

Low expression of ZMYND8 correlates with aggressive features and poor prognosis in nasopharyngeal carcinoma

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: ZMYND8 is closely correlated with cancerous proliferation and invasiveness. However, its prognostic value has not been estimated in a nasopharyngeal carcinoma (NPC). The purpose of this study was to elucidate the status of ZMYND8 expression and its prognostic significance in NPCs.

Methods: The status of ZMYND8 expression was investigated by immunohistochemistry for NPC samples in the study. The cutoff value of ZMYND8 expression was confirmed in NPCs using ROC-curve analysis. Correlations between ZMYND8 expression and clinico-pathological variables and patient prognosis were analyzed by various statistical methods.

Results: Our study showed that low expression of ZMYND8 strongly correlated with late T stage in NPCs ($P < 0.05$). Kaplan–Meier survival analysis revealed a significant association between low ZMYND8 expression and worse overall survival ($P < 0.05$). Most importantly, Cox regression analysis confirmed ZMYND8 expression in NPC could be an independent prognostic factor.

Conclusion: Low expression of ZMYND8 could be of importance, due to its displaying more aggressive behavior in NPC. Therefore, ZMYND8 expression might serve as an independent prediction factor in patients with NPCs.

Keywords: ZMYND8, nasopharyngeal carcinoma, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is the most common cancer in the nasopharynx, endemic in Southeast Asia, especially southern China, and seriously affects human health.¹ Most NPCs are undifferentiated nonkeratinized carcinoma by World Health Organization (WHO) pathological classification, with characteristics of fast growth, metastasis of regional lymph nodes, and/or metastasis to distant organs. Once the metastasis occurs, the prognosis for these patients is not extremely optimistic. The locoregional control rate for NPC has improved significantly in the past few years with improvements in therapeutic strategy, but the incidence of distant metastasis remains ineffectively controlled.² Although these advanced approaches attempting to resolve the dilemma have resulted in the development of NPC, there remain a considerable number of underdetermined factors were paid attention working for progression of NPC. To the best of our knowledge, it is closely related to genetic susceptibility, living customs, and Epstein–Barr virus infection,³ which induces tumorigenesis by multiple steps involved with genetic and epigenetic events.^{1,4} However, the mechanism in detail has yet to be addressed. In clinical practice, the

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TNM staging system is commonly used to predict the clinical outcome of NPC patients. However, patients at same clinical stage might manifest different prognoses. Therefore, there must be several unknown factors that play a crucial role in regulating the development of NPC. Consequently, there is an urgent need to find the signaling pathways associated with molecular and biological changes in NPC, and further to generate new prognostic biomarkers to determine the prognosis of patients more precisely, which would be beneficial for tailored treatment for NPC patients. As such, it is essential to explore novel biomarkers for predicting prognosis and investigate new effective therapeutic targets for NPC.

Research has indicated that ZMYND8 is initially employed as an activated protein kinase C– binding protein (also called PRKCBP1 or RACK7),⁵ which has a completely different domain architecture consisting of an MYND domain close to its C terminus and a PHD finger, with bromo- and PWWP domains located at its N terminus. The presence of a triple PHD–bromo–PWWP domain structure for ZMYND8 indicates that this protein has the potential to combine with chromatin.^{6,7} Further studies have demonstrated that ZMYND8 is the crucial regulatory factor for histone lysine 4 trimethyl (H3K4me3)-specific demethylase KDM5C binding to enhancers as their suppressor. Deficiency of ZMYND8 or KDM5C results in downregulation of S100A oncogenes and various cancer-related phenotypes,⁸ and ZMYND8 has also been identified as a transcriptional corepressor for downregulation of metastasis-linked genes via JARID1D mediation.⁹ Other research has identified that the MYND domain of ZMYND8 facilitates recruitment of GATAD2A/NuRD to sites of DNA damage and further promotes its repair.¹⁰ Delgado et al found that ZMYND8 combines with super-enhancers of B lymphocytes to achieve efficient somatic hypermutation of IgH-variable regions associated with immunity regulation.¹¹ Another recent study reported that ZMYND8 harbors an alteration of somatic copy number in high-grade serous ovarian cancer in the Cancer Genome Atlas Research Network,¹² and ZMYND8 with a high mutation frequency of 19% was shown in mismatch repair–deficient colorectal cancers, which supports ZMYND8 playing the role of tumor oncogene.¹³ More recently, another study showed that ZMYND8 inhibits tumor growth, proliferation, and tumorigenicity in prostate cancer, cervical cancer, and breast cancer cell lines.^{8,14} However, there have been no relevant studies on the prognostic value of ZMYND8 in NPCs. Therefore, the purpose

of this study was to elucidate the status of ZMYND8 expression by immunohistochemistry and its prognostic significance in NPCs.

Methods

Ethics statement

The study was supported by the Institute Research Medical Ethics Committee of Sun Yat-Sen University and conducted in accordance with the Declaration of Helsinki. As all samples were anonymized, patient consent was waived.

Patients and tissue specimens

We collected paraffin samples from September 2002 to November 2004 in the Department of Pathology, Sun Yat-Sen University Cancer Center. Diagnostic criteria for all tissue samples was based on the 2000 WHO criteria for tumor classification and tumor staging on the basis of the International Union Against Cancer and the American Joint Committee on Cancer.

Immunohistochemistry

ZMYND8 protein was stained by immunohistochemistry in accordance with standard EnVision procedures. We sliced paraffin blocks into 3 μ m sections and placed dry sections in an incubator at 60°C. Slides were deparaffinized with xylene, rehydrated in a graded ethanol series, immersed in 3% hydrogen peroxide for 10 minutes to inhibit endogenous peroxidase activity, and subsequently placed in boiled citric acid buffer for antigen retrieval. We incubated slides with antibody ZMYND8 (EPR16924, operative solution concentration 1:1,000; Abcam) at 37°C for 50 minutes. Thereafter, they were incubated with secondary antibody (K5007; Dako) at 37°C for 30 minutes. Then, staining was applied with 3,3-diaminobenzidine and the degree of staining observed by microscopy. Finally, slides were counterstained with hematoxylin, dehydrated in a graded ethanol series, cleared in xylene, and mounted with neutral gum. Positive and negative controls were set in the staining procedure.

Immunohistochemistry evaluation

ZMYND8 expression was assessed. The presence of dark-brown nuclei was taken to be positive for ZMYND8 expression, and scoring criteria were applied: each sample tissue harbored an intensity score (I score) of 0–3 (I0 means negative expression, I1 weak expression, I2 moderate expression,

and I3 strong expression). Subsequently, ZMYND8 was elucidated according to the percentage of positively stained cells in 5% increments of 0–100%, obtaining a percentage score (P score). Finally, the total H score (0–300) was calculated by multiplying each I score and P score. (eg, $[I1 \times P1] + [I2 \times P2] + [I3 \times P3]$).

Selection of cutoff value

The plot of true-positive fraction (sensitivity) versus false-negative fraction ($1 - \text{specificity}$) by various cutoffs generates an ROC curve in the unit square. ROC-curve analysis can determine the optimal cutoff value by point (eg, 0 or 1).^{15,16} The sensitivity and specificity for every clinicopathological variable was plotted, and constructing corresponding ROC curves for the ZMYND8 score, revealing both maximum sensitivity and specificity. Scores less than or equal to cutoff served as low expression of ZMYND8 and more than cutoff as high expression. Clinicopathological characteristics in ROC-curve analysis were T stage, N stage, M stage, clinical stage, relapse and survival status.

Statistical analysis

Statistical analyses were performed using SPSS 16.0. Correlations between ZMYND8 expression and clinicopathological variables of NPC patients were analyzed by χ^2 . Univariate analysis was used to determine associations between clinicopathological variables and overall survival and relapse-free survival of patients by the Kaplan–Meier method. Multivariate analysis was performed with the Cox regression model to identify independent prognostic factors. Two-tailed $P < 0.05$ served as statistical significance.

Results

Patient characteristics

Clinicopathological features of NPC patients are described in Table 1. There were 137 (72.1%) men and 53 (27.9%) women, with median age of 46 years. Follow-up was 3–185 months (median 81.3 months). A total of 157 patients (82.6%) at late stages (III and IV) were diagnosed, and the other 33 patients (17.4%) were at early stages (I and II). Seven of 190 patients had metastasis to distant organs.

Choice of cutoff score for ZMYND8 expression

The status of expression of ZMYND8 protein in NPC tissues was displayed in Figure 1. To choose a suitable

cutoff score of ZMYND8 for further analysis.^{15,17} Tumor tissue samples with scores more than the obtained cutoff value were identified as high ZMYND8 expression and those less or equal to cutoff as low ZMYND8 expression. As shown in Figure 2, ROC-curve points for survival status closest to 0 and 1). On the basis of this outcome, we choose a score of 155 as the cutoff value. Low expression of ZMYND8 was found in 42 of 190 (22.1%) patients with NPCs, and 148 of 190 (77.9%) patients had high expression.

Relationship between ZMYND8 expression and clinicopathological variables of NPC patients

Low and high expression of ZMYND8 in NPC patients linked to several clinicopathological variables are described in Table 1. The data demonstrated that low expression of ZMYND8 was significantly correlated with late T stage ($P < 0.05$), and no significant association was found between ZMYND8 expression and other clinicopathological variables, such as N stage, M stage, clinical stage, age, sex, relapse and therapy regimen. ($P > 0.05$).

Relationship between ZMYND8 expression and NPC-patient survival

Univariate analysis showed a significant impact of well-known clinicopathological prognostic factors on NPC patients' survival rates, such as T stage, N stage, clinical stage, and relapse ($P < 0.05$, Table 2). Univariate analysis also demonstrated that low expression of ZMYND8 was closely associated with worse overall survival ($P < 0.001$, Figure 3A), and presence of relapse, late T stage (T3 + T4), presence of lymph-node metastasis (N1 + N2 + N3) and advanced clinical stage (III + IV) were significantly correlated with poor overall survival ($P < 0.05$, Figure 3, B–F). No statistical significance was found between expression of ZMYND8 and relapse-free survival of patients with NPC (HR 1.091, 95% CI 0.526–2.264; $P = 0.815$; Table 3). Cox regression showed that low expression of ZMYND8 was an independent prognostic factor for overall survival (HR 0.300, 95% CI 0.164–0.547; $P < 0.001$; Table 4).

Discussion

NPC is characterized by high sensitivity to radiotherapy and chemotherapy. Tumor metastases lead to elevated mortality rates, despite new therapeutic strategies combining with conventional radiotherapy and chemotherapy.¹⁸ Different clinical outcomes are revealed for patients with

Table I Correlation between the ZMYND8 expression and clinicopathological variables in nasopharyngeal carcinoma patients

| | ZMYND8 expression | | | |
|------------------------|-------------------|------------|-------------|---------|
| | All | Low | High | P-value |
| Sex | | | | 0.617 |
| Female | 53 | 13 (24.5%) | 40 (75.5%) | |
| Male | 137 | 29 (21.2%) | 108 (78.8%) | |
| Age, years | | | | 0.080 |
| ≤46 | 95 | 16 (16.8%) | 79 (83.2%) | |
| >46 | 95 | 26 (27.4%) | 69 (72.6%) | |
| Clinical stage | | | | 0.550 |
| I-II | 33 | 6 (18.2%) | 27 (81.8%) | |
| III-IV | 157 | 36 (22.9%) | 121 (77.1%) | |
| T stage | | | | 0.028 |
| T1 + T2 | 63 | 8 (12.7%) | 55 (87.3%) | |
| T3 + T4 | 127 | 34 (26.8%) | 93 (73.2%) | |
| N stage | | | | 0.605 |
| N0 | 27 | 7 (25.9%) | 20 (74.1%) | |
| N1 + N2 + N3 | 163 | 35 (21.5%) | 128 (78.5%) | |
| M stage | | | | 0.611 |
| M0 | 183 | 41 (22.4%) | 142 (77.6%) | |
| M1 | 7 | 1 (14.3%) | 6 (85.7%) | |
| Relapse | | | | 0.573 |
| Presence | 47 | 9 (19.1%) | 38 (80.9%) | |
| Absence | 143 | 33 (23.1%) | 110 (76.9%) | |
| Therapy regimen | | | | 0.867 |
| ① | 56 | 13 (23.2%) | 43 (76.8%) | |
| ② | 82 | 16 (19.5%) | 66 (80.5%) | |
| ③ | 22 | 6 (27.3%) | 16 (72.7%) | |
| ④ | 30 | 7 (23.3%) | 23 (76.7%) | |

Notes: ①, Radiotherapy; ②, chemoradiotherapy; ③, radiotherapy + induce; ④, chemoradiotherapy + induce.

the same clinical stage after receiving the same treatment. Therefore, it is necessary to exploit new objective evidence that could effectively distinguish patients with different prognoses that belong to the same clinical stage. Reports have show abnormal gene expression in NPC,^{19,20} but exploring novel molecular biomarkers that might predict tumor progression or relapse remains an urgent task.

ZMYND8 was initially identified as a RACK protein that was able to interact with activated PKCβI,⁵ which has recently been found to be tumor-suppressive in various cancer types.²¹ ZMYND8 participates in DNA-damage response by binding to the NuRD chromatin- remodeling complex, which promotes transcriptional silencing induced by DNA damage and furthermore facilitates repair of DNA double-strand breaks.²² ZMYND8 links to H3K36me2 to further regulate genes that induced by

retinoic acid for neuronal differentiation.²³ Interestingly, several other studies have revealed ZMYND8 acts as an important regulator in controlling cell growth, invasion, and migration, possibly through regulating enhancer functions and interacting with JARID1D.^{8,9} Research has uncovered ZMYND8 to be a tumor suppressor in human breast cancer, cervical cancer, and prostate cancer by retinoic acid mediation or functioning as a transcriptional corepressor.^{9,14} However, in recent years, reports appeared pointing to acetylation of ZMYND8 mediating progression and metastasis of breast cancer by interacting with HIF-dependent transcriptional program,²⁴ and a ZMYND8–RELA fusion gene was found to increase dramatically via the NFκB signal pathway in acute erythroid leukaemia.²⁵ Copy numbers of ZMYND8 are also increased two- to threefold fold in several cancer cell lines according to

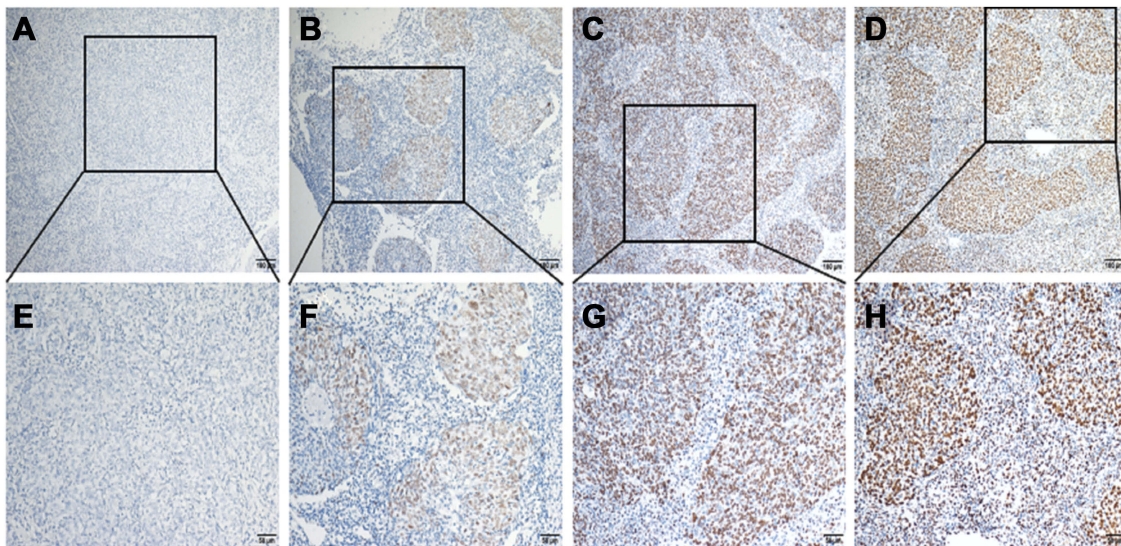


Figure 1 Expression of ZMYND8 protein in nasopharyngeal carcinoma tissue. Negative expression: (A) 10 \times ; (E) 20 \times ; Weak expression: (B) 10 \times ; (F) 20 \times ; Moderate expression: (C) 10 \times ; (G) 20 \times ; Strong expression: (D) 10 \times ; (H) 20 \times .

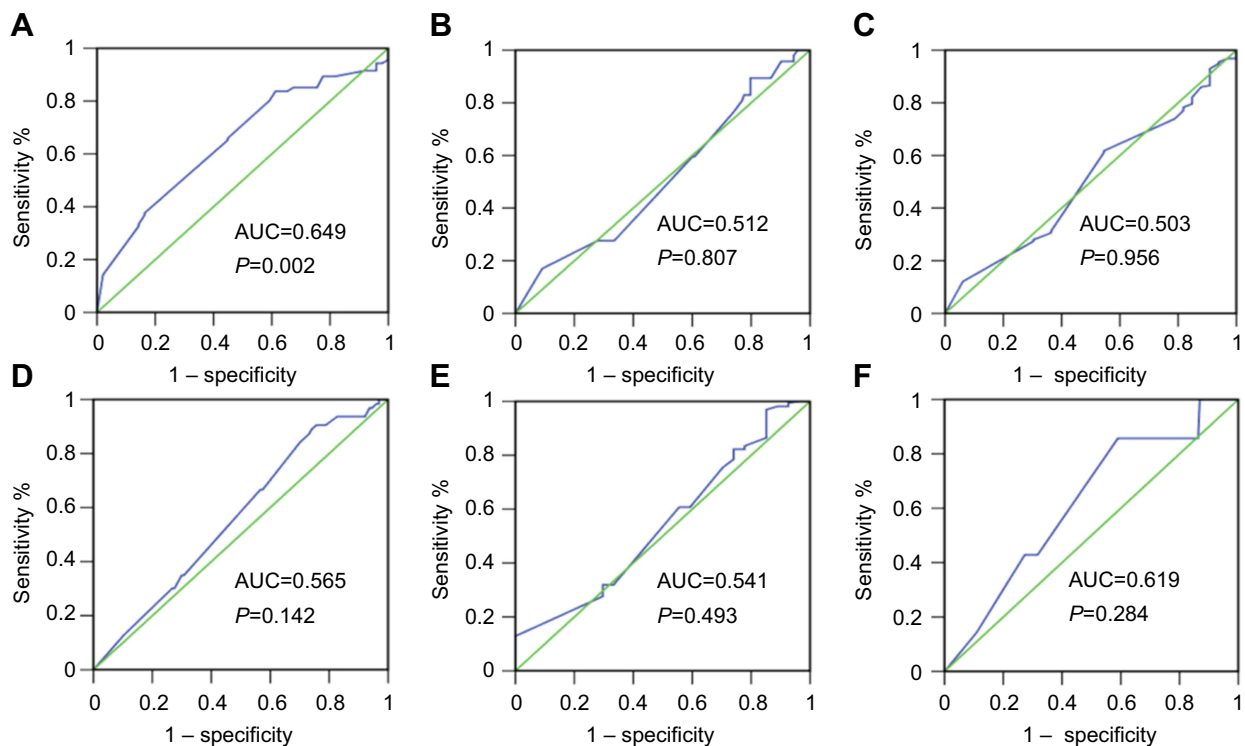


Figure 2 ROC-curve analysis of cutoff for high and low expression of ZMYND8 protein in nasopharyngeal carcinoma by various clinical parameters.

Notes: Sensitivity and specificity for each clinical parameter is plotted, with corresponding ROC curves for ZMYND8 scores. Cutoff values corresponding to points on curves closest to 0 and 1), meaning that the point had both maximum sensitivity and specificity. Green lines are reference lines and blue lines are movements in different cutoff values of corresponding curves by sensitivity (y-axis and 1 – specificity (y-axis). Survival status (A); clinical stage (B); relapse (C); T stage (D); M stage (E); N stage (F).

the UK Institute of Cancer Research and Catalogue of Somatic Mutations in Cancer (COSMIC). Mismatch repair-deficient colorectal cancers harbor a high inactivating mutation frequency (19%) of ZMYND8.¹³ These

studies implied that ZMYND8 can play a critical role in tumor progression and development. However, expression of the ZMYND8 protein and its prognostic significance in NPC remain unknown. In our study, we investigated

Table 2 Univariate analysis of different prognostic factors in 190 patients with nasopharyngeal carcinoma

| | All cases | Mean survival (months) | χ^2 | P-value |
|--------------------------|-----------|------------------------|----------|---------|
| Sex | | | 1.873 | 0.171 |
| Female | 53 | 153.3 | | |
| Male | 137 | 133.76 | | |
| Age, years | | | 2.167 | 0.141 |
| ≤46 | 95 | 148.19 | | |
| >46 | 95 | 129.25 | | |
| Clinical stage | | | 6.945 | 0.008 |
| I–II | 33 | 163.93 | | |
| III–IV | 157 | 134.15 | | |
| T stage | | | 5.966 | 0.015 |
| T1 + T2 | 63 | 158.87 | | |
| T3 + T4 | 127 | 129.89 | | |
| N stage | | | 7.666 | 0.006 |
| N0 | 27 | 170.1 | | |
| N1 + N2 + N3 | 163 | 134.09 | | |
| M stage | | | 2.764 | 0.096 |
| M0 | 183 | 142.04 | | |
| M1 | 7 | 70.43 | | |
| Relapse | | | 40.989 | <0.001 |
| Presence | 47 | 92.14 | | |
| Absence | 143 | 156.55 | | |
| Therapy regimen | | | 1.935 | 0.164 |
| ① | 56 | 124.84 | | |
| ② | 82 | 150.05 | | |
| ③ | 22 | 143.03 | | |
| ④ | 30 | 91.96 | | |
| ZMYND8 expression | | | 15.279 | <0.001 |
| Low | 42 | 92.29 | | |
| High | 148 | 150.72 | | |

Notes: ①, Radiotherapy; ②, chemoradiotherapy; ③, radiotherapy + induce; ④, chemoradiotherapy + induce.

ZMYND8 protein expression in 190 NPC tissue samples. Our results showed that low ZMYND8 expression was intensively correlated with late T stage, indicating that ZMYND8 inhibited differentiation and proliferation of NPC, in agreement with Shen et al.⁸ Our data suggest that a crucial role of ZMYND8 is as a tumor suppressor during the development and progression of NPC. In addition, these results support ZMYND8 acting as a suppressor of malignant tumor transformation, possibly through its inactivated role in human cancers. The inactivated mechanism of ZMYND8 might be correlated with its inactivating mutations (nonsense and frame shift; 9.5%; COSMIC), which have been reported in various cancer

subtypes. Moreover, low ZMYND8 expression was significantly associated with unfavorable survival statistics for NPC patients by univariate and multivariate analysis revealed that it is as an independent prognostic factor for predicting NPC patients' clinical outcomes. These findings indicated that inactivated ZMYND8 might result in aggressive proliferation of tumors and could be used as an important biomarker for the evaluation of prognosis in NPC.

A previous study reported that the *IGH* gene was regulated by the chromatin reader ZMYND8 in mature B lymphocytes to achieve antibody diversity.¹¹ In combination with our findings, we speculate that ZMYND8 is

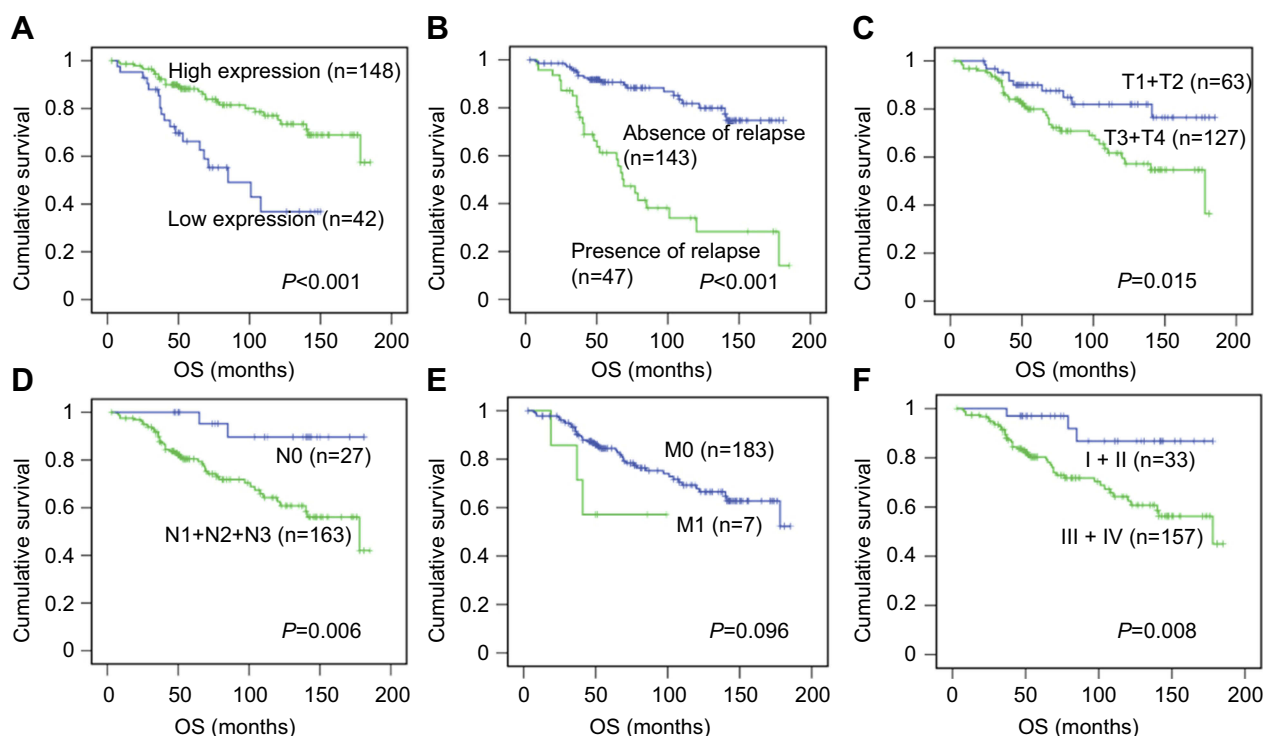


Figure 3 Kaplan-Meier survival analysis of associations between clinicopathological factors and overall survival (OS) in 190 patients with nasopharyngeal carcinoma (A–F).

Table 3 Univariate and multivariate analysis of ZMYND8 associated with relapse-free survival in nasopharyngeal carcinoma patients

| | Univariate analysis | | Multivariate analysis | |
|----------------------------------|----------------------|---------|-----------------------|---------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age, years (>46 vs ≤46) | 0.940 (0.529–1.669) | 0.832 | | |
| Sex | 1.249 (0.648–2.408) | 0.506 | | |
| Clinical stage (III–IV vs I–II) | 2.169 (0.857–5.489) | 0.102 | | |
| Therapy regimen (① + ② vs ③ + ④) | 0.888 (0.659–1.197) | 0.435 | | |
| T stage (T3 + T4 vs T1 + T2) | 1.189 (0.643–2.198) | 0.582 | | |
| N stage (N1 + N2 + N3 vs N0) | 3.299 (1.022–10.646) | 0.046 | 3.108 (0.960–10.067) | 0.059 |
| M stage (M1 vs M0) | 4.029 (1.423–11.409) | 0.009 | 3.566 (1.256–10.122) | 0.017 |
| ZMYND8 expression (high vs low) | 1.091 (0.526–2.264) | 0.815 | | |

Notes: ①, Radiotherapy; ②, chemoradiotherapy; ③, radiotherapy + induce; ④, chemoradiotherapy + induce.

essential for the modulation of an effective immunore-sponse to maintain a somewhat degree of level in NPC, and that it would activate the silencing sequence and further lead to loss of its expression in NPC when the immunity microenvironment is abnormal. Other studies have demonstrated that ZMYND8 interacts with members of H3K4me3-specific KDM5 family, such as KDM5C and KDM5D, to suppress cancer-linked genes across regulating transcription.^{8,9} ZMYND8 is also target gene of all-*trans* retinoic acid (ATRA), and can participate in ATRA-mediated inhibition of cancer-cell proliferation and invasion.^{14,23} These molecular studies provided a

multitude of underlying mechanisms that resulted in downregulation of ZMYND8. However, potential mechanisms by which ZMYND8 affects prognosis are still unclear and need to be further investigated. Therefore, we will deeply explore the potential mechanisms of ZMYND8-linked gene-mediated progression and metastasis of NPC in future experiments.

In a word, our study revealed that ZMYND8 expression might be an effective tool for assessment of those NPC patients at increased risk of tumor invasiveness and proliferation. Low expression of ZMYND8 acted as a new independent prognostic factor in NPC, and if we can

Table 4 Univariate and multivariate analysis of ZMYND8 associated with overall survival in nasopharyngeal carcinoma patients

| | Univariate analysis | | Multivariate analysis | |
|----------------------------------|----------------------|---------|-----------------------|---------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age, years (>46 vs ≤46) | 1.525 (0.865–2.689) | 0.145 | | |
| Sex | 1.596 (0.811–3.141) | 0.176 | | |
| Relapse (presence vs absence) | 5.310 (2.999–9.399) | <0.001 | 5.399 (3.029–9.624) | <0.001 |
| Clinical stage (III–IV vs I–II) | 4.227 (1.313–13.603) | 0.016 | 3.258 (0.877–12.109) | 0.078 |
| Therapy regimen (① + ② vs ③ + ④) | 0.795 (0.573–1.101) | 0.167 | | |
| T stage (T3 + T4 vs T1 + T2) | 2.319 (1.156–4.652) | 0.018 | 1.178 (0.533–2.605) | 0.685 |
| N stage (N1 + N2 + N3 vs N0) | 5.838 (1.414–24.095) | 0.075 | | |
| M stage (M1 vs M0) | 2.613 (0.804–8.493) | 0.110 | | |
| ZMYND8 expression (high vs low) | 0.331 (0.185–0.593) | <0.001 | 0.300 (0.164–0.547) | <0.001 |

Notes: ①, Radiotherapy; ②, chemoradiotherapy; ③, radiotherapy + induce; ④, chemoradiotherapy + induce.

upregulate ZMYND8 expression by activating its upstream regulatory factor in the associated signal pathway by a molecular biology approach, these patients with NPC would be suitable for individual treatment, possibly resulting in better prognoses.

Conclusion

Low ZMYND8 expression could be of importance, due to displaying more aggressive behavior in NPC. Therefore, ZMYND8 expression might serve as an independent prediction factor in patients with NPCs.

Acknowledgment

This work was supported by the Youth Foundation of the National Natural Science Foundation of China (81702755).

Disclosure

The authors report no conflicts of interest in this work.

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