated that GBM, LUAD, LUSC, BRCA, UCEC, CESC were notably relevanted to neoantigens (Fig. S3D). The correlation between the expression of *IL27* gene and TMB, MSI, DNMT3A, DNMT3B suggested that it has certain influences on the prognosis of patients with LIHC, THYM, CESC, COAD, GBM, HNSC, KIRC, KIRP, LUAD, LUSC, OV, SARC, SKCM, TGCT, and UCEC (Fig. S4).

And the expression of *IL27* gene was highly relevant to DNA repair gene EPCAM in KIRC and LIHC, MSH6 and MSH2 in SARC and THYM ($^{***}P < 0.001$), and slightly correlated with PMS2 in KIRP. It was moderately correlated with MLH1 in LUSC ($^{*}P < 0.05$), MLH1, MSH2 and PMS2 in GBM, and EPCAM in CESC and TGCT ($^{**}P < 0.01$) (Fig. S5A). Notably, we demonstrated a correlation between *IL27* gene expression and methyltransferase, these results indicated that the expression of *IL27* gene may affect the prognosis of patients with LIHC, THYM, CESC, COAD, HNSC, KIRC, LUAD, OV, SKCM, TGCT and UCEC.

In order to verify the results of the above database analysis, we used GSEA to analyze the enrichment of

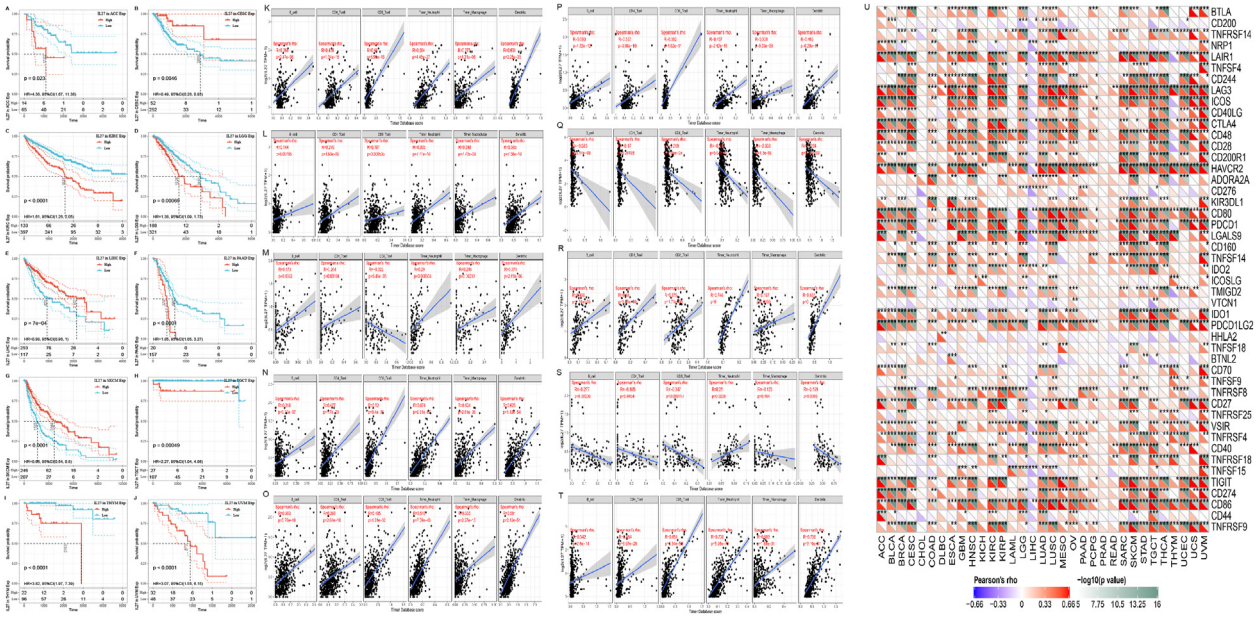

Figure 1 Correlation analysis of *IL27* gene expression with prognosis and immunity. **(A—J)** Overall survival curves of cancers with significant associated between *IL27* gene expression and prognosis. **(K—T)** Correlation analysis of *IL27* gene expression in immune infiltration in 33 tumors. **(U)** Correlation analysis between 33 tumors and more than forty common immune checkpoints. A *P value* < 0.05 was considered statistically significant. The symbols "*", "**", and "***" mean *P* values < 0.05, < 0.01, and < 0.001, respectively.

HALLMARK pathways and the Kyoto Encyclopedia of Genes and Genomes (KEGG) in the high and low expression groups. As a result, the analysis of the KEGG showed that *IL27* mediated NATURAL KILLER CELL MEDIATED_CYTOTOXICITY ($P = 0$), CHEMOKINE SIGNALING PATHWAY ($P = 0$) and FC GAMMA R_MEDIATED PHAGOCYTOSIS ($P = 0$) pathway was highly expressed (Fig. S5B and Table S1).

We performed additional verification, the results suggest that in CESC, LIHC and SKCM, the expression of IL27 in the tumor tissue of stage III patients is lower than that of stage I; while in KIRC, LGG and PAAD, its expression in tumor tissues of patients with stage III is higher than that in stage I (Fig. S6). The results of experimental verification were basically consistent with the results of data analysis.

We must acknowledge the potential limitations of our analysis. The relationship between the expression of *IL27* gene and prognosis of systemic cancer was analyzed by public database. Therefore, our work is retrospective rather than prospective. In addition, a few other important clinicopathological characteristics such as age, sex, TNM stage and risk score, were not included in the study. Subsequent animal studies and larger studies are needed to confirm the impact of *IL27* on patient outcomes and to explore more effective treatment strategies.

In conclusion, IL27 is linked with the prognosis of patients with various tumors and the infiltration levels of immune cells such as macrophages, $CD4^+$T cells, $CD8^+$T cells, neutrophils and dendritic cells. These findings suggest that IL27 can be used as a prognostic and immune indicator of some cancers such as CESC, KIRC, LUAD, and provided a theoretical basis for further study of the potential relationship and potential mechanism of IL27 in ubiquities. As a new prognostic biomarker of solid tumors, IL27 can help improve the level of clinical treatment decision of solid tumors.

Ethics declaration

This study was conducted in accordance with the recommendations of the Ethics Committee of the Second Affiliated Hospital of Nanchang University. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University.

Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

Data availability

The microarray data was obtained from the GTEx, TCGA, TIMER, CCLE, GSEA, KEGG and HPA Databases.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.08.016.

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