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Research on the Correlation Between miRNA, CMTM6, and PD-L1 Expression in Gastric Cancer

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Abstract: *Objective*: To investigate the correlation between miRNA, CMTM6, and PD-L1 expression in gastric cancer, providing new therapeutic targets for immunotherapy in gastric cancer. *Methods*: This study selected gastric cancer patients who were diagnosed and treated at our hospital from October 2022 to October 2024 as the research subjects. Based on the patients' PD-L1 examination results, they were divided into a positive group and a negative group. General patient data were collected, and qPCR and WB experiments were used to detect the levels of CMTM6 and miRNA in the patients. Univariate analysis was conducted to identify factors influencing PD-L1 expression, and variables with $p < 0.05$ were included in multivariate logistic regression analysis to clarify the correlation between miRNA, CMTM6, and PD-L1 expression in gastric cancer. *Results*: A total of 118 patients were included in this study, with 75 patients in the positive group and 43 patients in the negative group. Univariate analysis revealed that TNM stage, miRNA, and CMTM6 showed statistical significance in data comparison ($p < 0.05$). These variables were then included in multivariate logistic regression analysis, which found that TNM stage (OR = 2.849, 95% CI: 2.227–3.425), miRNA (OR = 3.038, 95% CI: 2.968–3.509), and CMTM6 (OR = 3.185, 95% CI: 2.995–3.810) all exhibited a positive correlation with PD-L1 expression in gastric cancer. *Conclusion*: There is a certain correlation between miRNA, CMTM6, and PD-L1 expression in gastric cancer. As miRNA and CMTM6 levels increase, the positive rate of PD-L1 examination in patients also rises, warranting clinical attention.

Keywords: miRNA; CMTM6; Gastric cancer; PD-L1; Correlation

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1. Introduction

Gastric cancer (GC) is a clinically common type of cancer with a relatively high mortality rate and a trend of affecting younger individuals. The pathogenesis of gastric cancer is mostly attributed to Helicobacter pylori

infection [1]. In addition, high-salt diets, gastritis, and Epstein-Barr virus (EB virus) infection are also major influencing factors for gastric cancer. Although traditional chemotherapy and targeted therapy have, to a certain extent, extended the survival period of patients, the five-year survival rate for patients with advanced gastric cancer remains below 30%, and treatment efficacy is often limited due to tumor heterogeneity, drug resistance, and immune microenvironment suppression [2]. In recent years, immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1) and its ligand (PD-L1) have achieved breakthrough progress in the treatment of gastric cancer [3]. However, their efficacy is highly dependent on the expression level of PD-L1 and the infiltration status of immune cells in the tumor microenvironment. As a core molecule of immunosuppression, PD-L1 expression is regulated at multiple levels, including chromatin remodeling, transcription factor activation, epigenetic modifications, and post-transcriptional regulation [4]. CKLF-like MARVEL transmembrane domain-containing 6 (CMTM6), a factor with a MARVEL domain, has been identified in recent years as a core positive regulator of PD-L1 expression. Studies have found that CMTM6 maintains the stability of PD-L1 on the cell membrane surface by directly binding to PD-L1 and preventing its ubiquitination-mediated degradation and lysosomal pathway degradation [5]. MicroRNAs (miRNAs), non-coding RNAs approximately 22 nucleotides in length, play a crucial role in tumor development and immune evasion by binding to the 3'-untranslated region (3'-UTR) of target gene mRNAs to inhibit their translation or promote their degradation [6]. However, the correlation between miRNAs, CMTM6, and PD-L1 expression in gastric cancer remains unclear. Based on this, this study selected gastric cancer patients who received diagnosis and treatment at our hospital from October 2022 to October 2024 as the research subjects to explore the correlation between miRNAs, CMTM6, and PD-L1 expression in gastric cancer. The specific report is as follows.

2. Materials and methods

2.1. General information

In this study, gastric cancer patients who sought diagnosis and treatment at our hospital from October 2022 to October 2024 were selected as the research subjects and divided into a positive group and a negative group based on the PD-L1 test results.

2.1.1. Inclusion criteria

(1) Complete clinical data
(2) Completion of the immunohistochemical examination for PD-L1 expression
(3) Patients and their family members signed informed consent forms, indicating their voluntary participation in this study

2.1.2. Exclusion criteria

(1) Non-primary gastric cancer
(2) Recent receipt of other adjuvant therapies, including chemotherapy and radiotherapy
(3) Incomplete data

2.2. Methods

In this study, immunohistochemistry was used to detect PD-L1, and based on the test results, patients were

divided into a positive group and a negative group. The specific detection steps are as follows [7].

(1) Dewaxing and hydration

Place the sections on a 60℃ baking machine for 30 minutes to prevent detachment. Then, immerse them sequentially in xylene → absolute ethanol → 95% ethanol → 70% ethanol → distilled water

(2) Antigen retrieval

Immerse the sections in EDTA retrieval solution, heat in a pressure cooker to 121℃ and maintain for 2 minutes, and then allow them to cool naturally to room temperature. After retrieval, rinse with PBS three times, each for 5 minutes

(3) Blocking

Add 3% hydrogen peroxide solution and incubate at room temperature for 10 minutes to block endogenous peroxidase activity. Rinse with PBS three times, each for 5 minutes. Add 5% goat serum or BSA and block at room temperature for 30 minutes to reduce non-specific binding

(4) Incubation

Add PD-L1 antibody and incubate overnight at 4℃ or for 1 hour at 37℃. Rinse with PBS three times, each for 5 minutes

(5) Color development

Add DAB working solution and observe under a microscope until the positive signal turns brown, then stop the color development

(6) Result determination

Calculate the percentage of positive tumor cells among all tumor cells. A tumor-specific staining percentage (TSP) ≥ 1% is considered positive, and < 1% is considered negative [7].

The independent variables selected include the patients' general information, as well as miRNA and CMTM6. The general information includes the patient's gender, age, pathological type, tumor size, and TNM stage.

2.3. Statistical methods

In this study, statistical software SPSS21.00 was utilized for data processing and calculation during data comparison. Measurement data were subjected to chi-square tests and expressed as (n, %), while count data were analyzed using *t*-tests and presented as (mean ± standard deviation). Variables with statistical significance in univariate analysis were included in multivariate logistic analysis. A calculated result of $p < 0.05$ indicated statistical significance in differences.

3. Results

3.1. Clinical data analysis

A total of 118 patients with gastric cancer were included in this study, consisting of 61 male patients and 57 female patients, with an average age of (57.49 ± 6.58) years. Among the pathological types, there were 81 cases of adenocarcinoma and 36 cases of other types. The average tumor size was (4.85 ± 1.16) cm. In terms of TNM staging, there were 27 cases in stage I, 40 cases in stage II, and 51 cases in stage III. There were 54 cases with high expression of CMTM6 and 74 cases with low expression. Regarding miRNA expression, there were 60 cases with high expression and 58 cases with low expression, as detailed in **Table 1**.

Table 1. Results of clinical data analysis

Variable	Category	Results
Gender [n (%)]	Male	61 (51.69)
	Female	57 (48.31)
Age (years)	Mean ± SD	57.49 ± 6.58
Pathological type [n (%)]	Adenocarcinoma	81 (68.64)
	Other	36 (31.36)
Tumor size (cm)	Mean ± SD	4.85 ± 1.16
TNM stage [n (%)]	Stage I	27 (22.88)
	Stage II	40 (33.90)
	Stage III	51 (43.22)
CMTM6 expression [n (%)]	High	54 (45.76)
	Low	74 (54.24)
miRNA expression [n (%)]	High	60 (50.85)
	Low	58 (49.15)

3.2. Univariate analysis results

After immunogenomic examination, 75 cases were included in the positive group and 43 cases in the negative group. Univariate analysis revealed that TNM staging, miRNA, and CMTM6 exhibited statistical significance in data comparison ($p < 0.05$), while other variables did not show statistical significance, as shown in **Table 2**.

Table 2. Results of univariate analysis

Variable	Category	Positive group (n = 75)	Negative group (n = 43)	χ^2/t	*p*-value
Gender [n (%)]	Male (n = 61)	39 (52.00)	22 (51.16)	0.008	0.930
	Female (n = 57)	36 (48.00)	21 (48.84)		
Age (years)	Mean ± SD	57.60 ± 6.61	57.47 ± 6.28		
Pathological type [n (%)]	Adenocarcinoma (n = 81)	50 (66.67)	31 (72.09)	0.374	0.541
	Other (n = 36)	25 (33.33)	12 (27.91)		
Tumor size (cm)	Mean ± SD	4.87 ± 1.16	4.85 ± 1.15		
TNM stage [n (%)]	Stage I (n = 27)	13 (17.33)	14 (32.56)	7.434	0.006
	Stage II (n = 40)	22 (29.33)	18 (41.86)		
	Stage III (n = 51)	40 (53.33)	11 (25.58)		
CMTM6 expression [n (%)]	High (n = 54)	42 (56.00)	12 (27.91)	8.690	0.003
	Low (n = 64)	33 (44.00)	31 (72.09)		
miRNA expression [n (%)]	High (n = 60)	48 (64.00)	12 (27.91)	14.246	< 0.001
	Low (n = 58)	27 (36.00)	31 (72.09)		

3.3. Multivariate logistic analysis results

Based on the findings from univariate analysis, three variables, including TNM staging, CMTM6, and miRNA were included. Multivariate logistic analysis indicated that TNM staging (OR = 2.849, 95% CI: 2.227–3.425), miRNA (OR = 3.038, 95% CI: 2.968–3.509), and CMTM6 (OR = 3.185, 95% CI: 2.995–3.810) all demonstrated positive correlations with PD-L1 expression in gastric cancer, as detailed in **Table 3**.

Table 3. Multivariate logistics regression results analysis

Variable	β	S.E.	*p*-value	OR	95% CI
TNM stage	0.87	0.83	< 0.05	2.849	2.227–3.425
CMTM6	0.92	0.90	< 0.05	3.038	2.968–3.509
miRNA	0.96	0.94	< 0.05	3.185	2.995–3.810

4. Discussion

As an immune checkpoint molecule, PD-L1 plays a pivotal role in immune evasion in gastric cancer. Its expression levels are regulated by various factors, among which microRNAs (miRNAs) and CMTM6 have emerged as research hotspots in recent years [8]. Both factors influence PD-L1 expression through distinct mechanisms, thereby modulating the immune microenvironment and therapeutic response in gastric cancer. miRNAs are a class of non-coding RNAs that regulate gene expression by binding to the 3' untranslated region (3'UTR) of target gene mRNAs, inhibiting their translation or promoting their degradation. In gastric cancer, miRNA regulation of PD-L1 exhibits bidirectionality, with certain miRNAs suppressing tumor immune evasion by negatively regulating PD-L1 expression. Studies have indicated that miR-375 is significantly downregulated in gastric cancer patients with high PD-L1 expression, showing a negative correlation between the two. Mechanistically, miR-375 inhibits PD-L1 expression by targeting the JAK2/STAT3 pathway [9]. CMTM6, on the other hand, reduces PD-L1 ubiquitination levels, thereby decreasing its degradation via the proteasome or lysosomal pathways and prolonging its half-life. Studies have shown that CMTM6 colocalizes with PD-L1 in the cell membrane and recycling endosomes, directly interacting to form a complex that protects PD-L1 from degradation, which is generally consistent with the findings of this study [10].

Based on this, this paper explores the correlation between miRNAs, CMTM6, and PD-L1 expression in gastric cancer. A total of 118 gastric cancer patients were included and categorized into positive and negative groups based on PD-L1 test results. Univariate analysis revealed that TNM stage, miRNAs, and CMTM6 were statistically significant ($p < 0.05$). Variables with statistical significance in the univariate analysis were then included in a multivariate logistic regression analysis, which found positive correlations between TNM stage, miRNAs, CMTM6, and PD-L1 expression in gastric cancer.

5. Conclusion

In summary, miRNAs and CMTM6 play crucial roles in regulating PD-L1 expression in gastric cancer. Through distinct mechanisms, they synergistically influence tumor immune evasion and therapeutic response, providing novel theoretical foundations and potential targets for gastric cancer immunotherapy. Future research should

further explore the interactions between miRNAs and CMTM6 in gastric cancer and elucidate the specific molecular mechanisms underlying their regulation of PD-L1.

Disclosure statement

The authors declare no conflict of interest.

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