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ORIGINAL PAPER

SIRT2 as a Potential Biomarker in Lung Adenocarcinoma: Implications for Immune Infiltration

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Abstract

SIRT2 play important roles in cell cycle and cellular metabolism in the development of non-small cell lung cancer (NSCLC), and SIRT2 exhibits its therapeutic effect on NSCLC tumors with high expression of SIRT2. Nevertheless, the clinical relevance of SIRT2 in lung adenocarcinoma (LUAD), particularly its impact on tumor growth and prognostic implications, remains obscure. This investigation entailed a comprehensive analysis of SIRT2 mRNA and protein expression levels in diverse tumor and corresponding healthy tissues, utilizing databases such as TIMER 2.0, UALCAN, and HPA. Prognostic correlations of SIRT2 expression in LUAD patients, stratified by distinct clinicopathological characteristics, were evaluated using the KM Plotter database. Additionally, the TCGA and TIMER 2.0 databases were employed to assess the relationship between SIRT2 and immune infiltration, as well as to calculate immunity, stromal, and estimation scores, thus elucidating the role of SIRT2 in modulating tumor immunotherapy responses. Furthermore, Gene Set Enrichment Analysis (GSEA) was utilized to elucidate SIRT2's biological functions in pan-cancer cells. Our findings revealed a marked reduction in both mRNA and protein levels of SIRT2 in LUAD tumors relative to healthy tissue. Survival analysis indicated that diminished SIRT2 expression correlates with adverse prognostic outcomes in LUAD. Furthermore, SIRT2 expression demonstrated a significant association with various clinicopathologic attributes of LUAD patients, influencing survival outcomes across different clinicopathologic states. Functional enrichment analyses highlighted SIRT2's involvement in cell cycle regulation and immune response. Notably, SIRT2 exhibited a positive correlation with immune cell infiltration, including natural killer (NK) cells, macrophages, and dendritic cells (DCs). In summary, SIRT2 was a potential prognostic biomarker for LUAD and and a new immunotherapy target.

Keywords SIRT2 · Lung adenocarcinoma (LUAD) · Biological functions · Expression · Immune response

Guining Zhang and Shuyu Lu contributed equally to this work and should be considered as equal first coauthors.

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Introduction

Lung cancer, notably arising from the bronchial mucosa or pulmonary glands, is distinguished by its alarmingly high morbidity and mortality rates. This malignancy is principally divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [1–4]. Lung adenocarcinoma (LUAD), a predominant subtype of NSCLC, not only represents a significant fraction of lung cancers but is also marked by an increasing incidence year by year [5, 6]. Characteristically, LUAD is known for features typical of aggressive tumors, including high rates of metastasis and invasion [7].

The landscape of lung cancer therapy has undergone substantial evolution in recent years, particularly with the introduction of novel treatments like immunotherapy and targeted therapy, which have markedly transformed the prognosis for patients, LUAD included [8, 9]. However, lung cancer's often asymptomatic early stages present a significant obstacle to early detection [10]. Further complicating the treatment paradigm is the development of resistance to drugs employed in targeted and immunotherapy regimens [11]. Consequently, despite advancements in treatment, the therapeutic efficacy for lung cancers, including LUAD, remains less than ideal, with a five-year survival rate for LUAD patients lingering at approximately 19% [12, 13]. However, the survival is significantly prolonged in those patients who have an EGFR mutation and who receive TKI inhibitors in NSCLC [14, 15].Although some TKIs have side effects, the advantage of drugs based on molecular analysis is significant [16].

Therefore, an in-depth exploration of NSCLC's pathogenesis, especially LUAD's pathogenesis is crucial and holds immense practical significance for improving treatment approaches for this disease.

SIRT2, a member of the sirtuin family of protein lysine deacetylases, utilizes nicotinamide adenine dinucleotide (NAD) as a cofactor. This gene, situated on human chromosome 19, encompasses 18 exons [17, 18]. Predominantly located in the cytoplasm, SIRT2's expression is observed in various organs, including the brain, heart, liver, and esophagus [19]. It plays a pivotal role in processes such as aging, differentiation, metabolism, and DNA damage repair [20, 21].

Moreover, SIRT2 exhibits a dualistic role in oncogenesis, acting as both a tumor suppressor and promoter, contingent on the tumor type [22, 23]. Elevated SIRT2 expression, observed in hepatocellular carcinoma, gastric carcinoma, and melanoma, suggests its tumor-promoting role in these cancers [24]. However, SIRT2 expression in glioma, ovarian cancer, and breast cancer tissues is lower compared to normal tissues, indicating an oncogenic role in these cancers [25]. Further, an increasing body of research highlights SIRT2's critical role in the pathogenesis of non-small cell lung cancer (NSCLC), functioning as a negative regulator [26]. Studies reveal that SIRT2 expression in NSCLC tissues is lower than in normal tissues and is intricately linked to the prognosis of NSCLC patients. Functionally, SIRT2 can suppress genes associated with tumor growth and development. For instance, it interacts with the promoter region of the methylase JMJD2A gene, inhibiting JMJD2A expression, thereby curbing NSCLC cell proliferation and impeding tumor development [27]. Additionally, SIRT2 enhances tumor drug sensitivity, potentially improving NSCLC prognosis and serving as a crucial target in NSCLC therapy [28]. Moreover, it is reported that SIRT2 play an important role in promoting the survival of LUAD through the KLF8-SIRT2-G6PD axis [29].

Nevertheless, the potential clinical utility of SIRT2 in NSCLC, particularly concerning growth development and prognosis in lung adenocarcinoma (LUAD), remains to be fully elucidated. The underlying mechanisms warrant further investigation.

Materials and Methods

Differential Analysis of SIRT2 Expression

To analyze the differential mRNA expression levels of SIRT2 across various cancer types, the TIMER2.0 database (http://timer.cistrome.org/) was employed. This involved navigating to the "Gene_DE" module within TIMER2.0, leading to the differential analysis interface where the SIRT2 gene was specifically input for investigation. Concurrently, UALCAN (https://ualcan.path.uab.edu/), a comprehensive public repository for TCGA gene expression analysis, was utilized. This database facilitated the examination of SIRT2 expression both at mRNA and protein levels in LUAD tissues compared to normal lung tissues, including an exploration of SIRT2 gene expression across diverse clinicopathological features. Furthermore, the Human Protein Atlas (HPA) database (https://www.proteinatlas.org/) provided an immunohistochemical perspective, delineating the expression of SIRT2 in cancerous versus normal tissues. A significance threshold was set at $P < 0.05$, with the analysis encompassing cancerous tissues and their corresponding normal counterparts.

Survival Analysis

The Kaplan–Meier Plotter database was instrumental in evaluating the overall survival profile of LUAD patients, in relation to SIRT2 expression levels across various

clinicopathological features. This analysis included the calculation of Hazard Ratios (HR) with 95% confidence intervals, along with logrank *p*-values.

Differential mRNA Analysis

For the analysis of differential mRNAs, the Xiantao Academic platform (https://www.xiantao.love/) was accessed. Utilizing the "Expression of Differences" module within the "All Tools" section, various parameters were input for comprehensive analysis. This process involved selecting the "[Cloud] Filter Molecules" option, followed by entering the relevant parameters. The resulting data were organized to facilitate the identification of significant molecular differences, leading to the creation of a volcano plot. The criteria for significance were established as an absolute log fold change (|logFC|) greater than 1.5 and an adjusted *P*-value (P.adj) of less than 0.05.

Single-Gene Correlation Screening

The examination of single-gene correlations with SIRT2 was conducted using the Xiantao Academic Online Analysis Tool. This process entailed accessing the "Interactive Network" module within the "All Tools" section, followed by the selection of "[Cloud] Single-gene Correlation Screening". After inputting various parameters for the analysis, the data were methodically organized. Consequently, the top 15 genes demonstrating a positive correlation with SIRT2 expression were identified and selected for further study.

Functional Enrichment Analysis

The functional enrichment analysis of SIRT2 in lung adenocarcinoma (LUAD) was executed through the Xiantao Academic Online Analysis Tool, leveraging data from the TCGA database. This involved selecting the "[Cloud] Single Gene-Differential Analysis" module and configuring the necessary parameters for the analysis. Post-data organization, mRNA extraction was performed, followed by screening of differentially expressed genes using threshold values of padj < 0.05 and |logFC|> 1.5. Subsequent to this, Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA) were conducted in distinct modules.

SIRT2 Immunocorrelation Analysis

The ssGSEA algorithm was utilized to assess the presence of 24 types of immune cells in LUAD tissue samples. This led to the individual analysis of the top 8 immune cells that exhibited the highest correlation with SIRT2 expression, culminating in the generation of correlation scatter plots for each. The Wilcoxon rank-sum test was employed to evaluate the enrichment of immune infiltrating cells in LUAD patients, particularly contrasting those in the high SIRT2 expression group with those in the ULBP2 low-expression group.

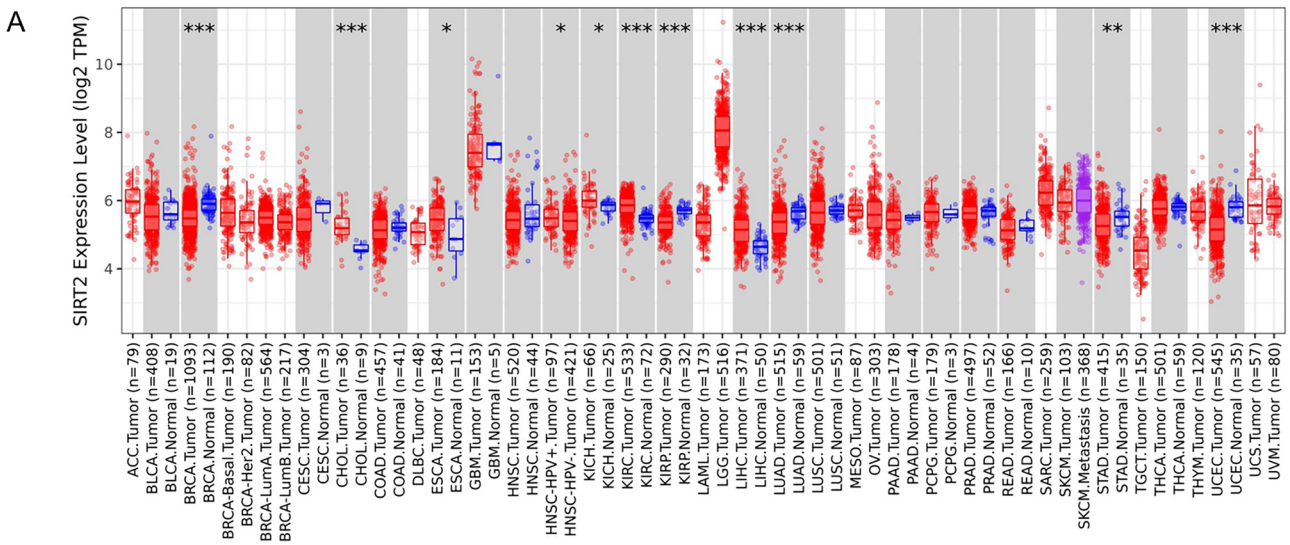
Results

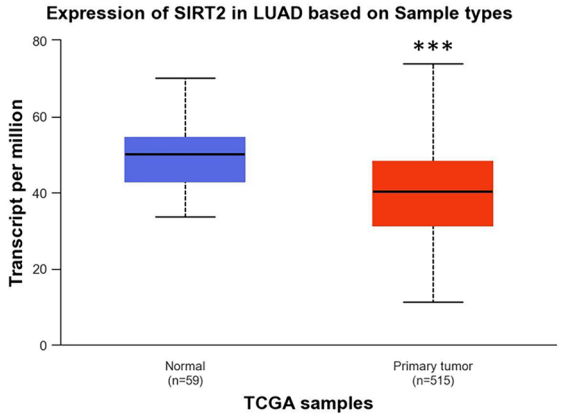
Diminished Expression of SIRT2 in LUAD

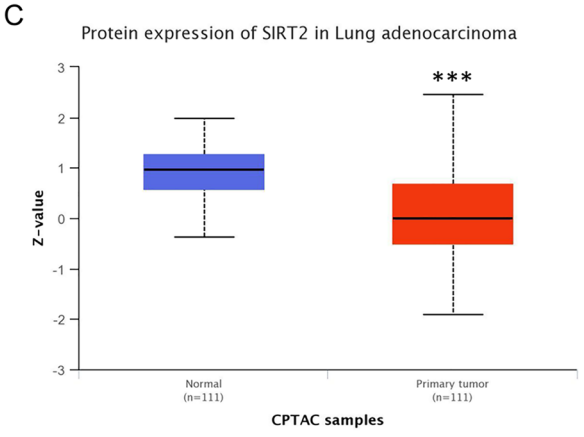
To ascertain the expression levels of SIRT2 in both normal and tumor tissues, we employed the TIMER 2.0 database for a comprehensive analysis of SIRT2 mRNA across various tumor types and their corresponding normal tissues. Our findings revealed a significant downregulation of SIRT2 expression in tumor tissues, notably in breast cancer (BRCA), kidney renal papillary cell carcinoma (KIRP), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), and uterine corpus endometrial carcinoma (UCEC), compared to their normal counterparts. Conversely, an upregulation of SIRT2 expression was observed in tumor tissues of cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), and liver hepatocellular carcinoma (LIHC) (Fig. 1A). Further analysis in the UALCAN database, focusing specifically on LUAD tumor tissues, corroborated these findings, indicating a significant reduction in SIRT2 mRNA expression in LUAD tumors relative to normal tissues (Fig. 1B). This trend was mirrored at the protein level, with SIRT2 protein expression markedly lower in LUAD tumors than in normal tissues, as demonstrated by both UALCAN and Human Protein Atlas (HPA) database analyses (Fig. 1C and D, respectively). Western blot results also showed that SIRT2 was lower in lung cancer cell lines compared with normal lung cells (Fig. 1E). These results collectively affirm that both mRNA and protein expression levels of SIRT2 are significantly decreased in LUAD tumor tissues.

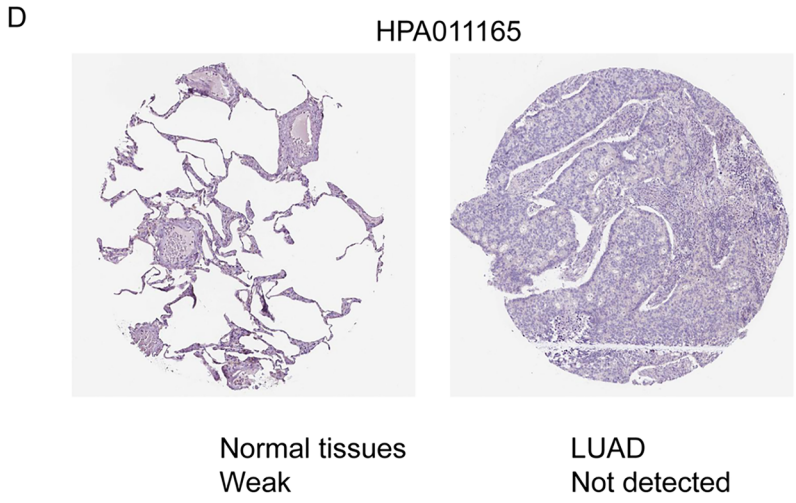
Association of SIRT2 Expression with Clinicopathological Features in LUAD

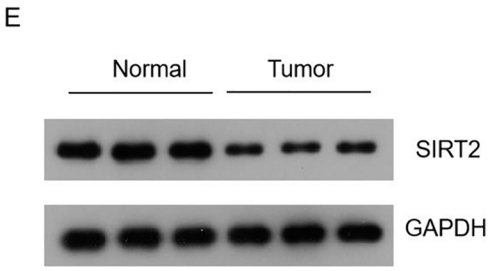
The relationship between SIRT2 expression and various clinicopathological characteristics in LUAD patients was examined using UALCAN, an online platform based on the TCGA database. Our analysis revealed a significant association of SIRT2 expression with several clinicopathologic features, including gender, age, smoking status, and lymph node metastatic stage (Figs. 2A–D). Notably, SIRT2 expression levels were considerably lower in male LUAD patients compared to females. Patients aged between 21–40 years exhibited a significantly reduced SIRT2 expression compared to


A
SIRT2 Expression Level (log2 TPM)
10
8
6
4
***
***
*
*
*
***
***
***
***
**
***
ACC.Tumor (n=79)
BLCA.Tumor (n=408)
BLCA.Normal (n=19)
BRCA.Tumor (n=1093)
BRCA.Normal (n=112)
BRCA-Basal.Tumor (n=190)
BRCA-Her2.Tumor (n=82)
BRCA-LumA.Tumor (n=564)
BRCA-LumB.Tumor (n=217)
CESC.Tumor (n=304)
CESC.Normal (n=3)
CHOL.Tumor (n=36)
CHOL.Normal (n=9)
COAD.Tumor (n=457)
COAD.Normal (n=41)
DLBC.Tumor (n=48)
ESCA.Tumor (n=184)
ESCA.Normal (n=11)
GBM.Tumor (n=153)
GBM.Normal (n=5)
HNSC.Tumor (n=520)
HNSC.Normal (n=44)
HNSC-HPV+.Tumor (n=97)
HNSC-HPV-.Tumor (n=421)
KICH.Tumor (n=66)
KICH.Normal (n=25)
KIRC.Tumor (n=533)
KIRC.Normal (n=72)
KIRP.Tumor (n=290)
KIRP.Normal (n=32)
LAML.Tumor (n=173)
LGG.Tumor (n=516)
LIHC.Tumor (n=371)
LIHC.Normal (n=50)
LUAD.Tumor (n=515)
LUAD.Normal (n=59)
LUSC.Tumor (n=501)
LUSC.Normal (n=51)
MESO.Tumor (n=87)
OV.Tumor (n=303)
PAAD.Tumor (n=178)
PAAD.Normal (n=4)
PCPG.Tumor (n=179)
PCPG.Normal (n=3)
PRAD.Tumor (n=497)
PRAD.Normal (n=52)
READ.Tumor (n=166)
READ.Normal (n=10)
SARC.Tumor (n=259)
SKCM.Tumor (n=103)
SKCM.Metastasis (n=368)
STAD.Tumor (n=415)
STAD.Normal (n=35)
TGCT.Tumor (n=150)
THCA.Tumor (n=501)
THCA.Normal (n=59)
THYM.Tumor (n=120)
UCEC.Tumor (n=545)
UCEC.Normal (n=35)
UCS.Tumor (n=57)
UVM.Tumor (n=80)


B
Expression of SIRT2 in LUAD based on Sample types
Transcript per million
80
60
40
20
0
***
Normal
(n=59)
Primary tumor
(n=515)
TCGA samples


C
Protein expression of SIRT2 in Lung adenocarcinoma
Z-value
3
2
1
0
-1
-2
-3
***
Normal
(n=111)
Primary tumor
(n=111)
CPTAC samples


D
HPA011165
Normal tissues
Weak
LUAD
Not detected


E
Normal
Tumor
SIRT2
GAPDH

◂**Fig. 1** Expression Levels of SIRT2 in Lung Adenocarcinoma (LUAD). **A** Evaluation of SIRT2 expression across different cancer types using the TIMER database. **B** Analysis of SIRT2 mRNA expression in LUAD versus normal lung tissues via the UALCAN database. **C** Assessment of SIRT2 protein expression in LUAD and normal lung tissues using the UALCAN database. **D** Determination of SIRT2 protein expression in LUAD and normal lung tissues, utilizing the Human Protein Atlas (HPA) database. **E** Western blot detected the protein expression of SIR2 in human normal lung epithelial cells BEAS-2B and human lung adenocarcinoma cell line A549 in three independent repeated experiments

those in the 41–60 and 81–100 age groups. Additionally, SIRT2 expression was lower in tumor tissues of smokers than in non-smokers. A striking observation was the higher expression of SIRT2 in LUAD patients with N0-stage lymph node metastasis compared to those with N2 stage. These findings suggest that reduced SIRT2 expression in LUAD tumor tissues is intricately linked to patient demographics and disease characteristics, such as gender, age, smoking habit, and lymph node metastatic status.

SIRT2 Expression and Prognostic Value in LUAD

We investigated the correlation between SIRT2 expression and patient survival in LUAD by utilizing the KM Plotter online analysis platform. Kaplan–Meier survival analyses, derived from both gene chip and RNA-seq data, consistently indicated that lower SIRT2 expression is associated with a poorer prognosis in LUAD patients (Fig. 3A, B). Subgroup analyses further revealed this trend to be significant across various demographics and clinical stages, including male and female patients, pathologic stages 1 through 3, Caucasians, and non-smokers (Fig. 3C–I).

Differential Gene Expression and Co-expression Analysis of SIRT2

In light of SIRT2's potential as a prognostic marker in LUAD, we identified differentially expressed mRNAs in SIRT2 low-expression LUAD samples versus normal tissues. The volcano plot (Fig. 4A) depicted a predominance of upregulated genes. A heatmap illustrated the co-expression patterns of SIRT2 and the top fifteen positively correlated genes, underscoring their positive correlation with SIRT2 expression (Fig. 4B).

Functional Enrichment Analysis

To elucidate SIRT2's functional role in LUAD, we conducted Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses on the differentially expressed genes associated with SIRT2. GO enrichment analysis pinpointed SIRT2's involvement predominantly in cell cycle regulation, encompassing aspects like chromosome assembly and DNA replication (Figs. 5A–C). KEGG analysis suggested SIRT2's associations with various immune disorders, including systemic lupus erythematosus and the formation of neutrophil extracellular traps, as well as with sensory perceptions of taste and smell (Fig. 5D). Furthermore, Gene Set Enrichment Analysis (GSEA) highlighted SIRT2's critical role in acetylation processes intrinsic to cellular life activities and cell cycle regulatory mechanisms (Fig. 6).

Correlation of SIRT2 Expression with Tumor Immunity

Building on the previously identified association of SIRT2 with immune-related disorders in the KEGG enrichment analysis, we postulated a role for SIRT2 in modulating tumor immune responses. Given the crucial interplay between tumor development and immune infiltration, we embarked on a detailed exploration of the relationship between SIRT2 expression levels and tumor immunity in lung adenocarcinoma (LUAD). Utilizing the Sento Academic Online analysis tool, based on the TCGA database, we assessed the immune infiltrability in LUAD with varying levels of SIRT2 expression. The ssGSEA algorithm facilitated the evaluation of the association between the relative abundance of 24 types of immune cells and SIRT2 expression in LUAD (Fig. 7A). The analysis highlighted eight immune cell types demonstrating the strongest correlation with SIRT2 expression. These included immature dendritic cells (iDCs; $P < 0.001$, $r = 0.308$), natural killer (NK) cells ($P < 0.001$, $r = 0.306$), T follicular helper (TFH) cells ($P < 0.001$, $r = 0.290$), mast cells ($P < 0.001$, $r = 0.264$), eosinophils ($P < 0.001$, $r = 0.254$), macrophages ($P < 0.001$, $r = 0.187$), mature dendritic cells (DCs; $P < 0.001$, $r = 0.186$), and neutrophils ($P < 0.001$, $r = 0.145$) (Fig. 7B–I).

Further examination of immune cell enrichment in LUAD samples revealed a pronounced disparity between high and low SIRT2 expression groups. Notably, iDCs, NK cells, TFH cells, mast cells, eosinophils, macrophages, DCs, and neutrophils exhibited higher enrichment in the SIRT2 high-expression group compared to the low-expression group (Fig. 8). In summary, these results indicate that the expression of SIRT2 was closely related to tumor immunity, with high expression in immune cells such as NK cells, DC cells, and macrophages.

Discussion

In the realm of lung adenocarcinoma (LUAD) treatment, molecularly targeted therapies and immunotherapy have demonstrated notable efficacy, particularly with drugs

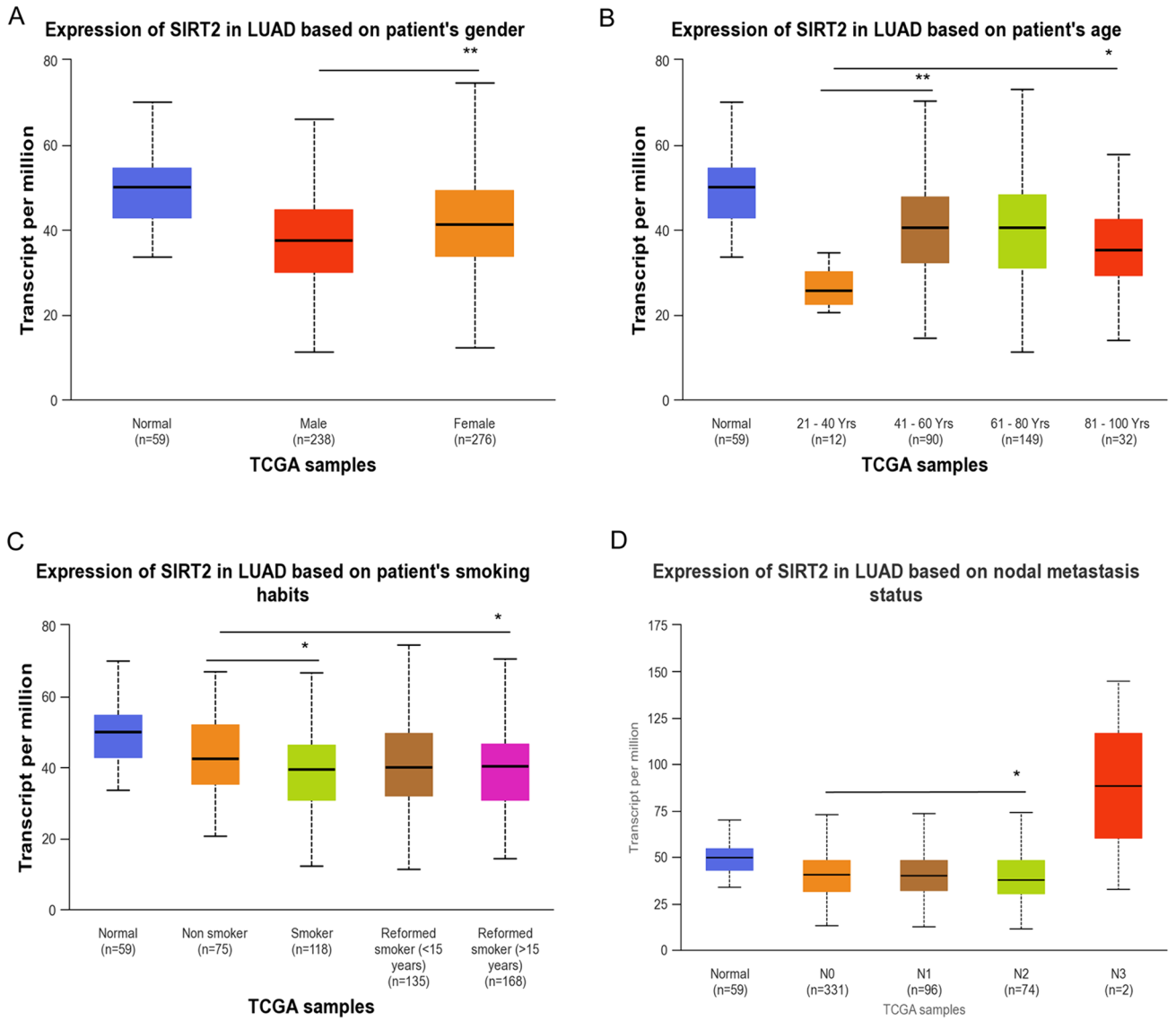


Fig. 2 Correlation between SIRT2 Expression and Clinicopathological Characteristics of LUAD Patients. **A** Relationship of SIRT2 expression with the gender of LUAD patients. **B** Correlation of SIRT2 expression with the age of LUAD patients. **C** Association between SIRT2 expression and smoking habits in LUAD patients. **D** Link between SIRT2 expression and lymph node metastasis status in LUAD patients

targeting immune checkpoints. However, the occurrence of adverse events has limited the effectiveness of immune checkpoint inhibitors in a majority of LUAD patients [30, 31]. This underscores the urgency of conducting comprehensive research into the pathogenesis of LUAD to identify potential therapeutic targets that could enhance patient prognosis.

Given the current ambiguity surrounding the pathogenesis of SIRT2 in tumors and the paucity of studies specifically examining its role, we adopted an extensive bioinformatics approach to elucidate SIRT2's involvement in LUAD development. Our initial analysis focused on comparing SIRT2 expression in LUAD tissues against normal lung tissues. This comparative study revealed a significant downregulation in both mRNA and protein levels of SIRT2 in LUAD tumors. Additionally, we observed that low SIRT2 expression was associated with poor clinicopathological status, exhibiting correlations with patient-specific factors such as gender, age, smoking history, and lymph node metastatic status.

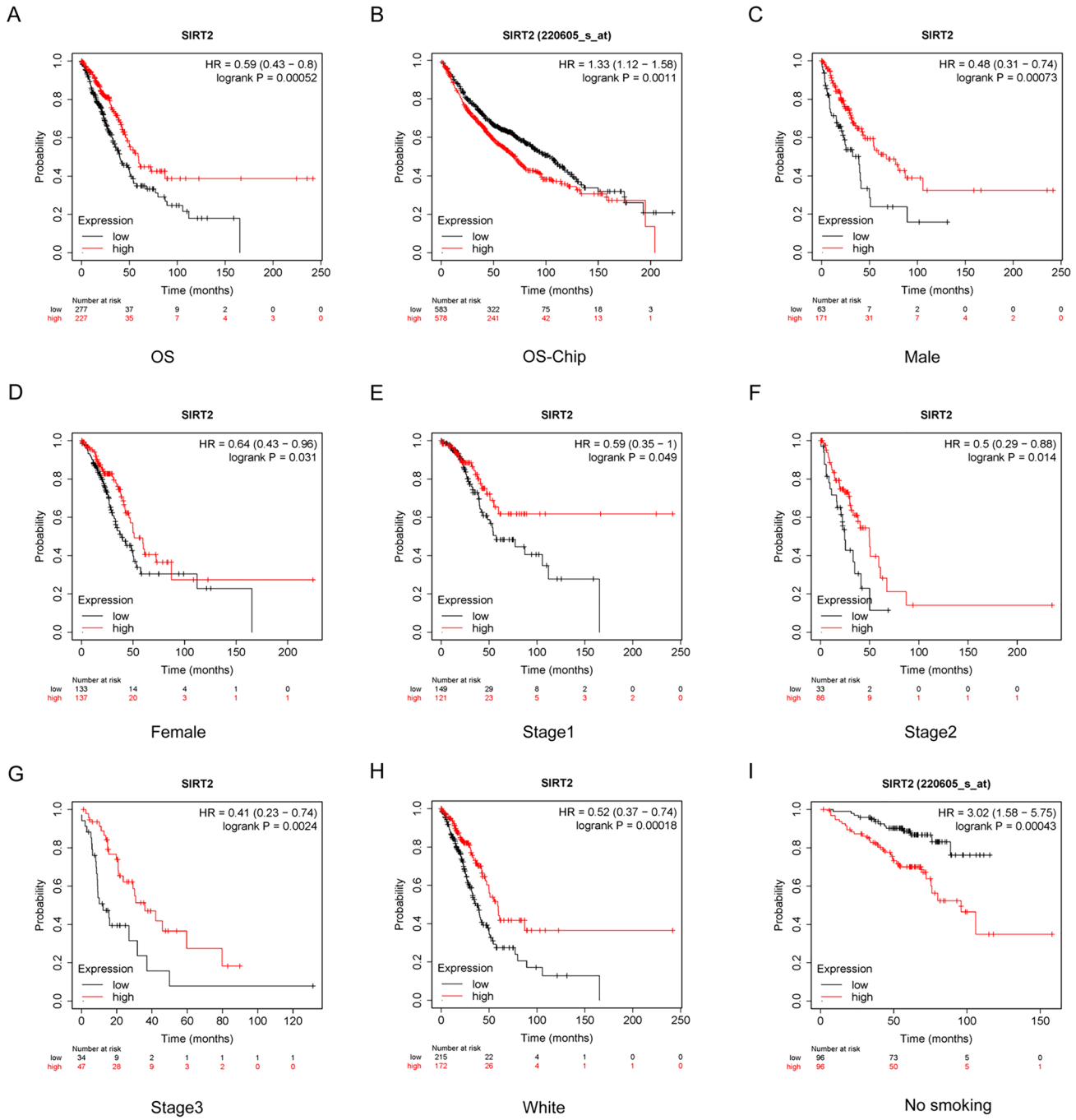


Fig. 3 SIRT2 Expression and Survival Rates in LUAD Patients Across Various Clinicopathological States. **A** Correlation of SIRT2 expression with overall survival in LUAD patients, based on RNA-seq data. **B** Association of SIRT2 expression with overall survival in LUAD patients, derived from microarray data. **C**–**I** Analysis of the relationship between SIRT2 expression and survival in LUAD patients across different clinicopathological states, including male patients, female patients, pathologic stages 1, 2, and 3, Caucasian patients, and non-smoking patients

Furthermore, our investigation into the prognostic value of the SIRT2 gene in LUAD highlighted its significance. We discovered that low SIRT2 expression is significantly linked to poorer prognosis in LUAD. This correlation extended to subgroups encompassing both male and female patients,

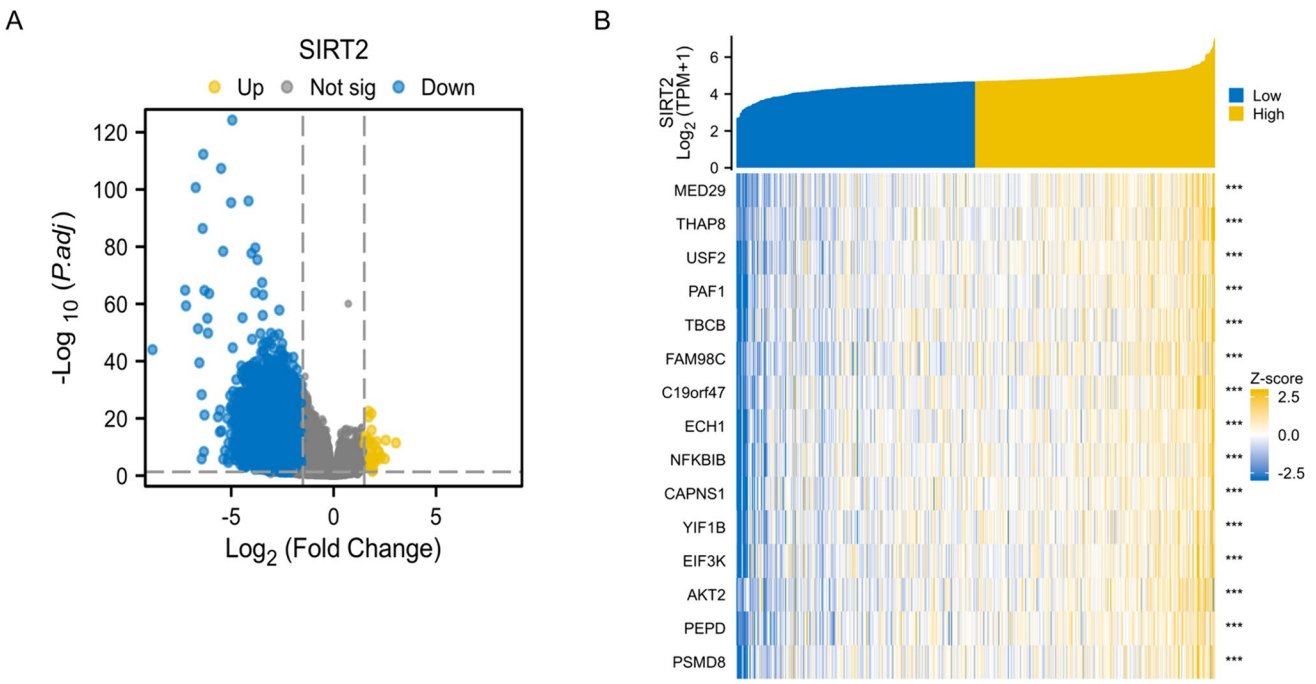


Fig. 4 Differential and Co-Expressed Genes Related to SIRT2 in Lung Adenocarcinoma (LUAD). **A** Volcano plot illustrating differential mRNA expression associated with SIRT2 in LUAD. **B** Heatmap displaying the pattern of genes co-expressed with SIRT2 in LUAD

across various pathological stages (stage1, stage2, stage3), and in specific demographics such as Caucasians and non-smoking individuals.

Tumors are fundamentally characterized by aberrant cell growth and proliferation, manifesting as a dysregulation in proliferation, apoptosis, and differentiation when compared to normal cells [32]. A prominent hallmark among these alterations is the disruption of the cell cycle, a critical aspect of tumorigenesis [33]. To investigate the molecular mechanisms underlying SIRT2's influence on the progression and prognosis of lung adenocarcinoma (LUAD), we conducted Gene Ontology (GO) functional enrichment analysis. This analysis substantiated the close association of SIRT2 expression in LUAD with cell cycle regulation. Complementary to this, the results of Gene Set Enrichment Analysis (GSEA) corroborated the connection between SIRT2 expression and cell cycle processes.

Cancer development is influenced by a confluence of factors including genetic predispositions, external environment, and notably, the tumor microenvironment [34]. The latter comprises immune cells, extracellular matrix, inflammatory mediators, and other constituents, playing a pivotal role in tumor progression, metastasis, and patient survival [35]. Perturbations in immune infiltration represent a significant aspect of tumor microenvironment alteration, critically impacting tumor progression and patient prognosis [36]. In tumor immunity, some immune cells, such as NK cells, DC cells and macrophages, play important roles in regulating the tumor microenvironment. NK cells are effectors of the body's immune defense, and various cytokines are key factors in cell maturation, activation, and survival, jointly maintaining the homeostasis of the tumor microenvironment [37]. At the same time, many tumor targeted therapeutic products targeting NK cells have been successively developed, such as rituximab (anti-cd20), etozumab (anti-slamf7), trastuzumab (anti-her2/neu), which are respectively used to treat some B cell malignant tumors, multiple myeloma and some forms of breast cancer [38]. DC cells participate in and regulate innate and adaptive immune responses by processing and presenting antigens, secreting cytokines and growth factors, and activating T cells, maintaining the immune homeostasis of the body and playing a key role in anti-tumor immune responses [39]. Macrophages play important roles in immune defense, immune regulation, and immune surveillance in the immune microenvironment (40). In LUAD, our findings from the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis revealed that SIRT2 expression is intricately linked to immunity. Further

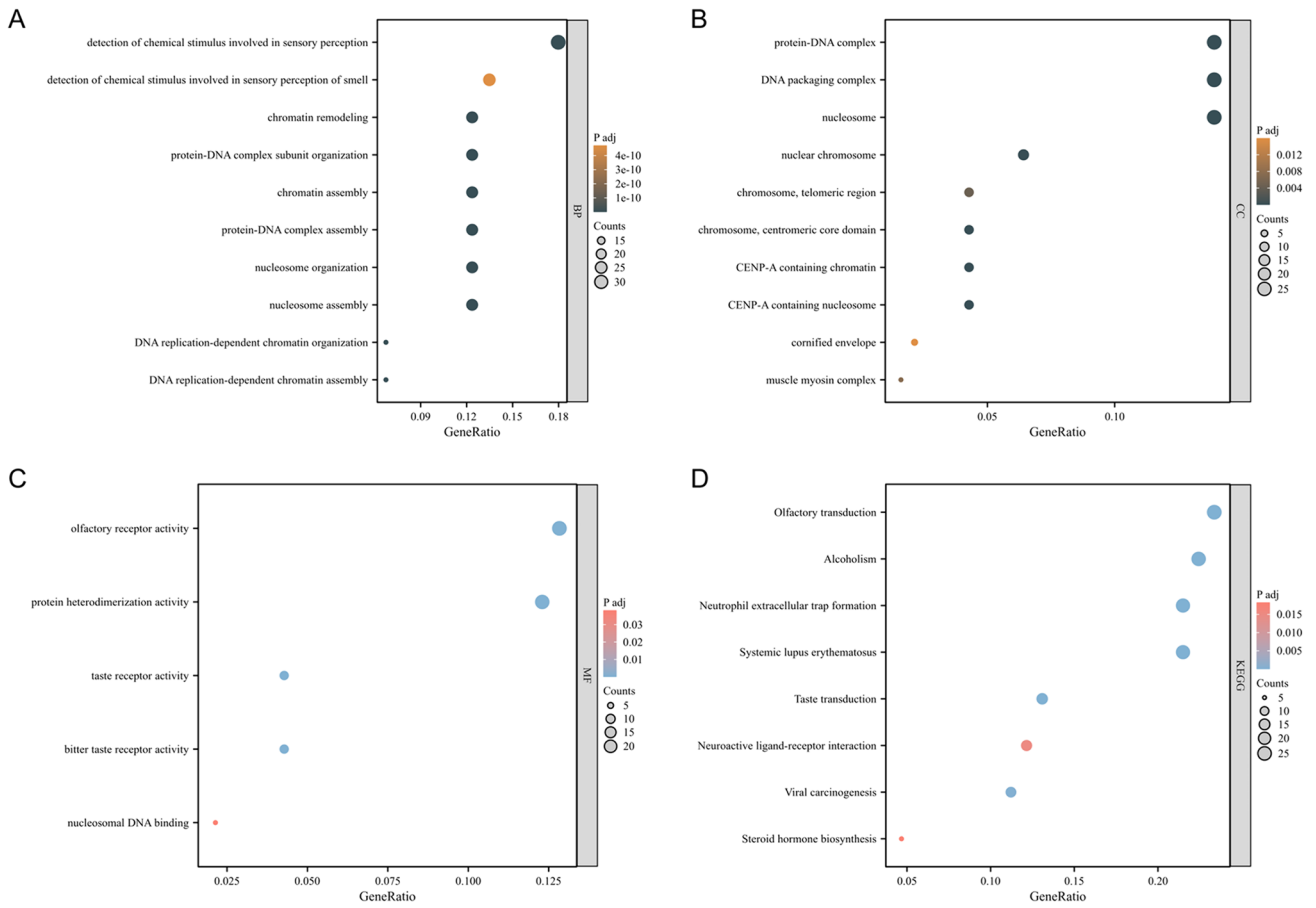


Fig. 5 Functional Enrichment Analysis of SIRT2 in LUAD. **A** Gene Ontology Biological Process (GO-BP) functional enrichment of SIRT2 and its co-expressed mRNAs. **B** Gene Ontology Cellular Component (GO-CC) functional enrichment related to SIRT2 and its co-expressed mRNAs. **C** Gene Ontology Molecular Function (GO-MF) functional enrichment associated with SIRT2 and its co-expressed mRNAs. **D** Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for SIRT2 and its co-expressed mRNAs

investigation into the association between SIRT2 expression and immune infiltrability in LUAD demonstrated a positive correlation of SIRT2 expression with the infiltration levels of various immune cells, including immature dendritic cells (iDCs), natural killer (NK) cells, T follicular helper (TFH) cells, mast cells, eosinophils, macrophages, dendritic cells (DCs), and neutrophils. Combined with previous studies, these observations suggest a profound association between SIRT2 and the tumor microenvironment in LUAD, potentially modulating the disease's developmental trajectory through alterations in the tumor microenvironment.

Conclusion

Despite our comprehensive and systematic analysis of SIRT2 in LUAD, corroborated by data from various databases, this study is not without limitations. Firstly, different online analysis platforms may process raw data from the same database in varied manners, potentially introducing systematic errors. Secondly, to validate the aberrant expression of SIRT2 in LUAD, its association with tumor immunity, and its prognostic implications, further in vivo or in vitro experimentation is warranted. These areas merit deeper investigation in future research endeavors.

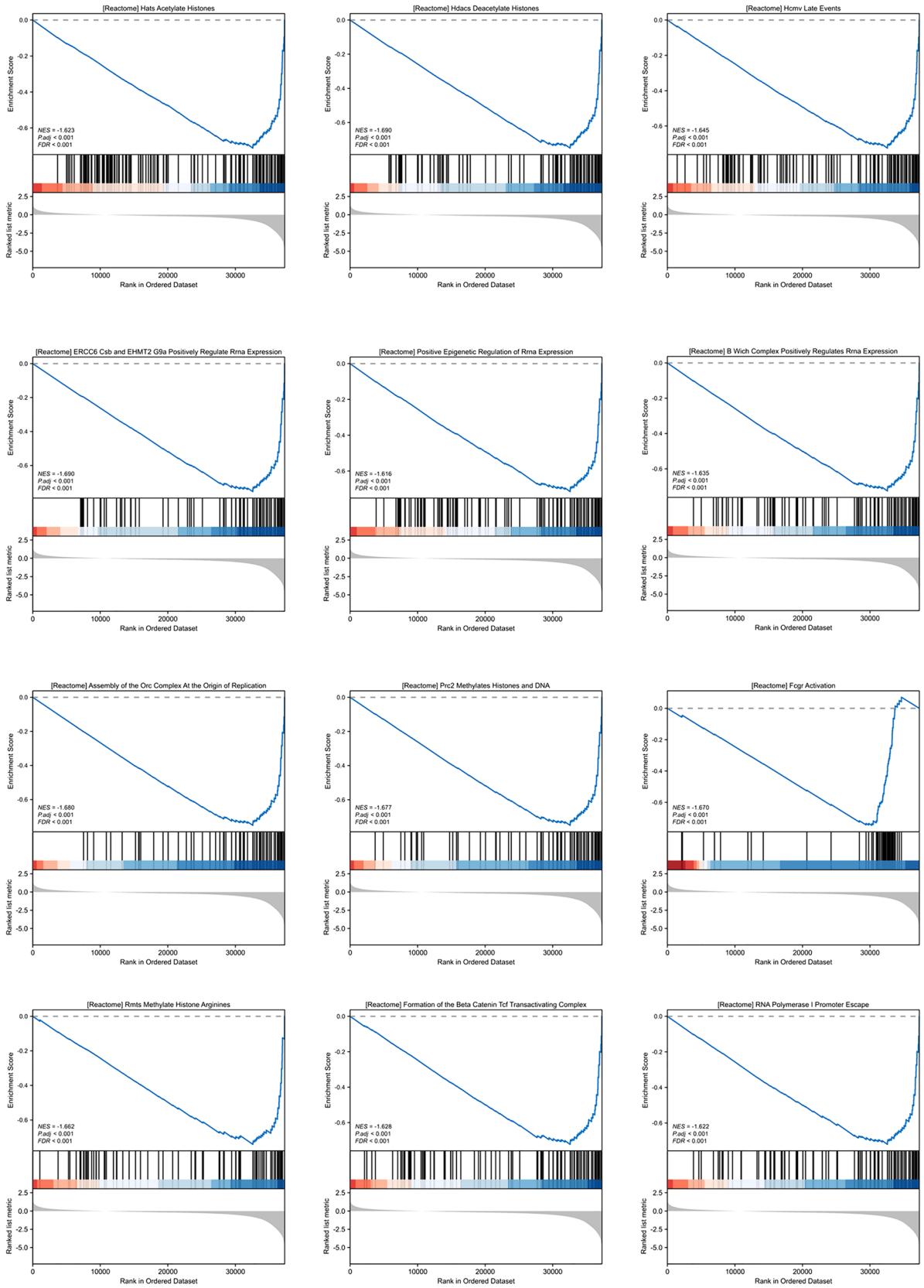


Fig. 6 Gene Set Enrichment Analysis (GSEA) in LUAD with Low SIRT2 Expression. GSEA revealing 12 signaling pathways predominantly enriched in LUAD patients exhibiting low SIRT2 expression

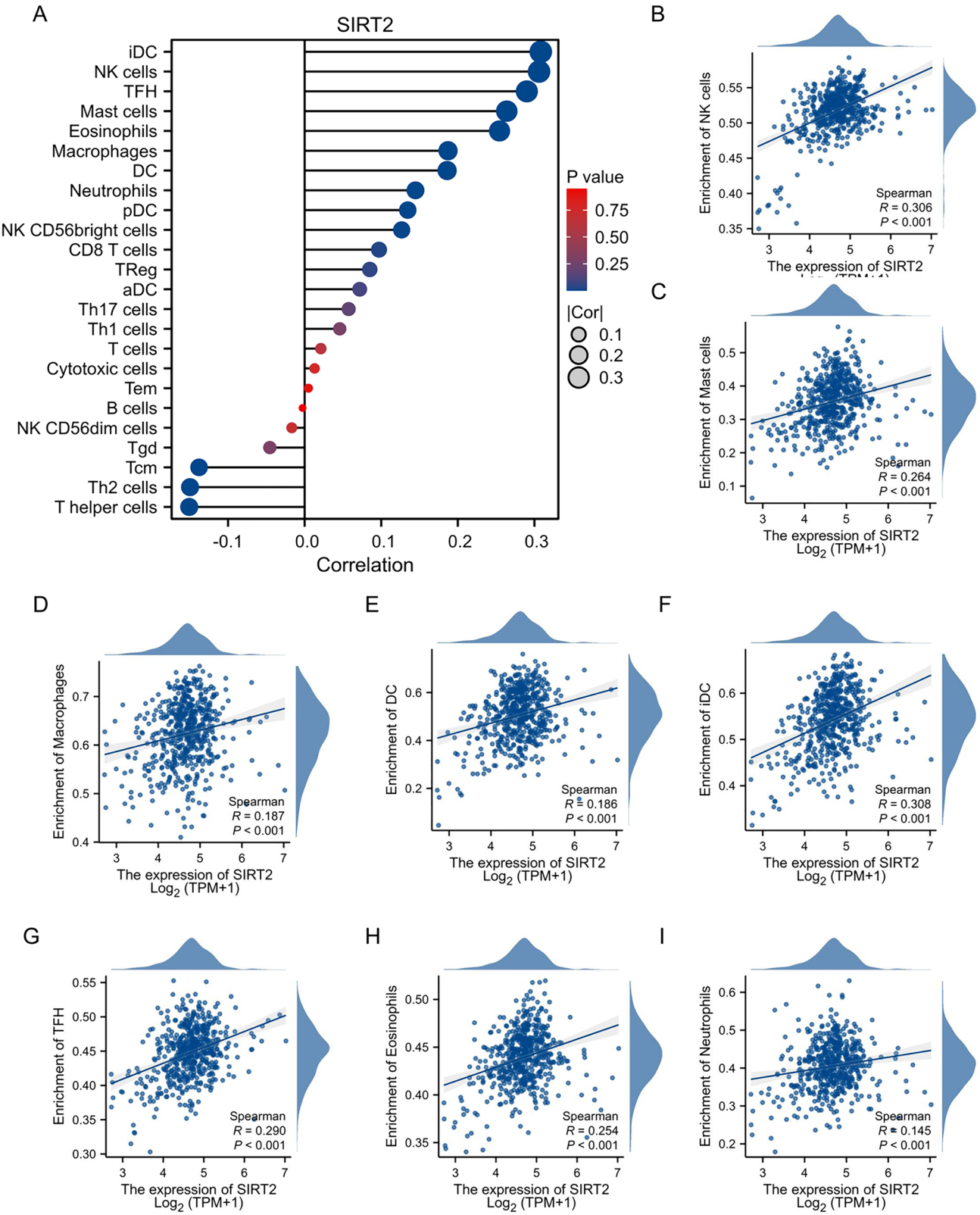


Fig. 7 Correlation Between SIRT2 Expression and Tumor Immunity in Lung Adenocarcinoma (LUAD). **A** Analysis of the correlation between SIRT2 expression and 24 types of immune cells in LUAD. **B–I** Detailed correlation analyses of SIRT2 expression with specific immune cell types: **B** immature dendritic cells (iDCs), **C** natural killer (NK) cells, **D** T follicular helper (TFH) cells, **E** mast cells, **F** eosinophils, **G** macrophages, **H** dendritic cells (DCs), and **I** neutrophils

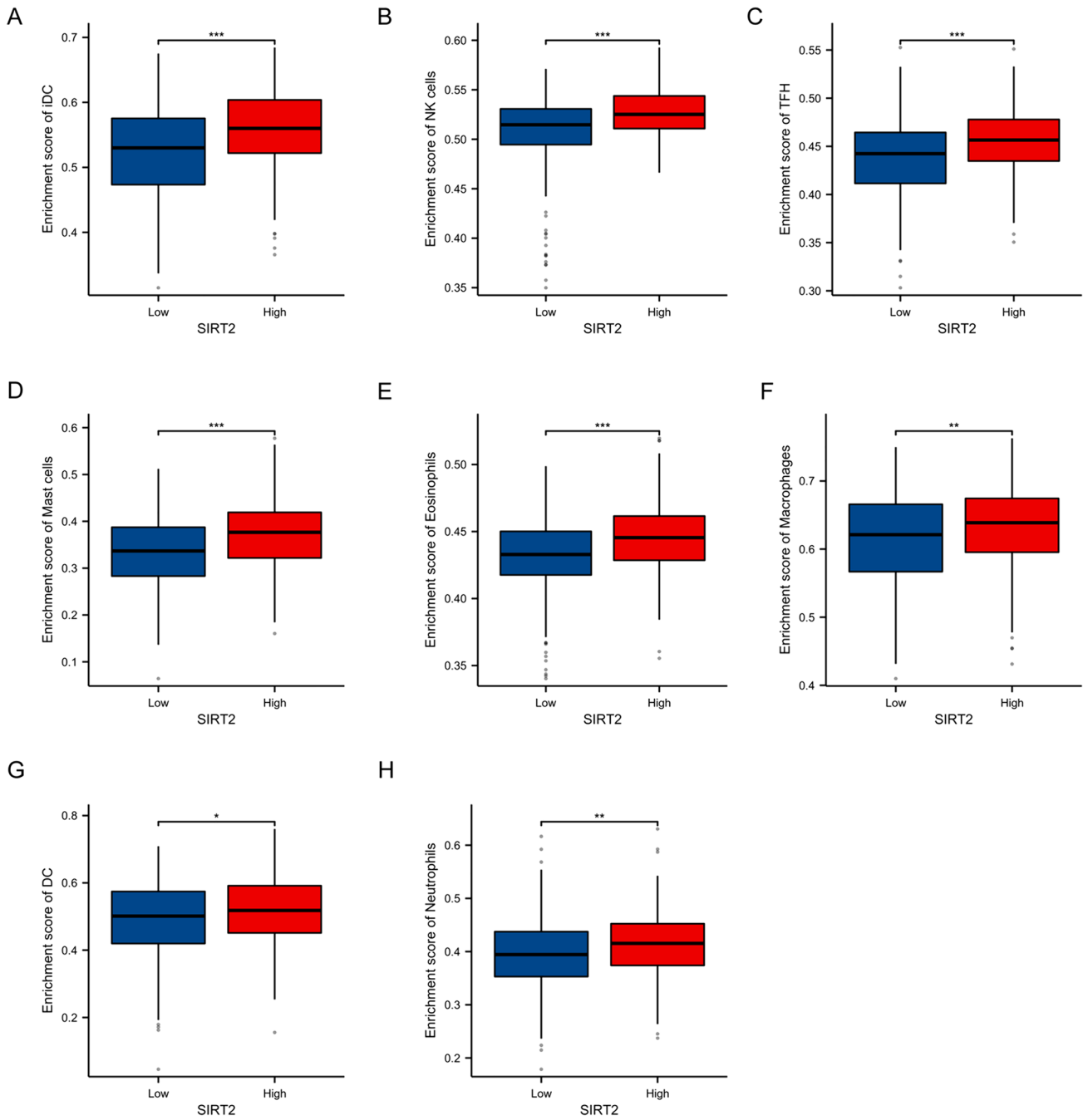


Fig. 8 Association of SIRT2 Expression with Immune Cell Enrichment in LUAD. Comparative analysis of immune cell enrichment between the SIRT2 low-expression and high-expression groups in LUAD, specifically focusing on: **A** iDCs, **B** NK cells, **C** TFH cells, **D** mast cells, **E** eosinophils, **F** macrophages, **G** DCs, and **H** neutrophils

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Declarations

Conflict of Interests The authors declare that there is no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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