REVIEW

The role of the cancer testis antigen PRAME in tumorigenesis and immunotherapy in human cancer

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Abstract

Preferentially expressed antigen in melanoma (PRAME), which belongs to the cancer/testis antigen (CTA) gene family, plays a pivotal role in multiple cellular processes and immunotherapy response in human cancers. PRAME is highly expressed in different types of cancers and is involved in cell proliferation, apoptosis, differentiation and metastasis as well as the outcomes of patients with cancer. In this review article, we discuss the potential roles and physiological functions of PRAME in various types of cancers. Moreover, this review highlights immunotherapeutic strategies that target PRAME in human malignancies. Therefore, the modulation of PRAME might be useful for the treatment of patients with cancer.

1 | INTRODUCTION

A cancer/testis antigen (CTA) termed preferentially expressed antigen in melanoma (PRAME) that encodes the human leucocyte antigen (HLA)-A24 antigen was first characterized in 1997.[1] The PRAME gene is localized on the reverse strand of chromosome 22 (22q11.22), is approximately 12 kilobases long and contains leucine-rich repeat domains.[2] PRAME, in addition to melanoma-associated antigen (MAGE), B melanoma antigen (BAGE), G antigen (GAGE), New York oesophageal squamous cell carcinoma 1(NY-ESO-1) and L antigen family member 1 (LAGE-1), belongs to the CTA gene family and encodes antigen peptides recognized by T lymphocytes.[3] PRAME often has specific expression profiles: PRAME can be detected in many human malignancies; aside from its expression in the testes and limited expression in ovaries, adrenals and endometrium, PRAME is not detected in healthy human tissues.[1] Male germline cells have genome-wide demethylation, which leads to high expression of PRAME in the testes.[1] It has been reported that the PRAME gene is hypermethylated in normal tissues; however, this gene is hypomethylated in most malignant cells. Ortmann et al observed that treatment with the demethylating agent 5′-Aza-2′dC contributes to a dose-related increase in PRAME expression in PRAME-negative U-937 and THP-1 cell lines with hypermethylation of PRAME, suggesting that treatment with the demethylating agents results in upregulation of PRAME expression in certain malignant cells.[4-6]

The PRAME gene encodes a membrane-bound protein and causes autologous cytotoxic T cell-mediated immune responses.[1,7] A group found that the overexpression of PRAME blocks retinoic acid (RA)-mediated cell differentiation, cell growth arrest and apoptotic death, suggesting that PRAME appears to serve as an inhibitor of retinoic acid receptor (RAR) signalling.[8] Hence, upregulation of PRAME contributes to tumorigenesis via inhibiting the RA/RAR signalling pathway.[8,9] In line with this, high expression of PRAME is observed in 88% of primary tissues and 95% of metastatic tissues in melanomas.[1] In addition to melanoma, PRAME is frequently expressed in numerous solid cancers, such as head and neck cancer, breast cancer, renal cell carcinoma and non–small-cell lung cancer (NSCLC).[10-13] Notably, it has been revealed that

PRAME is absent in normal hematopoietic tissues.[7,14] Nevertheless, some findings have uncovered that a high expression level of PRAME exists in acute and chronic leukaemia as well as in Hodgkin's lymphomas.[7,14,15] In addition, the expression level of PRAME is a prognostic biomarker for poor clinical outcomes in breast cancer and neuroblastoma.[16,17] However, the expression level of PRAME is associated with a better chemotherapy response and favourable survival in acute myeloid leukaemia (AML).[7,18] Therefore, the different roles of PRAME as an oncogene or a tumour suppressor gene in various malignancies may depend on the tumour types.

PRAME has been identified as a potential candidate for immunotherapy, eliciting a strong immune reaction in patients with AML, chronic myelogenous leukaemia (CML), acute lymphoblastic leukaemia (ALL) and melanoma.[19-22] Currently, the efficacy of anti-PRAME vaccines is being evaluated for PRAME-positive tumours in a clinical study.[23] Therefore, in this review article, we describe the role of PRAME in tumorigenesis. Moreover, we highlight whether PRAME might serve as a useful prognostic biomarker in numerous human cancers. Furthermore, we discuss whether PRAME might be a promising target for potential immunotherapy in human malignant tumours.

2 | ROLE OF PRAME IN CANCERS

2.1 | Breast cancer

Globally, there were approximately 2.1 million newly diagnosed cases of female breast cancer in 2018, accounting for a quarter of cancer cases in females.[24] The PRAME antigen is expressed widely among diverse breast cancer subtypes, including hormone-sensitive tumours.[25,26] Moreover, PRAME expression is involved in poor clinical outcome and is useful in conjunction with clinical parameters to predict breast cancer outcomes.[16,27] Notably, the expression level of PRAME is correlated with negative oestrogen receptor status, lower rates of overall survival and elevated rates of distant metastases.[28] It has been reported that PRAME could serve as a tumour-promoting factor in triple-negative breast cancer. Mechanistically, this phenomenon is due to the promotion of cancer cell motility through EMT-related gene reprogramming.[29] Moreover, Sun et al revealed that PRAME might be a biomarker candidate for breast cancer.[30] Controversially, another report revealed that PRAME inhibits the proliferation and metastasis of breast cancer cells, demonstrating that PRAME might be a tumour suppressor in breast cancer.[31] Thus, due to the limited research on the functions of PRAME in breast cancer, it is necessary to further determine the role of PRAME in the development and progression of mammary malignancy.

2.2 | Cervical cancer

Cervical cancer is responsible for 570 000 cancer cases worldwide, ranking fourth in incidence in 2018.[24] A study showed that overexpression of PRAME in HeLa cervical cancer cells leads to an apparent change in morphology.[32] Concomitantly, PRAME-transfected HeLa cells show cytoplasmic vacuolization and blebbing. Later, HeLa cells disintegrated into apoptotic bodies, suggesting that PRAME might act as a tumour suppressor gene in cervical cancer progression.[32]

2.3 | Haematological malignancies

Haematological malignancies comprise three major groups: leukaemia (acute leukaemia and CML), B and T/natural killer (NK) cell lymphomas, and plasma cell malignancy (multiple myeloma, MM).[33] Numerous investigations have shown that increased PRAME expression is associated with poor outcomes, drug resistance and disease progression in chronic leukaemia (CL), MM, Hodgkin's lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) patients.[34-37] For instance, in DLBCL patients treated with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (R-CHOP) therapy, higher expression of PRAME is associated with shorter overall survival (OS) and shorter progression-free survival (PFS) indicating that PRAME expression level might be a novel prognostic factor for DLBCL patients treated with R-CHOP therapy.[36] Additionally, PRAME is highly expressed in Down's syndrome-acute megakaryoblastic leukaemia (DS-AMKL) patients who are more likely to progress, but not in Down's syndrome-transient myeloproliferative disorder (DS-TMD) patients that are likely to self-regress. This suggests that PRAME might be a potentially ideal indicator for the distinction between DS-AMKL and DS-TMD cases.[38] Furthermore, it is well known that Wilms' tumour gene 1 (WT1) gene is a tumour biomarker for a wide variety of haematological malignancies.[39] Hence, the combination of these two tumour biomarkers might cover a broad range of patients with leukaemia.[40] Furthermore, malignant plasma cells from the majority of MM patients express MAGE-1, MAGE-3 and PRAME. However, polyclonal reactive plasma cells do not express any of these genes.[41] Another study found that expression of ETS-related genes (ERGs), ecotropic viral integration site-1 (EVI1) and PRAME could allow a greater distinction between AML and cytogenetically normal AML (CN-AML) patients, which could be useful for improving their individual prognostic significance and patient risk stratification.[42] In the CML cell line model, PRAME overexpression inhibits RAR-mediated cell differentiation, growth arrest and apoptosis. When the PRAME/RAR effect is blocked, CML cells can differentiate and undergo apoptotic death, even when CML is in the advanced phase.[8] Consistent with this finding, Tanaka et al found that PRAME expression is associated with cell cycle progression from the G0/G1 phase to the S phase.[43] Overexpression of PRAME also leads to the suppression of apoptosis and the blockade of erythroid differentiation in the CML cell line.[43] In support of the oncogenic role of PRAME, one report demonstrated that knockdown of PRAME could evoke the expression of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and increase the sensitivity of CML cells to imatinib, suggesting that PRAME may be associated with tumour progression via blockade of the TRAIL pathway.[44]

PRAME hypomethylation might lead to its increased expression in CML blast crisis and AML, resulting in an enhancement of

the oncogenic activity of PRAME.[4,5] Controversially, there are several reports showing that PRAME may be a tumour suppressor in haematological malignancies. One study uncovered that PRAME expression is associated with a better outcome in haematological malignancies such as AML and ALL.[42,45,46] It has been found that a high level of PRAME expression has a favourable prognosis in leukaemia, and PRAME overexpression increases leukaemia cell apoptosis and suppresses proliferation by downregulation of S100A4 and upregulation of p53.[47,48] Tajeddine et al indicated that overexpression of PRAME causes a decrease in the expression of heat shock protein 27 (Hsp27) and S100A4 at the transcriptional level, thus correlating with a better prognosis in leukaemia. In animal models, downregulation of PRAME induces tumour growth in leukaemia.[32] Altogether, the high expression level of PRAME could have a favourable prognosis in acute leukaemia.

Haematological malignances such as CML and AML as well as lymphomas could be vulnerable to control by the immune system, and effector T cells, which recognize minor histocompatibility antigens and tumour-associated antigens (TAAs) that are overexpressed in tumour cells, play a key role in this process.[49-53] PRAME is overexpressed in many haematological malignancies but is absent in normal tissues. Therefore, it may be a suitable candidate for T cell-mediated immunotherapy.[54] Strikingly, PRAME-specific cytotoxic T lymphocyte (CTL) lines induce high-avidity CTLs that do not affect normal hematopoietic progenitors, indicating that this could be valuable for immunotherapy of haematological malignancies with high expression of PRAME.[54] PRAME could be a potential target antigen for adoptive T-cell therapy and vaccination of patients with CML.[19] HLA-B62-restricted PRAME peptides are presented on adult T-cell leukaemia (ATL) cells, and CTLs induced by this peptide that were obtained from healthy volunteers were able to kill PRAME-positive ATL cells.[55] Moreover, the antigen receptors for hyaluronic acid-mediated motility (RHAMM), PRAME, M-phase phosphoprotein 11 (MPP11) and G250 might be candidates for immunotherapies of leukaemia patients. Because of their simultaneous expression, these antigens also constitute targets for polyvalent vaccines.[22,23] Therefore, CTLs in combination with peptide vaccines could maintain long-term immune surveillance. Similar to these reports, PRAME and other HL-associated CTAs might be useful for monitoring HL-directed immune responses or as targets for HL-specific immunotherapy.[56] Additionally, PRAME is highly expressed in chemoresistant HL cells, indicating that immunotherapy might be a promising approach for patients with chemoresistant HL.[57] PRAME-positive AML dendritic cells (DCs) are recognized by specific T cells, which might be a powerful tool for AML immunotherapy.[58] Several studies have shown that PRAME could be an attractive target for monitoring minimal residual disease (MRD).[59-61] On the other hand, patients with positive PRAME expression and MRD after hematopoietic stem cell transplantation (HSCT) treatment do not respond well to pre-emptive immunotherapy. Choosing appropriate interventions can further improve the clinical outcomes of PRAME- and MRD-positive patients.[62] One study found that epigenetic upregulation of PRAME by a demethylating agent could lead to increased expression of PRAME, suggesting that epigenetic regulators in combination with specific CTA can improve the effect of immunotherapy in patients with AML.[63] These results demonstrate that the PRAME protein could be processed by a demethylating agent and present on the cell surface of leukaemia cells and might be the target antigen for immunotherapy in leukaemia patients.

2.4 | Lung cancer

Lung cancer remains the primary cause of cancer morbidity and mortality worldwide, with 2.1 million new cases and 1.8 million deaths in 2018.[24] PRAME has been identified as an essential player in the development of NSCLC.[64] In NSCLC patients, it has been reported that higher levels of MAGE-A3 and PRAME expression are found in squamous cell carcinomas compared to adenocarcinomas, as well as in smokers compared to nonsmokers.[13] Similarly, another study reported that the expression of PRAME and MAGE-A3 is more frequent in NSCLC squamous cell carcinomas than in adenocarcinomas.[65] These results indicate that high expression of PRAME might be considered during the clinical development of antigen-specific cancer immunotherapy. PRAME expression is decreased in lung adenocarcinoma and lung bone metastasis tissues compared to normal lung tissues.[66] In addition, in vitro experiments revealed that downregulation of PRAME could promote the metastasis of lung cancer cells, suggesting that PRAME might play a key role in preventing the progression and metastasis of lung adenocarcinoma.[66]

Non–small-cell lung cancer patients treated with recombinant PRAME protein exhibit a humoral response and thereby stimulate CD4-positive responses and enhance anti-tumour activity.[67] The percentage of patients with PRAME-specific CD4-positive T cells at a dose of 500 μg of PRAME is higher than that at lower doses.[67] At the same time, it has been shown that the PRAME immunotherapeutic dose of 500 μg is a safe and clinically acceptable dose.[67] Similarly, PRAME-derived peptides trigger frequent specific T-cell responses in patients with lung cancer and are an appropriate candidate for targeted immunotherapy.[68] Moreover, in the adjuvant setting, the most relevant and promising vaccine directly targeting PRAME could be a potential therapeutic approach for NSCLC patients.[69]

2.5 | Melanoma

Melanoma is a common deadly cancer, with approximately 90 000 new invasive cases and approximately 10 000 deaths per year.[70] Increasing evidence supports the important roles of PRAME in melanoma tumorigenesis. It has been reported that PRAME is highly overexpressed in melanoma tumour samples and that PRAME is considered an immunotherapy target for the treatment of melanoma.[71,72] PRAME-positive status is significantly correlated with the largest basal diameter (LBD), tumour volume and worsening gene expression profiling (GEP) class in uveal melanoma (UM).[73] Two studies confirmed that PRAME is significantly associated with

an increased risk of metastasis in uveal melanomas.[74,75] In addition, one study confirmed that the prognostic accuracies of GEP and PRAME are superior to that of tumour-node-metastasis (TNM) staging in UM. Furthermore, GEP combined with PRAME enhanced the prognostic accuracy of the molecular prognostic model.[76]

One study revealed that downregulation of miR-211 triggered elevated PRAME expression in melanoma cells.[77] In addition, DNA methylation is negatively correlated with PRAME expression in melanoma cells. After treatment with a DNA methylation inhibitor, the expression of myeloid zinc finger 1 (MZF1) and PRAME significantly increases at both the protein and mRNA levels. Moreover, MZF1 promotes PRAME expression, leading to enhancement of the colony-forming capability of melanoma cells.[78] Because of the heterogeneous expression of CTAs including PRAME in human cutaneous melanoma, the DNA hypomethylating agent 5-AZA-dCyd could reverse the CTA-negative and weakly positive phenotype of different melanoma cells in tumour lesions, producing a group of tumour cells homogeneously expressing therapeutic CTA to be targeted by CTA-specific CTL.[79] Gezgin et al noticed that PRAME-specific T cells efficiently recognized UM cell lines expressing PRAME, suggesting that PRAME-directed immunotherapy might play a potential role in selected patients with metastatic UM.[72] Notably, in the phase I clinical study of melanoma patients, the PRAME immunotherapeutic approach using intramuscular injections of the recombinant PRAME protein with AS15 immunostimulant exhibits an acceptable safety profile and triggers similar anti-PRAME–specific cellular and humoral immune responses.[80]

2.6 | Ovarian cancer

In 2018, ovarian cancer was one of the most deadly malignancies in women, with 295 414 new ovarian cancer cases and 184 799 deaths.[24] PRAME expression is increased in ovarian cancer tissues compared with normal ovarian tissues.[81,82] For instance, PRAME is frequently expressed in epithelial ovarian cancer at the mRNA and protein levels due to demethylation of PRAME, and its DNA methylation level is inversely correlated with its expression.[83] Several possible tumour-associated antigens, mucin 1 (MUC1), MUC20, folate receptor 1 (FOLR1) and PRAME have elevated expression levels in all high-grade serous ovarian cancer cell lines.[84] Furthermore, PRAME expression is absent in mesothelial cells lining the peritoneal cavity and in the fibroblasts of ovarian cancer patients.[84] The expression level of PRAME is high in tumours from deceased patients, indicating that PRAME might act as a poor prognostic factor in patients with late-stage serous ovarian adenocarcinoma.[85] Consistent with this study, Partheen et al showed a similar result, in which PRAME expression is lower in ovarian cancer tissues from survivors compared with tissues from deceased patients.[86] However, one group found that the expression of PRAME was not significantly different between survivors and deceased ovarian cancer patients.[87] Thus, the different results of the two studies indicate that the function of PRAME needs to be further explored in ovarian cancer.

2.7 | Sarcoma

Sarcomas consist of more than one hundred diverse bone and soft tissue cancers that are rare and heterogeneous, accounting for approximately 1% of adult tumours and 15% of paediatric cancers.[88] The antigen PRAME is highly expressed in numerous types of sarcomas, such as synovial sarcoma, liposarcomas and myxoid/round cell liposarcoma.[89-92] Moreover, myxoid liposarcomas have higher levels of PRAME and NY-ESO-1 than other liposarcomas at both the transcriptional and translational levels. Their expression levels are positively associated with tumour grade and poor prognosis.[91] By microarray dataset analysis, hypomethylation of PRAME is observed in osteosarcoma (OS), which leads to an increase in PRAME expression contributing to OS progression, indicating that PRAME could be useful for cancer diagnosis and treatment.[93] Additionally, PRAME is homogeneously expressed in OS tissue, and knockdown of PRAME inhibits cell proliferation and colony formation and causes cell cycle arrest at G1 phase.[94] In addition, one study indicated that PRAME is one of the candidate antigens in Ewing sarcoma (EwS), but even under optimal conditions, EwS-associated antigens do not induce effective T-cell receptor (TCR)-mediated anti-tumour immune responses. Hence, TCR engineering strategies could provide a more effective means to manipulating T-cell immunity to target tumour cell elimination.[95] The expression of NY-ESO-1 and PRAME could be induced by 5-Aza-dC treatment in chondrosarcoma cell lines, including in cell lines with absent or almost undetectable expression.[96] These findings indicate that with adoptive immunotherapy following 5-Aza-dC treatment, NY-ESO-1/LAGE-1s and PRAME-specific CD8+ effector T cells can treat chondrosarcoma, which might be a promising way to treat patients with unresectable or metastatic chondrosarcoma.[96]

2.8 | Other tumours

An elevated expression level of PRAME is found in hepatocellular carcinoma (HCC), and patients with a higher level of PRAME expression have a poorer prognosis in HCC, indicating the potential for the use of PRAME as a biomarker for unfavourable prognosis in HCC.[97] Furthermore, PRAME expression is positively correlated with alpha fetoprotein levels, tumour size and American Joint Committee on Cancer (AJCC) clinical tumour stage in HCC.[97] Biologically, the decreased expression of PRAME inhibits cell growth and induces cell apoptosis by activating p53/B-cell lymphoma 2 (Bcl-2)-mediated apoptosis pathway and increasing p21 expression.[97] PRAME is also expressed at a high frequency in head and neck squamous cell carcinoma (HNSCC) cell lines and HNSCC tissues.[98] In addition, PRAME expression is positively associated with clinicopathologic markers of poor outcome in HNSCC,[98] and PRAME expression is always present in metastatic lymph nodes of HNSCC.[10] In addition, elevated PRAME expression is found in medulloblastoma (MB), and its higher expression indicates poorer prognosis in MB.[99] Further mouse modelling studies found that tumour growth could efficiently be controlled in MB by using genetically modified T

TABLE 1 Role of PRAME in human cancers

Cancer type	Function	Target	References
Breast cancer	Involved in poor survival and distant metastases; relates with negative oestrogen receptor status	N/A	16,27,28
Cervical cancer	Associates with cell apoptosis	N/A	32
Haematological malignancies	Inhibits cell differentiation, growth arrest and apoptosis; increases the sensitivity to chemotherapy; and promotes cell apoptosis and favourable prognosis	Inhibits RAR signal and TRAIL; promotes p53; and downregulates S100A4, HSP27 and p21	8,32,44,45
Lung cancer	Exhibits higher expression in squamous cell carcinomas lung cancer patients than adenocarcinomas	N/A	65
Melanoma	Associates with an increased risk of metastasis; enhances cell colony-forming capability	Promotes by MZF1 and inhibits by miR-211	74,75,77,78
Ovarian cancer	Exhibits higher expression in tumours from deceased patients, and its function remains unknown	N/A	85,86
Sarcoma	Associates with tumour grade and poor prognosis; inhibits cell proliferation and colony formation; and causes cell arrest at G1 phase	N/A	91,94
Other tumours			
Seminomas	Regulation of cell differentiation and pluripotency	Activates by SOX17	102
HCC	Correlates with alpha fetoprotein levels, tumour size, AJCC stage and poor survival prognosis; induces cell growth; and inhibits cell apoptosis	Inhibits p53/Bcl2 and p21	97
HNSCC, MB, prostate cancer and bladder carcinoma	Related to poor prognosis, but function remains unknown; associates with poor response to chemotherapy	Inhibits by miR-421	98,99,101,103

cells with a PRAME-specific TCR. PRAME-specific TCRs might represent an attractive novel approach for treating patients with MB.[99] A high frequency of PRAME expression is observed in salivary duct carcinoma (SDC) but not in normal salivary gland tissues, immune cells or stromal cells.[100] The high frequency and selective expression of PRAME in tumour tissues make PRAME a promising diagnostic biomarker for monitoring malignancy and might be an attractive target for cancer vaccination in SDC.[100] In prostate cancer, it has been uncovered that PRAME is one of the downstream targets of miR-421, and miR-421 binds to the 3′-untranslated region (UTR) of PRAME to inhibit the expression of PRAME.[101] One group revealed that PRAME acts downstream of SRY-box transcription factor 17 (SOX17) by repressing the regulation of germ cell differentiation and pluripotency in seminomas.[102] Additionally, it has been reported that PRAME expression is associated with a poor response to chemotherapy in bladder urothelial carcinoma patients.[103] These studies reveal that PRAME might be a carcinogenic gene and that targeting the PRAME oncoprotein might be a promising anti-cancer therapeutic strategy.

3 | CONCLUSION AND PERSPECTIVE

In summary, PRAME is not only expressed in the normal testis but is also widely expressed in numerous cancers. Moreover, PRAME can act as an oncogene or a tumour suppressor gene in different cancer types (Table 1). PRAME exerts its biological functions via regulation of its downstream targets, such as p53, p21, Bcl-2, TRAIL,

RAR, Hsp27 and S100A4 in human malignancies (Figure 1). Notably, PRAME is critical in the immunotherapy response and may be an attractive target for human cancer immunotherapy. Indeed, several clinical trials of PRAME immunotherapies have shown their safety and potent immune responses in melanoma, lung cancer and other advanced solid tumours.[67,80,104] Antigen delivery and target specificity might affect the efficacy of PRAME immunotherapy. In addition, we have described a number of modulators, such as demethylating agents, to improve the effect of PRAME-based immunotherapy in human malignancies.
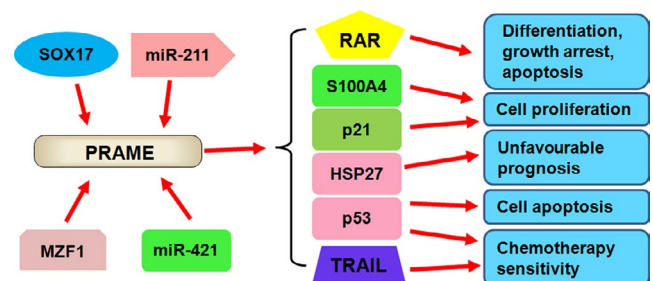
FIGURE 1 PRAME is regulated by upstream molecules and exerts its biological functions via the regulation of downstream targets in cancer. SOX17, MZF1, miR-211 and miR-421 regulate the expression of PRAME. PRAME exerts its biological functions via targeting p21, p53, RAR, TRAIL, S100A4 and HSP27, leading to the control of several cellular processes, including cell proliferation, apoptosis, differentiation, growth arrest and chemotherapy sensitivity

Although the function of PRAME has been discussed, there are still several remaining questions. For instance, what are the upstream signalling pathways that regulate PRAME? How does PRAME govern their downstream targets? What other innovative technologies can improve the effect of PRAME-based immunotherapy? To address these issues, we will need to use whole-body or tissue-specific knockout or knock-in mouse models that will help us determine the carcinogenic effects of PRAME in human cancers. Altogether, in-depth studies could contribute to the development of novel countermeasures and innovative technologies to target PRAME in immunotherapy for fighting human malignancies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Y.X. searched the literature and wrote the manuscript. R.Z. and J.W. made the figure and table. ZW.W. and X.Z. critically viewed, edited and approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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