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Original Article

Expression of MYB protein and its clinicopathological significance in adenoid cystic carcinoma of salivary gland

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Abstract: Objective: Recent studies revealed the existence of ectopic gene at t(6;9)(q22-23;p23-24) in adenoid cystic carcinoma (ACC), resulting in MYB-NFIB fusion gene formation. In this study, we discuss the expression of MYB of ACC in salivary gland and its clinicopathological significance. Methods: We examined 98 samples of salivary gland adenoid cystic carcinoma and 68 samples of salivary non-ACC neoplasms among patients at the Department of Oral Pathology, Nanjing Stomatological Hospital, Medical School of Nanjing University (China). The expression of Ki67 and MYB was analyzed by immunohistochemical analysis and followed up with survival analysis. Results: Of the 98 cases of salivary ACC, 87 (88.8%) stained positive for MYB, including 59.2% (58/98) strongly positive and 29.6% (29/98) weakly positive. Among the non-ACC neoplasms, 11.8% (8/68) cases stained weakly positive for MYB. No salivary gland tissue adjacent to ACC (0/20) or salivary gland tissue of non-neoplastic lesions (including submandibular gland calculus and inflammation) (0/5) was MYB positive. No significant relation was seen between MYB expression and age, gender, size, site, histological type, distant metastasis, Ki67 proliferation index and prognosis. Conclusion: Immunohistochemical analysis of MYB facilitates clinical pathological diagnosis and differential diagnosis of ACC in salivary gland. A strong positive expression of MYB is a significant ACC-specific marker in salivary gland.

Keywords: Gene fusion, MYB-NFIB, MYB, adenoid cystic carcinoma, salivary gland neoplasms

Introduction

Adenoid cystic carcinoma (ACC) is one of the most common epithelial malignancies in salivary glands. It may also occur in the breast, skin and other organs. Variations in histology and morphology between ACC and a variety of benign and malignant tumors, and the lack of specific tumor markers, lead to errors in clinicopathological diagnosis. Persson Met et al [1] found that ectopic gene t(6;9)(q22-23;p23-24) in ACC resulted in MYB-NFIB fusion gene formation, which plays a key role in the development of ACC. West RB et al [2] found a persistent and elevated expression of MYB protein or RNA amplification in part of the ACC following loss of MYB-NFIB fusion gene, suggesting a potential role of MYB in the formation and development of ACC.

Currently, fluorescence in situ hybridization (FISH) and gene sequencing are used to detect MYB-NFIB fusion gene, which can differentiate ACC from other salivary gland tumors with high specificity. However, the operation are complex, expensive, with a low sensitivity, and not conducive to large-scale application. Immunohistochemical detection of MYB antibody facilitates rapid and convenient diagnosis, and has already been used in some cases. The role of MYB expression in ACC and its differential diagnosis, clinical pathology and prognosis is not clear. In this study, the expression of MYB in different salivary gland tumors was detected using immunohistochemistry, and its significance in the differential diagnosis of ACC as well as clinical pathological parameters and prognosis were analyzed.

Materials and methods

Clinical data

Paraffin-embedded specimens of salivary gland tumors were collected from March 2007 to March 2015 at the Department of Oral

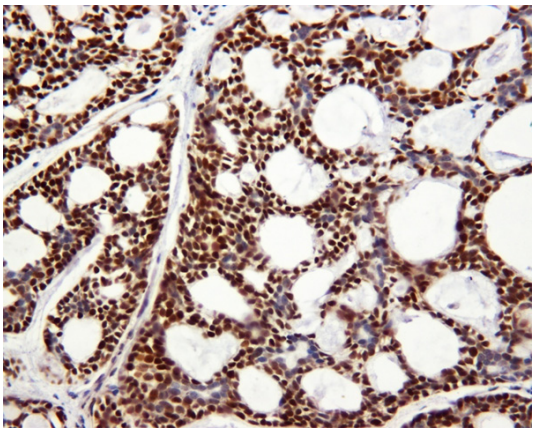

Figure 1. Immunohistochemical staining of MYB, ACC cribriform type, positive in the nucleus of neoplastic myoepithelial cells, but negative in nucleus of epithelial cells lining duct (original magnification ×400).

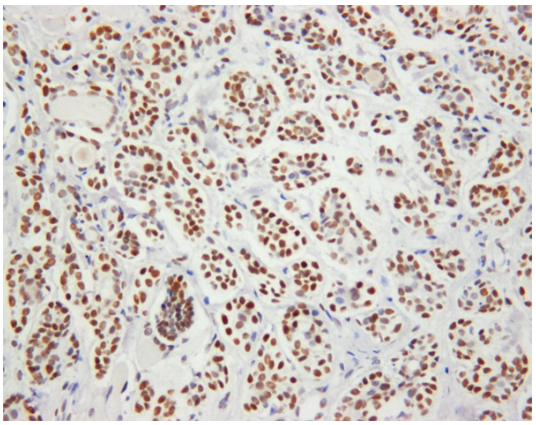

Figure 2. Immunohistochemical staining of MYB, ACC tubular type, positive in the nuclei of neoplastic myoepithelialcells and epithelial cells lining ducts (original magnification ×400).

Pathology, Nanjing Stomatological Hospital, Medical School of Nanjing University (China), including 98 cases of ACC and 68 cases of non-ACC neoplasms (20 cases of basal cell adenoma, 12 cases of pleomorphic adenoma, 11 cases of myoepithelioma, 10 cases of Warthin tumor, 6 cases of oncocytoma and 9 cases of basal cell carcinoma). All the cases were primary tumors resected for the first time. None of them was treated with radiotherapy, chemotherapy or immunotherapy pre- or post-operatively. The 20 wax blocks of salivary gland tissue adjacent to ACC and 5 wax blocks of salivary gland tissue of non-neoplastic lesions (including submandibular gland calculus and inflammation) were selected as controls. According to the 2005 WHO histological classification of tumors of salivary glands for pathological diagnosis and histology typing, all the cases were confirmed by two senior pathologist. Among the 98 ACC cases including 44 males and 54 females, the median age was 50 years old (range, 30 to 87). The ACC included 46 cases involving major salivary glands (including parotid, submandibular and sublingual), and 52 cases involving minor salivary glands (including palate, cheek, tongue, and others). They included 19 cases of solid type and 79 cases of non-solid type. Follow-up of the 98 patients with ACC was conducted in April 2015.

Immunohistochemistry

The slides were deparaffinized and rehydrated, then boiled in Tris-EDTA buffer (pH 9.0), for 15 minutes in a pressure cooker. After cooling for 30 minutes, they were incubated for 1 h at 37°C with the following primary antibodies: anti-MYB antibody (EP769Y, Abcam, UK) at 1:2000 dilution, Ki-67 (DAKO, Denmark) at 1:200 dilution. EnVision method (DAKO, Denmark) was used for detection, employing diaminobenzidine as the chromogen. Hematoxylin was used in the counterstaining of the sections. A specimen each of ACC and basal cell adenoma was used as negative control, respectively, along with an internal control when interpreting the results.

As described in previous studies [2, 4], the case was deemed positive only when its nuclei stained positive in the tumor cells as follows: strongly positive (++): stained brown yellow, and the positive cells accounted for no less than 50%; weakly positive (+): stained light to brown yellow, and the positive cells accounted for less than 50%, but more than 5%; negative (-): positive cells accounted for less than 5%.

Statistical analysis

Normally distributed data of continuous variables were represented as “mean ± SD”, and compared using Student’s t test. The data were measured as “n (%) ”, and statistical data were analyzed with chi-square test or Fisher’s exact chi-square test. Survival time was estimated using Kaplan-Meier methods, and survival was analyzed using the log-rank test. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc, Chicago, Illinois, US). Differences were considered statistically significant when $P<0.05$.

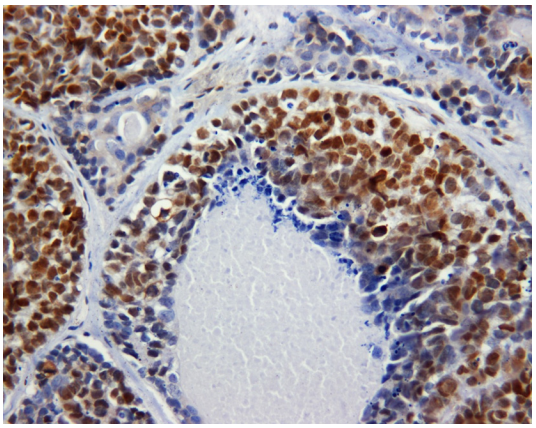

Figure 3. Immunohistochemical staining of MYB, ACC solid type, positive in the nuclei of neoplastic myoepithelial cells, acne-like necrosis in the centre (original magnification ×400).

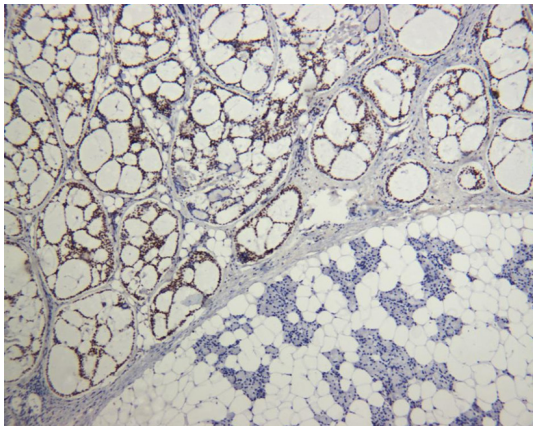

Figure 4. Immunohistochemical staining of MYB, positive expression of ACC (upper left); negative expression of salivary glands adjacent to ACC in the right lower area (original magnification ×40).

Results

Expression of MYB in ACC and salivary gland tissue adjacent to ACC, non-ACC neoplasm and salivary glands of non-neoplastic lesions

MYB stained mainly in the nucleus of tumor cells. MYB was expressed in different histological types of ACC: cribriform (**Figure 1**), tubular (**Figure 2**) and solid (**Figure 3**). In a few ACC cases, the expression of MYB was positive in the neoplastic myoepithelial cells, but negative in epithelial cells lining duct (**Figure 1**). In a few ACC cases, the expression of MYB was positive in epithelial cells lining ducts and neoplastic myoepithelial cells (**Figure 2**). No MYB was expressed only in the lining duct of epithelial

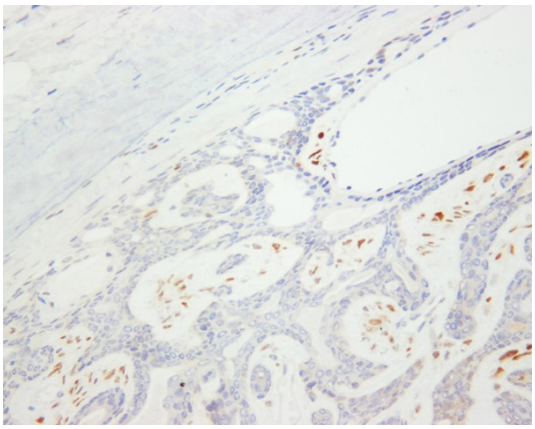

Figure 5. Immunohistochemical staining of MYB, basal cell adenoma, fibrous envelope in the upper left, negative expression of tumor in the right lower area, and positive nuclei of spindle cells in the stroma (original magnification ×200).

cells. In some cases, MYB expression was observed in the lymphocytes or fibroblasts of mesenchyme, but was not considered as positive. The 20 samples of salivary glands adjacent to ACC were all negative (**Figure 4**).

In 98 cases of ACC in salivary gland, the MYB expression was positive in 87 cases, accounting for 88.8%. Robust MYB expression was observed in 58 cases, accounting for 59.2%. The expression of MYB was weakly positive in 29 cases, accounting for 29.6%. The 20 cases of salivary gland tissue adjacent to ACC were all negative for MYB. In 8 out of 68 cases of non-ACC neoplasm, MYB stained weakly positive, accounting for 11.8%, and the remainder were all negative (-) (**Figure 5**). The MYB was expressed weakly in 6 out of 20 cases of basal cell adenoma (+), accounting for 30%. The expression of MYB in 1 out of 12 cases in polymorphic adenoma was weakly positive (+), accounting for 8.3%. In 1 out of 11 myoepithelioma cases, MYB was weakly positive (+), accounting for 9.3%. However, MYB was negative in 10 cases of Warthin tumor, 6 cases of oncocytoma and 9 cases of basal cell carcinoma. In the control group of 5 cases of non-neoplastic salivary glands, MYB was negative (**Table 1**).

Correlation of MYB expression and clinicopathological parameters in ACC

The maximum diameter of MYB-expressing tumor was slightly smaller than in other tumors,

Table 1. Immunohistochemistry of MYB in ACC and non-ACC tumors of salivary gland

	Cases	++ Cases (%)	+ Cases (%)	Total cases (%)
ACC	98	58 (59.2)	29 (29.6)	87 (88.8)
Salivary gland tissue adjacent to ACC	20	0 (0)	0 (0)	0 (0)
Non-ACC neoplasms	68	0 (0)	8 (11.8)	8 (11.8)
Basal cell adenoma	20	0 (0)	6 (30.0)	6 (30.0)
Pleomorphic adenoma	12	0 (0)	1 (8.3)	1 (8.3)
Myoepithelioma	11	0 (0)	1 (9.1)	1 (9.1)
Warthin tumor	10	0 (0)	0 (0)	0 (0)
Oncocytoma	6	0 (0)	0 (0)	0 (0)
Basal cell carcinoma	9	0 (0)	0 (0)	0 (0)
Salivary gland tissue	5	0 (0)	0 (0)	0 (0)

Table 2. Correlation analysis of MYB expression and clinicopathological parameters of ACC

		Positive expression of MYB (including strong and weakly positive)	Negative expression of MYB	*P* value
		87	11	
Age		52.4±13.5	52.8±11.8	0.923
Sex	Male	37 (37. 8%)	7 (7.1%)	0.185
	Female	50 (51.0%)	4 (4.1%)	
Size		3.04±1.36	4.45±2.29	0.071
Site	Minor salivary glands	46 (46.9%)	6 (6.1%)	0.917
	Major salivary glands	41 (41.8%)	5 (5.1%)	
Histological type	Solid type	18 (18.4%)	1 (1.0%)	0.359
	Non-solid type	69 (70.4%)	10 (10.2%)	
Ki67 (%)		31.4±17.0	30.0±14.1	0.820

but the difference was not significant (P = 0.071). No significant relationship was observed between MYB expression and age, gender, site, histological type and proliferation index of Ki67 (**Table 2**).

Prognostic significance of MYB expression and clinicopathological parameters of ACC in salivary gland

Seventy-five out of 98 ACC patients were successfully followed up. The follow-up rate was 76.5%. The follow-up time ranged from 1 month to 79 months. Results showed that 64 cases survived with or without tumor, among which 5 cases showed recurrence, and 19 cases exhibited distant metastasis. There were 11 deaths including 8 from pulmonary metastasis, and 3 due to unknown causes.

There was no significant association between MYB expression and ACC prognosis. The prognosis of solid type ACC was worse than that of the cribriform and tubular types. The prognosis of minor salivary gland was worse than that of major salivary gland. The prognosis of ACC with diameter >3 cm was worse than those ≤3 cm. However, there was no significant association between clinicopathological parameters and prognosis in ACC (**Figure 6**).

Discussion

The MYB gene family includes a-MYB, b-MYB and c-MYB. It is an ancient conserved gene. V-MYB gene is also found in viruses. c-MYB is located on chromosome 6q24. It is composed of 16 exons and 1914 bp of coding sequence. The gene product MYB consists of 637 amino acids. It is a transcription factor combined with DNA. c-MYB plays a role in stem cell differentiation, especially in angiogenesis [5]. The MYB gene knockout mice are significantly smaller than normal mice, and lethal. Currently, MYB is considered as a proto-oncogene, which induces tumorigenesis and tumor proliferation [6]. MYB was first found to induce blood tumors [5]. Its role in oncogenesis has also been reported in cancers of colon [7] and breast [8].

Recent studies suggest that MYB aberrations are significantly higher in ACC than in other tumors. Persson M et al [1] first reported the

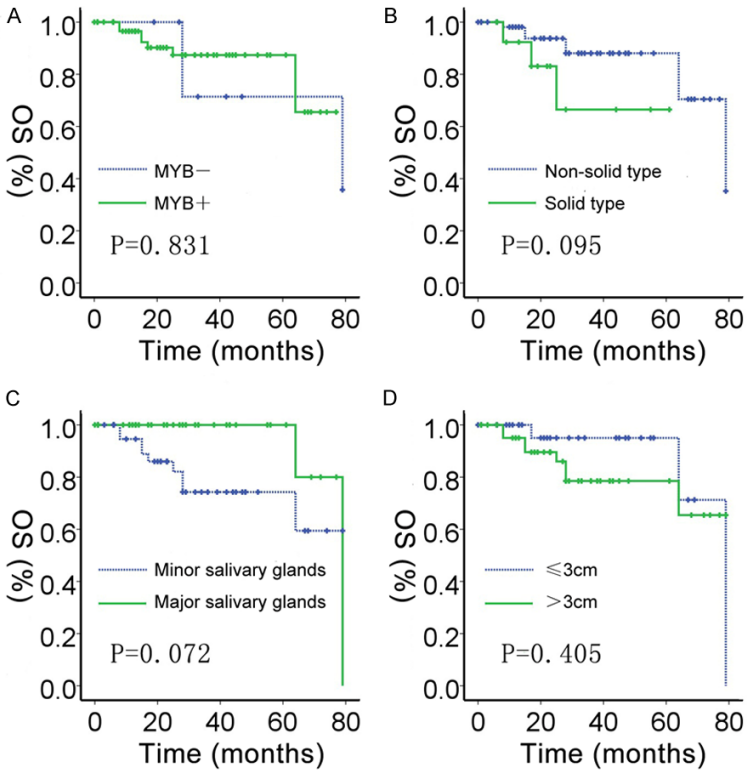

Figure 6. Overall survival curves of ACC in salivary gland. A. Positive and negative expression of MYB in ACC; B. Cribriform, tubular and solid types of ACC; C. ACC of minor and major salivary glands; D. ACC of tumor diameter ≤ 3 cm and tumor diameter >3 cm.

occurrence of MYB-NFIB fusion gene in 6/6 cases of ACC. MYB-NFIB fusion gene was subsequently localized in 49% to 57% cases of ACC [2, 9-11]. The detection of MYB transcripts in ACC was as high as 62% to 100% [1, 12-16]. MYB was found largely in ACC, even though the MYB-NFIB fusion gene was not detected, which implied that MYB played a key role in the formation of ACC.

The MYB-NFIB fusion gene and MYB expression are highly specific to ACC, and therefore, represent a reliable index for the differential diagnosis of ACC. In the study of Hudson JB et al [17], ACC and non ACC were diagnosed by fine needle aspiration from different parts of the biopsy specimens. The MYB-NFIB fusion gene was detected in 50% (5/10) of ACC, but none of the 13 cases of non-ACC neoplasm. The MYB-NFIB fusion gene was detected in 49% (18/37) cases of ACC by West RB [2]. And no MYB-NFIB fusion gene was detected in 16% (6/37) of the cases, but MYB transcription was high. The expression of MYB was not detected in other 112 cases of non ACC tumors in salivary gland. Mitani Y et al [12] reported MYB expression in 85% (17/20) of MYB-NFIB-positive patients. The MYB expression was also detected in 61% (25/41) of MYB-NFIB-negative patients, which indicated that MYB-NFIB fusion gene formation was not completely consistent with MYB expression.

MYB protein is expressed in nucleus. Brill LB et al [13] reported the expression of MYB in neoplastic myoepithelial cells of ACC, but not in the epithelial cells lining the duct. The MYB-positive expression in the peripheral region was stronger than in the central region of the tumor. This study revealed a similar phenomenon. However, MYB expression was also positive in both epithelial cells lining the ducts and neoplastic myoepithelial cells of the tumor in some of the ACC cases studied. Brill LB et al [13] found MYB-positive expression in 14% (16/113) of non-ACC tumors, with a higher expression in basal-like squamous cell carcinoma (4/5), as well as in individual polymorphic adenoma and basal cell adenoma. Similar results were observed in this study. In the study of West et al [2], tissue microarray was used to detect MYB expression. In 65% (24/37) of the ACC cases studied, a strong MYB expression was observed, and mostly in neoplastic myoepithelial cells. The expression was weakly positive in 9% (10/115) of the non-ACC tumors in salivary gland. The tumors included carcinoma in pleomorphic adenoma, myoepithelial carcinoma, myoepithelial tumor, pleomorphic adenoma, mucoepidermoid carcinoma, but the expression rate was below 50%. In this study of 98 cases diagnosed with ACC of the salivary gland, 87 were positive, accounting for 88.8%. Among the positive cases, the expression of MYB protein was strong in 58 cases, accounting for 59.2%, and was weak in 29 cases, accounting for 29.6%. Among the 68 cases of non-ACC tumors, it was weakly positive in only

8 cases (11.8%, including 6 cases of basal cell adenoma, 1 case of pleomorphic adenoma, and 1 case of myoepithelioma). The MYB-positive cell number in non-ACC tumors were less than in ACC samples. The staining intensity was all lower and appeared to be light yellow. Notably, MYB was occasionally positive but not strongly expressed in basal cell adenoma, prompting the need for differential diagnosis.

Thus, detection of MYB expression immunohistochemically facilitated diagnosis and differential diagnosis of ACC and non-ACC tumors in salivary gland. The expression rate of MYB protein in ACC of salivary gland was high, and most of which was strongly positive. In contrast, the MYB expression in non-ACC tumors was poor and weakly positive. In our clinical study, basal cell adenoma is the most difficult to distinguish from ACC. West et al [2] reported negative expression of MYB in 9 cases of basal cell adenoma. However, in this study, MYB expression was weakly positive in basal cell adenoma in 6 out of 20 patients suggesting that biopsy specimens weakly expressing MYB should be analyzed with a combination of clinical and histological morphology. It is also necessary to identify polymorphic adenoma with ACC in the salivary gland. It was suggested by Mendoza PR et al [18] that these two tumor types could be identified by the combination of PLAG1. Our results indicated that MYB expression in polymorphic adenoma was low (1/12). West et al [2] reported that MYB expression was also found in about 29% of breast cancer, 33% of spermocytoma and 27% of colon cancer, but was significantly lower than in ACC of salivary gland, and MYB facilitated the differential diagnosis of ACC by immunohistochemical staining.

Based on the correlation of clinicopathological parameters in ACC, Mitani Y et al [12] found that MYB-NFIB fusion gene formation was only related to patients' age. More specifically, the fusion gene formation was significantly higher in patients aged over 50 years than in younger cases, and had a statistical significance. It was reported by scholars [2] that the probability of MYB-NFIB fusion gene formation in males was higher than in females. The changes in histological grade 3 of ACC were significantly higher than grades 1-2 [14]. However, these results were obtained from single-center study and were not uniform. The significant clinicopathological parameters relating to MYB expression were not found in this study.

The prognosis of ACC is not consistent in recent research. It was reported by West et al [2] that no significant differences were seen between the occurrence of MYB-NFIB fusion gene and ACC prognosis. von HSL et al [15] suggested the absence of any direct correlation between MYB expression and ACC prognosis, consistent with our study. Bell et al [4] concluded that the prognosis of patients with MYB+/c-kit+/cox-2+ was better than in patients with MYB-/c-kit+/cox-2+. Meanwhile, Mitaniet al [9] reported that high MYB expression, age above 60 years old and solid pattern were related to worse prognosis for ACC. Until now, no study reported the high expression of MYB as an independent factor for ACC prognosis. The mechanism underlying the role of MYB in ACC is not clear. Ho et al [10] claimed that MYB-NFIB fusion gene and amplification of MYB consolidated multiple mutations and accelerated tumorigenesis. Most of these mutations are associated with FGF-IGF-PI3K signaling pathway. The significance of screening for MYB-NFIB fusion gene and high MYB expression in salivary gland not only facilitate clinicopathological diagnosis and differential diagnosis of ACC, but also provide important clues underlying the molecular mechanism and targeted therapy of ACC.

Acknowledgements

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Disclosure of conflict of interest

None.

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