Research Article

Expression and Clinical Significance of CMTM6 and PD-L1 in Triple-Negative Breast Cancer

Shuai Shi, Hong-Yan Ma, Yin-zhou Sang, Ying-Bo Ju, Xiao-Yun Liu, and Zhi-Gang Zhang

Department of Pathology, Cangzhou People’s Hospital, Cangzhou 061000, China

Correspondence should be addressed to Zhi-Gang Zhang; zhzhg001518@126.com

Received 18 April 2022; Revised 15 June 2022; Accepted 21 June 2022; Published 7 July 2022

Academic Editor: Valeria D’Argenio

Copyright © 2022 Shuai Shi et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The CKLF-like MARVEL transmembrane domain containing 6 (CMTM6) plays an extremely important role of the programmed death receptor ligand-1 (PD-L1) protein. Our study is aimed at investigating the expression of CMTM6 and PD-L1 proteins in triple-negative breast cancer and their correlation with the clinical pathological data of patients. We selected 89 cases of triple-negative breast cancer and 62 cases of normal breast tissue specimens. Immunohistochemical methods were used to detect the expression levels of CMTM6 and PD-L1 and to carefully study differences in their expression. The expression of CMTM6 and PD-L1 in TNBC was higher than that in normal breast tissue, and the expression of the two was positively correlated ($p < 0.05$). In TNBC, CMTM6 expression is positively correlated with tumor size, lymph node metastasis, Ki67 proliferation index, and TNM stage ($p < 0.05$). PD-L1 expression is positively correlated with tumor size, lymph node metastasis, Ki67 proliferation index, TNM stage, and vascular infiltration ($p < 0.05$). Kaplan-Meier analysis showed that the positive expression of CMTM6 and PD-L1 had no correlation with the survival rate of patients ($p > 0.05$). According to KM-plotter, we found that a higher CMTM6 expression was positively related with relapse-free survival rate of patients ($p < 0.05$). A higher PD-L1 expression was positively correlated with relapse-free, overall, and distant metastasis survival rate of patients ($p < 0.05$). In timer database, we found a positive correlation between the expression of CMTM6 and PD-L1 in triple-negative breast cancer. Both CMTM6 and PD-L1 are highly expressed in TNBC, and their expressions are positively related. In the future, the two gene might become targets for the treatment of TNBC, providing a basis of clinical treatment of TNBC.

1. Introduction

Breast cancer is a common malignant tumor for women. As the incidence of breast cancer has gradually increased, it has made an important threat to women’s health [1]. Breast cancer is divided into four subtypes based on receptor types: luminal A, luminal B, Her2 +, and triple-negative. Triple-negative breast cancer (TNBC) has the characteristics of high transfer rate, low degree of differentiation, poor treatment, and low survival rate. Chemokine plays an important role in the process of tumors and autoimmune diseases [2]. Triple-negative breast cancer is a clinicopathological classification based on the results of immunohistochemistry. The basel-like group of triple-negative breast cancer and molecular typing (PAM50) has a high degree of overlap [3]. At present, the standard treatment of TNBC is mainly chemotherapy, and targeted therapy and immunotherapy are constantly being explored [4]. Peking University first discovered 8 new genes of the chemokine family. It has the characteristics of MARVEL structures, so the chemokine-containing factor super family 1-8 (CKLF-like MARVEL transmembrane domain containing 1-8 (CMTM1-8)) is named MARVEL transmembrane structure [5]. Chemokine-like factor super family member 6 (CMTM6) is one of the members of the CMTM family. CMTM6 is located in chromosome P22, with 183 amino acids, and molecular weight is 20.4 kD. CMTM6 is widely expressed in normal human tissues, mainly located on the cell membrane,
and participates in epigenetic regulation and tumorigenesis [6]. Studies have shown that CMTM6 is abnormally expressed in colorectal cancer, lung cancer, and glioma [7–9].

PD-L1 is also known as CD274 and belongs to the B7 family. The PD-L1 is the type I transmembrane protein, the molecular weight is 33 kD, and the PD-1 gene encoding chemical assembly instruction inside of living things of human 9 chromosome is encoded, which is the ligand of PD1. When PD1 binds to PD-L1, it inhibits the activation of tumor antigen-specific T cells, thereby downregulating the expression of antiapoptotic molecules and proinflammatory factors [10]. The combination of PD-1 and PD-L1 can affect the cell cycle, make tumor cells evade the body’s immune killing, and ultimately lead to the occurrence and development of tumors [11]. There are studies targeting programmed cell death ligand 1 (PD-L1) with monoclonal antibodies (mAbs) such as atezolizumab to treat various tumors. Molecular mechanisms of response to atezolizumab use the PD-L1-expressing human TNBC cell line MDA-MB-231. Atezolizumab downregulates genes that promote cell migration/invasion and metastasis, epithelial-mesenchymal transition (EMT), cell growth/proliferation/survival, and hypoxia. Conversely, genes related to apoptosis and DNA repair were upregulated after atezolizumab treatment. The findings suggest that monoclonal antibodies (mAbs) such as atezolizumab target programmed cell death ligand 1 (PD-L1) to inhibit TNBC molecular mechanisms/signaling pathways provide new insights [12]. Previous studies have shown that CMTM6 can be used as a key regulator of PD-L1 in a variety of tumor cells, binds to PD-L1 and maintains its stable expression of the cell surface, and does not make PD-L1 lysosome-mediated degradation target [13, 14]. The deletion of the CMTM6 gene will cause the degradation of PD-L1 protein and reduce its expression of the surface of tumor cells. The specific binding of CMTM6 and PD-L1 can maintain the recycling of the PD-L1/CMTM6 protein complex in the inclusion body and protect the PD-L1 protein from being recognized and degraded by lysosomes and ultimately maintain the high expression of PD-L1 [15].

In our study, we detected the expression of CMTM6 and PD-L1 in triple-negative breast cancer, analyzed their relationship with clinicopathological characteristics, and explored the clinical significance of CMTM6 and PD-L1 in triple-negative breast cancer.

2. Material and Methods

2.1. Tissue Samples. Collected paraffin specimens of triple-negative breast cancer (n = 89) and normal breast tissue (n = 62) are from Cangzhou People’s Hospital. The patients were 26-81 years old, with an average age of 51.0 years. During the preoperative interview, we provided written informed consent for the patient to describe the use of his tissue. This study was reviewed by the Ethics Committee of Cangzhou People’s Hospital (approval number: J2022-001(0121)). All cases did not undergo radiotherapy, chemotherapy, and biological therapy before surgery. All specimens were histologically diagnosed by two pathologists, including 38 histological grade I cases and 51 histological grade II-III cases. According to the American Joint Committee on Cancer (AJCC), triple-negative breast cancer was classified by TNM, including 73 cases of stage I and 16 cases of stages II-III.

2.2. Immunohistochemistry. All specimens were fixed in neutral formaldehyde solution at 37°C, embedded in paraffin, sectioned at 4 μm, and stained with HE. After dewaxing and hydration, the tissue chip was repaired under high pressure, and the primary antibody was added dropwise for 15 min and then incubated at 4°C overnight. After washing with PBS, the secondary antibody was added and incubated at room temperature for 17 min. The bag used for the primary antibody incubation is transparent and sealed. The primary antibody is rabbit CMTM6 (Abcam; 1:100; ab264067) and PD-L1 (Abcam; 1:100; ab205921). Then, anti-rabbit antibodies conjugated to HRP (Abcam, 1:200, ab996979) were subjected to incubation as the secondary antibody. Use 3, 3′-diaminobenzidine to observe the binding sites and then counterstained with Mayer’s hematoxylin. Both CMTM6 and PD-L1 proteins are located on the cell membrane.

Two independent observers score the slices separately (Shi S and Ma HY). The inconsistent data were confirmed by both persons until final agreements were reached. The expression positivity was graded and counted as follows: 0 = negative, 1 = 1–50%, 2 = 50–74%, and 3 ≥ 75%. The staining intensity score was graded as follows: 1 = weak, 2 = intermediate, and 3 = strong. The scores for CMTM6 [16] and PD-L1 [17] positivity and staining intensity were multiplied to obtain a final score, which determines their expression as (- = 0 – 2; + = 3–9).

2.3. Kaplan-Meier Plotter and TIMER Analysis. The prognosis of CMTM6 and PD-L1 was analyzed using KM-plotter (http://www.kmplot.com) and TIMER (https://cistrome.shinyapps.io/timer/) database, and the correlation of CMTM6 and PD-L1 in triple-negative breast cancer was analyzed.

2.4. Statistical Analysis. The results are analyzed by the SPSS 17.0 software (SPSS). The chi-square test was used to compare the expression differences between TNBC and normal breast tissues. Fisher’s exact test was used to analyze the correlation between CMTM6 and PD-L1 in TNBC. Kaplan-Meier method was used for survival analysis, and COX risk regression models were used for univariate multivariate analysis. p value of < 0.05 was considered statistically significant.

3. Results

3.1. Expression of CMTM6 and PD-L1 in TNBC and Normal Breast Tissue. As shown in Figures 1(a) and 1(d), we performed HE staining on triple-negative breast cancer tissue and normal breast tissue. The results of immunohistochemistry showed that CMTM6 and PD-L1 proteins were located on the cell membrane, and their expression in TNBC (Figures 1(e) and 1(f)) was higher than that in normal breast tissues (Figures 1(b) and 1(c)). The positive rates of CMTM6
in TNBC and normal breast tissue were 56.2% (50/89) and 16.1% (10/62), respectively (p < 0.05, Table 1). PD-L1 expression was detected in 29.2% (26/89) of TNBC and 8.1% (5/62) of normal breast tissue (p < 0.05, Table 1). The expression of CMTM6 and PD-L1 in TNBC (c, f).

### Table 1: CMTM6 and PD-L1 expression in normal tissue and TNBC.

| Groups  | n  | CMTM6 expression | PD-L1 expression |
|---------|----|------------------|------------------|
|         |    | —    | +   | PR (%) | —    | +   | PR (%) |
| Normal  | 62 | 52   | 10  | 16.1   | 57   | 5   | 8.1   |
| Cancer  | 89 | 39   | 50  | 56.2*  | 63   | 26  | 29.2* |

PR: positive rate. *p < 0.01.

3.2. Association of CMTM6 and PD-L1 Expression with the Clinicopathological Parameters of TNBC. We collected the clinicopathological data of 89 patients with TNBC, including patient age, tumor size, TNM staging, histological grade, vascular infiltration, nerve invasion, lymph node status, TP53, Ki67, and distant metastasis. As shown in Table 3,
CMTM6 expression is positively correlated with tumor size, lymph node metastasis, Ki67 proliferation index, and TNM staging \( (p < 0.05) \). PD-L1 expression is positively correlated with tumor size, lymph node metastasis, Ki67 proliferation index, TNM staging, and vascular infiltration \( (p < 0.05) \). With the increase of TNM stage, the expression of CMTM6 and PD-L1 in triple-negative breast cancer patients also increased.

3.3. Relationship between CMTM6 and PD-L1 Expression and Prognosis of TNBC. Kaplan-Meier analysis showed that the positive expression of CMTM6 and PD-L1 had no correlation with the survival rate of patients (Figures 2(a) and 2(b), \( p > 0.05 \)). During the cox survival analysis, due to the small number of samples and the short follow-up time of patients, no prognostic indicators and independent risk factors were found to affect the prognosis of patients with triple-negative breast cancer \( (p > 0.05, \text{Tables 4 and 5}) \).

According to KM-plotter, we found that a higher CMTM6 expression was positively related with relapse-free survival rate of patients (Figure 3(a)). A higher PD-L1 (CD274) expression was positively correlated with relapse-free, overall, and distant metastasis survival rate of patients (Figure 3(b)). In TIMER database, we found a positive correlation between the expression of CMTM6 and PD-L1 in triple-negative breast cancer(Figure 3(c)).

### 4. Discussion

Breast cancer is a common malignant tumor that endangers women’s health. With the advancement of medicine, the early diagnosis and treatment of breast cancer have made great progress, but for advanced patients, radiotherapy and chemotherapy are still the main treatment methods. Studies have shown that the overall survival rate of patients with triple-negative breast cancer is

| Clinicopathological features | \( n \) | — | + | CMTM6 PR (%) | \( p \) value | — | + | PD-L1 PR (%) | \( p \) value |
|-----------------------------|-------|---|---|-------------|-----------|---|---|-------------|-----------|
| Age \( \leq 50 \) | 36    | 14 | 22 | 61.1        | 0.147     | 24 | 12 | 33.3        | 0.181     |
| >50              | 53    | 25 | 28 | 52.8        |           | 39 | 14 | 26.4        |           |
| Size \( <3 \)    | 50    | 25 | 25 | 50.0        | 0.043     | 38 | 12 | 24.0        |           |
| \( \geq 3 \)     | 39    | 14 | 25 | 64.1        |           | 25 | 14 | 35.9        | 0.022     |
| Lymph node metastasis - | 54    | 27 | 28 | 51.9        |           | 47 | 8  | 14.8        |           |
| +               | 34    | 12 | 22 | 64.7        |           | 16 | 18 | 52.9        |           |
| Distant metastasis - | 81    | 36 | 45 | 55.6        | 0.298     | 60 | 21 | 25.9        | 0.273     |
| +               | 8     | 3  | 5  | 62.5        |           | 3  | 5  | 62.5        |           |
| TNM stage I      | 73    | 34 | 39 | 53.4        | 0.003     | 57 | 16 | 21.9        | 0.039     |
| II-III           | 16    | 5  | 11 | 68.8        |           | 6  | 10 | 62.5        |           |
| Histological grade I | 38    | 15 | 23 | 60.5        | 0.187     | 31 | 7  | 18.4        |           |
| II-III           | 51    | 24 | 27 | 52.9        |           | 32 | 19 | 37.3        |           |
| Vascular infiltration - | 52    | 25 | 27 | 51.9        | 0.091     | 41 | 11 | 21.2        | 0.001     |
| +               | 37    | 14 | 23 | 62.2        |           | 22 | 15 | 40.5        |           |
| Nerve invasion -  | 75    | 34 | 41 | 54.7        | 0.076     | 53 | 22 | 29.3        | 0.909     |
| +               | 14    | 5  | 9  | 64.3        |           | 10 | 4  | 28.6        |           |
| TP53 -           | 23    | 11 | 12 | 52.2        | 0.531     | 17 | 6  | 26.1        | 0.429     |
| +               | 66    | 28 | 38 | 57.6        |           | 46 | 20 | 30.3        |           |
| Ki67 -           | 10    | 8  | 2  | 20.0        |           | 10 | 0  | 0.0         |           |
| +               | 79    | 31 | 48 | 60.8        |           | 53 | 26 | 32.9        |           |

| PR: positive rate. |
significantly lower than that of patients with non-triple-negative breast cancer [18]. In recent years, immunotherapy has been widely used in cancer treatment in recent years. In recent years, immunotherapy had been widely used in tumor treatment. Compared with traditional radiotherapy and chemotherapy, immunotherapy can target tumors, thereby inhibiting immune escape pathways and ultimately inhibiting tumor growth. Therefore, finding new immunotherapy targets is of great significance for the early diagnosis, treatment, and prognosis of breast cancer patients.

As a member of the CMTM family, CMTM6 is widely expressed in human tissues, mainly on cell membranes. Studies have found that the high expression of CMTM6 can negatively regulate T cells to kill tumors, thereby participating in the occurrence and development of tumors [19]. Previous studies have shown that CMTM6 is elevated in colorectal cancer, non-small-cell lung cancer, glioma, melanoma, and other tissues [7–9, 14, 20]. Our study found that CMTM6 is also highly expressed in triple-negative breast cancer. Yang et al. found that the expression of CMTM6 was correlated with the pathological type of breast cancer patients and HER2 positivity. Breast cancer pathological classification, TNM stage, triple-negative breast cancer, and high expression of CMTM6 could be used as independent risk factors to judge the prognosis of patients [21]. Our research in triple-negative breast cancer showed that CMTM6 was not an independent risk factor for triple-negative breast cancer. The paradoxical results might be due to the selection of samples and the number of samples, the small number of samples in our hospital, and the short follow-up time for patients. On the contrary, the expression of CMTM6 in hepatocellular carcinoma and esophageal cancer tissues is lower than that in normal tissues, which indicates that CMTM6 expression is different in different tissues [20, 22]. This difference

![Figure 2: Relationship between CMTM6 and PD-L1 expression and prognosis of TNBC. Kaplan-Meier analysis of overall survival associated with CMTM6 (a) and PD-L1 (b).](image-url)
determines the biological characteristics of different tumors. The specific reasons need to be further explored.

The PD-1/PD-L1 signaling pathway is a pair of costimulatory molecules in the process of T cell immune response. It induces antigen-specific T cell apoptosis by negatively regulating T lymphocyte activation, proliferation, and effector functions and exerts an immunosuppressive effect. Monoclonal antibodies targeting the PD-1/PD-L1 pathway had been developed into tumor immunotherapy by improving the function of T lymphocytes, and its clinical trials had also shown exciting effects. As the ligand of PD-1, PD-L1 is mainly expressed on mature immune cells and is highly expressed on the surface of a variety of tumor cells [23]. The expression of PD-L1 in melanoma, non-small-cell lung cancer, and gastric cancer was higher than that in adjacent tissues, and survival analysis suggests that PD-L1 might be a predictor of tumor prognosis [24–26]. Studies had shown that the expression of PD-L1 protein and mRNA in triple-negative breast cancer was higher than that of adjacent

### Table 4: Univariate analysis of prognostic risk factors in the patients with TNBC.

| Characteristics                        | CMTM6 Relative risk (95% CI) | p value | PD-L1 Relative risk (95% CI) | p value |
|----------------------------------------|------------------------------|---------|------------------------------|---------|
| Size                                   |                              |         |                              |         |
| <3                                     | 0.698 (0.062-7.835)          | 0.771   | 0.202 (0.018-2.262)          | 0.194   |
| ≥3                                     |                              |         |                              |         |
| Age (years)                            |                              |         |                              |         |
| <60                                    | 0.680 (0.060-7.694)          | 0.755   | 0.235 (0.020-2.747)          | 0.248   |
| ≥60                                    |                              |         |                              |         |
| Lymph node metastasis                  |                              |         |                              |         |
| -                                       | 0.897 (0.081-9.893)          | 0.929   | 0.530 (0.048-5.853)          | 0.605   |
| +                                       |                              |         |                              |         |
| Distant metastasis                     |                              |         |                              |         |
| -                                       | 0.752 (0.068-8.314)          | 0.816   | 0.442 (0.035-5.541)          | 0.527   |
| +                                       |                              |         |                              |         |
| TNM stage                              |                              |         |                              |         |
| I                                       | 0.907 (0.081-10.118)         | 0.937   | 0.444 (0.035-5.716)          | 0.534   |
| II–III                                 |                              |         |                              |         |
| Histological grade                     |                              |         |                              |         |
| I                                       | 0.729 (0.065-8.130)          | 0.797   | 0.186 (0.016-2.147)          | 0.178   |
| II–III                                 |                              |         |                              |         |
| Vascular infiltration                  |                              |         |                              |         |
| -                                       | 0.790 (0.070-8.945)          | 0.849   | 0.241 (0.021-2.808)          | 0.256   |
| +                                       |                              |         |                              |         |
| Nerve invasion                         |                              |         |                              |         |
| -                                       | 0.551 (0.048-6.352)          | 0.632   | 0.172 (0.015-1.922)          | 0.153   |
| +                                       |                              |         |                              |         |
| TP53                                   |                              |         |                              |         |
| -                                       | 0.608 (0.055-6.725)          | 0.685   | 0.202 (0.018-2.228)          | 0.191   |
| +                                       |                              |         |                              |         |
| Ki67                                   |                              |         |                              |         |
| -                                       | 0.822 (0.074-9.085)          | 0.873   | 0.248 (0.022-2.734)          | 0.255   |
| +                                       |                              |         |                              |         |

CI: confidence interval; TNM: tumor-node-metastasis.

### Table 5: Multivariate analysis of clinicopathological variables for the survival of the patients with TNBC.

| Clinicopathological parameters | p     | p     |
|--------------------------------|-------|-------|
| CMTM6/PD-L1 expression (+)     | 0.982 | 0.827 |
| Size (≥3)                      | 0.814 | 0.767 |
| Age (≥60 years)                | 0.966 | 0.929 |
| Lymph node metastasis (+)      | 0.937 | 0.837 |
| Distant metastasis (+)         | 0.719 | 0.632 |
| TNM staging (III–IV)           | 0.999 | 0.954 |
| Histological grade (III–IV)    | 0.398 | 0.529 |
| Vascular infiltration (+)      | 0.998 | 0.982 |
| Nerve invasion (+)             | 0.822 | 0.733 |
| TP53 (+)                       | 0.997 | 0.943 |
| Ki67 (+)                       | 0.934 | 0.961 |

CI: confidence interval; TNM: tumor-node-metastasis.
Figure 3: Continued.
Figure 3: Correlation and prognostic significance of CMTM6 and PD-L1 expression in triple-negative breast cancer. According to KM-plotter, we found that a higher CMTM6 expression was positively related with relapse-free survival rate of patients (a). A higher PD-L1 expression was positively correlated with relapse-free, overall, and distant metastasis survival rate of patients (b). In TIMER database, we found a positive correlation between the expression of CMTM6 and PD-L1 in triple-negative breast cancer (c).
tissues, and PD-L1 expression was positively correlated with lymph node metastasis, ki67 proliferation index, and histological grade [27, 28]. Our research showed that the expression of PD-L1 in TNBC was higher than that in normal breast tissue. PD-L1 expression was positively correlated with tumor size, lymph node metastasis, Ki67 proliferation index, TNM stage, and vascular infiltration.

Burr et al. [13] found that the deletion of the CMTM6 gene can cause the degradation of PD-L1 protein and reduce its expression on the cell surface. The specific binding of CMTM6 and PD-L1 can maintain the recycling of the PD-L1/CMTM6 complex in the inclusion body, thereby protecting the PD-L1 protein from being recognized and degraded by lysosomes, and maintaining the high expression of the PD-L1 protein. PD-L1 can regulate the stability of RNA, but when the interaction between CMTM6 and PD-L1 is eliminated, the stability of PD-L1 is destroyed, and the binding of PD-L1 to the RNA of the target gene is also destroyed, eventually leading to degradation of target RNA [29]. The stability regulation of CMTM6/PD-L1 on gene group RNA indirectly proves that CMTM6/PD-L1 plays a more important role in tumor development and the survival status of tumor cells themselves.

5. Conclusions

In conclusion, upregulated expression of CMTM6 and PD-L1 may play a role in the occurrence and development of TNBC. It might be considered a good biomarker to indicate the aggressiveness of TNBCs. In the future, whether CMTM6 and PD-L1 can be used as prognostic indicators of triple-negative breast cancer requires a large number of samples to verify. The study of CMTM6 and PD-L1 in the pathogenesis of triple-negative breast cancer requires further research.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] J. Pandy, J. C. Balolong-Garcia, M. Cruz-Ordinario, and F. V. F. Que, “Triple negative breast cancer and platinum-based systemic treatment: a meta-analysis and systematic review,” BMC Cancer, vol. 19, no. 1, p. 1065, 2019.
[2] C. M. Perou, T. Sorlie, M. B. Eisen et al., “Molecular portraits of human breast tumours,” Nature, vol. 406, no. 6797, pp. 747–752, 2000.
[3] X. Chen, J. Li, W. H. Gray et al., “TNBCtype: a subtyping tool for triple-negative breast cancer,” Cancer Informatics, vol. 11, no. 11, article CIN.S9983, 2012.
[4] X. Liu, Y. Q. Li, F. C. Mu et al., “New advances in molecular staging of triple negative breast cancer,” Chinese Journal of Clinical and Experimental Pathology, vol. 36, no. 3, pp. 316–319, 2020.
[5] W. Han, P. Ding, M. Xu et al., “Identification of eight genes encoding chemokine-like factor superfamily members 1-8 (CKLFSF1-8) by in silico cloning and experimental validation,” Genomics, vol. 81, no. 6, pp. 609–617, 2003.
[6] A. Yafune, M. Kawai, M. Ihashi et al., “Global DNA methylation screening of liver in piperonyl butoxide-treated mice in a two-stage hepatocarcinogenesis model,” Toxicology Letters, vol. 222, no. 3, pp. 295–302, 2013.
[7] Y. Miyakawa, T. Kishikawa, T. Seimiya et al., “Expression of circular RNA CDR1-AS in colon cancer cells increases cell surface PD-L1 protein levels,” Oncology Reports, vol. 42, no. 4, pp. 1459–1466, 2019.
[8] Y. W. Koh, J. H. Han, S. Haam, J. Jung, and H. W. Lee, “Increased CMTM6 can predict the clinical response to PD-1 inhibitors in non-small cell lung cancer patients,” Onco Immunology, vol. 8, no. 10, pp. 1–7, 2019.
[9] S. Delic, A. Thuy, M. Schulze et al., “Systematic investigation of CMTM family genes suggests relevance to glioblastoma pathogenesis and CMTM1 and CMTM3 as priority targets,” Genes Chromosomes & Cancer, vol. 54, no. 7, pp. 433–443, 2015.
[10] G. J. Freeman, A. H. Sharpe, and M. E. Keir, “PD-1 and its ligands in tolerance and immunity,” Annual Review of Immunology, vol. 26, no. 1, pp. 677–704, 2008.
[11] R. V. Parry, J. M. Chemnitz, K. A. Frauwirth et al., “CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms,” Molecular and Cellular Biology, vol. 25, no. 21, pp. 9543–9553, 2005.
[12] R. Saleh, R. Z. Taha, V. Sasidharan Nair, N. M. Alajez, and E. Elkord, “PD-L1 blockade by atezolizumab downregulates signaling pathways associated with tumor growth, metastasis, and hypoxia in human triple negative breast cancer,” Cancers, vol. 11, no. 8, p. 1050, 2019.
[13] M. L. Burr, C. E. Sparbier, Y. C. Chan et al., “CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity,” Nature, vol. 549, no. 7670, pp. 101–105, 2017.
[14] R. Mezzadra, S. Chong, and L. T. Jae, “Identification of CMTM6 and CMTM4 as PD-L1 protein regulators,” Nature, vol. 549, no. 7670, pp. 106–110, 2017.
[15] M. Emilie, D. J. Birnbaum, and F. Pascal, “CMTM6 stabilizes PD-L1 expression and refines its prognostic value in tumors,” Annals of Translational Medicine, vol. 6, no. 3, pp. 54–54, 2018.
[16] L. Li, X. He, Z. C. Zhou, and X. Y. Gao, “Expression and correlation of CARD9 PMK2 and CMTM6 in breast cancer tissue,” Hebei Medicine, vol. 27, no. 9, p. 6, 2021.
[17] R. Nanda, L. Chow, E. C. Dees et al., “Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study,” Journal of Clinical Oncology, vol. 34, no. 21, pp. 2460–2467, 2016.
[18] N. U. Lin, A. Vanderplas, M. E. Hughes et al., “Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network,” Cancer, vol. 118, no. 22, pp. 5463–5472, 2012.
[19] X. D. Guan, C. B. Zhang, J. Y. Zhao, G. R. Sun, Q. K. Song, and W. Jia, “CMTM6 overexpression is associated with molecular and clinical characteristics of malignancy and predicts poor prognosis in gliomas,” Ebiomedicine, vol. 35, pp. 233–243, 2018.
[20] H. Li, J. Li, Y. Su et al., “A novel 3p22.3 gene CMTM7 represses oncogenic EGFR signaling and inhibits cancer cell growth,” Oncogene, vol. 33, no. 24, pp. 3109–3118, 2014.
[21] X. J. Yang, L. Wei, X. Zheng et al., “Expression of CMTM6 in breast cancer tissues and its correlation with patients’ clinicopathological characteristics and prognosis,” Chinese Journal of Cancer Biotherapy, vol. 4, p. 391, 2020.

[22] X. Zhu, G. Qi, C. Li et al., “Expression and clinical significance of CMTM6 in hepatocellular carcinoma,” DNA and Cell Biology, vol. 38, no. 2, pp. 193–197, 2019.

[23] S. F. Zhang and J. X. Yang, “PD-1/PD-L1 signaling pathway and its application in breast cancer,” Medical Innovation of China, vol. 14, pp. 145–148, 2017.

[24] D. Massi, D. Brusa, B. Merelli et al., “PD-L1 marks a subset of melanomas with a shorter overall survival and distinct genetic and morphological characteristics,” Annals of Oncology Official Journal of the European Society for Medical Oncology, vol. 25, no. 12, pp. 2433–2442, 2014.

[25] Z. Yang, L. Wang, and L. Yuan, “Protein expression of programmed death 1 ligand 1 and ligand 2 independently predict poor prognosis in surgically resected lung adenocarcinoma,” Oncotargets & Therapy, vol. 7, pp. 567–573, 2014.

[26] M. Zhang, Y. Dong, and L. Hl, “The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: a meta-analysis of 10 studies with 1,901 patients,” Scientific Reports, vol. 6, no. 1, article 37933, 2016.

[27] T. P. Miao, Z. Y. Zhang, and Z. Li, “Expression of PD-1/PD-L1 pathway in triple negative breast cancer patients and its clinical significance,” Journal of Hunan Normal University (Medical Science), vol. 17, pp. 176–178, 2020.

[28] X. R. Huang and C. G. Yang, “Relationship between expression of PD-L1 and epithelial-mesenchymal transition in triple-negative breast cancer and its significance,” Chinese Journal of Clinical and Experimental Pathology, vol. 37, pp. 541–545, 2021.

[29] X. Tu, B. Qin, Y. Zhang et al., “PD-L1 (B7-H1) competes with the RNA exosome to regulate the DNA damage response and can be targeted to sensitize to radiation or chemotherapy,” Molecular Cell, vol. 74, no. 6, pp. 1215–1226.e4, 2019.