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Pan-Cancer Analysis of the Expression and Prognostic Value of S-Phase Kinase-Associated Protein 2

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Abstract

BACKGROUND: S-Phase Kinase-Associated Protein 2 (SKP2) is essential in modulating metabolism processes, cell proliferation, and carcinogenesis DUE to its capacity to ubiquitinate and degrade various tumor-suppressive substrates. However, the actual biological and mechanism significance of SKP2 in the development of tumors and as a possible therapeutic target remains to be completely understood.

AIM: This study aimed to explore the potential roles of the SKP2 gene in the oncologic pathogenesis of various cancers through an in-depth pan-cancer analysis including gene expression assessment, survival analysis, genetic alteration, and enrichment analysis.

METHODS: Public databases including the Cancer Genome Atlas database, Genotype-Tissue Expression Project database, cBioPortal database, Gene Expression Profiling Interactive Analysis 2 database, Tumor Immune Estimation Resource version 2.0 database, and STRING database were used to detect the SKP2 expression, molecular mechanism, and its association with the prognosis across pan-cancer.

RESULTS: SKP2 was significantly highly expressed in most types of cancers and was substantially correlated to the poor survival of patients with specific cancers based on the log-rank test. SKP2 had the highest frequency of alteration in lung cancer and amplification was the most common genetic alteration type. Finally, SKP2-related genes were identified and enrichment analyses were conducted.

CONCLUSION: This study presented the first demonstration of the pan-cancer landscape of abnormal SKP2 expression, it could potentially serve as a predictive indicator and prospective therapeutic target.

Introduction

With the dramatic growth and aging of the world's population, cancer-related mortality has become the leading reason for premature death in numerous countries and seriously threatens public health globally [1]. Although multimodal therapy and advances in medical technology have increased cancer patients' chances of survival, these treatments are still not perfect and are not suitable for all patients. Furthermore, the economic burden that cancer takes on nations throughout the world keeps rising [1], [2]. Therefore, it is vital and needed to determine the key genes to develop diagnostic and prognostic indicators as well as novel therapeutic targets. Pan-cancer analysis has emerged as an effective method for identifying and revealing gene features among cancers and provides a more thorough knowledge of molecular pathobiology in oncology [3].

S-Phase Kinase-Associated Protein 2 (SKP2), alternatively called F-Box and Leucine-Rich Repeat Protein 1 (FBXL1) or p45, belongs to the FBXL subgroup of the F-box family. Due to its capacity to ubiquitinate and degrade various tumor-suppressive substrates, SKP2 is essential in modulating metabolism processes, cell proliferation, and carcinogenesis [4], [5], [6]. Various research has been conducted over a long period of time to investigate the pro-oncogenic activity of SKP2 and uncovered the different functions of SKP2 in numerous cancer types. SKP2 overexpression was widely observed in hematologic cancers such as lymphoma, leukemia, and multiple myeloma [7], [8], [9], as well as solid sarcomas and carcinomas of various organs [10], [11], [12], [13], [14], [15], [16]. In addition, many publications have demonstrated that SKP2 targeting may be therapeutically useful for a variety of malignancies [17], [18], [19], [20], [21], [22], [23].

The actual biological and mechanism significance of SKP2 in the development of tumors and as a possible therapeutic target, however, remains to be completely understood. Moreover, from a pan-cancer viewpoint, there is little comprehension of the common or varied roles of SKP2 in cancers. Therefore, understanding the connection between SKP2 and pan-cancers is crucial. In this study, we aimed to explore the potential

roles of the SKP2 gene in the oncologic pathogenesis of various cancers through an in-depth pan-cancer analysis including gene expression assessment, survival analysis, genetic alteration, and enrichment analysis.

Methods

Databases

The Cancer Genome Atlas (TCGA) project, which is constructed by the National Cancer Institute, seeks to collect and find key cancer-causing genetic changes to develop an integrated map of cancer genomic profiles [24]. The Genotype-Tissue Expression Project (GTEx) is a huge database aimed at deciphering the intricate patterns of genetic diversity and gene regulation in numerous human tissue types [25].

Expression analysis

Tumor Immune Estimation Resource version 2.0 (TIMER2) is a webserver with special capabilities for analyzing and visualizing tumor immunity and its relationship to other oncogenic molecular and clinical characteristics [26]. The differential expression of SKP2 between different tumors and corresponding adjacent normal tissues in the TCGA database was obtained by using the module "GeneDE" of the TIMER2.

Regarding gene expression of several tumors which are not available in TIMER2, we used the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) database as an alternative pathway. GEPIA2, an updated version of the GEPIA, is a powerful tool to explore and compare the genomic data in TCGA and GTEx, such as differential expression analysis, correlation analysis, prognostic analysis, similar gene detection, and dimensionality reduction analysis.

Moreover, the "PathologicalStagePlot" module of GEPIA2 was used to extract and compare SKP2 expression in different pathological stages of each malignancy.

Survival analysis

In each tumor type, the median value of SKP2 expression was used as the cutoff value. Based on this value, the samples were classified into the high SKP2 group and the low SKP2 group. Then, survival analysis was conducted using the GEPIA2 "Survival Analysis" panel and the Kaplan–Meier Plotter tool.

Genetic alteration analysis

The cBio Cancer Genomics Portal (cBioPortal) is a public resource for interactive exploration of multidimensional cancer genomics datasets [27]. The variation information of the gene in all tumors was queried using the modules "Cancer_Type_Summary" and "Mutation" in the "Quick Search" function.

Enrichment analysis

We first explored the SKP2-interacted and correlated genes. The STRING database was used to find the genes that interacted with SKP2. It has been demonstrated that the repetitive presence of genes close to one another on genomes denotes a functional relationship between the proteins those genes encode. To identify correlated functions for a particular gene, STRING offers a framework for finding and analyzing conserved patterns in the structure of the genome [28]. The correlated targeting genes from the TCGA database were obtained based on the "SimilarGeneDetection" function of GEPIA2. Then, the Pearson correlation analysis between SKP2 and the top 5 SKP2-correlated genes was conducted.

The SKP2-related gene dataset was defined as the combination of the interacted genes and correlated genes. We used this gene set for further analyses of functional and pathway enrichment, including Kyoto Encyclopedia of Genes and Genomes and Gene ontology (GO).

Results

Overexpression of S-phase kinase-associated protein 2 in human pan-cancer

We used the TIMER2 method to examine SKP2 expression levels across diverse TCGA cancer types (Figure 1a). Consistent upregulated expression of SKP2 was seen in bladder urothelial carcinoma (BLCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head-and-neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), and uveal melanoma (UVM) compared with normal tissues. Because several cancers lack corresponding normal tissue controls, we therefore combined the data from the TCGA and GTEx (Figure 1b). SKP2 was

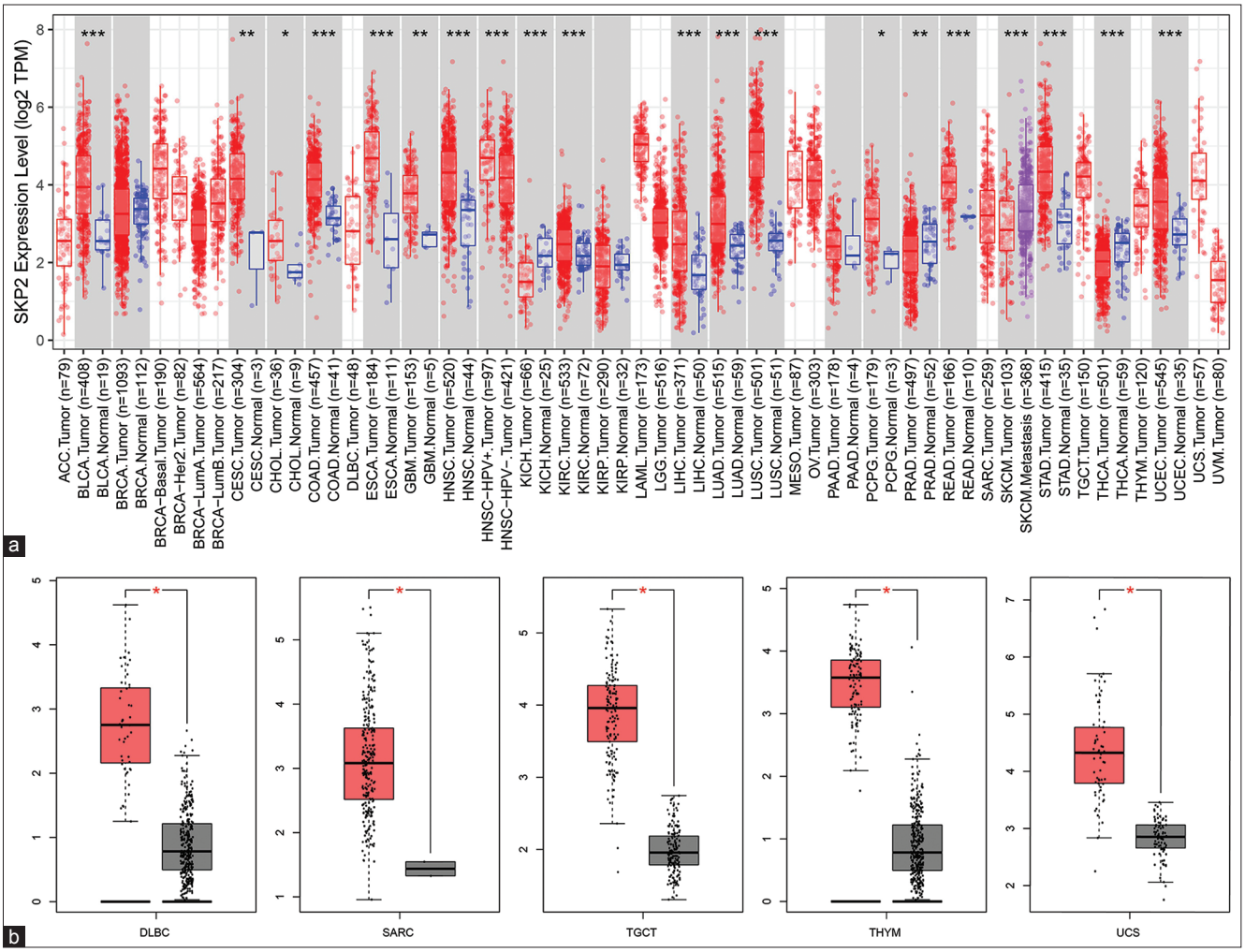

*Figure 1: Box plots of the SKP2 mRNA expression status in different cancer types and the corresponding normal tissues. (a) The expression level of the SKP2 mRNA in different cancer types in the TIMER2 database. (b) The expression level of the SKP2 mRNA in DLBC, SARC, TGCT, THYM, and UCS in TCGA and GTEx. * p < 0.05, ** p < 0.01, *** p < 0.001*

significantly highly expressed in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), sarcoma (SARC), testicular germ cell tumors (TGCT), thymoma (THYM), and uterine carcinosarcoma (UCS).

We subsequently assessed the association between SKP2 expression and the clinicopathological characteristics of patients with various tumors depending on distinct cancer stages. As shown in Figure 2, the gene expression was significantly increased in adrenocortical carcinoma (ACC), KICH, kidney renal papillary cell carcinoma (KIRP), LIHC, and LUAD. In contrast, the expression was dramatically decreased in COAD, SKCM, and UCS.

Prognostic value of S-Phase Kinase-Associated Protein 2 in cancers

The cutoff value was established as the mean SKP2 expression level across all tumor types. We separated cancer patients into high-expression and low-expression groups based on this cutoff value, and then we looked into the relationship between SKP2 expression and patient prognosis. The log-rank test indicated that the high expression level of SKP2 was substantially correlated to the poor overall survival (OS) of patients with ACC, KIRP, brain lower grade glioma, mesothelioma (MESO), and THYM, whereas the low SKP2 expression was related to poor OS prognosis in patients with ovarian serous cystadenocarcinoma (OV) and SKCM (Figure 3).

In addition, the results of survival analysis were subsequently conducted through the Web-Based Survival Analysis Tool “Kaplan–Meier Plotter.” Figure 4a demonstrated that the elevated expression of SKP2 gene was correlated with poor OS, diseasefree survival (DFS), and post-progression survival (PPS) in breast cancer. In contrast, the decreased expression of the gene was associated with poor OS, first progression (FP), and PPS prognosis for gastric cancer (Figure 4b). In liver cancer, the elevated SKP2 expression was correlated with poor OS, diseasespecific survival (DSS), and progression-free survival (PFS) (Figure 4c). Regarding lung cancer, the high expression group had a poorer OS than the low expression group, but there was not a significant difference in FP and PPS prognosis

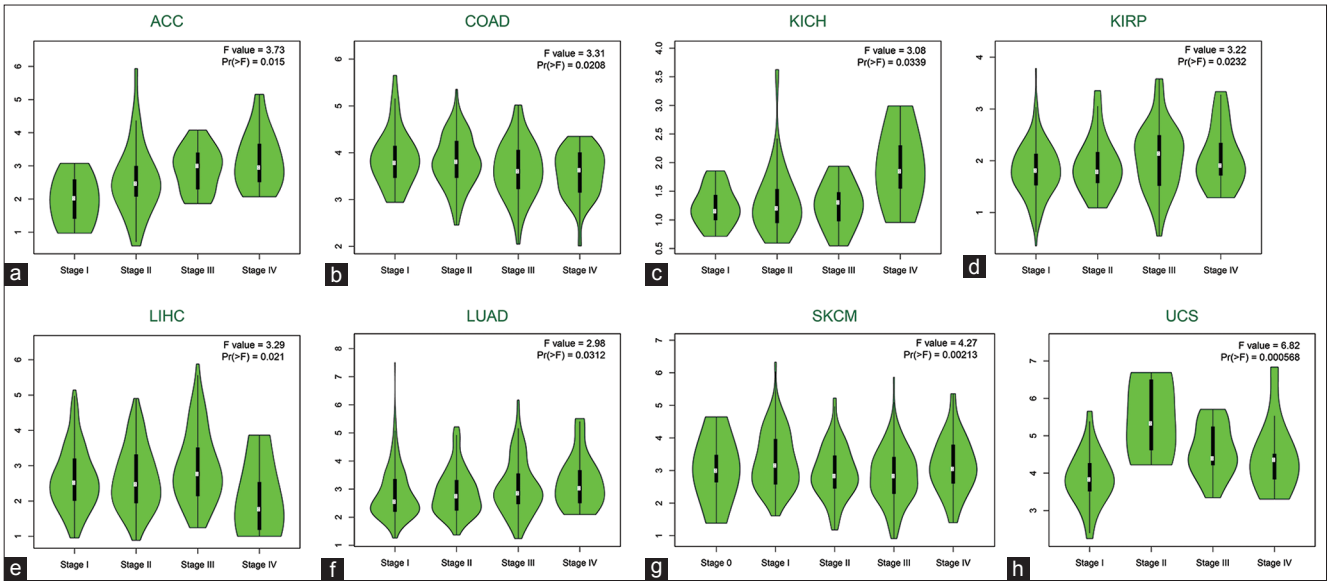

Figure 2: Violin plots of the SKP2 mRNA expression status in different pathological stages (Stage I-IV) in ACC (a), COAD (b), KICH (c), KIRP (d), LIHC (e), LUAD (f), SKCM (g), and UCS (h)

(Figure 4d). In ovarian cancer, as shown in Figure 4e, the increased SKP2 expression could predict the poor PFS prognosis. Subgroup studies were also performed utilizing certain clinicopathological and demographic criteria and noted various results in these five cancers (Tables 1-5).

Genetic alteration landscape of S-phase kinase-associated protein 2

We investigated the genetic alteration landscape of SKP2 in various cancers using the cBioPortal platform. Figure 5a demonstrated that patients with LUSC had the highest frequency of SKP2 alteration (10.47%), followed by those with LUAD (8.83%), BLCA (8.27%), ESCA (7.69%) and STAD (7.50%). "Amplification" was the most common genetic alteration type in most cancers, except UCEC ("Mutation" type accounting for 51.1%), DLBC ("Deep Deletion" type accounting for 100%), COAD/READ ("Mutation" type accounting for 62.5%), and TGCT ("Deep Deletion" type accounting for 100%). Figure 5b presents the SKP2 genetic alteration's locations

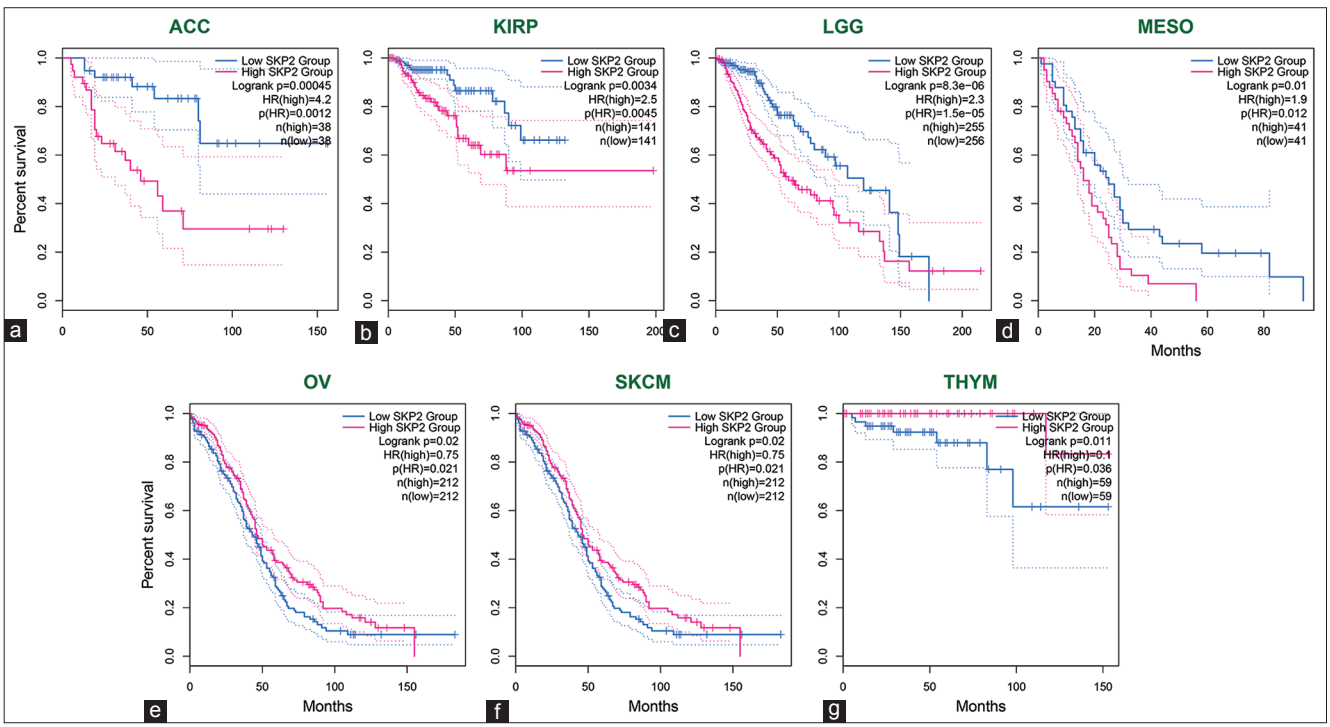

Figure 3: Kaplan–Meier curves show different overall survival in patients with ACC (a), KIRP (b), LGG (c), MESO (d), OV (e), SKCM (f), and THYM (g) based on the different expression levels of SKP2 in the GEPIA2 platform

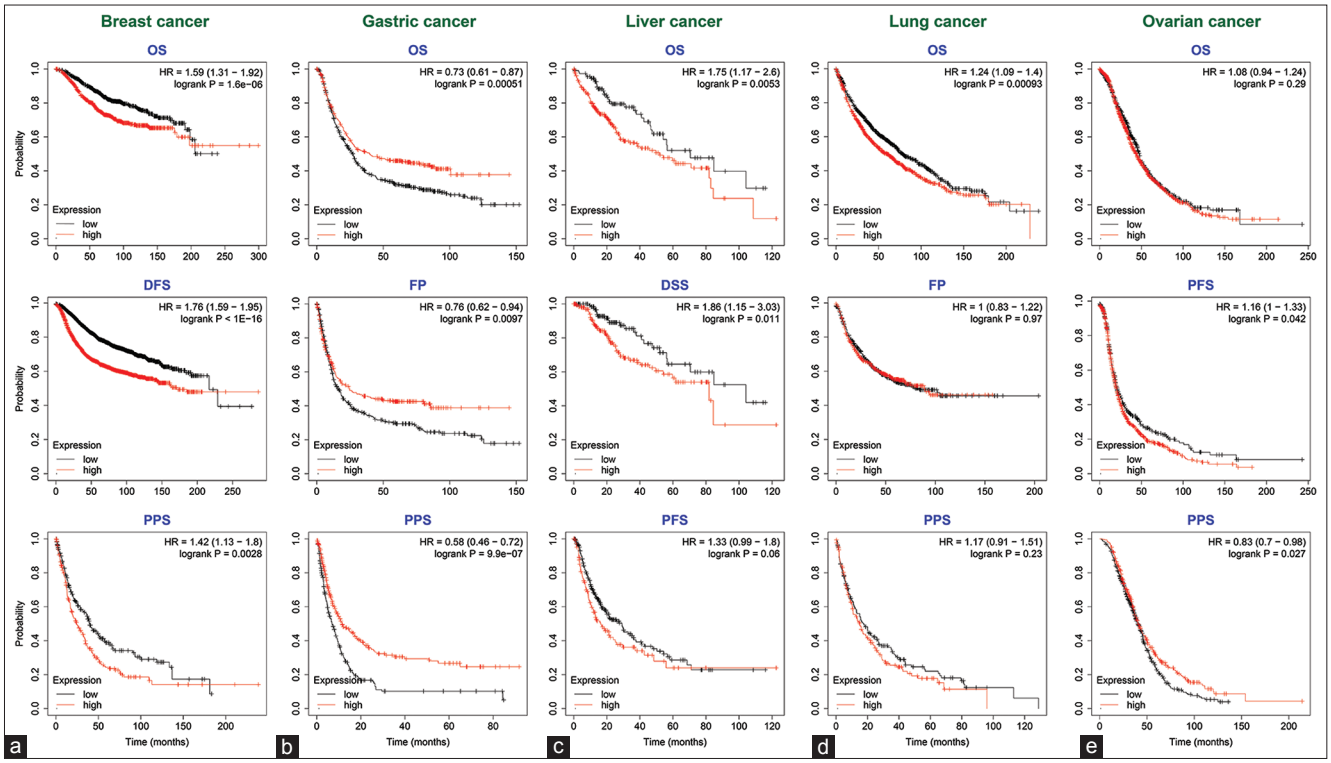

Figure 4: Survival analysis of in patients with breast cancer (a), gastric cancer (b), liver cancer (c), lung cancer (d), and ovarian cancer (e) based on the different expression levels of SKP2 in the Kaplan–Meier Plotter tool. OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; FP, first progression; PFS, progression-free survival; PPS, post-progression survival

in more detail. We discovered that the N229Kfs*8 mutation, which was reported in one case of STAD, one case of OV and one case of UCEC, can cause a frameshift mutation of the SKP2 gene, translation from N (Asparagine) to K (Lysine) at the 229th location of SKP2 protein. The 3D structure of the SKP2 protein was illustrated in Figure 5c, and the N229 location was marked in yellow.

Identifying S-phase kinase-associated protein 2-related genes and enrichment analysis

We sought to screen out the targeted SKP2-interacted proteins and the SKP2 expression-correlated

Table 1: Association of S-phase kinase-associated protein 2 expression and survival in breast cancer subgroups

Factor	Subgroup	Sample size	OS		RFS		DMFS		PPS	
			HR	p	HR	p	HR	p	HR	p
ER	ER +	3499	1.42	0.028	1.57	<0.001	1.56	0.002	1.29	0.172
	ER −	2168	0.86	0.364	0.93	0.473	0.77	0.050	1.14	0.591
PR	PR +	1559	1.53	0.268	1.58	0.002	1.92	0.007	1.16	0.769
	PR −	1989	0.78	0.355	1.04	0.728	1.01	0.937	0.61	0.330
HER2	HER2 +	1273	1.38	0.085	1.31	0.015	1.42	0.037	1.08	0.742
	HER2 −	6262	1.62	<0.001	1.79	<0.001	1.57	<0.001	1.48	0.004
Intrinsic subtype	Basal	1494	0.59	0.007	0.83	0.097	0.61	0.002	1.15	0.620
	Luminal A	3511	1.62	0.003	1.61	<0.001	1.48	0.003	1.39	0.072
	Luminal B	2015	1.08	0.671	1.52	<0.001	1.36	0.034	1.01	0.975
	HER2 +	515	1.51	0.159	1.26	0.197	1.25	0.376	1.56	0.238
Lymph node status	Positive	2153	1.09	0.610	1.72	<0.001	1.71	<0.001	1.03	0.881
	Negative	2829	1.75	0.001	1.63	<0.001	1.63	<0.001	1.68	0.012
Grade	I	576	1.43	0.416	1.83	0.023	1.37	0.452	0.88	0.800
	II	1795	1.6	0.022	1.45	0.001	1.55	0.003	1.58	0.050
	III	2058	0.99	0.951	1.14	0.176	1.18	0.201	0.99	0.972
TP53 status	Mutated	272	0.95	0.870	0.8	0.358	0.8	0.564	1.16	0.740
	Wild type	388	1.53	0.175	1.44	0.091	1.11	0.776	1.22	0.566
Pietenpol subtype	Basal-like 1	418	0.84	0.648	1.62	0.030	0.92	0.783	1.33	0.640
	Basal-like 2	165	0.96	0.938	0.94	0.853	0.52	0.095	NA	NA
	Immunomodulatory	462	2.41	0.036	0.71	0.152	0.81	0.462	1.79	0.296
	Mesenchymal	382	0.52	0.053	0.84	0.403	0.51	0.028	0.86	0.722
	Mesenchymal stem-like	201	2.17	0.135	1.72	0.137	2.22	0.122	NA	NA
	Luminal androgen receptor	413	1.02	0.939	1.17	0.421	1.42	0.233	1.01	0.974
Endocrine therapy	Include	1813	1	0.988	1.34	0.008	1.57	0.002	1.05	0.874
	Exclude	2038	1.66	0.002	1.44	<0.001	1.49	<0.001	1.61	0.010
	Tamoxifen only	1063	1.5	0.250	1.26	0.111	1.6	0.009	0.91	0.829
Chemotherapy	Include all	2342	0.99	0.953	1.51	<0.001	1.37	0.019	1.06	0.825
	Adjuvant only	746	0.93	0.775	1.48	0.007	1.68	0.028	0.89	0.684
	Neoadjuvant only	1615	0.81	0.508	1.54	0.006	1.51	0.012	NA	NA
	Exclude all	2104	1.47	0.031	1.49	<0.001	1.45	0.003	1.18	0.413

OS: Overall survival, RFS: Recurrence free survival, DMFS: Distant metastasis free survival, PPS: Post-progression survival, HR: Hazard ratio, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor-2, TP53: Tumor protein P53, NA: Not applicable.

Table 2: Association of S-phase kinase-associated protein 2 expression and survival in lung cancer subgroups

Factor	%	Subgroup	Sample size	FP		OS		PPS	
				HR	p	HR	p	HR	p
Histology		Adenocarcinoma	865	0.97	0.853	0.75	0.016	0.69	0.120
		Squamous cell carcinoma	675	0.93	0.776	0.79	0.049	0.77	0.618
Stage		1	652	0.97	0.897	1.15	0.298	0.85	0.597
		2	320	1.37	0.230	0.75	0.125	0.72	0.321
		3	70	NA	NA	0.89	0.675	NA	NA
		4	4	NA	NA	NA	NA	NA	NA
Grade		I	202	0.98	0.944	0.84	0.337	1.67	0.042
		II	310	1.3	0.207	1.38	0.045	0.98	0.932
		III	77	1.09	0.831	1.76	0.093	2.54	0.066
AJCC stage T		1	475	1.17	0.535	1.42	0.016	1.32	0.383
		2	686	1.22	0.190	1.3	0.020	0.95	0.749
		3	99	0.76	0.568	0.66	0.094	NA	NA
		4	48	NA	NA	1.1	0.767	NA	NA
AJCC stage N		0	863	1.59	0.005	1.53	<0.001	1.17	0.429
		1	296	0.77	0.272	1.2	0.247	0.96	0.873
		2	113	1.28	0.470	1.44	0.076	1.87	0.084
AJCC stage M		0	818	1.52	0.106	1.48	<0.001	0.99	0.981
		1	10	NA	NA	NA	NA	NA	NA
Gender		Female	817	0.94	0.695	1.14	0.263	1.25	0.242
		Male	1387	1.13	0.360	1.27	0.003	0.98	0.929
Smoking history		Exclude those never smoked	970	1.16	0.229	1.22	0.059	1.33	0.059
		Only those never smoked	247	0.65	0.076	0.59	0.063	0.9	0.736
Surgery		Only surgical margins negative	730	0.84	0.161	0.93	0.523	1.12	0.447
Chemotherapy		No	317	1.1	0.633	1.54	0.011	1.69	0.027
		Yes	178	1.25	0.296	1.22	0.348	1.31	0.267
Radiotherapy		No	276	1.11	0.582	1.19	0.334	1.2	0.422
		Yes	73	1.42	0.187	1.49	0.141	1.69	0.081

FP: First progression, OS: Overall survival, PPS: Post-progression survival, HR: Hazard ratio, AJCC: American Joint Committee on Cancer, NA: Not applicable.

genes for a series of pathway and functional enrichment studies to better explore the biological mechanisms of the SKP2 gene in carcinogenesis. The gene expression matrices of all cancers in the TCGA database were combined through the GEPIA2 platform, we then extracted 100 genes having the highest correlation coefficient with SKP2 (Table 6). Figure 6a showed the top 5 genes that correlated with SKP2 expression, which were NUP155 (Nucleoporin 155, R = 0.71, p < 0.001), BRIX1 (Biogenesis Of Ribosomes BRX1, R = 0.68, p < 0.001), CCT5 (Chaperonin Containing TCP1 Subunit 5, R = 0.63, p < 0.001), GINS1 (GINS Complex Subunit 1, R = 0.61, p < 0.001), and CENPI (Centromere Protein I, R = 0.61, p < 0.001). Besides, we screened out a total of 50 SKP2-interacted proteins using the STRING tool (Table 6). The protein-protein interaction network of these proteins was constructed and illustrated in Figure 6b. The Venn diagram of the two datasets mentioned above revealed two similar subjects, CCNA2 (Cyclin A2) and CDK1 (Cyclin Dependent Kinase 1) (Figure 6c).

The SKP2-related gene dataset creating from both the SKP2-interacted genes and SKP2-correlated genes was used for functional and pathway enriched analysis. GO analysis classified the functions of the gene dataset into three categories: Biological process (BP), cellular component (CC), and molecular function (MF). With regard to BP, the genes were significantly enriched in organelle fission, nuclear division, mitotic cell cycle phase transition, regulation of mitotic cell cycle, and regulation of cell cycle phase transition (Figure 7a). Figure 7b showed the result of the CC analysis, in which the SKP2-related genes were significantly enriched in spindle, chromosomal region, chromosome-centromeric region, condensed chromosome, and microtubule. For MF, the gene set was highly enriched in tubulin binding, microtubule binding, ATP hydrolysis activity, protein kinase regulator activity, and catalytic activity acting on DNA (Figure 7c). Pathway analysis results showed that the SKP2-related genes were mainly involved in cell cycle, cellular senescence, human T-cell leukemia

Table 3: Association of S-phase kinase-associated protein 2 expression and survival in ovarian cancer subgroups

Factor	Subgroup	Sample size	PFS		OS		PPS	
			HR	p	HR	p	HR	p
Histology	Endometrioid	62	3.57	0.070	0.46	0.471	NA	NA
	Serous	1232	0.86	0.035	0.89	0.127	0.83	0.035
Stage%	1	107	3.57	0.012	2.16	0.179	NA	NA
	2	72	2.17	0.078	0.37	0.071	0.42	0.132
	3	1079	0.74	<0.001	0.88	0.136	0.84	0.077
	4	189	0.72	0.087	0.7	0.086	0.57	0.018
Grade	I	56	2.97	0.047	1.67	0.276	NA	NA
	II	325	0.79	0.155	0.84	0.314	1.22	0.306
	III	1024	0.77	0.002	0.81	0.014	0.78	0.013
	IV	21	NA	NA	0.53	0.224	NA	NA
TP53 mutation	Mutated	516	0.64	<0.001	0.64	<0.001	0.62	<0.001
	Wild type	102	0.54	0.026	0.65	0.154	1.26	0.444
Debulk	Optimal	802	1.21	0.075	1.21	0.096	1.25	0.115
	Suboptimal	536	0.8	0.037	0.83	0.113	0.81	0.124
Chemotherapy	Contains platin	1438	0.88	0.044	0.89	0.113	0.8	0.014
	Contains taxol	821	0.76	0.002	0.89	0.218	0.87	0.179
	Contains taxol+platin	804	0.77	0.003	0.89	0.243	1.19	0.147
	Contains avastin	50	1.43	0.335	0.61	0.270	0.53	0.185
	Contains docetaxel	108	1.91	0.013	1.87	0.026	2.2	0.010
	Contains gemcitabine	135	1.37	0.112	0.7	0.085	0.66	0.071
	Contains paclitaxel	248	0.68	0.029	0.51	0.003	0.48	0.005
	Contains topotecan	119	1.31	0.187	0.65	0.031	0.67	0.055

PFS: Progress free survival, OS: Overall survival, PPS: Post-progression survival, HR: Hazard ratio, TP53: Tumor protein p53, NA: Not applicable.

Table 4: Association of S-phase kinase-associated protein 2 expression and survival in gastric cancer subgroups

Factor	Subgroup	Sample size	OS		FP		PPS	
			HR	p	HR	p	HR	p
Stage	1	69	0.47	0.136	2.17	0.171	0.5	0.364
	2	145	0.45	0.007	0.45	0.009	0.5	0.039
	3	319	0.64	0.005	0.64	0.027	0.42	<0.001
	4	152	0.4	<0.001	0.57	0.004	0.51	0.004
AJCC stage T	1	14	NA	NA	NA	NA	NA	NA
	2	253	0.74	0.159	1.55	0.042	0.58	0.017
	3	208	0.7	0.040	0.75	0.095	0.51	<0.001
	4	39	0.27	0.007	0.33	0.006	0.47	0.160
AJCC stage N	0	76	0.4	0.035	0.41	0.043	0.16	<0.001
	1	232	0.54	0.003	0.56	0.003	0.37	<0.001
	2	129	0.41	<0.001	0.5	0.002	0.42	<0.001
	3	76	0.57	0.042	0.6	0.057	0.65	0.145
AJCC stage M	0	459	0.56	<0.001	0.63	<0.001	0.42	<0.001
	1	58	0.24	<0.001	0.38	0.005	0.22	<0.001
Lauren classification	Instestinal	336	0.51	<0.001	0.59	0.004	0.35	<0.001
	Diffuse	248	0.57	0.001	0.57	0.001	0.59	0.007
	Mixed	33	2.07	0.216	3.03	0.073	NA	NA
Differentiation	Poorly	166	1.42	0.119	1.4	0.168	1.5	0.223
	Moderately	67	1.74	0.108	1.35	0.368	0.35	0.048
	Well	32	0.45	0.147	NA	NA	NA	NA
Gender	Female	244	0.59	0.007	0.57	0.007	0.44	<0.001
	Male	566	0.7	0.003	0.79	0.064	0.58	<0.001
Perforation	No	169	1.367	0.122	1.22	0.311	1.45	0.169
	Yes	4	NA	NA	NA	NA	NA	NA
Treatment	Surgery alone	393	0.68	0.009	0.76	0.061	0.44	<0.001
	5-Fluorouracil-based adjuvant	157	2.23	<0.001	2.27	<0.001	1.52	0.020
	other adjuvant	80	0.46	0.078	0.41	0.020	0.53	0.170
HER2 status	HER2 −	641	0.6	<0.001	0.64	0.001	0.5	<0.001
	HER2 +	424	1.19	0.217	1.22	0.228	0.5	0.001

OS: Overall survival, FP: First progression, PPS: Post-progression survival, HR: Hazard ratio, AJCC: American Joint Committee on Cancer, HER2: Human epidermal growth factor receptor-2, NA: Not applicable.

virus 1 infection, viral carcinogenesis, FoxO signaling pathway, and oocyte meiosis (Figure 7d).

Discussion

As the most extensive E3 ubiquitin ligase grouping in humans, Cullin-Really Interesting New Gene ligases (CRLs) ubiquitinate up to one-fifth of all proteins degraded through the ubiquitin-proteasome system, and CRL1, or S-phase kinase-associated protein 1 (Skp1)-Cullin1-F-box (SCF) is the most intensively studied and documented CRL [29]. F-box proteins serve as CRL1 subunits that recognize substrates and attract target proteins for ubiquitination and degradation; therefore, they play a crucial part in numerous physiological functions in the body [16]. Despite the fact that most F-box proteins have been known for a long time, only a few of these have received thorough research, and SKP2 is the best-described mammalian F-box protein.

The pan-cancer analysis is a comprehensive and systematic approach to investigating and assessing the function and mechanism of a specific gene in tumorigenesis. Using the TCGA database, several genes were identified that may have a role in human cancers, such as FGL1 [30], CARM1 [31], CBX [32], LCK [33], and MNX1 [34]. In the present study, we conducted a systematic analysis of SKP2 expression across a variety of tumor forms, and the results revealed that practically most tumor types overexpressed SKP2

Table 5: Association of S-phase kinase-associated protein 2 expression and survival in liver cancer subgroups

Factor	Subgroup	Sample size	OS		RFS		PFS		DSS	
			HR	p	HR	p	HR	p	HR	p
Stage	1	171	1.66	0.148	0.68	0.198	1.3	0.326	0.55	0.274
	2	86	3.53	0.008	0.67	0.228	0.78	0.414	9.4	0.009
	3	85	1.87	0.048	1.99	0.062	1.63	0.132	1.78	0.159
	4	5	NA	NA	NA	NA	NA	NA	NA	NA
Grade	I	55	2.29	0.135	0.32	0.024	0.49	0.074	2.01	0.295
	II	177	1.95	0.015	1.43	0.166	1.6	0.052	2.31	0.019
	III	122	1.44	0.256	1.67	0.072	2.04	0.007	1.91	0.098
	IV	12	NA	NA	NA	NA	NA	NA	NA	NA
AJCC stage T	1	181	1.52	0.197	0.7	0.208	1.35	0.254	0.71	0.462
	2	94	3.61	0.003	0.78	0.432	1.3	0.411	6.64	0.004
	3	80	1.97	0.032	1.71	0.138	1.66	0.131	1.58	0.274
	4	13	NA	NA	NA	NA	NA	NA	NA	NA
Vascular invasion	None	205	1.8	0.045	0.81	0.416	1.39	0.155	1.53	0.281
	Micro	93	1.77	0.182	0.63	0.151	0.65	0.146	1.53	0.454
	Macro	16	NA	NA	NA	NA	NA	NA	NA	NA
Gender	Male	250	1.56	0.073	1.17	0.436	1.14	0.514	2.01	0.026
	Female	121	2.11	0.010	2.44	0.003	2.32	0.002	2.51	0.011
Race	White	184	1.85	0.011	0.77	0.281	1.48	0.081	1.77	0.057
	Black	17	NA	NA	NA	NA	NA	NA	NA	NA
	Asian	158	2.06	0.019	1.46	0.141	1.65	0.036	3.57	0.027
Sorafenib treatment	Treated	30	0.32	0.074	0.53	0.193	0.47	0.080	0.32	0.074
Alcohol consumption	Yes	117	1.63	0.140	1.58	0.151	1.55	0.126	2.22	0.039
	None	205	1.64	0.063	1.16	0.551	1.38	0.116	1.77	0.076
Hepatitis virus	Yes	153	1.69	0.152	0.73	0.269	1.26	0.421	2.21	0.073
	None	169	1.92	0.008	1.88	0.018	2.12	0.001	1.92	0.032

OS: Overall survival, RFS: Recurrence free survival, PFS: Progress free survival, DSS: Disease specific survival, HR: Hazard ratio, AJCC: American Joint Committee on Cancer, NA: Not applicable.

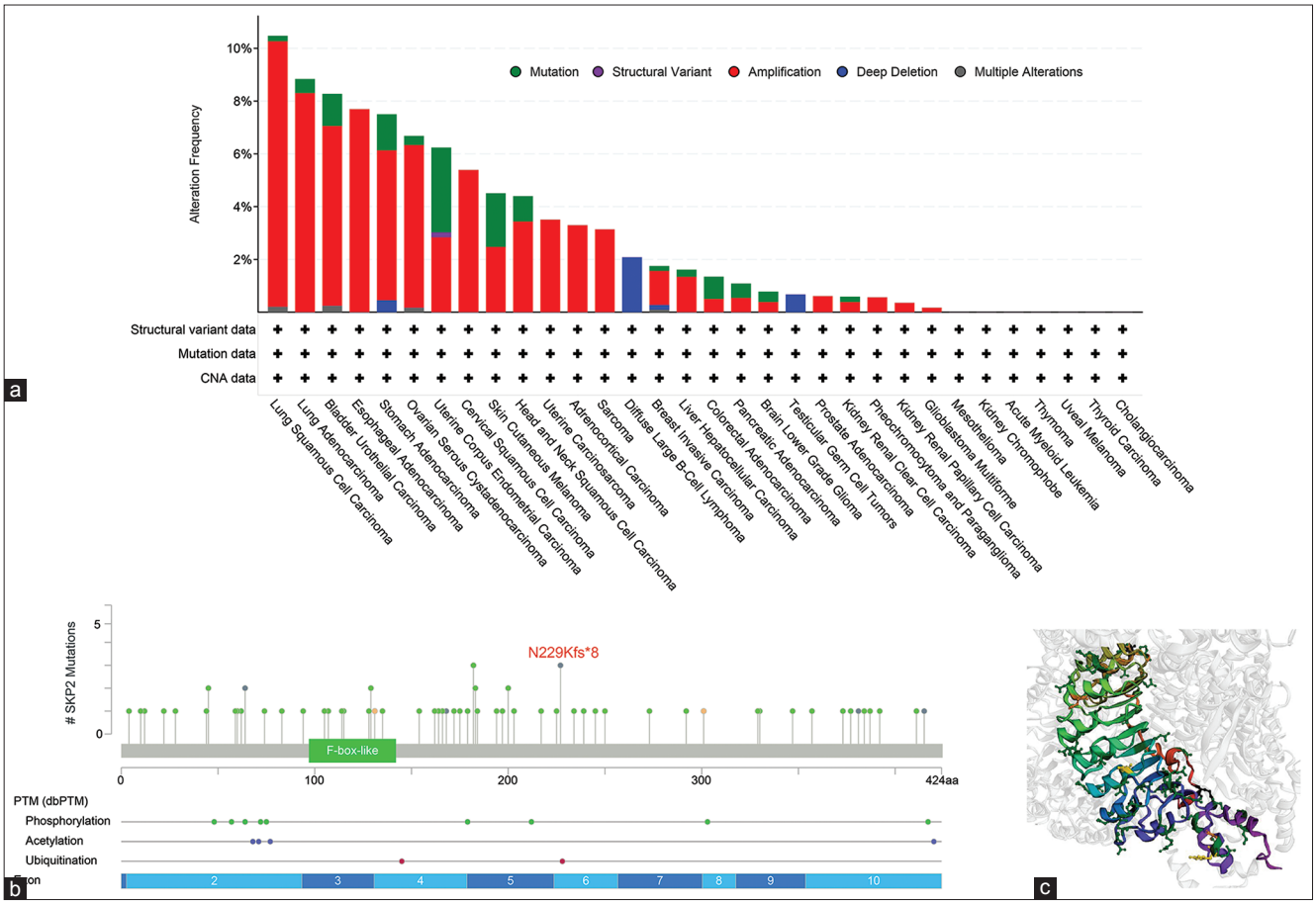

Figure 5: Characteristics of SKP2 mutation in various cancers. (a) Alteration frequency with mutation type. (b) Frequency of mutation site. (c) The 3D model of SKP2 protein

and there were certain differences in the level of SKP2 expression in different cancer stages. This finding highly recommended that SKP2 may contribute to the development of human malignancies. In addition, the survival analysis indicated that SKP2 may serve as a prognostic marker for various human malignancies.

In breast cancer, we found that the high expression of the gene was correlated with poor prognosis including OS (hazard ratio [HR]: 1.59, 95% confidence interval [CI]: 1.31–1.92, p < 0.001), DFS (HR: 1.76, 95% CI: 1.59–1.95, p < 0.001), and PPS (HR: 1.42, 95% CI: 1.13–1.80, p < 0.001). Subgroup analysis also demonstrated the high expression level of SKP2 in estrogen receptor (ER) positive, progesterone receptor (PR) positive, and human epidermal growth factor receptor-2 (HER2) negative tumors, and this expression level was associated with poor prognosis. Mechanistically, SKP2 strongly encourages the phosphorylation, ubiquitination, and degradation of PDCD4, which is well-known as a tumor-suppressive protein that prevents the development of pre-initiation complexes by interacting with eIF4A, thereby promoting breast cancer tumorigenesis and radiation tolerance [11], [35]. Notably, maintaining mH2A1 stability through the SKP2-mH2A1-CDK8 axis as a crucial channel for orchestrating G2/M transition, polyploidy, cell proliferation, and migration is another potential molecular mechanism of SKP2 in breast carcinogenesis [36].

We investigated the TCGA-LIHC samples, and the finding indicated that aberrant SKP2 expression was an unfavorable factor of OS (HR: 1.75, 95% CI: 1.17–2.60, p = 0.005) and DSS (HR: 1.86, 95% CI: 1.15–3.03, p = 0.011) in liver cancer. Numerous publications

Table 6: S-phase kinase-associated protein 2-related gene list based on STRING and gene expression profiling interactive analysis 2

Feature	Gene name
SKP2-interacted genes	AKT1 BRCA1 BTG2 CCNA1 CCNA2 CCNE1 CDC14B CDC20 CDC34 CDH1 CDK1 CDK2 CDK4 CDK9 CDKN1A CDKN1B CDKN1C CDT1 CKS1B COPS5 CUL1 CUL5 DDB1 DUSP1 E2F1 EP300 FBXW2 FOXO1 FOXO3 FZR1 HSP90AA1 KMT2A KPNA1 KPNA6 MYC ORC1 PHB PSMD9 RASSF1 RBL2 RBX1 RUNX2 SIRT3 SKP1 TCF3 UBB SMAD4 TEN1-CDK3 USP18 TRIM49
SKP2-correlated genes	NUP155 BRIX1 CCT5 GINS1 CENPI NCAPH KIF18A MCM2 TPX2 TTK BUB1 RAD1 MMS22L MCM8 KIF18B MCM10 KIF11 KIF2C DDIAS KIF14 CKAP2L FANCI GMPS CHEK1 KIF23 NCAPD2 POLQ KIAA1524 CKAP2 CENPO TICRR MCM4 SASS6 KIF4A DEPDC1 LMNB2 TARS CCNA2 SKA1 DNAJC21 AUNIP RACGAP1 CCNB2 CLSPN CDCA5 RAD51AP1 PLK1 CCDC138 TDG C5orf34 PARPBP PAPD7 SGOL2 TOPBP1 DLGAP5 BORA CDK1 TMPO ARHGAP11A ZNF131 RFC5 ZWILCH FIGNL1 TRA2B ASPM GSG2 NUSAP1 FOXM1 NDC1 SGOL1 MCM6 INCENP NSUN2 MAD2L1 NCAPG OIP5 RP11-443B20.1 RQCD1 DNA2 STIL MKI67 TRIP13 FANCB SUV39H2 MELK ESPL1 HJURP RRM2 XRCC2 MTBP RFC4 TIMELESS ECT2 CDCA8 EXO1 C17orf53 KIFC1 CENPL MTFR2 DBF4

SKP: S-phase kinase-associated protein.

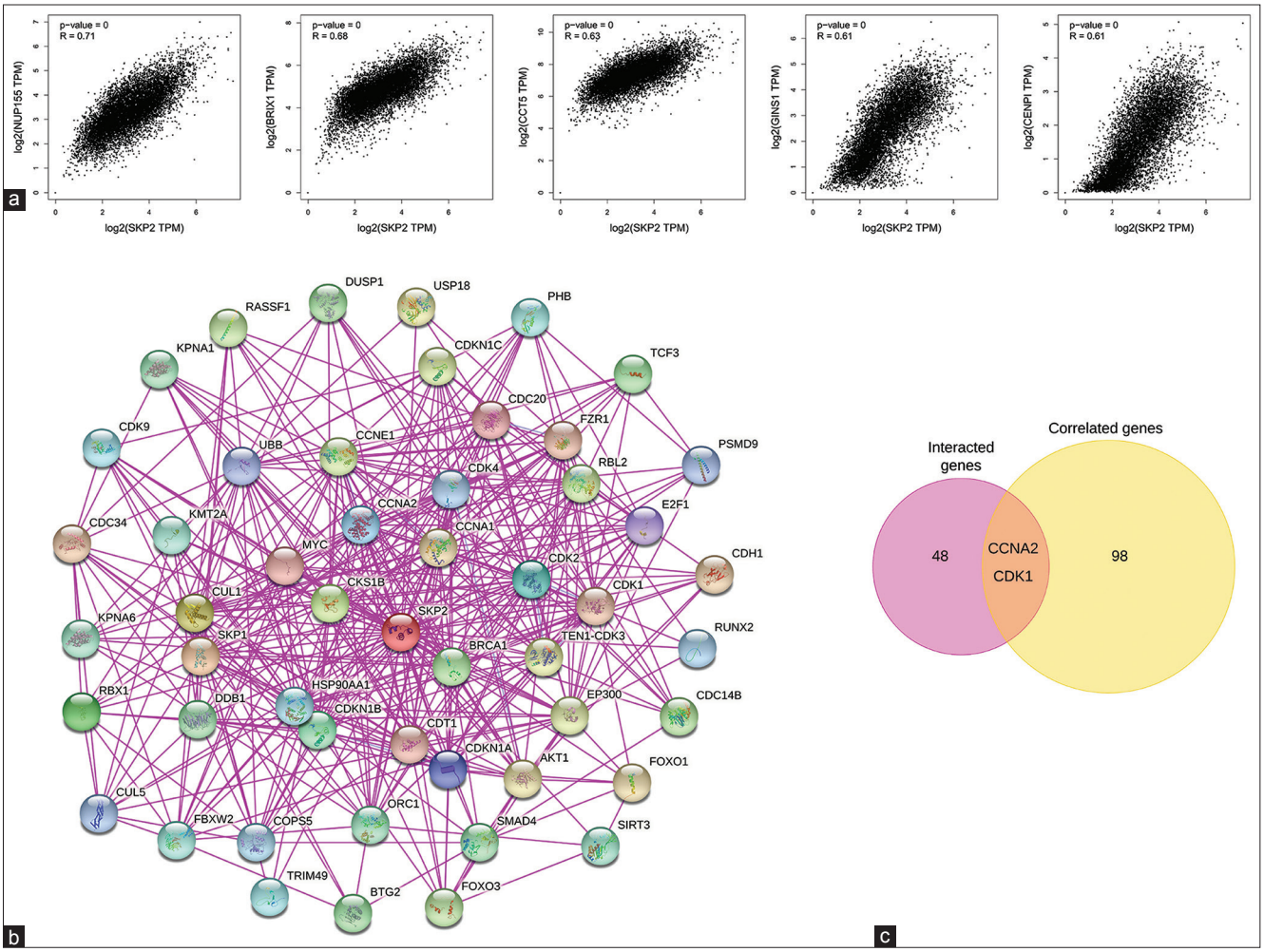

Figure 6: SKP2-related gene enrichment analysis. (a) Pearson correlation analysis and dot plots of the expression of SKP2 and the top 5 SKP2-correlated genes (NUP155, BRIX1, CCT5, GINS1, and CENPI). (b) Protein-protein interaction network of SKP2 and the top 100 interacted proteins. (c) Venn diagram of the SKP2-correlated and interacted genes

have shown that SKP2 may act as an oncogene in the formation and progression of liver cancer, especially hepatocellular carcinoma (HCC). Delogu *et al*. reported that SKP2 facilitated the onset of HCC via the Ras/MAPK and AKT/mTOR pathways [37]. A recent research revealed that SKP2 promoted hepatocarcinogenesis through nuclear AMPK-SKP2-CARM1 signaling transcriptionally regulating nutrient-deprived autophagy induction [38]. Furthermore, emerging studies have highlighted the critical role of SKP2 in lung cancer. Elevated expression of SKP2 in nonsmall cell lung cancer enhanced the potential for invasion and is linked to metastases and high mortality [39]; besides, in small cell lung cancer, SKP2 stimulates tumor cell invasion and migration and shields them from programmed cell death [40]. Similar to this, the analyses of the TCGA-LUAD and TCGA-LUSC data in this study confirmed lung cancer tissues significantly expressed SKP2 in contrast to adjacent non-tumor tissues, and patients with high expression of the gene had an HR of 1.75 (95% CI: 1.09–1.40, p < 0.001) compared to those with low expression.

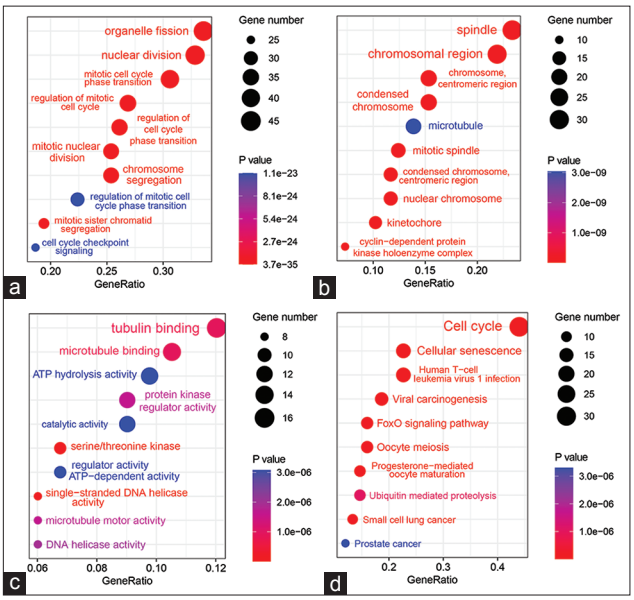

Figure 7: Functional and pathway enrichment analysis of the SKP2-related genes. (a) Biological processes; (b) Cell composition; (c) Molecular function; (d) KEGG

To more thoroughly comprehend the molecular mechanism of SKP2 in cancer, we first sought to identify the targeted SKP2-related molecules, and CDK1 and CCNA2 were found as the two most related genes

due to their interaction and correlation with SKP2. These two genes, like SKP2, also play an important role in the cell cycle, and a large body of literature has reported their relationship in regulation and controlling of cell cycle as well as tumorigenesis. Recently, a functional relationship of the SKP2-CDK1 loop was found, in which increased expression of SKP2 led to the expression of CDK1 indicating SKP2 as a positive driver for CDK1 [41]. In addition to boosting CDK activity, overexpressed SKP2 could also disrupt the excellent time-related balance of the CDK signaling pathway to make a significant contribution to the uncontrolled proliferation and unstable genomic characteristics of tumor cells [42]. Concerning CCNA2, it is an important modulator of the G2-M transition and S-phase [43]. In S-phase, CCNA2 is commonly linked to CDK2, while in late S-phase, the majority of CCNA2 is connected to CDK1 [44], [45]. CCNA2 is widely expressed and upregulated in a variety of cancer types, due to its crucial pathogenic involvement in the immune-oncology context of the tumor microenvironment, increased CCNA2 expression was associated with unfavorable clinicopathological characteristics [46].

Conclusion

We presented the first demonstration of the pan-cancer landscape of abnormal SKP2 expression. Our findings will enable us to take the next step into a further mechanistic investigation of SKP2 and the therapeutic applicability of SKP2 suppression in particular tumors, offering fresh perspectives and treatment choices for cancer.

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