· Original article ·

Expression of Skp2, p27, PTEN proteins in B – cell non—Hodgkin lymphoma of ocular adnexa

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Abstract

• AIM: To investigate the expression of Skp2, p27 and PTEN proteins in B-cell non—Hodgkin lymphoma (NHL) of ocular adnexa.

• METHODS: Paraffin sections were collected from patients suffering from B – cell NHL (n = 30) and lymphadenosis (n = 10) of ocular adnexa in Qingdao Affiliated Hospital from 1995 to 2011. Features (age, gender, pathogenetic locations, pathological type) can be used as factors to classify 30 cases of B – cell NHL. Lymphadenosis sections were selected to the control group. The expression of Skp2, p27 and PTEN proteins were detected by immunohistochemistry and the positive expression rate between lymphomas and lymphadenosis was compared. Spearman rank correlation was used to estimate the relationships among Skp2, p27 and PTEN in ocular lymphoma.

• RESULTS: The expression of three proteins were not related to age, gender, pathogenetic locations but related to pathologic type of tumors. In B-cell NHL specimens, the expression of $p27^{kip1}$ and PTEN was lower than that in lymphadenosis ($P<0.05$), while the expression of Skp2 was higher. Skp2 labeling frequency was increased dramatically in plasmacytoma (PL) and diffuse large B-cell lymphoma (DLBCL) compared with mucosa – associated lymphoid tissue (MALT) ($P<0.01$). While $p27^{kip1}$ and PTEN labeling frequency in PL and DLBCL was significantly lower than that of MALT ($P<0.05$, $P<0.01$). There was a negative correlation between $p27^{kip1}$ and Skp2 in MALT ($r=-0.134$, $x^2=12.58$, $P<0.05$) while there was a positive correlation between $p27^{kip1}$ and PTEN ($r=0.828$, $x^2=20.66$, $P<0.05$). The relationship between Skp2 and PTEN was also negative ($r=-0.883$, $x^2=20.52$, $P<0.05$).

• CONCLUSION: Over expression of Skp2 and lower expression of $p27^{kip1}$ and PTEN play an important role in the tumorigenesis and different pathologic type in ocular adnexal tumors. The expression of three proteins correlates with each other in MALT. Combined examination of Skp2, p27 and PTEN is a valuable marker to predict the presence of the B-cell NHL of ocular adnexa and differentiate the pathologic type of tumors.

• KEYWORDS: ocular adnexa; non—Hodgkin lymphoma; Skp2; $p27^{kip1}$; PTEN; immunohistochemistry
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INTRODUCTION

Ocular adnexal lymphoma is the most common malignant tumor and its incidence is increasing proportionally with the rise of the average survival rate of the general population[1]. The disorder cell cycle is considered to be the common process for oncogenisis. $p27^{kip1}$ is known as a cyclin-dependent kinase inhibitor which is crucial for cell cycle progression from G1 into S phase[2]. Skp2 is a number of ubiquitin – mediated proteolysis, which is involved in the ubiquitination and subsequent degradation of cyclin—dependent kinase inhibitor $p27^{kip1}$, thus promoting cell cycle progression of late G1 to S-phase transition and accelerating the process of cell proliferation. PTEN gene (Phosphatase and tensin homology residing in chromosome 10q23, identified as a candidate tumor suppressor gene) is a newest phosphatas oncongen suppressor which can specifically induce cyclin – dependent kinases inhibitor $p27^{kip1}$ and then decelerate the process of cell proliferation. Emphasis on the expressions of Skp2, $p27^{kip1}$, PTEN and the relationship among them in lymphoma is now increasingly put by present researches. In this study, we examined the expression levels of three proteins in B-cell non—Hodgkin lymphoma (NHL) and estimated the correlation among them for further detecting the pathological features of lymphoma in molecular mechanism.

MATERIALS AND METHODS

Materials Paraffin sections were collected from patients suffering from NHL (n=30) and lymphadenosis (n=10) of ocular adnexa from 1995 to 2011 by the Ophthalmic Pathology Department in Affiliated Hospital of Qingdao University. Subjects accepted no treatment before surgery. Lymphadenosis sections were selected as the control group. Among 30 lymphoma cases, 19 cases were mucosa-associated lymphoid tissue type (MALT), 6 cases were plasmacytoma (PL) and 5 cases were diffuse large B-cell lymphoma (DLBCL). The subjects' age ranged from 52 to 88 (mean 70. 2±5. 9) years. Among them, males were 23 cases (58%) while females were 17 cases (42%). Among 40 cases in ocular adnexa, 4 cases from eyelid, 25 cases from orbit, 11 cases from conjunctiva.

Table 1 Relationship between Skp2, p27 and PTEN immunostaining and B-cell NHL classification

Classification	No. of cases	Expression of Skp2		Expression of p27		Expression of PTEN	
		High Skp2(%)	Low Skp2(%)	High p27(%)	Low p27(%)	High PTEN(%)	Low PTEN(%)
Lymphadenosis	10	0(0.0)	10(100.0)	10(100.0)	0(0.0)	10(100.0)	0(0.0)
MALT	19	13(68.4)	6(31.5)	16(84.2)	3(15.8)	14 (73.7)	5(26.3)
PL	6	5(83.3)	1(16.7)	4(66.7)	2(33.3)	2(33.3)	4(66.7)
DLBCL	5	5(100.0)	0(0.0)	2(40.0)	3(60.0)	1(20.0)	4(90.0)
χ^2		19.79		8.37		13.48	
P		0.001		0.039		0.004	

* Statistical significance of Skp2, p27 and PTEN percentages and classification($P<0.05$).

Methods HE staining was used to differentiate histological type of 40 cases. Paraffin sections (3um thickness) were stained with immunohistochemistry tests using the streptavidin-peroxidase method. The primary antibodies were Skp2, $p27^{kip1}$, and PTEN (mouse polyclonal antibody, Beijing Biot Biotechnology Corporation, China), $p27^{kip1}$ was biotin-conjugated anti-mouse second antibody. The immunostaining was graded by the percentage of the three proteins positive rate. <25%, >25% -<50%, >50% -<75%, and >75% of tumor cells showing positive staining was defined as (-), (+), (++)and (+++), respectively. Samples scored (-) were considered negative and low expression, and those that scored (+)-(+++) were considered positive and high expression[3].

Statistical Analysis The positive expression rates of Skp2, $p27^{kip1}$ and PTEN between lymphomas and lymphadenosis were compared, and the different expression rates among three subtypes of NHL sections were also compared using the X^2 test. Spearman rank correlation was used to estimate the relationships among Skp2, $p27^{kip1}$ and PTEN in lymphoma sections. All statistical analysis was performed by SPSS 17.0. $P<0.05$ was considered statistically significant.

RESULTS

The Expression of Skp2 in Lymphoma Skp2 expression had no correlation with gender, age and location of neoplasm. The Skp2 immunoreactivity was predominantly localized to the cytoplasm of lymphomatic cells. Negative control slides were performed using PBS with no dyeing. Skp2 showed negative staining in lymphadenosis (Figure 1) while high expression in MALT(Figure 2), PL (Figure 3) and DLBCL (Figure 4). Positive rates of Skp2 proteins in cell cytoplasm of MALT was 68.4%. In NHL, Skp2 labeling frequency was increased dramatically in PL and DLBCL compared with MALT. The concrete data was showed in Table 1.

The Expression of p27 in Lymphoma p27 expression had no correlation with gender, age and location of neoplasm. The p27 immunoreactivity was predominantly localized to the nuclei of lymphomatic cells. p27 expression in lymphadenosis showed high expression (Figure 5). p27 positive membrane and cytoplasmic staining pattern with uneven dyeing in MALT and PL (Figure 6, 7), while negative staining in DLBCL (Figure 8). Positive rates of p27 proteins in cell nucleus of MALT, PL and DLBCL respectively were 84.2% (Figure 6), 66.7% (Figure 7), 40% (Figure 8), which were significant differences with lymphadenosis ($P<0.05$). Negative control slides were performed using PBS have no dyeing too. The concrete data was showed in Table 1.

The Expression of PTEN in Lymphoma PTEN expression had no correlation with gender, age and location of neoplasm. The PTEN immunoreactivity was predominantly localized to the cytoplasm of lymphomatic cells. While PTEN labeling frequency was significantly lower in lymphoma than that in lymphadenosis (Figure 9). In low-grade malignancies, samples of MALT were with high PTEN expression(Figure 10). PTEN expression in PL showed a moderate membrane and cytoplasmic staining(Figure 11) uneven dyeing. However, in high-grade malignancies samples of DLBCL, PTEN staining was low (Figure 12). In NHL of ocular adnexa, with the increase of pathologic grade, PTEN labeling frequency decrease gradually($P<0.01$). The concrete data was showed in Table 1.

The Relationship between Skp2, p27 and PTEN in MALT Interestingly, we found that increased Skp2 expression is significantly correlated with loss of p27 and PTEN staining in MALT. In 19 cases of tumour samples, 3 cases with negative expression of p27 have 2 cases of Skp2 and no case of PTEN positive. Vice versa, 16 cases with positive or high expression of p27 show 11 cases of Skp2 and 14 cases of PTEN positive. Spearman analysis demonstrates an inverse correlation between Skp2 and p27 expression (Spearman's rho = -0.134, $P<0.05$) and a positive correlation between PTEN and p27 expression(Spearman's rho = 0.828, $P<0.05$). 6 cases with negative expression of PTEN have 6 cases of Skp2 positive. In 13 cases with positive or high expression of PTEN show 8 cases of Skp2 positive. Our study found that there was negative correlation between expression of PTEN and Skp2 in lymphoma tissue (Spearman's rho =-0.883, $P<0.05$).

DISCUSSION

Histologically almost all of the lymphomas are derived from NHL, mostly for small lymphocytic types which are a diverse group of clinically and genotypically well defined disease entities. It was reported that MALT, PL and DLBCL were the front three subtypes of B-cells lymphoma [4], which was consistent with the results we selected from all NHL patients. MALT, the most common subtype in ocular adnexa, is now recognized as a distinct clinicopathologic subtype of small B-cell NHL and constitutes approximately 70%-80% of all NHLs[5].

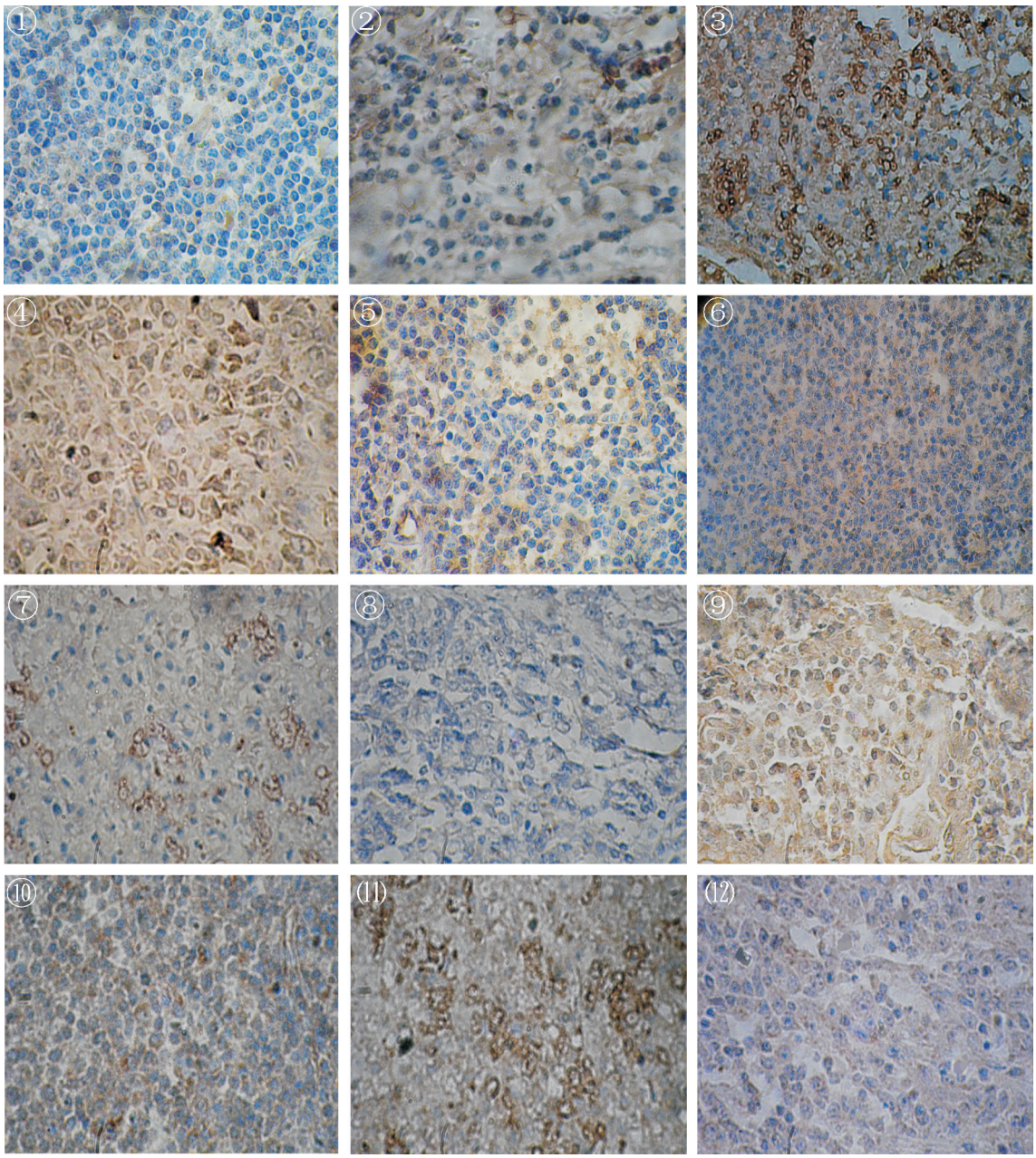

Figure 1 The whole lymphadenosis cells stained for Skp2 was low(SP×400).
Figure 2 Skp2 in MALT had high expression in cytoplasm of the neoplastic cells(SP×400).
Figure 3 Skp2 in PL had high expression in cell nucleus and cell wall of the lymphomatic cells(SP×400).
Figure 4 Skp2 in DLBCL had high expression in cytoplasm of the neoplastic cells(SP×400).
Figure 5 p27 had high expression in cytoplasm and nucleus in lymphadenosis cells(SP×400).
Figure 6 p27 in MALT had high expression in cell nucleus of the lymphomatic cells(SP×400).
Figure 7 p27 in PL had high expression in cell nucleus and cell wall of the lymphomatic cells (SP×400).
Figure 8 The whole DLBCL cells stained for PTEN was low(SP×400).
Figure 9 PTEN had high expression in cytoplasm of the lymphadenosis cells(SP×400).
Figure 10 PTEN had high expression in cytoplasm of normal lymphomatic cells of MALT(SP×400).
Figure 11 PTEN in PL had moderate expression in cell nucleus and cell wall of the lymphomatic cells(SP×400).
Figure 12 The whole DLBCL cells stained for PTEN was low(SP×400).

Progression through the mammalian cell cycle requires the activities of Cdks which composed of catalytic Cdk subunits and regulatory cyclin subunits. These enzymes are opposed by a family of Cdk inhibitors typified by $p27^{kipl}$ [2]. p27, residing in chromosome 12p13, expressed at its highest levels in G0 and G1 cells and its levels decrease as the cell cycle begins. It prevents cell cycle progression of late GI to S-phase transition. Deregulation of $p27^{kipl}$ expression is a relatively common feature in many solid tumors, but alterations of the gene are infrequent[6,7]. In mouse models, p27 worked as a haplo-insufficient tumor suppressor. In human cancer, a low level of p27 is correlated with higher tumor grade and poor survival [8,9].

In this study, nuclear p27 level in lymphoma was significantly

lower than that in lymphadenosis, which is similar to the study of Zhang *et al*[10]. Meanwhile nuclear p27 staining in lymphoma cells was quantified and the expressions became lower when the progression grade became severer. It declares that a low level of p27 may lead to the happening of lymphoma and be related to clinical progression of tumor cells in lymphoma, in Favor of Kiviniemi *et al*[11].

The F-box protein Skp2 is a positive regulator of G1-S transition and promotes ubiquitin-mediated proteolysis of the cyclin-dependent kinase inhibitor p27[9,12]. Loss of Skp2 in mice leads to increased levels of p27, consistent with a role for Skp2 in p27 turn over. In appropriate expression of Skp2 in G0 cells can promote S-phase entry concomitant with loss of p27. Its overexpression has been implicated in cell transformation and oncogenesis in both in many other tumors[13-15]. MALT sections in the present study had very low Skp2 levels, while PL and DLBCL sections had increased Skp2 levels even labeling frequency, which is similar to the study of Seki *et al*[16]. These results indicated that higher expression of Skp2 in NHL had been clearly associated with tumorigenesis and with the increase of pathologic grade, Skp2 labeling frequency increased gradually.

PTEN gene is a newest phosphatas oncongen suppressor which worked as a phosphatase of phosphatidylinositol 3, 4, 5 trisphosphate (PIP3) and negatively regulates the PI3kinase signaling pathway[17]. This pathway has been shown to regulate multiple cellular processes including growth, apoptosis, migration, and cell cycle progression [18,19]. Concomitant with this arrest is the posttranscriptional upregulation of cyclin dependent kinase inhibitor $p27^{kip1}$ which is located in lower reaches of PTEN[20,21]. Thereby PTEN is a key regulator of the G1 to S phase cell cycle transition. A complex relationship also exists between p27 and the tumor suppressor protein PTEN. PTEN expression has been observed to lead to upregulation of p27[22]. The decreases of p27 protein expression caused by the deletion or the mutation of PTEN gene expression cannot effectively play the anti-oncogene role in negative regulation of the cell cycle , which makes the tumor cells more malignant.

Our experiment observed a higher expression of PTEN (100%) in lymphadenosis than that in MALT (73.6%), indicating PTEN played an important role in maintaining the stabilization of lymphocytes and the reduction of PTEN protein expression in lymphoma might be an important event in the pathogenesis of the disorders. We also found decreased levels of PTEN in MALT, PL and DLBCL sections, which might imply the lower expression of PTEN correlating with progression of lymphoma.

Generally recognizing, there was negative correlation between expression of Skp2 and $p27^{kip1}$[23]. Levels of p27 decrease with the passage of cells from quiescence and early G1 into S phase. This change is primarily due to ubiquitin dependent proteolytic degradation of p27 through the SCFSkp2 ubiquitin E3 ligase complex. Cyclin E/Cdk2 is able to phosphorylate p27 on threonine 187, and this phosphorylated form of p27 is then recognized by the SCFSKP2 complex and targeted for ubiquitin mediated degradation by the 26S proteasome[24-26]. Overexpression of Skp2 is frequently observed in human cancers of diverse histology, while in most human cancers reduced level of p27 represents an adverse prognostic marker[27,28]. The relationship between Skp2 expression and loss of PTEN is particularly interesting in light of the finding that deletion of PTEN in mouse fibroblasts leads to increased levels of Skp2 with concomitant reductions in p27 levels [29]. Thus, it would appear that PTEN worked as a negative regulator of the Skp2 pathway that is normally used to control S-phase entry.

According to the reports above, more accounts have been made on the relationship among Skp2, p27 and PTEN as well as their functions on the cell cycle recently. In this study, we examined the expression of p27, Skp2, and PTEN in B-cell NHL of ocular adnexa and observed Skp2 levels dramatically increased with advance in grading of tumors, which correlating with the loss of p27 and PTEN. The similar results were also seen in colon, lymphoid and oral epithelial tumors [30-32]. The possible mechanism is that PTEN ensure a proper level of SCFSkp2 activity for the degradation of p27, thus allowing subsequent activation of cyclin E/Cdk2 and progression from G1 phase to S phase.

It was found that over expression of Skp2 and the loss of p27, PTEN in a number of different cancers give us a selection for drug therapeutic development by targeting these molecules. Continued investigations into the molecular mechanisms of lymphoma may provide to establish novel biomarkers for this disease and generate therapeutic targets for improved treatment[33].

The over expression of Skp2 and the loss of p27 and PTEN may play an important role in NHL of ocularadnexa and differentiating pathological type of B cell NHL. As targets to control the early event in tumorigenesis, the understanding of this novel molecular pathway on Skp2, p27 and PTEN proteins may prove valuable in designing new therapeutic approaches for responding to lymphoma of ocular adnexa.

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Skp2,p27,PTEN 在眼附属器 B 细胞非霍杰金淋巴瘤中的表达

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摘要

目的:探讨眼附属器 B 细胞非霍杰金淋巴瘤(B-cell non-Hodgkin lymphoma, NHL)中 Skp2,p27 和 PTEN 的表达。

方法:收集 1995 年到 2011 年青岛大学附属医院眼科石蜡包埋标本,用免疫组化法分别检测眼附属器 B 细胞 NHL ($n=30$) 标本中 Skp2,p27 和 PTEN 的表达,以眼部反应性淋巴组织增生($n=10$)作为对照组。以患者的年龄、性别、发病部位,病理类型作为眼附属器 B 细胞 NHL 的的分类标准。

结果:Skp2,p27 和 PTEN 的表达与患者的年龄、性别、发病部位无关,而与病例类型有关。眼附属器 B 细胞 NHL Skp2 表达率与眼部反应性淋巴组织增生相比显著增高。p27,PTEN 表达率与反应性淋巴组织增生相比显著降低。随眼附属器 B 细胞 NHL 病理分级的提高,Skp2 的表达显著增高,p27 和 PTEN 的表达显著降低。在黏膜相关淋巴组织结(mucosa-associated lymphoid tissue, MALT)外边缘区 B 细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)中,Skp2 分别与 p27,PTEN 成负相关,p27 和 PTEN 成正相关。

结论: Skp2 的表达升高,p27,PTEN 蛋白的缺失以及可能与眼附属器 B 细胞 NHL 的发生有关;其中在 MALT 外边缘区 DLBCL 中,三种蛋白存在相关性。联合三种蛋白的检测眼附属器 B 细胞 NHL 的不同病理类型有重要意义。

关键词:眼附属器;非霍杰金淋巴瘤;Skp2;$p27^{kip}$;PTEN;免疫组织化学检验