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·Original Article·

The role of Skp2 in extranodal NK/T-cell lymphoma

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[**Abstract**] **Background and Objective:** Expression of Skp2 was related with the prognosis of several tumors. However, there was no intensive study on the relationship between Skp2 and extranodal NK/T-cell lymphoma. This study was to explore the role of Skp2 in extranodal NK/T-cell lymphoma. **Methods:** The clinicopathological data of 39 patients with extranodal NK/T-cell lymphoma were analyzed. The expression of Skp2 was examined by immunohistochemistry on formalin-fixed, paraffin-embedded tissue sections. **Results:** Among the patients with high expression of Skp2, complete remission (CR) rate was only 14.3% (2/14). However, CR rate among the patients with low expression of Skp2 was 68.0% (17/25). Significant difference was shown between these two groups ($P < 0.001$). In the group of low expression, the median overall survival (OS) was 85.59 months (95% CI: 35.83-135.34 months), the 1- and 2-year OS rates were 81% and 71%, respectively. However, in the group of high expression, the median OS was only 9.73 months (95% CI: 2.05–17.40 months), the 1- and 2-year OS rates were 42% and 14%, respectively. There was statistical difference between these two groups ($P < 0.001$). Multivariate analysis showed that Skp2 expression ($P < 0.001$), LDH ($P = 0.026$) and ECOG PS ($P = 0.003$) were dependent prognostic factors of extranodal NK/T-cell lymphoma. **Conclusion:** High expression of Skp2 is an independent unfavorite adverse prognostic factor of extranodal NK/T-cell lymphoma.

Key words: Extranodal NK/T-cell lymphoma, Skp2, CR rate, prognosis

The new WHO comprehensive classification of neoplasms classified the extranodal NK/T-cell lymphoma as a distinct disease. It is rare in Europe and North America, while common in Asia and Latin America. In western countries, extranodal NK/T-cell lymphoma accounts for only 0.44% of all extranodal lymphomas and 0.17% of all lymphomas; however, in Asia, it accounts for about 2.6% –10.7% of all non-Hodgkin's lymphomas (NHL) and 40%–70% of all nasal and nasopharyngeal lymphomas [1-4]. It is reported that Epstein-Barr virus (EBV) is involved in the pathogenesis of Burkitt's lymphoma, Hodgkin's lymphoma, NK/T-cell lymphoma and nasopharyngeal carcinoma (NPC)[5-16]. NPC has high an incidence in Guangdong, China. We categorized 4396 patients with lymphoma in reference to the WHO classification and found that the incidence of NK/T-cell lymphoma in Guangdong is also very high (unpublished data). EBV maintains its latency by interaction with ubiquitin-proteasome system (Skp1-Cullin-F-box, SCF), and it can activate certain oncogenes to dysfunction the ubiquitin-dependent protein degradation system[17].

Reports showed that down-regulation of $P27^{kip1}$, a CDK inhibitor, is related with prognosis of various tumors, including colon cancer[18], breast cancer [19] and prostate cancer[20], while $P27^{kip1}$ is degraded by ubiquitin-proteasome system[21]. Skp2 is the substrate-recognizing subunit of SCF complex, which can recognize $P27^{kip1}$ and then degrade it [22-24]. In mammalian cells, EBV nuclear antigen (EBNA) can regulate SCF-Skp2-dependent ubiquitination and effect P27 expression[25].

Skp2, found by Demetrick *et al*. with fluorescent in situ hybridization (FISH) in 1995, is a key regulator of cell cycle and localizes at 5p13, which has been involved in karyotype transform [26]. The protein SKP2, about 45 kDa and 436 amino acids long, is a nuclear protein. It contains an F-box, 10 leucine-rich repeats (LLR) and a C-terminal motif. The F-box spans about 40 amino acids and comprises of 3 α-helix motifs, which can bind Skp1 regulator. Each LRR contains a β-sheet and an α-helix. The LLRs are directly involved in the recognition of substrates during ubiquitination. The function of the N-terminal region (about 100 amino acids) is not clear[27].

Several groups showed that Skp2 expression is negatively correlated with the prognosis of various carcinoma, including

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laryngocarcinoma[28], gastric cancer[29], colorectal cancer[30], breast cancer[31], urinary tract transitional epithelial carcinoma[32] and certain soft tissue sarcoma[33]. We detected the expression of SKP2 in extranodal NK/T-cell lymphoma tissues by immunohistochemistry to explore its relationship with treatment efficacy and survival and provide evidence for treatment and prognosis.

Patients and Methods

Patient information

Thirty-nine patients with extranodal NK/T-cell lymphoma were firstly treated in Sun Yat-sen University Cancer Center between March 1997 and July 2009. Complete clinicpathologic data and follow-up records are available. The patients were 18–71 years old, with a median age of 42 years (Table 1). All the diagnoses were confirmed by two experienced pathologists, and categorized by Ann Arbor staging system (9 at stage I, 8 at stage II, 22 at stage IV). All stage IV patients were treated with simple chemotherapy; 2 stage II patients were treated chemotherapy alone and achieved CR; another 2 stage II patients were in chemotherapy when this study ended, planning to have radiotherapy after chemotherapy; 2 stage I patients with nasal cavity lesions were treated with radiotherapy at the clinics; 7 stage I patients and 4 stage II patients were treated with radiochemotherapy. Chemotherapy regimens included CHOP-like, DHAP, IMVP-16, EPOCH, and L-ASP-containing regimens. Median dosage of radiotherapy was 54 Gy (range, 5-74 Gy). The treatment efficacy was assessed according to WHO standard classification (2005): complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The patients were followed up by clinical visiting and telephone for 1-230 months (median, 26 months) till August 10, 2009.

Detection of the Skp2 expression in lymphoma tissues

Biopsies from the patients were fixed with 4% neutral formaldehyde, and embedded in paraffin. Immunohistochemical staining was done with Envison kit (Dako Co.) according to the manufacturer's instruction. Sodium citrate with high pressure were sued for antigen repair. PBS was used as the negative control and tonsil tissue was used as the positive control of Skp2. Skp2 mainly localizes in the nuclei, and a few in the cytoplasm. Positive cells in each section were counted under high magnification objective. High expression of Skp2 was denoted when the proportion of positive cells was > 50%, while low expression when the proportion < 50%[34] (Figure 1).

Statistical methods

All statistical analysis was done with SPSS13.0 package. X^2 test was used when analyzing the relationship between Skp2 and CR. Survival probability was estimated by Kaplan-Meier method, and log-rank analysis was used to test the significance. Multivariate analysis used the Cox risk model and the factors were screened by Forward Stepwise LR method. A P value of < 0.05 was regarded as significance.

Table 1 Clinical characteristics of 39 patients with extranodal NK/T-cell lymphoma

Factor	Patient No.	Percentage (%)
Gender		
Male	25	64.1
Female	14	35.9
Age(years)		
⩽ 60	33	84.6
> 60	6	15.4
Skp2 expression		
Low	25	64.1
High	14	35.9
ECOG PS		
< 2	33	84.6
⩾ 2	6	15.4
B symptoms		
Yes	17	43.6
No	22	56.4
Hb (g/L)		
⩾ 110	37	94.9
< 110	2	5.1
WBC ($\times10^9$/L)		
⩾ 4.0	33	84.6
< 4.0	6	15.4
PLT ($\times10^9$/L)		
⩾ 100	36	92.3
< 100	3	7.7
LDH		
Normal	28	71.8
Elevated	11	28.2
ALB		
Normal	31	79.5
Decreased	8	20.5
Bone involvement		
Yes	27	69.2
No	12	30.8
Skin involvement		
Yes	33	84.6
No	6	15.4
Bone marrow involvement		
Yes	22	56.4
No	17	43.6
Lymph node involvement		
Yes	7	17.9
No	32	82.1
Primary sites		
Nasal cavity or nasopharynx	24	61.5
Extranasal sites	15	38.5
Efficacy after primary therapy		
CR + CRu	19	48.7
Non-CR	20	51.3
Therapeutic modality		
Chemotherapy only	26	66.7
Radiotherapy only	2	5.1
Radiochemotherapy	11	28.2

ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; LDH, lactate dehydrogenase; ALB, albumin; CR, complete response; CRu, uncertain complete response.

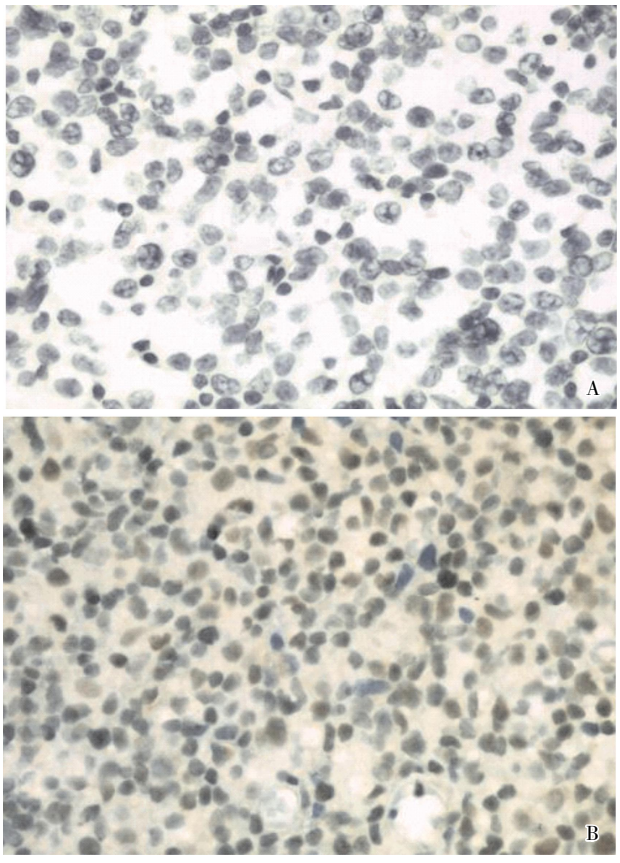

Figure 1 Skp2 expression in extranodal NK/T-cell lymphoma detected by immunohistochemistry (IHC ×400)
A, negative Skp2 expression; B, Skp2 is strongly expressed in nucleolus of extranodal NK/T-cell lymphoma.

Results

The relationship between Skp2 and clinical characteristics

The expression level of Skp2 had no significant relationship with the clinical characteristics, including gender, age, physical state, B symptoms, hemoglobin, white blood cells, platelet, lactate dehydrogenase (LDH), albumin, primary site and invasiveness (Table 2).

The relationship between Skp2 and CR rate

The CR rate was 49.0% in all the patients. It was significantly lower in the 14 patients with high Skp2 expression than in the 25 with low Skp2 expression (14.3% vs. 68.0%, P = 0.001) (Table 3).

The relationship between SKP2 and survival time

The median overall survival (OS) time of all patients was 25.53 months (95% CI: 0–64.31 months) (Figure 2). The 1- and 2-year OS rates of all patients were 68.0% and 43.0%. In low Skp2 expression group, the median OS was 85.59 months (95% CI: 35.83–135.34 months), and the 1- and 2-year OS rates were 81.0% and 71.0%. In high Skp2 expression group, the median OS was only 9.72 months (95% CI: 2.05-17.40 months), the 1- and 2-year OS rates were 42.1% and 14.1%. The differences between the two groups were significant (P < 0.001) (Figure 3). Univariate analysis found that OS was related with Skp2 expression, skin invasion, physical state, LDH elevation, down

Table 2 The relationship between Skp2 and clinical characteristics of 39 patients with extranodal NK/T–cell lymphoma

Factor	Skp2		P
	High expression	Low expression	
Gender			0.986
Male	9	16	
Female	5	9	
Age(years)			0.434
≤60	11	22	
> 60	3	3	
ECOG PS			0.434
<2	11	22	
≥2	3	3	
B symptoms			0.945
Yes	6	11	
No	8	14	
Hb (g/L)			0.052
≥110	12	25	
<110	2	0	
WBC ($\times10^9$/L)			0.887
≥4.0	12	21	
<4.0	2	4	
PLT ($\times10^9$/L)			0.923
≥100	13	23	
<100	1	2	
LDH			0.128
Normal	8	20	
Elevated	6	5	
ALB			0.916
Normal	11	20	
Decreased	3	5	
Bone involvement			0.617
Yes	9	18	
No	5	7	
Skin involvement			0.286
No	13	20	
Yes	1	5	
Bone marrow involvement			0.546
Yes	7	10	
No	7	15	
Lymph node involvement			0.672
Yes	11	21	
No	3	4	
Primary sites			0.431
Nasal cavity or nasopharynx	8	11	
Extranasal sites	6	14	

Table 3 The relationship between Skp2 expression and CR rate

Skp2 expression	CR	Non-CR	CR rate (%)
High	2	12	14.3
Low	17	8	68.0
Total	19	20	48.7

Significant difference between the two groups was found (P=0.001).

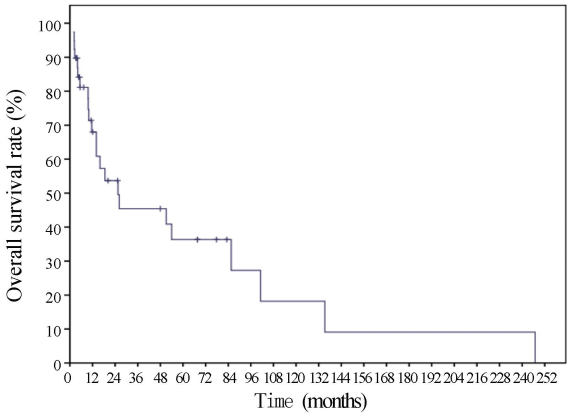

Figure 2 Overall survival curve of 39 patients with extranodal NK/T-cell lymphoma

The median overall survival (OS) was 25.53 months (95% CI: 0–64.31 months); the 1- and 2-year OS rates were 68% and 43%.

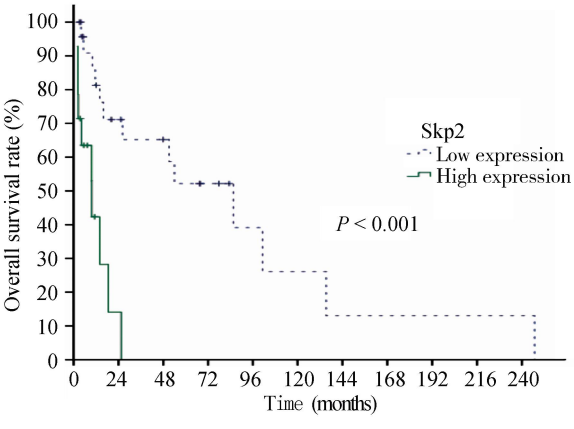

Figure 3 Overall survival curves of extranodal NK/T-cell lymphoma patients with high and low Skp2 expression

The median OS of low Skp2 expression group was 85.59 months (95% CI: 35.83–135.34 months), and the 1- and 2-year OS rates were 81% and 71%. The median OS of high Skp2 expression group was 9.37 months (95% CI: 2.05–17.40 months), and the 1- and 2-year OS rates were 42% and 14%. Significant difference was found between these two groups ($P < 0.001$).

regulation of albumin and CR state. Multivariate analysis found that Skp2 ($P < 0.001$), LDH ($P < 0.026$) and physical state ($P = 0.003$) were independent prognosis factors.

Discussion

Precise regulation of cell division is very important in cell proliferation. Dysregulation of cell cycle can induce tumorigenesis. Latres *et al.*[35] found that Skp2 transgenetic mice had shorter survival time and higher incidence of tumor. Several other groups reported that Skp2, an oncogene which is overexpressed in various epithelial carcinomas, is an independent prognosis factor[36-38]. Chiarle *et al.*[39] found that Skp2 was lowly expressed in slowly growing lymphoma, while highly expressed in invasive lymphoma, indicating that Skp2 is related with the malignant extent of lymphoma and has potent diagnostic and prognostic relevance. Other studies found that Skp2 can be used as a marker for prognosis of certain subtypes of lymphoma[40,41]. However, the role of Skp2 in NK/T-cell lymphoma has not been investigated yet. In this study, we found that 35.9% of the extranodal NK/T-cell lymphoma patients had high expression of Skp2, which was related with OS and could be used as an independent prognosis factor, but it showed no relationship with gender, age and other hematological index.

Extranodal NK/T-cell lymphoma is a highly aggressive cancer that is insensitive to chemotherapy, especially the CHOP protocol[42]. Xiao *et al.*[43] showed that HL-60/A, a leukemia cell line with drug resistance, had higher expression of P-gp and Skp2 than HL-60, which has no drug resistance. They concluded that Skp2 is a potent factor in drug resistance of leukemia. Wang *et al.*[44] reported that 67% of the nasal NK/T-cell lymphomas were P-gp-positive and the CR rate was significantly lower in P-gp-positive group than in P-gp-negative group ($P = 0.045$). We also analyzed the relationship between Skp2 expression and CR rate to address whether the drug resistance of NK/T-cell lymphoma is related to Skp2. We found that the CR rate was significantly higher in low Skp2 expression group than in high Skp2 expression group, indicating that Skp2 is related with drug resistance of NK/T-cell lymphoma. Some reports showed that inhibiting the expression of Skp2 by siRNA technique could up-regulate $P27^{kip1}$ and induce cell apoptosis. MG-132, an proteasome inhibitor, can induce apoptosis and up-regulate the expression of apoptosis-related proteins[45-47]. This indicates that targeting ubiquitin-proteasome system is a new potent therapeutic strategy for extranodal NK/T-cell lymphoma. A phase I clinical trial with Boetezomib and CHOP showed certain efficacy[48]. Our study showed that Skp2 is involved in drug resistance and survival, indicating that Skp2 is a new target for NK/T-cell lymphoma therapy.

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