Associations and prognostic significance of $p27^{Kip1}$, Jab1 and Skp2 in non-Hodgkin lymphoma

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Received March 3, 2016; Accepted July 26, 2016

DOI: 10.3892/mco.2016.986

Abstract. Non-Hodgkin lymphoma (NHL) is a primary tumor arising in lymph nodes and lymphoid tissue. The incidence of NHL is increasing at an annual rate of 3%. The human Jun activation domain-binding protein 1/COP9 signalosome subunit 5 (Jab1/CSN5) is a negative regulator of the cell cycle inhibitor $p27^{Kip1}$ and abnormal expression of Jab1 is correlated with reduced p27 expression and associated with advanced tumor stage and poor prognosis in several human cancers. F-box protein S-phase kinase-interacting protein-2 (Skp2), the substrate recognition subunit of the Skp1-Cul1-F-box protein ubiquitin protein ligase complex, is required for the ubiquitination and consequent degradation of p27. The Skp2 protein is overexpressed in several human cancers and is associated with the degree of differentiation and the prognosis. The aim of the present study was to investigate the expression status of $p27^{Kip1}$, Jab1 and Skp2 by immunohistochemistry, and assess their prognostic significance in patients with NHL. Immunohistochemical analysis revealed an inverse association between Jab1 and p27 in NHL tissue samples. Kaplan-Meier analysis demonstrated that Jab1 overexpression, Skp2 overexpression and low p27 expression were significantly associated with poor prognosis. Among clinicopathological parameters, overexpression of Jab1 was significantly associated with tumor size and International Prognostic Index (IPI), whereas Skp2 expression was significantly associated with metastasis and IPI. These findings suggest that the overexpression of Jab1 or Skp2 plays an important role in the pathogenesis of NHL. Thus, the expression of $p27^{Kip1}$, Jab1 and Skp2 provided a clinical reference for the treatment of NHL.

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Key words: non-Hodgkin lymphoma, $p27^{Kip1}$, Jun activation domain-binding protein 1/COP9 signalosome subunit 5, S-phase kinase-interacting protein-2

Introduction

Non-Hodgkin lymphoma (NHL) accounts for ~85% of all malignant lymphomas and consists of a complex group of cancers arising mainly from B lymphocytes, and occasionally from T lymphocytes. NHL is heterogeneous regarding its clinical, immunophenotypic and genetic characteristics. With the accelerated process of industrialization and environmental pollution, the incidence of NHL is increasing annually. In China, the incidence of lymphoma is 1.39/100,000 in men and 0.84/100,000 in women. Lymphoma ranks from eleventh to thirteenth in overall cancer mortality (1.5/100,000) (1). NHL ranks twelfth in overall cancer morbidity and tenth in overall cancer mortality, with a cumulative NHL risk of 0.54 and a cumulative mortality risk of 0.26 (2). NHL severely affects the physical and mental health of the patients. NHL is characterized by an onset with distinct regional differences, and the etiology is unknown. There are several difficulties in current cancer research, including diversity of clinical status and complex pathological type, whereas the molecular pathogenesis has not been fully elucidated.

Uncontrolled cell proliferation is the main characteristic of tumors. Disorders of the cell cycle and an unbalance between cell proliferation and death due to various causes play a crucial role in tumorigenesis and tumor progression. $p27^{Kip1}$, a negative cell cycle regulator, is a universal cyclin-dependent kinase (CDK) inhibitor (CKI) that belongs to the Cip/Kip group of CDK inhibitors. $p27^{Kip1}$ shares a sequence homology with p21 and p57 (3) and it may bind to and inhibit the activity of cyclin-CDK complexes. Due to the inhibition of $p27^{Kip1}$, cyclin-CDK cannot effectively phosphorylate the retinoblastoma protein; thus, E2F transcription factors cannot be released, downstream genes cannot be transcribed and the cell cycle process is blocked (4). $p27^{Kip1}$ inhibits the G1-S phase transition in the cell cycle, resulting in cell cycle arrest in the G1 phase and cessation of cell proliferation (5). Low p27 expression is associated with higher tumor grade (6). Therefore, $p27^{Kip1}$ is considered to be a tumor suppressor.

The human Jun activation domain-binding protein 1/COP9 signalosome subunit 5 (Jab1/CSN5) was initially identified as a coactivator of the gene regulatory activator protein (AP-1), which is involved in the control of cell proliferation (7). Jab1 is also referred to as the fifth component of the COP9 signalosome (CSN) complex. CSN is a multiprotein complex involved in

modulating signal transduction, gene transcription and protein stability (8,9). Jab1 is a nuclear export protein that targets $p27^{Kip1}$ for transportation from the nucleus to the cytoplasm and promotes its subsequent degradation (10). Jab1/CSN5 interacts with a number of proteins and regulates their function, and is involved in different signal transduction pathways, including degradation of target proteins by regulating gene transcription and cell cycle through phosphorylation (8). Jab1 regulates cell proliferation through p27 (11). These findings indicate that Jab1 may play a significant role in oncogenesis. Jab1 expression is inversely correlated with $p27^{Kip1}$ protein expression, and is significantly associated with adverse clinicopathological characteristics. Recent research indicates that Jab1 participates in the nuclear export of the $p27^{Kip1}$ protein (10). Jab1 overexpression may induce p27 downregulation by nuclear export (12). Some scholars investigated the expression of Jab1 in pancreatic (13) and ovarian cancer (14), and found that the increase of Jab1 expression level is correlated with a decrease of $p27^{Kip1}$ levels and poor prognosis.

F-box protein S-phase kinase-interacting protein-2 (Skp2), the substrate recognition subunit of the Skp1-Cul1-F-box protein (SCF) ubiquitin protein ligase complex, targets substrates such as p27, p21, p57, or p130 for degradation (15). Skp2, as an important cell cycle regulatory factor, is able to identify phosphorylated substrates specifically and mediate ubiquitin degradation. It has been demonstrated that Skp2 is able to specifically recognize $pThr187p27^{Kip1}$, then mediate the ubiquitination and subsequent proteolysis of $p27^{Kip1}$ (16). Due to the important role of Skp2, scholars have investigated it and found Skp2 protein overexpression in gastric carcinoma (17), small-cell lung cancer (18) and oral squamous cell carcinoma (19), which is associated with the degree of differentiation and prognosis. The role of Skp2 in controlling $p27^{Kip1}$ levels has been reported in several types of cancer, including colon, breast, prostate and oral squamous cell carcinoma (20-23).

Jab1 and Skp2 dysfunction in NHL may cause a decrease in the level of $p27^{Kip1}$ and disrupt its function, leading to the occurrence of this malignancy. To the best of our knowledge, an investigation of both Skp2 and Jab1 has not been reported in NHL to date. Thus, the aim of the present study was to concurrently evaluate the abnormal expression of Jab1 and Skp2 by immunohistochemistry, with a comparative analysis of p27 expression and proliferative activity in NHL.

Materials and methods

Patients. Fresh surgical specimens from 50 patients with NHL were provided by the Department of Pathology of the Affiliated Hospital of Nantong University (collected from 2005 to 2009, following an Institutional Review Board-approved human subjects study protocol. Informed consent was obtained from all patients (34 men and 16 women; age range, 10-90 years; mean age, 55.6 years). The histology of the disease was determined based on hematoxylin and eosin-stained preparations, according to the criteria of the World Health Organization (24).

Immunohistochemistry. Paraffin sections (5 μm) from the samples were deparaffinized in 100% xylene and rehydrated in descending ethanol-water ratio solutions according to the standard protocol. The sections were treated with 10 mmol/l citrate buffer (pH 6.0) and heated to 121˚C for 20 min to enhance the accessibility of the antigens. The slides were incubated at 4˚C overnight with anti-Jab1 (monoclonal, mouse anti-human, dilution 1:100; Santa Cruz Biotechnology, Dallas, TX, USA; sc-13157), anti-Skp2 (polyclonal, rabbit anti-human, dilution 1:50; Santa Cruz Biotechnology, sc-7164), anti-p27 (polyclonal, rabbit anti-human, dilution 1:50; Santa Cruz Biotechnology, sc-528), or anti-Ki-67 (polyclonal, rabbit anti-human, dilution 1:150; ZSGB-Bio, Beijing, China; ZM-0165). After washing, the sections were treated with rabbit anti-mouse/rabbit immunoglobulin for 30 min at room temperature. Staining for Jab1, Skp2, p27 and Ki-67 were completed by using the streptavidin-biotin-peroxidase complex method with diaminobenzidine (DAB) as a chromogen. Counterstaining was performed using haematoxylin. The stained sections were examined under a light microscope. At least 10 high-power fields were randomly selected and at least 300 cells/field were counted per section. Jab1, Skp2, p27 and Ki-67 indices were scored as the percentage of positive cells for each antigen. The staining results were scored semiquantitatively. Intensity was estimated compared with the control and scored as follows: 0, negative staining; 1, weak staining; 2, moderate staining; and 3, strong staining. Scores representing the percentage of tumor cells that stained positive were as follows: 0, <1%; 1, 1-10%; 2, 10-50%; 3, 50-75%; and 4, >75% positive tumor cells. A final score was calculated by adding the scores for percentage and intensity, resulting in scores of 0 and 2-7. A score of 0 was considered as negative; 2-3 was considered weak; 4-5 was considered moderate; and 6-7 was considered strong. For statistical analysis, scores 0-3 were considered as low expression, while scores 4-7 were considered as overexpression (25). In half of the samples, staining was repeated twice to avoid technical errors, but similar results were obtained in these samples.

Statistical analysis. The correlations among clinicopathological factors and the expression levels of Jab1, p27, Skp2 and Ki-67 were analyzed using the Chi-square test, the Mann-Whitney U test and logistic regression analysis. Survival analysis was performed by the Kaplan-Meier method and survival curves were compared with the log-rank test. The Cox proportional hazard model with a forward stepwise procedure was used in the multivariate analysis to determine independently significant prognostic factors. Data are expressed as mean ± standard error. P-values <0.05 were considered to indicate statistically significant differences. All the statistical analyses were performed with SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Expression of $p27^{Kip1}$, Jab1, Skp2 and Ki-67 and their correlation in NHL. Immunohistochemical analysis revealed that the tumor cells expressed $p27^{Kip1}$, Jab1 and Skp2. The pattern of $p27^{Kip1}$, Jab1 and Skp2 expression varied in the same sample as follows: $p27^{+}/Jab1^{-}/Skp2^{-}$; $p27^{+}/Jab1^{+}/Skp2^{-}$; $p27^{+}/Jab1^{-}/Skp2^{+}$; $p27^{+}/Jab1^{+}/Skp2^{+}$ (Fig. 1); $p27^{-}/Jab1^{-}/Skp2^{-}$; $p27^{-}/Jab1^{+}/Skp2^{-}$; $p27^{-}/Jab1^{-}/Skp2^{+}$; and $p27^{-}/Jab1^{+}/Skp2^{+}$ (Fig. 2). The positivity ratio of $p27^{Kip1}$, Jab1 and Skp2 was 38, 70 and 32%, respectively. The correlation among the

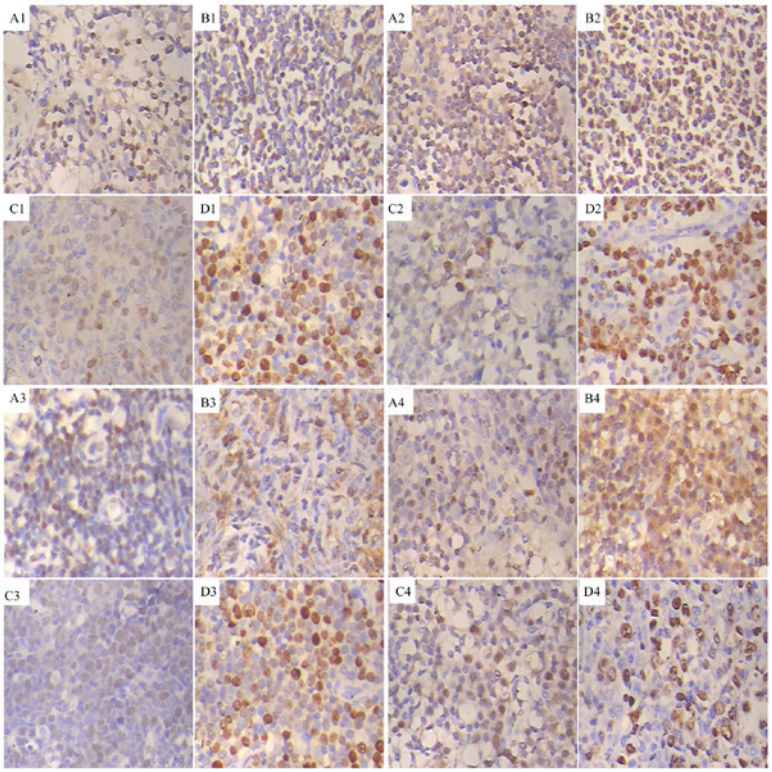

Figure 1. Expression patterns of p27, Jun activation domain-binding protein 1 (Jab1), S-phase kinase-interacting protein-2 (Skp2) and Ki-67 in non-Hodgkin lymphoma tissues (immunohistochemical staining; magnification, x400). (A1) p27 overexpression; (B1) low expression of Jab1; (C1) low expression of Skp2; and (D1) Ki-67 overexpression. (A2) p27 overexpression; (B2) Jab1 overexpression; (C2) low expression of Skp2; and (D2) Ki-67 overexpression. (A3) p27 overexpression; (B3) low expression of Jab1; (C3) Skp2 overexpression; and (D3) Ki-67 overexpression. (A4) p27 overexpression; (B4) Jab1 overexpression; (C4) Skp2 overexpression; and (D4) Ki-67 overexpression. The positive ratio of $p27^{Kip1}$, Jab1 and Skp2 was 38, 70 and 32%, respectively.

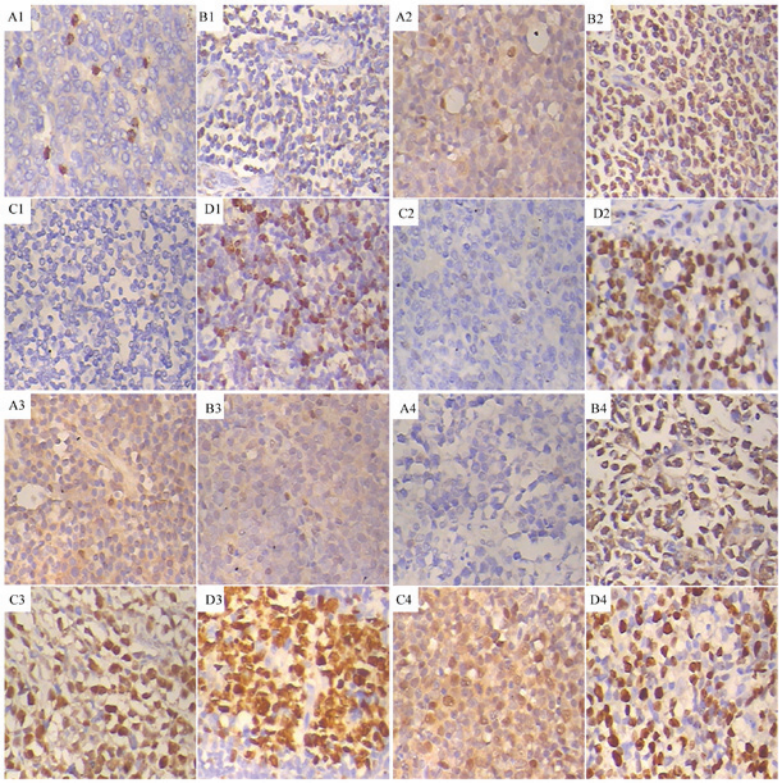

Figure 2. Expression patterns of p27, Jun activation domain-binding protein 1 (Jab1), S-phase kinase-interacting protein-2 (Skp2) and Ki-67 in non-Hodgkin lymphoma tissues (immunohistochemical staining; magnification, x400). (A1) Low expression of p27; (B1) low expression of Jab1; (C1) low expression of Skp2; (D1) Ki-67 overexpression. (A2) Low expression of p27; (B2) Jab1 overexpression; (C2) low expression of Skp2; (D2) Ki-67 overexpression. (A3) Low expression of p27; (B3) low expression of Jab1; (C3) Skp2 overexpression; (D3) Ki-67 overexpression. (A4) Low expression of p27; (B4) Jab1 overexpression; (C4) Skp2 overexpression; (D4) Ki-67 overexpression.

Table I. Correlations among p27^{Kip1}, Jab1, Skp2 and Ki-67.

Marker expression	p27^{Kip1}		Jab1		Skp2		Ki-67	
	P-value	r	P-value	r	P-value	r	P-value	r
p27^{Kip1}	-	-	0.003[a]	-0.410	0.28	0.177	0.614	-0.073
Jab1	0.003[a]	-0.410	-	-	0.097	0.237	0.011[a]	0.355
Skp2	0.28	0.177	0.097	0.237	-	-	0.001[a]	0.459
Ki67	0.614	-0.073	0.011[a]	0.355	0.001[a]	0.459	-	-

[a]P<0.05 was considered statistically significant. Jab1, Jun activation domain-binding protein 1; Skp2, S-phase kinase-interacting protein-2.

Table II. Correlations of p27, Jab1 and Skp2 expression with clinicopathological parameters in NHL.

Variables	Patients, n (%)	p27^{Kip1}			Jab1			Skp2			Ki-67		
		High	Low	P-value	High	Low	P-value	High	Low	P-value	High	Low	P-value
Age, years				0.018[a]			1.0			0.126			0.095
≥60	22 (44)	4	18		19	3		10	12		18	4	
<60	28 (56)	15	13		16	12		6	22		17	11	
Gender				1.0			1.0			0.746			0.572
Male	34 (68)	13	21		24	10		10	24		24	10	
Female	16 (32)	6	10		11	5		6	10		11	5	
Tumor size, cm				1.0			0.033[a]			0.076			0.287
≥2	22 (44)	8	14		11	10		4	18		14	8	
<2	28 (56)	11	17		23	5		12	16		21	7	
Metastasis				0.284			0.298			0.008[a]			0.227
Positive	4 (8)	0	4		4	0		4	0		4	0	
Negative	46 (92)	19	27		30	15		12	34		31	15	
Surgery				1.0			0.470			0.256			0.018
Yes	40 (80)	15	25		28	11		11	29		25	15	
No	10 (20)	4	6		6	4		5	5		10	0	
IPI score				0.000[a]			0.001[b]			0.001[a]			0.002[a]
0 or 1	19 (38)	14	5		9	10		2	17		10	9	
2	8 (16)	3	5		4	4		0	8		3	5	
3	3 (6)	0	3		3	0		2	1		3	0	
4 or 5	20 (40)	2	18		19	1		12	8		19	1	

[a]P<0.05 was considered significant. NHL, non-Hodgkin lymphoma; IPI, International Prognostic Index; Jab1, Jun activation domain-binding protein 1; Skp2, S-phase kinase-interacting protein-2.

expressions of p27^{Kip1}, Jab1, Skp2 and Ki-67 was investigated by Spearman's rank correlation (Fig. 3). A negative correlation between Jab1 and p27^{Kip1} expression was identified (Table I, r=-0.410, P=0.003). The result was consistent with previous findings (26). The expressions of Jab1 (r=0.355, P=0.011) and Skp2 (r=0.459, P=0.001) were positively correlated with Ki-67 expression. The expressions of Jab1 and Skp2 exhibited a trend for positive correlation (r=0.237, P=0.097). There was no correlation between the expressions of Skp2 and p27 (Table I, r=0.177, P=0.218).

Correlation of p27^{Kip1}, Jab1 and Skp2 with clinicopathological parameters. The correlation of the expressions of p27^{Kip1}, Jab1 and Skp2 with clinicopathological parameters, such as age, gender, tumor size, metastasis and surgery, is summarized in Table II. In this study, we found that decreased expression of p27 was associated with age (P=0.018), and increased expression of Jab1 was significantly associated with tumor size (P=0.033). In addition, increased expression of Skp2 was significantly associated with metastasis (P=0.008). Finally, the expressions of p27, Jab1, Skp2 and Ki-67 were all associated

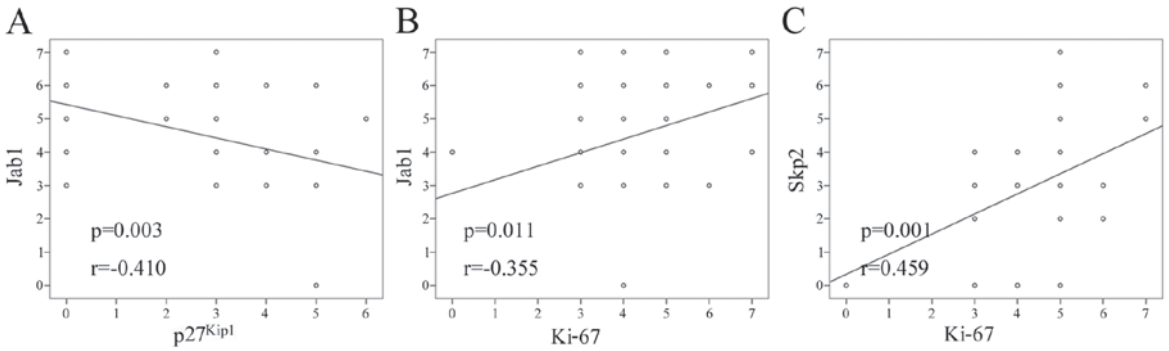

Figure 3. Correlation of immunohistochemical Jun activation domain-binding protein 1 (Jab1), S-phase kinase-interacting protein-2 (Skp2), $p27^{Kipl}$ and Ki-67 expression in 50 non-Hodgkin lymphoma samples. (A) A negative correlation was observed between Jab1 and $p27^{Kipl}$ expression (r=-0.410, P=0.003). (B) A positive correlation was observed between Jab1 and Ki-67 expression (r=0.355, P=0.011). (C) A positive correlation was observed between Skp2 and Ki-67 expression (r=0.459, P=0.001).

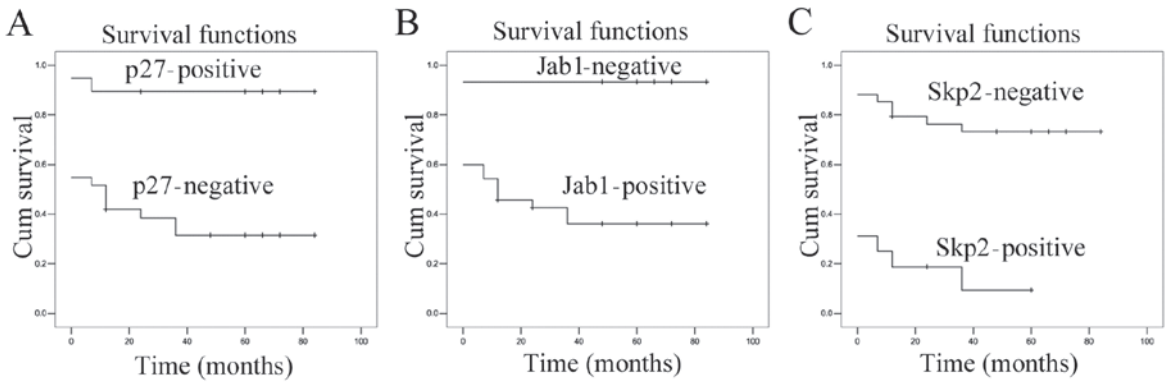

Figure 4. Kaplan-Meier analysis of p27, Jab1 and Skp2. Comparison was made according to the status of p27, Jun activation domain-binding protein 1 (Jab1) and S-phase kinase-interacting protein-2 (Skp2) expression in non-Hodgkin lymphoma. (A) The 5-year survival rate of the positive p27 expression group was significantly higher compared with that of the negative expression group (P<0.05). (B) The 5-year survival rate of the negative Jab1 expression group was significantly higher compared with that of the positive Jab1 expression group (P<0.05). (C) The 5-year survival rate of the negative Skp2 expression group was significantly higher compared with that of the positive Skp2 expression group (P<0.05).

with IPI. Other clinicopathological parameters exhibited no association with p27, Jab1 or Skp2.

Prognostic value of $p27^{Kipl}$, Jab1 and Skp2 expression. The Kaplan-Meier survival analysis demonstrated that Jab1 (P=0.000) and Skp2 (P=0.000) overexpression had a significant adverse effect on overall survival (Fig. 4B and C). This result was consistent with previous findings (27). However, $p27^{Kipl}$ expression exerted a beneficial effect on overall survival (Fig. 4A, P=0.000). We also observed that age was associated with survival rate (Table III, P=0.020). In present study, other parameters exhibited no association with survival.

The Cox proportional hazard regression analysis demonstrated that age [P=0.020, hazard ratio (HR)=1.038, 95% confidence interval (CI): 1.006-1.072], Skp2 (P=0.022, HR=2.893, 95% CI: 1.162-7.203) and IPI (P=0.000, HR=6.000, 95% CI: 2.576-13.971) were independent prognostic factors (Table IV).

Discussion

The cell cycle is the basic process in cell life and uncontrolled cell proliferation is the main characteristic of tumors. The unbalance between cell proliferation and death and disorders of the cell cycle play an important role in tumorigenesis and tumor progression. $p27^{Kipl}$ is a universal CKI that is able to bind to and inhibit the activity of cyclin-CDK complexes. $p27^{Kipl}$ inhibits the G1-S phase transition in the cell cycle resulting in cell cycle arrest in the G1-phase and cessation of cell proliferation (5). $p27^{Kipl}$ protein levels are increased in quiescent cells and rapidly decrease after cells are stimulated with mitogens (28). Cellular abundance of the $p27^{Kipl}$ protein is regulated by various mechanisms, the most important of which is the ubiquitin-proteasome pathway. Studies have demonstrated that improving the level of Jab1 expression may induce a decrease of CDK specifically; furthermore, $p27^{Kipl}$ is also degraded (29). Skp2 may mediate the degradation of $p27^{Kipl}$ in liver cancer (30). There is an inverse correlation between $p27^{Kipl}$ and Skp2 expression in intrahepatic cholangiocarcinomas (31). The expression of Skp2 was significantly negatively correlated with the expression of p27 in gastrointestinal stromal tumors (23). Our study demonstrated that low expression of the $p27^{Kipl}$ protein is associated with poor prognosis (P<0.01), which is consistent with a previous report that reduced expression of p27 is associated with poor prognosis (32).

Jab1 interacts with a wide range of proteins, regulates their function, and plays a role in different signal transduction

Table III. Correlation between clinicopathological variables and survival rate.

Variables	Patients, n (%)	Patients, n (%)			P-value
		Survival	Mortality	Survival rate (%)	
Age (y)					0.020[a]
≥60	22 (44)	5	17	22.7	
<60	28 (56)	22	6	78.6	
Gender					0.288
Male	34 (68)	27	17	79.4	
Female	16 (32)	10	6	62.5	
Tumor size					0.219
≥2 cm	22 (44)	14	8	63.6	
<2 cm	28 (56)	13	15	46.4	
Metastasis					0.617
Positive	4 (8)	0	4	0	
Negative	46 (92)	27	19	58.7	
Surgery					0.091
Yes	40 (80)	24	16	60	
No	10 (20)	3	7	30	
IPI					0.000[a]
0 or 1	19 (38)	19	0	100	
2	8 (16)	8	0	100	
3	3 (6)	0	3	0	
4 or 5	20 (40)	0	20	0	
p27^{Kip1}	19 (38)				0.176
Positive	19 (38)	17	2	89.5	
Negative	31 (62)	9	22	29	
Jab1					0.052
Positive	35 (70)	13	22	37.1	
Negative	15 (30)	14	1	93.3	
Skp2					0.022[a]
Positive	16 (32)	2	14	12.5	
Negative	34 (68)	25	9	73.5	
Ki-67					0.052
Positive	35 (70)	13	22	37.1	
Negative	15 (30)	14	1	93.3	

IPI, international prognostic index. [a]P<0.05 was considered significant. Jab1, Jun activation domain-binding protein 1; Skp2, S-phase kinase-interacting protein-2.

pathways, including degrading target proteins by regulating gene transcription and cell cycle by phosphorylation (8). Jab1 may lead to cell proliferation and regulate the cell cycle; it also interacts with p53 inducing phosphorylation mediated by CSN and subsequent degradation (33). These results indicate that Jab1 may play a significant role in oncogenesis. Jab1 overexpression may induce p27 downregulation (12). In addition, the chromosome region maintenance 1 protein homolog and 26S proteasome-dependent proteolysis is accelerated (34). The Jab1 expression level is correlated with a decrease of the p27^{Kip1} level and poor prognosis. Our immunohistochemical staining results demonstrated that Jab1 expression was inversely correlated to p27^{Kip1} protein expression (P<0.01), which is consistent with previous results demonstrating that Jab1 negatively regulates p27 in nasopharyngeal carcinoma (35). The expression of Jab1 was positively correlated with Ki-67 expression (P=0.011), a proliferating cell marker, expressed specifically in the cell nucleus from the late G1 to the S phase. Overexpression of Jab1 is associated with poor prognosis (P<0.01). These results suggest that Jab1 may play an important role in the development and progression of NHL and controlling Jab1 expression may be a novel therapeutic target in NHL.

Skp2, as an important cell cycle regulatory factor, is able to identify phosphorylated substrates specifically and mediate

Table IV. Multivariate analysis with Cox regression model.

Variable	Hazard ratio	95% CI	P-value
Age	1.038	1.006-1.072	0.020[a]
Gender	1.676	0.647-4.342	0.288
Tumor size	0.524	0.186-1.471	0.219
Metastasis	0.712	0.188-2.697	0.617
Surgery	0.438	0.168-1.140	0.091
IPI	6.000	2.576-13.971	0.000[a]
$p27^{Kip1}$	0.340	0.071-1.624	0.176
Jab1	7.638	0.987-59.135	0.052
Skp2	2.893	1.162-7.203	0.022[a]
Ki-67	1.573	0.158-14.363	0.722

[a]P<0.05 was considered statistically significant. CI, confidence interval; IPI, International Prognostic Index; Jab1, Jun activation domain-binding protein 1; Skp2, S-phase kinase-interacting protein-2.

ubiquitin degradation. Skp2 may mediate ubiquitination and subsequent proteolysis of $p27^{Kip1}$ (16). Carrano *et al* (29) demonstrated that the rate-limiting factor of $p27^{Kip1}$ degradation is SCF ubiquitin ligase complex, including Skp2 as the special substrate recognition sites. It was previously demonstrated that Skp2 protein overexpression decreased $p27^{Kip1}$ expression level in mantle cell lymphoma, whereas inhibition of Skp2 by small interfering RNA, increased the $p27^{Kip1}$ and $p21^{WAF1}$ levels (36). In the present study, we observed that Skp2 was associated with poor prognosis (P=0.000). However, there was no inverse correlation between $p27^{Kip1}$ and Skp2 expression (r=0.177, P=0.218). The role of Skp2 in controlling $p27^{Kip1}$ level has been reported in a number of cancers, including colon, breast, prostate and oral squamous cell carcinoma (20-23). However, the p27 level was not found to be inversely correlated with increasing Skp2 expression in carcinoma of the uterine cervix, and our result is consistent with that study (37). The different association between p27 and Skp2 may be elucidated by the difference in the tumor types, the patients' selection and the cut-off values.

Jab1 is associated with degradation of $p27^{Kip1}$, which is the key protein in cell cycle regulation. It is possible that Jab1 dysfunction causes a decrease in the level of $p27^{Kip1}$ and/or loss of function, thereby leading to the occurrence of NHL. In conclusion, the overexpression of Jab1 and Skp2 and the low expression of $p27^{Kip1}$ are associated with oncogenesis and poor prognosis. Jab1 expression was found to be inversely correlated with $p27^{Kip1}$ protein expression. Thus, the expression of $p27^{Kip1}$, Jab1 and Skp2 may provide a clinical reference for the treatment of NHL.

Acknowledgements

The present study was supported by the Six Talent Peaks foundation (WSN-061), the Post-doctoral Program of Jiangsu Province (1201028C), the National Natural Scientific Foundation of China (31370803), the Science and Technology Program of Nantong City (MS22015071), the Scientific Research Program of Jiangsu Province Health Department (H201423), and the Doctoral Program of Nantong University (14B44).

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