Observational Study

Medicine

OPEN

Elevated STIL predicts poor prognosis in patients with hepatocellular carcinoma

Huangqin Song, MS[a], Haichao Zhao, MD[a], Changzhou Chen, MD[b], Donglin Zhang, MS[a], Xiaoxiao Wang, MS[a], Jiefeng He, MD[a,c,d,*]

Abstract

Overexpression of SCL/TAL1 interrupting locus (STIL) has been observed in various cancer types. However, the clinical significance of STIL in hepatocellular carcinoma (HCC) remains unknown. Cox regression and Kaplan–Meier survival analyses were performed to evaluate the prognostic value of STIL. Go and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analyses were also carried out. Immune infiltrates analyses were conducted based on TIMER (Tumor Immune Estimation Resource) and GAPIA databases. STIL expression was highly expressed in HCC tissues, based on multiple databases. KEGG and GO enrichment analysis showed STIL-related to tumorigenesis and progress. Furthermore, STIL was significantly correlated with immune infiltration. STIL serves as a biomarker for the prediction of patient survival.

Abbreviations: AFP = alphafetoprotein, CI = confidence interval, DEGs = differently expressed genes, DSS = disease-specific survival, GO = gene ontology, HCC = hepatocellular carcinoma, HR = hazard ratio, KEGG = Kyoto encyclopedia of genes and genomes, OS = overall survival, PFI = progression-free interval, STIL = SCL/TAL1 interrupting locus, TAMs = tumor-associated macrophages.

Keywords: hepatocellular carcinoma, immune infiltrates analyses, STIL

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, ranking 6th in incidence and 4th in mortality according to the Global Cancer Report 2020.[1] Presently, the 5-year survival rate of HCC patients in China is about 14.1%.[2] Although surgical resection is considered the best treatment approach for patients with early but high post-operative recurrence rates, the overall prognosis of patients with HCC is poor.[3,4] Therefore, potent prognostic biomarkers for HCC need to be identified at the earliest.

SCL/TAL1 interrupting locus (STIL) is a critical regulator of the mitotic centrosome to promote centriolar replication and cell cycle. The centrosome is composed of a pair of centromeres and its surrounding material, and STIL protein is a key regulator of human cell centriole replication and is directly involved in the formation of new centrosomes.[5] STIL mutation makes it stable in the cytoplasm without degradation, resulting in abnormal centrosome amplification.[6] Tumorigenesis is closely related to abnormal cell proliferation, and studies have shown that STIL has a crucial impact on the occurrence and development of cancer.[7–12] In colorectal cancer, STIL promotes cell proliferation and tumor growth by activating the Wnt/β-catenin signaling pathway and Sonic hedgehog (Shh) signaling pathway.[7] Reportedly, STIL is one of the 17 upregulated genes in primary adenocarcinoma, and its elevated expression is associated with metastasis.[12] Furthermore, the high expression of STIL protein promotes the occurrence and development of various tumor types, including osteosarcoma, pancreatic cancer, gastric cancer, and prostate cancer.[8–11] However, the role of STIL in HCC has not yet been explored.

In this study, we investigated STIL expression in patients with HCC and assessed its correlation with clinicopathological features and its prognostic value in HCC. Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were used to explore the underlying functions and mechanisms of STIL in HCC. Finally, the correlation between STIL expression and immune cells was also evaluated.

HS and HZ contributed equally to this work.

This work was supported by Shanxi Province 136 Medical Project and Project of Science and Technology Department of Shanxi Province (No.201901D111404, 201903D026).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

Supplemental Digital Content is available for this article.

[a] Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, China, [b] Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education; Institute of Biomedical Sciences, Fudan University, Shanghai, China, [c] Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China, [d] Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

**Correspondence: Jiefeng He, Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, 030032, China (e-mail: hejiefeng1995@163.com).*

How to cite this article: Song H, Zhao H, Chen C, Zhang D, Wang X, He J. Elevated STIL predicts poor prognosis in patients with hepatocellular carcinoma. Medicine 2023;102:7(e33004).

Received: 12 October 2022 / Received in final form: 26 January 2023 / Accepted: 27 January 2023

http://dx.doi.org/10.1097/MD.0000000000033004

2. Materials and methods

2.1. STIL expression analysis in HCC

The mRNA expression data of 424 HCC cases of level 3 HTSeq-FPKM data were downloaded from the TCGA dataset (https://tcga-data.nci.nih.gov/tcga/), including 50 adjacent nontumor liver samples and 374 HCC tissues. Patients with missing clinical data and the absence of follow-up prognosis information were excluded. Next, level 3 HTSeq-FPKM data were transformed into TPM (transcripts per million reads), and then TPM information and corresponding patients' clinical data of 371 HCC samples were utilized for further analyses. The TPM data were used to analyze STIL expression in paired and unpaired HCC tissues and adjacent tissues. Furthermore, gene expression profiles, GSE121248 and GSE14520, were obtained from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/) to analyze the STIL expression level. Oncomine (https://www.oncomine.org/) and HCCDB (http://lifeome.net/database/hccdb) data resources were also used to explore the STIL expression level in various HCC datasets. It is necessary to note that we searched the Oncomine database in November 2021, but this database is no longer available now. That site was taken offline on January 17, 2022.

2.2. Screening of STIL-related differently expressed genes (DEGs)

According to the median expression of STIL, HCC samples in the TCGA dataset were divided into high/low-expression groups. Then, DEGs between groups (STIL-high vs STIL-low) were assessed using the R package "DESeq2." DEGs with an adjusted $P < .05$ and $|LogFC| > 1$ were identified and used for subsequent analysis.

2.3. Biological function and pathway enrichment analysis

KEGG and GO analyses of DEGs in the high-and low-STIL groups were carried out using the R package "clusterProfiler." GO analysis included the biological process, molecular function, and cellular component.

2.4. Immune infiltration analysis

The correlation between STIL expression level of HCC samples and several immune cells was evaluated in Tumor Immune Estimation Resource (TIMER) platform, used to estimate immune infiltration among multiple cancer types.[13] Furthermore, the correlation between STIL expression and immune cells markers was explored based on TIMER and GEPIA databases.

2.5. Statistical analysis

The expression of STIL in HCC patients was assessed compared to adjacent normal tissue in various databases by box plots. According to the median expression level of STIL, HCC samples in TCGA-LIHC dataset were divided into STIL-high- and STIL-low groups. Then, the correlation between STIL-and clinical features in HCC was established using Wilcoxon signed-rank test and logistic regression. Kaplan–Meier survival analysis was used to analyze the overall survival (OS), disease-specific survival (DSS), and progression-free interval between the STIL-high-and STIL-low-expression groups. Univariate and multivariate Cox analyses were performed to investigate whether STIL expression is an independent prognostic factor.

3. Results

3.1. Pan-cancer analysis of STIL expression levels

We utilized different datasets to systematically analyze the mRNA expression of STIL in 33 types of cancers. Firstly, in the Oncomine database, we found that STIL was significantly upregulated in most types of cancers, including HCC (Fig. 1A). Furthermore, TIMER database was employed to verify the STIL expression in different tumor types, and the results were consistent with those of Oncomine (Fig. 1B). Given the overexpression of STIL in multiple malignant tumors, STIL may function as an oncogene and promote tumorigenesis. Thus, we analyzed whether STIL expression could serve as a potential prognostic biomarker for HCC.

3.2. Overexpression of STIL in HCC

Accumulating evidence stated that STIL is a key regulator in promoting tumor progression in multiple tumors. However, its expression levels and functions in HCC have not been studied systematically. Therefore, we used TCGA database to compare the expression of STIL between HCC cancer samples and normal samples at the transcriptional level and found that the mRNA expression of *STIL* was significantly increased in

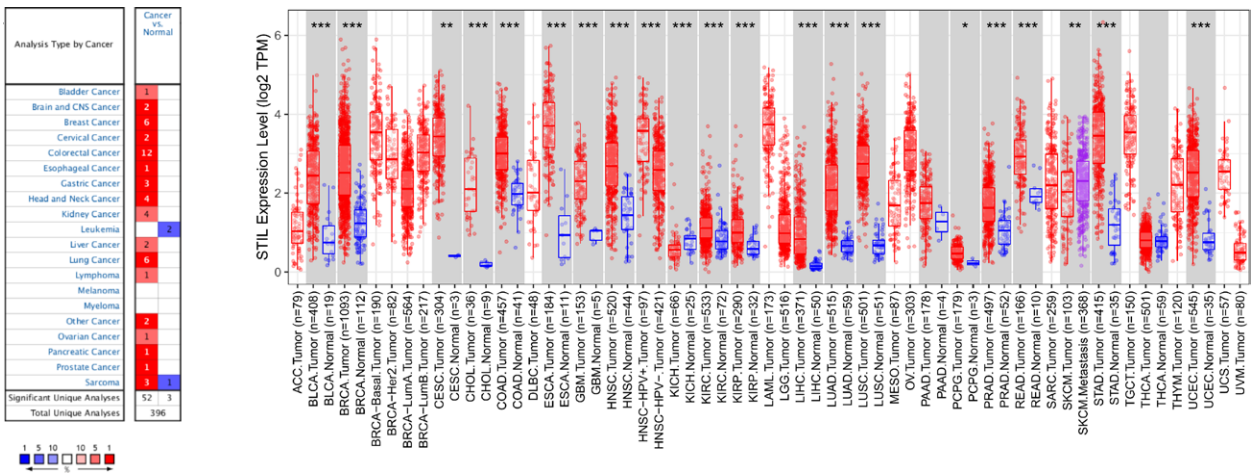

Figure 1. STIL expression levels in different tumors. (A) Expression of STIL in various cancer tissues compared to normal tissues using the Oncomine database. (B) Expression status of STIL in different types of tumors was analyzed by Tumor Immune Estimation Resource database. Note: *$P < .05$, **$P < .01$, ***$P < .001$. STIL = SCL/TAL1 interrupting locus.

cancer samples, and the conclusion is consistent with 50 pairs of matched tumor/normal samples (Fig. 2A and B). We also compared STIL expression between normal and HCC samples in the HCCDB dataset and found high expression of STIL in HCC (Fig. 2C). Then, we used GSE121248 and GSE14520 in gene expression omnibus databases for verification and found that the results were consistent with those above (Fig. 2D and E). The same conclusion was further confirmed in the ONCOMINE data. The consistent result was corroborated to that of the ONCOMINE data. Specifically, the Roessler, Roessler2, and Wurmbach datasets indicated that STIL was overexpressed in HCC tumors relative to normal tissues (Fig. 2F–H). These results indicated that STIL was significantly increased in HCC tissues.

3.3. Correlation between STIL expression and clinical parameters in HCC

The expression levels of STIL were related to age (P = .03), alphafetoprotein (AFP) (P = .002), and tumor status (P = .026) (Fig. 3A–C). Moreover, STIL expression was significantly correlated with T stage (P < .001), histological grade (P < .001), and pathological stage (P < .001) (Fig. 3D–F). We also applied logistic analysis to verify the correlation of STIL with clinical parameters and received basically the same results (Supplementary Table S1, Supplemental Digital Content, http://links.lww.com/MD/I505). Furthermore, we evaluated the correlation between the mRNA levels of STIL with several survival parameters. The results indicated that high STIL was significantly associated with OS, DSS, and progression-free interval (PFI) of HCC patients compared to low-STIL (P < .05) (Fig. 3G–I). In order to explore the independent prognostic value of STIL, we conducted univariate and multivariate analyses based on the clinical information, including age, gender, residual tumor, AFP, fibrosis Ishak score, vascular invasion, T stage and histologic grade, and STIL expression data obtained from the TCGA dataset. The results confirmed that a high mRNA level of STIL was significantly and independently correlated with short OS (hazard ratio [HR] = 1.466, 95% confidence interval [CI]: 1.018–2.054, and P = .039), DSS (HR = 1.860, 95% CI: 1.171–2.954, and P = .009), and PFI (HR = 1.724, 95% CI: 1.233–2.411, and P = .001) for HCC patients (Supplementary Tables S2, S3, and S4, Supplemental Digital Content, http://links.lww.com/MD/I506). These findings suggested that STIL expression was an independent prognostic factor for OS, DSS, and PFI in HCC patients.

3.4. GO and KEGG enrichment analysis of STIL-related DEGs in HCC patients

To explore the potential enrichment functions and pathways driven by high STIL expression, the transcriptomes of HCC

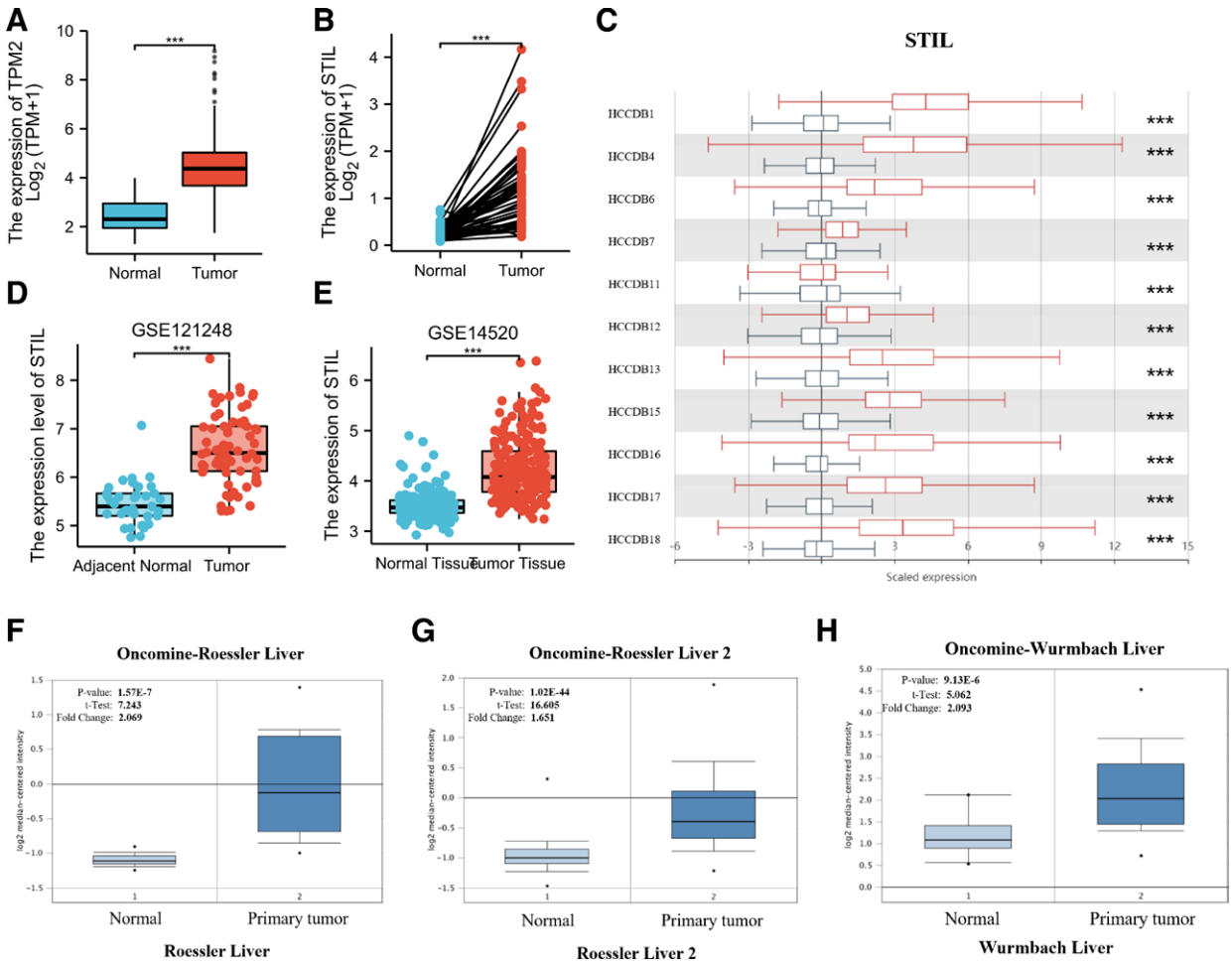

Figure 2. STIL expression was compared between cancer and normal tissues in HCC, according to different databases. (A) *STIL* mRNA expression in normal and tumor tissues in TCGA datasets. (B) STIL expression in paired samples in TCGA datasets. (C) Expression levels of STIL in various HCC datasets of HCCDB. (D, E) mRNA level of *STIL* in normal and tumor samples in GSE121248 and GSE14520, respectively. (F, G, H) *STIL* mRNA expression in various HCC datasets in ONCOMINE. *P < .05, **P < .01, ***P < .001. HCC = hepatocellular carcinoma, STIL = SCL/TAL1 interrupting locus, TCGA = The Cancer Genome Atlas.

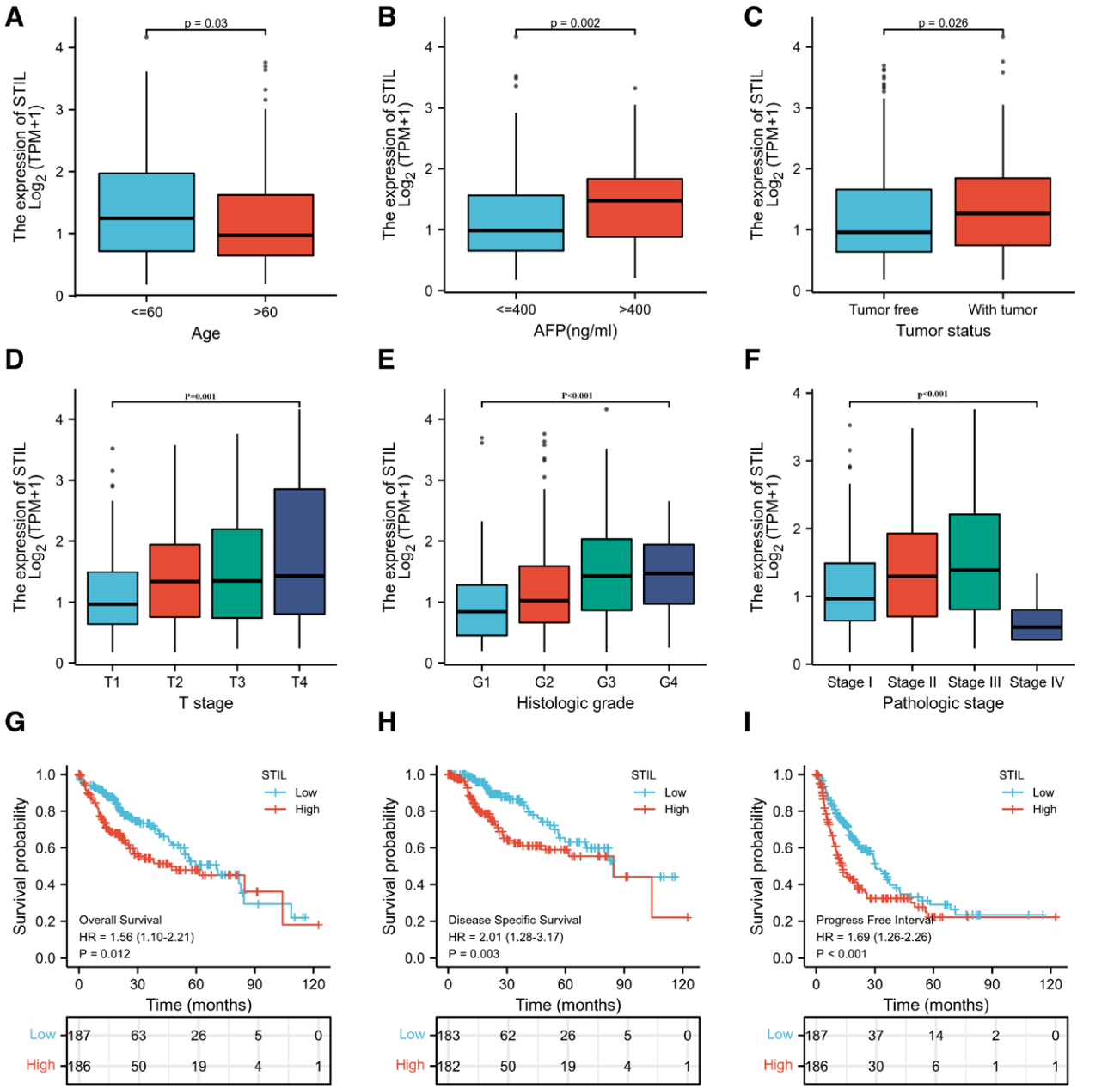

Figure 3. Association of STIL expression with clinicopathological characteristics of HCC patients and its prognostic significance. (A) Age; (B) AFP; (C) Tumor status; (D) T stage; (E) Histological grade; (F) Pathological stage. (G–I) Kaplan–Meier survival curves of (G) OS, (H) DFS, and (I) PFI. AFP = alphafetoprotein, HCC = hepatocellular carcinoma, PFI = progression-free interval, STIL = SCL/TAL1 interrupting locus.

samples in TCGA with STIL-high-and STIL-low mRNA expression were compared to obtain the list of DEGs. A total of 4079 DEGs, including 3139 upregulated and 940 downregulated DEGs, were obtained. Volcano plots and bar graphs were used to visually display the results of DEGs (Fig. 4A and B), and heatmaps showed the top 10 significantly up- and downregulated DEGs between the STIL-and low-expression groups (Fig. 4C and D). Then, the top 100 upregulated and downregulated STIL-related DEGs were used for GO functions and KEGG pathway enrichment (Supplementary Table S5, Supplemental Digital Content, http://links.lww.com/MD/I507). The molecular function for these genes were predominantly enriched in microtubule motor activity, microtubule binding, tubulin binding, ATPase activity, and motor activity (Fig. 4E). The STIL-related DEGs were mainly enriched in organelle fission, chromosome segregation, mitotic nuclear division, nuclear division, and DNA replication in terms of the biological processes category (Fig. 4F). The cellular component for these genes mainly included the spindle, centromeric region, condensed chromosome, and mitochondrial matrix (Fig. 4H). KEGG enrichment analysis revealed several crucial pathways, including cell cycle, oocyte meiosis, and homologous recombination (Fig. 4G). All the above enriched functions and pathways were significantly related to tumorigenesis and tumor development.

3.5. Correlation analysis between STIL expression and tumor-infiltrating immune cell abundance

Tumor-infiltrating immune cells are crucial components of the tumor microenvironment, which are also independent indicators of prognostic and lymph node involvement status. The study showed that immune infiltrations have a significant impact on the development and progression of HCC.[14] Therefore, the

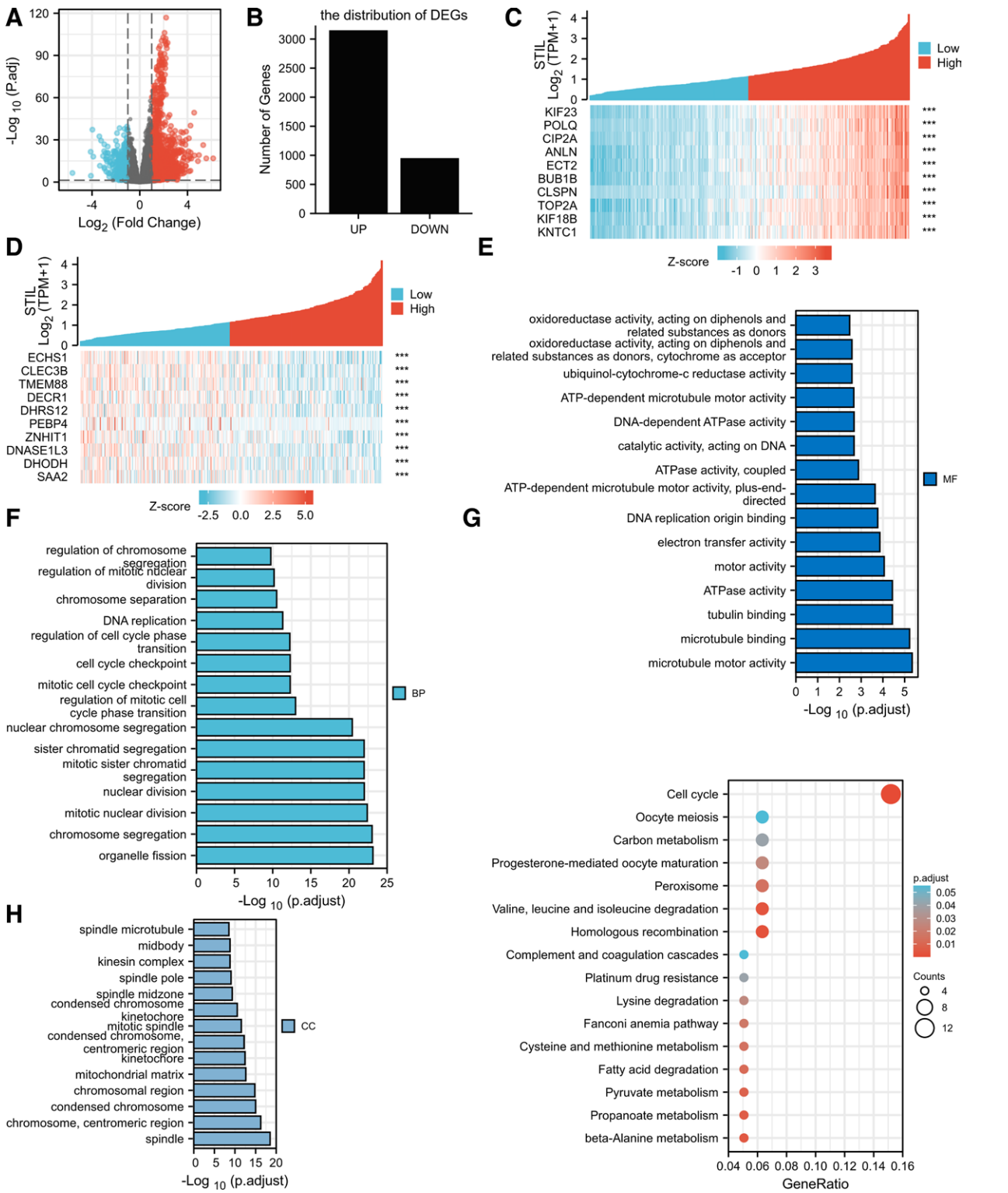

Figure 4. GO and KEGG enrichment analysis of STIL-related DEGs. (A) The volcano plot describes 4079 DEGs (|log2fold change| > 1 and adjusted *P* value < 0.05). (B) The histogram shows the number of upregulated or downregulated genes. (C, D) The heatmaps depict the expression of 10 significantly upregulated and downregulated genes in HCC samples related to STIL expression. (E–G) GO and KEGG enrichment results of STIL-related DEGs. ***$P < .001$. DEGs = differently expressed genes, GO = gene ontology, HCC = hepatocellular carcinoma, KEGG = Kyoto encyclopedia of genes and genomes, STIL = SCL/TAL1 interrupting locus.

correlation between STIL expression and immune cell infiltration was analyzed. These results showed that STIL levels were strongly positively correlated with the infiltration level of B cells (partial.cor = 0.442, $P = 7.43 \times 10^{-18}$), CD8 + T cells (partial.cor = 0.333, $P = 2.63 \times 10^{-10}$), CD4 + T cells (partial.cor = 0.445, $P = 3.80 \times 10^{-18}$), macrophage (partial.cor = 0.524, $P = 1.90 \times 10^{-25}$), neutrophil (partial.cor = 8.21, $P = 2.34 \times 10^{-19}$), and dendritic cells (partial.cor = 0.511, $P = 5.02 \times 10^{-24}$) in HCC. Notably, a positive correlation was established between STIL expression and tumor purity (COR = 0.144, $P = 7.13 \times 10^{-3}$, Fig. 5A). Thus,

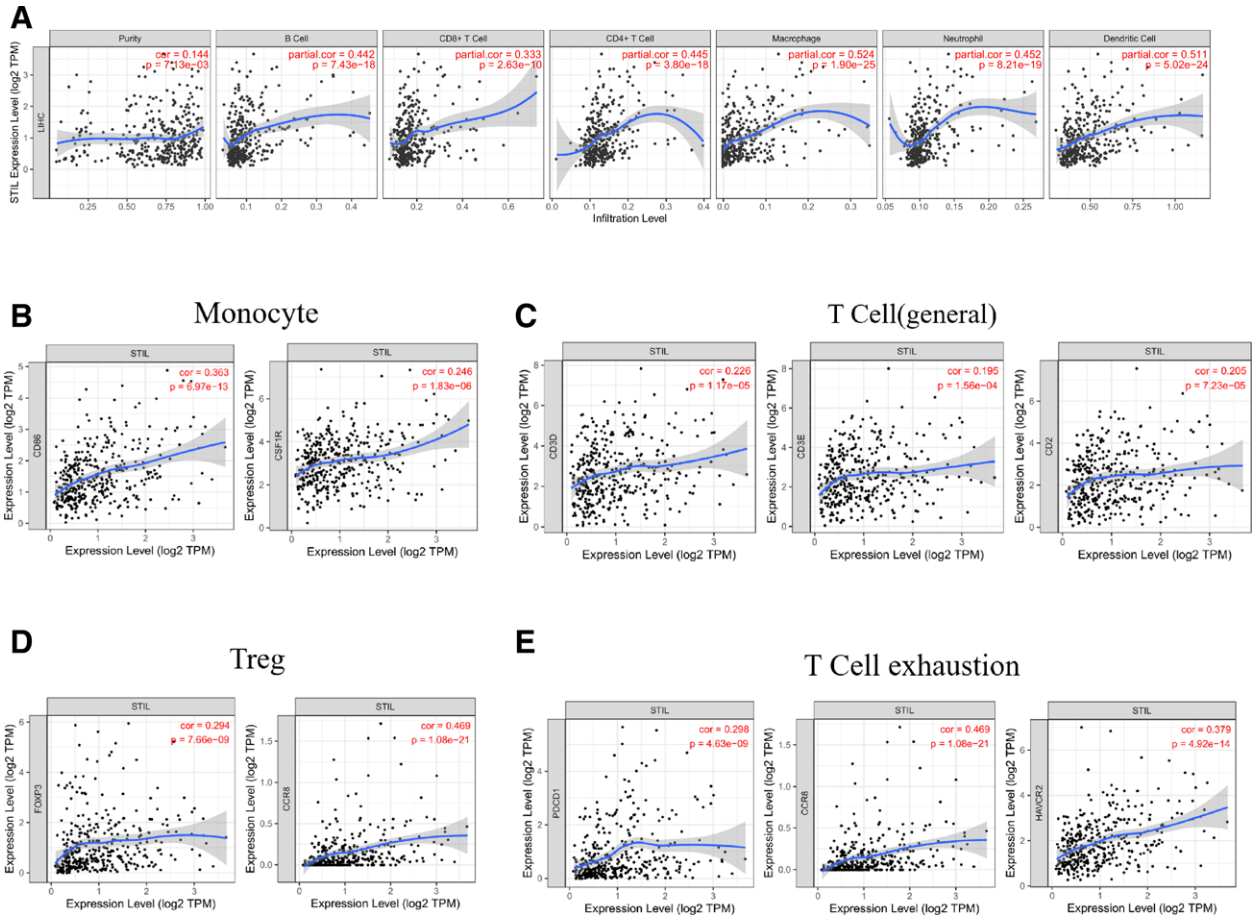

Figure 5. Correlation between STIL levels and immune infiltration analyzed by TIMER. (A) Correlation between STIL expression and the proportion of immune cells. (B–D) Correlation between STIL expression and immunological markers (B) Monocyte; (C) T cells (general); (D) Tregs; (E) T cell exhaustion. STIL = SCL/TAL1 interrupting locus, TIMER = Tumor Immune Estimation Resource.

the expression level of STIL is associated with immune infiltration in HCC.

For an in-depth understanding of the connection between STIL expression and immune infiltration, we analyzed the association between STIL-and immune cell markers by mining the TIMER database. Tumor ecosystems are comprised of tumor cells and stromal components, which can accurately analyze the correlation between STIL expression and immune infiltration in tumor cells. The correlation was adjusted by tumor purity, which displayed that the most immune cell markers had a significant positive link with STIL expression (Supplementary Table S6, Supplemental Digital Content, http://links.lww.com/MD/I508). The mRNA levels of CD86 and CD115 were specifically expressed by monocytes; CD3D, CD3E, and CD2 were specifically expressed by T cells; CCR8 and TGFβ were specifically expressed by Tregs; and PD-1, cytotoxic T lymphocyte associated antigen-4, and TIM3 were specifically expressed by exhausted T cells; all these were closely related to STIL expression (Fig. 5B–E). In addition, the correlation between the expression of STIL-and the immune cell markers was also verified by GEPIA database and the results were consistent with that of TIMER database (Supplementary Table S7, Supplemental Digital Content, http://links.lww.com/MD/I509). In conclusion, the data above indicated that STIL may play a critical role in mechanisms controlling immune infiltration in HCC.[13,15]

3.6. Development of a nomogram based on STIL

In order to make a more adequate assessment of the prognosis of HCC patients, we developed a nomogram combining STIL-and other independent clinical risk factor (T stage) to predict the 1-, 3-, and 5-year OS of HCC, the C-index for the nomogram was 0.640 (95% CI: 0.613–0.667) (Supplementary Tables S2, Supplemental Digital Content, http://links.lww.com/MD/I506 and Fig. 6A). We also developed calibration plots of the nomogram, and the results showed that the calibration line was close to the ideal curve, indicating that the nomogram had a good calibration effect (Fig. 6B). Furthermore, the time-dependent ROC curve showed that nomogram had high prognostic specificity and sensitivity, and the area under the ROC curve (AUC) of 1-year, 3-year and 5-year OS prediction was 0.711, 0.670 and 0.646, respectively (Fig. 6C). In total, these results indicated that the nomogram was a good prognostic model for HCC patients.

4. Discussion

Although recent advances have been made in the treatment of HCC, the prognosis remains unsatisfactory. Therefore, identifying potential prognostic biomarkers and therapeutic targets for HCC is an urgent requirement. Accumulating evidence has demonstrated that abnormal DNA replication and uncontrolled cell cycle progression are major hallmarks of tumor genesis, invasion, and progression.[16] STIL functions as a cell cycle regulatory protein recruited at the mitotic centrosome to promote the duplication of centrioles in dividing cells.[17] A current study reported that STIL overexpression causes chromosomal instability in cancer cells.[18] However, the exact role of STIL proteins in HCC remains unknown.

In this study, we found that STIL expression was upregulated in most types of cancers, including HCC. The high expression

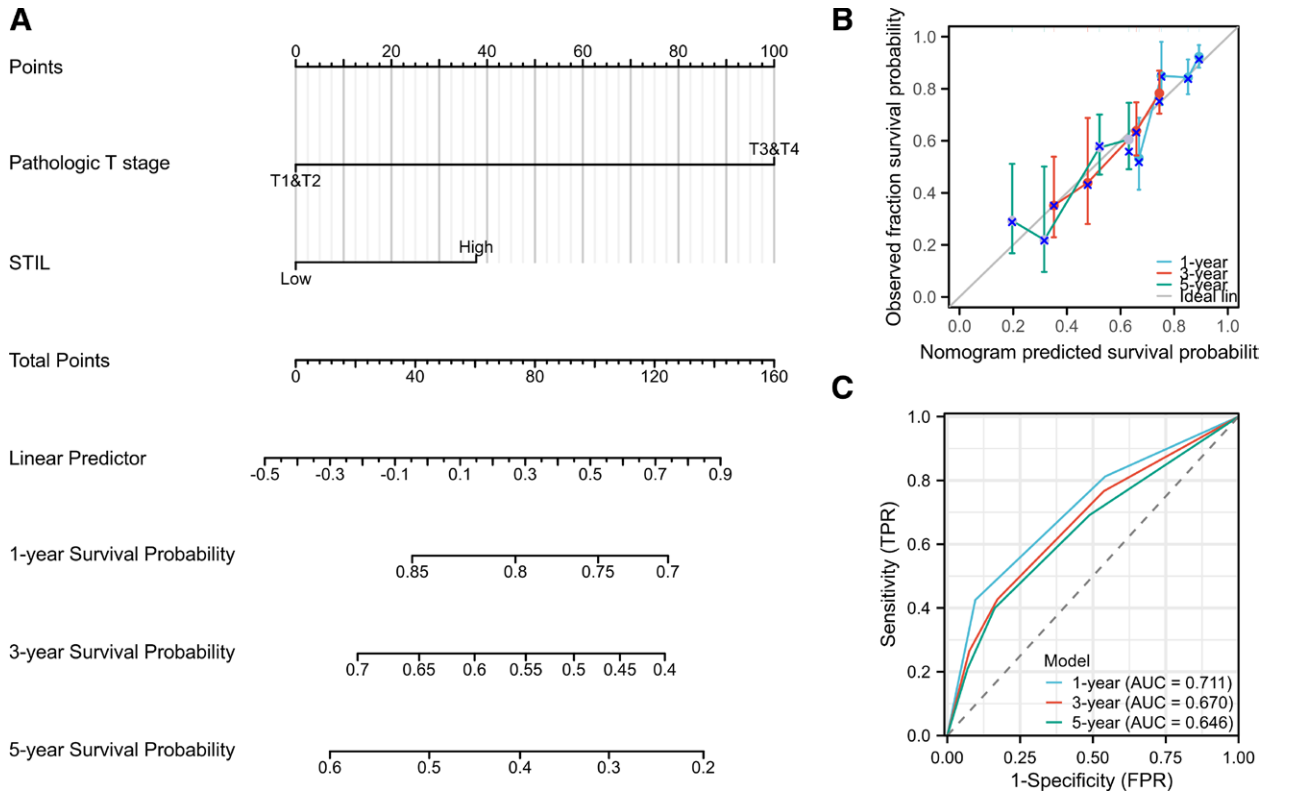

Figure 6. Construction of a prognostic model for HCC patients. (A) Nomogram for predicting the probability of 1-, 3-, and 5-year OS for HCC patients. (B) Calibration plot of the nomogram for predicting the probability of 1-, 3-, and 5-year OS. (C) Time-dependent ROC curve analyses of the prognostic model for 1-, 3-, and 5-year OS. HCC = hepatocellular carcinoma, OS = overall survival, ROC = receiver operating characteristic.

of STIL was positively correlated with several clinical features in patients with HCC, including AFP, T stage, histological grade, and pathological stage. Furthermore, a high expression level of STIL was an independent prognostic factor associated with adverse prognosis. The STIL-related signal transduction pathways included the cell cycle and DNA replication in HCC. Finally, STIL expression was strongly correlated with various infiltrating immune cells based on the level of markers for various tumor-infiltrating cells in HCC.

To explore the biological function and the mechanisms underlying STIL in HCC patients, GO and KEGG analyses were carried out. The most enriched GO terms of the co-expressed genes were "chromosome segregation," "DNA replication," and "nuclear division" and KEGG pathways were "DNA replication," "spliceosome," and "cell cycle." The dysregulation of cell cycle activities, such as uncontrolled proliferation and abnormal replication, are fundamental characteristics of the pathogenesis of cancer,[19] and novel small-molecule inhibitors of triple-negative breast cancer are shown to promote cell cycle arrest.[20] Similarly, chromosome segregation at M-phase and DNA replication at S-phase are indispensable processes of cell mitosis. In the event of cancer, abnormal chromosome separation caused by DNA replication stress induces genomic instability.[21] Furthermore, analysis of survival-related miRNAs enriched in ovarian carcinomas identified several signaling pathways, such as oocyte meiosis.[22] These findings revealed that STIL regulates the development and progression of HCC by modulating DNA replication and cell cycle. However, further investigation of the putative molecular mechanisms is required to elucidate the role of STIL in HCC.

The biological interactions between immune cells and tumors are crucial for tumor progression.[23] In addition, TIICs show a tendency of preferential enrichment and massive amplification in HCC,[24] and accumulation of TIICs is positively associated with poor prognosis in patients with HCC.[14] The current study showed that the expression level of STIL was positively correlated with various immune cells, such as macrophages and T cells. Tumor-associated macrophages (TAMs) are the leading inflammatory components of a tumor matrix with varied effects on adaptive immune regulation in a tumor environment.[25–30] Reportedly, TAMs inhibit the activity of inflammatory cells, such as effector T cells and monocytes, by regulating the infiltration density of Tregs in HCC.[25–28] Some studies have shown that PD-1 is expressed on the surface of TAM and Kupffer cells in HCC patients, which inhibits the function of T and B cells, mediates the immune escape of HCC, and promotes tumor growth.[29,30] T cell exhaustion is a dysfunctional state of CD8 + T cells that is effectuated by inhibiting proliferation, promoting apoptosis, and decreasing the secretory capacity of effector cytokines, such as IL-6, TNF-α, and IFN-γ, caused by continuous stimulation of tumor antigen and inhibition of immunosuppressive cells.[31] Furthermore, complete exhaustion CD8 + T cells does not elicit a response to immune checkpoint inhibitors.[32] This phenomenon could be ascribed to the ineffectiveness of antibody therapy using programmed death receptor-1 and cytotoxic T lymphocyte associated antigen-4 in many patients with HCC. Also, the expression of STIL is closely related to Tregs, monocytes, neutrophils, and dendritic cells in HCC. In conclusion, the current findings indicated a crucial role of STIL in immune infiltrating cell modulation in HCC.

Nevertheless, the present study has several limitations. Firstly, we could not obtain all clinical information from public databases, such as the approach of treatment for each patient, to elucidate the role of STIL in the progression of HCC. Secondly, the expansion of the clinical sample size is needed to validate the correlation between the expression of STIL-and prognosis. Finally, additional studies are required to explore the mechanism of STIL in HCC.

In summary, the present study revealed that STIL expression was higher in HCC and was an essential prognostic biomarker.

High STIL might promote the development of HCC by modulating the cell cycle, DNA replication, and immune infiltration. Nevertheless, these findings need to be substantiated further by experimental investigation to analyze the biological functions and the mechanisms underlying STIL in HCC patients.

Author contributions

Conceptualization: Huangqin Song, Haichao Zhao, Xiaoxiao Wang.
Data curation: Huangqin Song, Haichao Zhao, Donglin Zhang, Xiaoxiao Wang, Jiefeng He.
Formal analysis: Haichao Zhao, Changzhou Chen, Xiaoxiao Wang, Jiefeng He.
Investigation: Changzhou Chen, Donglin Zhang.
Methodology: Changzhou Chen, Donglin Zhang, Jiefeng He.
Resources: Huangqin Song.
Writing – original draft: Huangqin Song, Haichao Zhao, Changzhou Chen, Donglin Zhang, Xiaoxiao Wang, Jiefeng He.
Writing – review & editing: Huangqin Song, Haichao Zhao, Changzhou Chen, Donglin Zhang, Xiaoxiao Wang, Jiefeng He.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
[2] Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023–75.
[3] Fujiwara N, Friedman SL, Goossens N, et al. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol. 2018;68:526–49.
[4] Famularo S, Di Sandro S, Giani A, et al. Recurrence patterns after anatomic or parenchyma-sparing liver resection for hepatocarcinoma in a western population of cirrhotic patients. Ann Surg Oncol. 2018;25:3974–81.
[5] Arquint C, Sonnen KF, Stierhof YD, et al. Cell-cycle-regulated expression of STIL controls centriole number in human cells. J Cell Sci. 2012;125:1342–52.
[6] Arquint C, Nigg EA. STIL microcephaly mutations interfere with APC/C-mediated degradation and cause centriole amplification. Curr Biol. 2014;24:351–60.
[7] Pradhan T, Kumar V, Surya HE, et al. STIL endows oncogenic and stem-like attributes to colorectal cancer plausibly by Shh and Wnt signaling. Front Oncol. 2021;11:581671.
[8] Ji SF, Wen SL, Sun Y, et al. The biological function and clinical significance of STIL in osteosarcoma. Cancer Cell Int. 2021;21:218.
[9] Ye Z, Zhu Z, Xie J, et al. Hsa_circ_0000069 knockdown inhibits tumorigenesis and exosomes with downregulated hsa_circ_0000069 suppress malignant transformation via inhibition of STIL in pancreatic cancer. Int J Nanomed. 2020;15:9859–73.
[10] Wu X, Xiao Y, Yan W, et al. The human oncogene SCL/TAL1 interrupting locus (STIL) promotes tumor growth through MAPK/ERK, PI3K/Akt and AMPK pathways in prostate cancer. Gene. 2019;686:220–7.
[11] Wang J, Zhang Y, Dou Z, et al. Knockdown of STIL suppresses the progression of gastric cancer by down-regulating the IGF-1/PI3K/AKT pathway. J Cell Mol Med. 2019;23:5566–75.
[12] Neyaz A, Husain N, Deodhar M, et al. Synchronous cervical minimal deviation adenocarcinoma, gastric type adenocarcinoma and lobular endocervical glandular hyperplasia along with STIL in Peutz-Jeghers syndrome: eliciting oncogenesis pathways. Turk Patoloji Derg. 2019;35:247–53.
[13] Li T, Fan J, Wang B, et al. TIMER: a web server for comprehensive analysis of tumor-infiltrating immune cells. Cancer Res. 2017;77:e108–10.
[14] Sun H, Liu L, Huang Q, et al. Accumulation of tumor-infiltrating CD49a(+) NK cells correlates with poor prognosis for human hepatocellular carcinoma. Cancer Immunol Res. 2019;7:1535–46.
[15] Zhang X, Park JE, Kim EH, et al. Wip1 controls the translocation of the chromosomal passenger complex to the central spindle for faithful mitotic exit. Cell Mol Life Sci. 2021;78:2821–38.
[16] Zheng L, Meng Y, Campbell JL, et al. Multiple roles of DNA2 nuclease/helicase in DNA metabolism, genome stability and human diseases. Nucleic Acids Res. 2020;48:16–35.
[17] Arquint C, Nigg EA. The PLK4-STIL-SAS-6 module at the core of centriole duplication. Biochem Soc Trans. 2016;44:1253–63.
[18] Nigg EA. Centrosome aberrations: cause or consequence of cancer progression? Nat Rev Cancer. 2002;2:815–25.
[19] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
[20] Hwang SY, Park S, Kwon Y. Recent therapeutic trends and promising targets in triple negative breast cancer. Pharmacol Ther. 2019;199:30–57.
[21] Zhang BN, Bueno Venegas A, Hickson ID, et al. DNA replication stress and its impact on chromosome segregation and tumorigenesis. Semin Cancer Biol. 2019;55:61–9.
[22] Kuznetsov VA, Tang Z, Ivshina AV. Identification of common oncogenic and early developmental pathways in the ovarian carcinomas controlling by distinct prognostically significant microRNA subsets. BMC Genomics. 2017;18:692.
[23] Domingues P, Gonzalez-Tablas M, Otero A, et al. Tumor infiltrating immune cells in gliomas and meningiomas. Brain Behav Immun. 2016;53:1–15.
[24] Zheng C, Zheng L, Yoo JK, et al. Landscape of infiltrating T cells in liver cancer revealed by single-cell sequencing. Cell. 2017;169:1342–1356.e16.
[25] Sica A. Role of tumour-associated macrophages in cancer-related inflammation. Exp Oncol. 2010;32:153–8.
[26] Ju MJ, Qiu SJ, Fan J, et al. Peritumoral activated hepatic stellate cells predict poor clinical outcome in hepatocellular carcinoma after curative resection. Am J Clin Pathol. 2009;131:498–510.
[27] Smyth MJ, Teng MW, Swann J, et al. CD4+CD25+ T regulatory cells suppress NK cell-mediated immunotherapy of cancer. J Immunol. 2006;176:1582–7.
[28] Sakaguchi S. Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. Nat Immunol. 2005;6:345–52.
[29] Wu K, Kryczek I, Chen L, et al. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. Cancer Res. 2009;69:8067–75.
[30] Kuang DM, Zhao Q, Peng C, et al. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J Exp Med. 2009;206:1327–37.
[31] Wang X, Lu XJ, Sun B. The pros and cons of dying tumour cells in adaptive immune responses. Nat Rev Immunol. 2017;17:591.
[32] Reading JL, Galvez-Cancino F, Swanton C, et al. The function and dysfunction of memory CD8(+) T cells in tumor immunity. Immunol Rev. 2018;283:194–212.