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The clinical significance of CD97, NF-kB and COX-2 in gastric MALT lymphomas

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ABSTRACT

Background and Objectives: Increased expression of the CD97, nuclear factor-kB (NF-kB) and cyclooxygenase-2 (COX-2) has been found to play an important role in development of many cancers, including gastric neoplasm. However, the expression and biological behavior of CD97, NF-kB and COX-2 in gastric MALT (mucosa-associated lymphoid tissue) lymphoma has not been well investigated. Methods: The expressions of CD97, COX-2 and NF-kB in 47 cases of gastric MALT lymphoma were detected immunohistochemically, and the relevance between their expressions and the biological behavior was analyzed retrospectively. Results: 1) The expressions of CD97, NF-kB and COX-2 were 87.2%, 36.2% and 48.9%, respectively; 2) The difference of CD97 expression between depth of invasion limited in mucosa and submucosa and beyond muscularis propria was significant (100.0% vs. 71.4%, $P < 0.01$). Moreover, the expression of nuclear CD97 between stage IIE, III, IV and stage I patients showed significant difference (96.4% vs. 73.7%, $P < 0.05$); 3) The expression of NF-kB was significantly correlated with tumor size, depth of invasion and stage; 4) The expression of COX-2 was significantly correlated with Helicobacter pylori infection, clinical stage, depth of invasion and tumor size ($P < 0.05$). Conclusions: Expressions of CD97, NF-κB and COX-2 were correlated with tumor invasion and metastasis in gastric MALT lymphoma.

Keywords: Stomach Neoplasm; CD97; Nuclear Factor-Kb (NF-Kb); Cyclooxygenase-2 (COX-2); Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

1. INTRODUCTION

Gastric mucosa associated lymphoid tissue (MALT) lymphoma has recently been incorporated into the World Health Organization (WHO) lymphoma classification, termed as extranodal marginal zone B-cell lymphoma of MALT-type [1,2]. Low grade gastric MALT lymphoma is a neoplasia with a very indolent course and an excellent prognosis, and it has a tendency to remain localized to the gastric wall and seldom involve lymph nodes and bone marrow [1-5]. As with other malignancies, the accumulation of genetic abnormalities is required for malignant transformation of human lymphocytes.

CD97 is known as a leukocyte-restricted, cell surface glycoprotein expressed constitutively by human granulocytes, monocytes, and, at low levels, resting T and B cells [6], and it regulates the expression of genes that are involved in inflammation, cell proliferation, and apoptosis [7]. Recent studies suggest that CD97 expression correlates with tumor dedifferentiation, migration, and invasion in many tumors, such as thyroid, colorectal, and gastric cancer [8-15]. Furthermore, CD97 has features of a multifunctional protein that may play a role in signal transduction associated with the development or establishment of the inflammatory processes [6,7]. However, CD97 has never been systemically investigated in gastric MALT lymphoma.

Nuclear factor kappa B (NF-kB), a transcription factor, plays an important role in carcinogenesis as well as in the regulation of immune and inflammatory responses, and it induces the expression of diverse target genes that promote cell proliferation, regulate apoptosis, facilitate angiogenesis and stimulate invasion and metastasis [16-25]. And the transcription factor NF-kB is a tightly regulated positive mediator of T- and B-cell development, proliferation, and survival [16-22,24,26-29]. Various molecular events lead to deregulation of NF-kB signaling in Hodgkin disease and a variety of T- and B-cell non-Hodgkin lymphomas either up-stream or down-stream of the central IkppaB kinase. These alterations are prerequisites for lymphoma cell cycling and blockage of apoptosis.

Epidemiological and clinical studies demonstrated a link between gastric MALT lymphoma and chronic infection

with Helicobacter pylori (*H pylori*) [30]. Cyclooxygenase-2 (COX-2) is one of important enzymes that mediate inflammatory processes. In recent years, it has been demonstrated that both COX-2 play an important role in various tumors, including gastric lymphoma [3,31-36]. Cyclooxygenase-2 (COX-2) is a key biosynthetic enzyme of COX enzyme family, which is the rate-limiting enzyme for prostaglandin H synthesis. It is an inducible enzyme, and normally absent in cells, but its expression is rapidly and transiently induced in response to growth factors, tumor promoters or cytokines, and it has an important role in the development and progression of various malignancies [31-34,36]. COX-2 has been studied in solid tumors; however, there is little data on the potential role of COX-2 in gastric MALT lymphoma pathogenesis. In this study, we conducted to determine the expressions of CD97, NF-kB and COX-2 with the clinicopathological data in 47 gastric MALT lymphomas and 10 adjacent mucosal specimens by using immunohistochemistry.

2. MATERIAL AND METHODS

2.1. Patients and Specimens

A total of 47 Chinese patients with gastric MALT lymphoma, who were treated surgically from January 1994 to May 2007 at the University Hospital of Wenzhou Medical College, participated in this study. All the patients were pathologically confirmed as low grade gastric MALT lymphoma. The diagnosis of low grade gastric MALT lymphoma was made according to the criteria of Isaacson [1,2], which are composed of centrocyte-like cells, lymphoid follicles and plasma cell differentiation, and scoring system of Wotherspoon *et al.* [5], and the stains of immunohistochemical markers, such as leukocyte common antigen (LCA), L26, CD5 and CD10 was performed. The initial staging procedures included a complex physical examination, chest roentgenogram, bone marrow examination, abdominal CT scan and endoscopy. Normal gastric mucosal samples were located at least 8 cm from the margin of the tumors of surgical specimens. The average age was 56.4 years, ranging from 32 years to 81years, and the ratio of male to female was 30 to 17.

2.2. Immunohistochemistry

The expressions of CD97, NF-kB and COX-2 were studied by immunohistochemicl Envision method according to the manufacturer's recommendations. Briefly, all the tissue specimens were preserved with 10% v/v formalin and embedded in paraffin. Sections (5-μm-thick) were cut, placed on glass slides, and depaffinized. One section from each block was stained with hematoxylin-eosin for evaluating the diagnosis of gastric MALT lymphoma. After depaffinization and dehydration, the tissue sections were subjected to microwave oven treatment in 0.01 mol/L sodium citrate buffer (pH 6.0) for 8 minutes at 600W and then exposed to 0.3% H_2O_2 for 30 minutes to block endogenous peroxidase. After washing with PBS, sections were incubated in PBS supplemented with 10% goat serum for 20 min at room temperature to block non-specific binding of secondary antibody, then incubated overnight at 4˚C with CD97 (1:50), NF-kB (1:100) and COX-2 (1:50) in PBS containing 1% bovine serum albumin. After rinsing three times in PBS, sections were treated with biotinylated anti-immunoglobulin for 1h at room temperature, then washed again and reacted with the streptavidinbiotin system by using 0.04% 3, 3'-diaminobenzidine tetrahydrochloride for1min as chromogen. Negative control was established by replacing the primary antibody with PBS.

The primary antibody of rabbit polyclonal CD97 (ab13345) was purchased from Cambridge Science Park (Abcam plc332, Cambridge, UK), monoclonal mouse anti-human NF-kB oncoprotein were purchased from Beijing Zhongshan Godden Bridge Biotechnology Co. LTD., and rabbit polyclonal anti-human COX-2 IgG from (Santa Cruz, CA, USA).

2.3. Evaluation of Immunohistochemical Staining

Immunoreactivity was scored semiquantitatively by two independent investigators who were unaware of the histological results using a light microscope in the terms of proportion of cells in gastric MALT lymphoma tissues. The criteria for grade referenced to the report of Wu *et al*. [37]: grade 0, stained cells accounted for less than 10%; grade 1, between 10% and 29%; grade 2, between 30% and 49%; and grade 3, more than 50%. Grades 1 through 3 were considered positive. And the level of staining intensity was estimated to grades between 0 and 3 (0, negative; 1, weak; 2, moderate; 3, strong staining). CD97-positive tumors were further examined for the presence of more strongly stained scattered cells or scattered cell groups near or on the invasion front.

2.4. Statistical Analysis

Statistical analysis was performed with SSPS 13.0; the parameters were compared with the χ^2 test. Spearman correlation test was used for the correlation between positive rates. A level of P 0.05 was considered significant.

3. RESULTS

3.1. CD97 Protein Expression Correlates with Clinicopathological Variables

Forty-one of 47 gastric MALT lymphoma tissues showed CD97 positive staining, including 8 weak, 15 moderate and 18 strong staining (**Figure 1(a)**). All three cases with large cell differentiation stained strongly,

whereas, in normal gastric mucosa tissue, no immunoreactivity of CD97 was found. The relationship between CD97 protein expression and a number of clinical indexes, including depth of tumor invasion and clinical staging, as well as patient's age and sex, tumor size, and H pylori infection, were also investigated and summarized in **Table 1**. The difference of CD97 expression between depth of invasion limited in mucosa and submucosa and beyond muscularis propria was significant (100.0%, 26/26 vs. 71.4%, 15/21, $P < 0.01$). Moreover, the expression of nuclear CD97 between stage IIE, III, IV and stage Ⅰ patients showed significant difference (27 of 28, 96.4% vs. 14 of 19, 73.7%, $P < 0.05$), but not with the age and gender of patients, H pylori infection, and tumor size ($P > 0.05$, **Table 1**).

There was no correlation between CD97 and NK-kB ($r = 0.243$, $P = 1.00$) or COX-2 expression ($r = 0.263$, $P = 0.74$).

3.2. NF-kB Protein Expression Correlates with Clinicopathological Variables

In this study, no immunoreactivity of NF-kB was found in all normal gastric mucosa tissues, the positive expression of NF-kB protein (**Figure 1(b)**) in the patients with gastric MALT lymphoma was 36.2% (17/47), moreover, tumors with low expression of NF-kB were significantly smaller in size (17 of 47, 36.2%, $P < 0.05$) than those with high expression (9 of 21, 42.8% and 5 of 7, 71.4%). The incidence of deeper invasion was significantly higher ($P < 0.05$) than that in tumor with low expression (13 of 26, 50% vs. 4 of 21, 26.7%). Furthermore, the expression of nuclear NF-kB between stage IIE, IV and stage I and stage II patients showed significant difference(16 of 19, 84.2% vs. 4 of 19, 21.1% vs. 4 of 15, 26.7%, $P < 0.05$).Whereas, not with the age and gender of patients, or H pylori infection ($P > 0.05$, **Table 1**).

3.3. COX-2 Protein Expression Correlates with Clinicopathological Variables

Twenty-three of 47 gastric MALT lymphoma tissues showed COX-2 positive staining, immunohistochemically, COX-2 was stained diffusely in cytoplasm of the tumor cells (**Figure 1(c)**). In contrast, no or very faint signal was found in neighboring normal tissues. The expression of COX-2 gastric MALT lymphoma patients with H pylori infection was significantly higher than those in patients without H pylori infection (19 of 29, 65.5% vs. 4 of 18, 22.2%) ($P<0.05$), moreover, COX-2 expression was significantly correlated with clinical stage, depth of invasion, tumor size ($P<0.05$). Univariate factor analysis showed that the overall survival of gastric MALT lymphoma patients with positive COX-2 protein

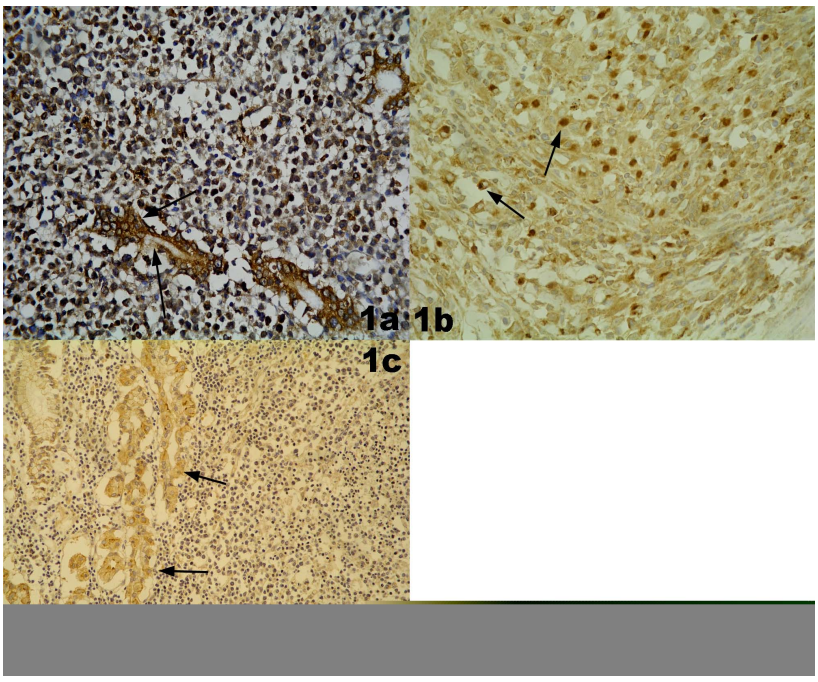

Figure 1. (a) Strong immunohistological stain of CD97 in gastric MALT lymphoma (original magnification × 200). (b) The gastric MALT lymphoma stained NF-kB nuclear immunity (original magnification × 200). (c) Strong immunohistological stain of COX-2 in gastric MALT lymphoma (original magnification × 200).

Table 1. The relationship between CD97, NF-kB and COX-2 positive expression and the clinicopathological factors in gastric MALT lymphoma.

Clinicopathological factors	CD97 positive expression (%)	NF-kB positive nuclear expression (%)	COX-2 expression (%)
Age			
>60year (n = 20)	18 (90.0%)	11 (55.0%)	10 (50.0%)
≤60year (n = 27)	23 (85.2%)	10 (43.5%)	13 (48.1%)
Sex			
male (n = 30)	26 (86.7%)	13 (50.0%)	14 (46.7%)
female (n = 17)	15 (88.2%)	8 (53.3%)	9 (52.9%)
H pylori infection			
yes (n = 29)	24 (82.8%)	10 (41.7%)	10 (34.5%) **
no (n = 18)	17 (94.4%)	7 (29.9%)	14 (77.8%)
Tumor size			
≤5 cm (n =19)	14 (73.7%)	3 (15.7%)	
5 - 10 cm (n = 21)	20 (95.2%)	9 (42.8%)*	14 (73.7%)*
>10 cm (n = 7)	7 (100.0%)	5 (71.4%) **	10 (35.7%)
Depth of invasion			
m + sm (n = 21)	15 (71.4%) **	4 (19.0%)*	15 (71.4%)*
pm + s (n = 26)	26 (100.0%)	13 (50.0%)	9 (34.6%)
Staging			
stage I (n = 19)	14 (73.7%)*	4 (21.1%)*	12 (63.2%)*
stage II (n = 15)	14 (93.3%)	4 (26.7%)*	9 (60.0%)
stage IIE + IV (n = 13)	13 (100.0%)	9 (69.2%)	2 (15.4%)
Tumor recurrence			
yes (n = 4)	3 (75.0%)	3 (33.3%)	5 (29.4%)*
no (n = 43)	38 (88.4%)	14 (36.8%)	19 (63.3%)

Note: *$P < 0.05$; **$P < 0.01$

(59.9 months) was shorter than that of patients with negative COX-2 protein (77.8 months), but this difference was no statistically significant ($P > 0.05$).

There was a significant correlation between COX-2 and NK-kB expression (r = 0.442, $P = 0.02$).

4. DISCUSSION

Normal human gastric mucosa is devoid of MALT, and MALT accumulates within gastric mucosa as a result of long-standing H pylori infection in a subset of infected patients, and from this acquired MALT, low-grade B cell MALT lymphoma may eventually develop [1-3,5]. H pylori can be demonstrated in the gastric mucosa of the majority of cases of gastric MALT lymphoma [23,30]. Additionally, eradication of H pylori was reported to result in the complete regression of the majority of these tumors [5,38]. However, the exact mechanism responsible for the development of MALT lymphoma still remains obscure.

It has been showed that expression of CD97 was found in various epithelial tumours, for example, thyroid, colorectal, gastric, oesophageal and pancreatic carcinomas [30-36,39]. A study from Steinert *et al*. [14] suggests a strong correlation between the appearance of moderate of severe tumor budding and accumulating of CD97 in these scattered tumor cells. Recent studies suggest that molecule CD97 are contributing to cell-matrix and cell to cell interactions and identify a subset of carcinoma cells prone to invade focally, spread, and metastasis in colorectal cancer [10,12]. In addition, the level of CD97 in cancer cell line correlates with migration and invasion in vitro, and this result was confirmed in CD97-inducible Tet-off HT1080 cells [14]. However, there is no data on CD97 expression in MALT lymphoma. Our observation for the first time demonstrated that CD97 protein was strongly expressed in 87.2% gastric MALT lymphoma tissues, moreover, CD97 protein was diffusely expressed in the gastric MALT lymphoma tissues, and very highly expressed in the tumor with large cell differentiation, but it remarkably differed from the characteristics of CD97 in gastric or colorectal cancer tissues [12,14]. Moreover, our data showed that CD97 protein expression was inversely correlated with tumor size, depth of invasion and clinical staging in gastric MALT lymphoma ($P < 0.01$ or 0.05), namely, the immunoassaying of CD97 in gastric MALT lymphoma suggests that CD97 expression may play an important role in the development and aggressiveness of gastric MALT lymphoma.

NF-kB is a family of important transcription factors that regulate B-cell development, maintenance, and stimulation [19,20,23,25] ;it is constitutively present in the cytosol and inactivated by its association with IkB family inhibitors [17,22]. B-cell receptor signaling and some tumor necrosis factor (TNF) cytokine signaling induce NF-kB activation through the NF-kB1 pathway [24], where phosphorylation of the NF-kB inhibitor IkB by the IkB kinase (IKK) complex allows the cytoplasmic

NF-kB proteins p65 and p50 to translocate to the nucleus when their nuclear localization sequence (NLS) is exposed. Once phosphorylated, IkB is targeted for ubiquitination and degradation by the 26S proteasome, allowing translocation of NF-kB into the nucleus where it binds to specific DNA sequences in the promoters of target genes, thereby stimulating transcription [16,21]. Recently, genetic and biochemical evidence has accumulated, suggesting that constitutive activation of NF-kB proteins plays an important role in the development/progression of B and T cell lymphoid malignancies [19,22,29]. In particular, genetic and molecular alterations of NF-kB family members and their transcriptional target genes have been implicated in the development of diffuse large B cell lymphoma and mucosa-associated lymphoid tissue lymphoma. Various molecular events lead to deregulation of NF-kB signaling in Hodgkin disease and a variety of T- and B-cell non-Hodgkin lymphomas either up-stream or downstream of the central IkappaB kinase. Although NF-kB proteins represent an integrating point of several pathways, potentially contributing to several diseases, their unique activation depends on cell type and stimulus [26,28].

H pylori activate the alternative NF-kB pathway in B lymphocytes. The effects on chemokine production and antiapoptosis mediated by H. pylori-induced processing of NF-kB2/p100 to p52 may drive lymphocytes to acquire malignant potential [10]. Merzianu M *et al.* [27] reported that nuclear expression of the p65 subunit of NF-kB in lymphoplasmacytic lymphoma was 34%, suggesting that NF-kB is active in these tumors. In this study, expression of NF-kB was examined in gastric MALT lymphoma, and found NF-kB nuclear expression was inversely correlated with tumor volume, depth of tumor invasion and clinical staging in gastric MALT lymphoma. These results suggest that nuclear expression of NF-kB involve in the tumorogenesis and development of gastric MALT lymphoma and inhibition of NF-kB pathway may be an alternative for prevention and treatment of this disease.

Cyclooxgenases (COXs) are the key enzymes in arachidonate metabolism and catalyze the biosynthesis of prostaglandin H2, which is the precursor for prostanoids. There are at least two isoformers, COX-1 and COX-2, the former, which is constitutively expressed in many tissues, and involved in the homeostasis of various physiologic functions, and the latter, which is involved in many inflammatory reactions with its expression rapidly induced by growth factors, tumor promoters or cytokines [30,33]. Under normal conditions, COX-2 is absent in tissue cells. Over-expression of COX-2 in adenocarcinoma cells has also been linked to increased angiogenesis and metastasis [32-34]. COX-2 can be regulated at both transcriptional and posttranscriptional levels [33]. The transcriptional activation of COX-2 is mediated by the binding of inducible transcriptional factors to *cis*-acting elements in the COX-2 promoter. Binding sites for the regulatory elements, including NF-kB, nuclear factor for interleukin-6 (NF-IL-6), cyclic AMP response element (CRE), PEA-3, SP-1, activator protein-2 (AP-2), and T-cell factor 4 (TCF-4), have been identified in the 5'-flanking region of the COX-2 gene [19,20,29]. COX-2 has been found to be overexpressed in various B-cell lymphoma cell lines [32,34,36,40].

With respect to lymphoma, Paydas *et al*.'s study suggested that there was an important association between aggressive histology and COX-2 expression: COX-2 was negative in about half of the cases with indolent morphology, while two thirds of the COX-2 positive cases had aggressive histology ($P = 0.036$) [32]. Furthermore, though the difference was not significant statistically, the overall survival of COX-2-positive patients was less than for those without COX-2 expression [31]. Our study showed COX-2 positive staining, and the expression of COX-2 gastric MALT lymphoma patients with H pylori infection was significantly higher than those in patients without H pylori infection ($P < 0.05$), moreover, COX-2 expression was significantly correlated with clinical stage, depth of invasion, tumor size in gastric MALT lymphoma($P < 0.05$), and gastric MALT lymphoma patients with positive COX-2 protein lived shorter than patients with negative COX-2 protein ($P > 0.05$) in univariate factor analysis. This is in agreement with the report of Yang *et al.* [41], the COX-2 expression correlated with clinical stage and COX-2 negative patients had lower survival than COX-2 positive patients ($p = 0.014$). Lymphoma cells treated with COX-2 inhibitor (celecoxib) revealed apoptotic induction of greater than 85% in all cell lines examined at 50 microM celecoxib, these findings suggest that increased COX-2 expression and activity, contributes to the pathogenesis of B cell lymphomas and point to a possible role for COX-2 inhibition in their treatment [34]. These findings suggest that increased COX-2 expression and activity, contributes to the pathogenesis of gastric MALT lymphomas and point to a possible role for COX-2 inhibition in their treatment.

COX-2 over-expression parallels NF-kB expression in oral precancer and cancer[40], and synchronism between individual expressions may denote a regulatory role of the latter in COX-2 tansactivation[41]. Our results indicate that there was a significant correlation between COX-2 and NK-kB Expression ($r = 0.02$, $P < 0.05$), but no correlation was found between CD97 and NK-kB ($r = 1.00$, $P > 0.05$) or COX-2 expression ($r = 0.74$, $P > 0.05$).

Taken together, our findings was the first to indicate

that CD97 strongly expressed in gastric MALT lymphoma tissues, and expressions of CD97, NF-kB and COX-2 may play a synergistic role in the pathogenesis of gastric MALT lymphoma, moreover, their expressions were correlated with tumor invasion and metastasis.

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