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Review Article

The expression of cancer-testis antigen in ovarian cancer and the development of immunotherapy

Jianhang Zhao[1*], Zhaoxu Xu[1*], Yan Liu[2], Xiaobin Wang[3], Xinli Liu[4], Yanan Gao[1], Ying Jin[2]

[1]Department of Pharmacology, School of Pharmacy, China Medical University, Shenyang, Liaoning, China; [2]Liaoning Research Institute of Family Planning (Reproductive Hospital Affiliated to China Medical University), Key Laboratory of Reproductive Health and Genetic Medicine, National Health Commission of China, Shenyang, Liaoning, China; [3]Center of Reproductive Medicine, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China; [4]Medical Oncology Department of Gastrointestinal Cancer, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang, Liaoning, China. [*]Equal contributors.

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Abstract: Ovarian cancer is a relatively common tumor in women with the highest mortality among female reproductive system tumors. The lack of apparent early symptoms and effective screening strategies often leads to ovarian cancer being diagnosed at an advanced stage. Immunotherapy relying on tumor-associated antigens might improve the treatment of ovarian cancer. Cancer-testis antigens (CTAs) are ideal tumor-associated antigens, and MAGE-A, NY-ESO-1, CT45, and Sp17 are classic CTAs highly expressed in ovarian cancer. Here, we review the research on CTAs in ovarian cancer, including prognostic value and advances in immunotherapy, all of which are essential for developing a theoretical basis for targeted therapy strategies.

Keywords: Cancer-testis antigen, ovarian cancer, immunotherapy, MAGE-A/NY-ESO-1/CT45/Sp17

Introduction

Ovarian cancer is the seventh most common cancer among women and the eighth-most common cause of cancer death worldwide [1]. According to the latest model-based estimates issued by Cancer Statistics in the US, the estimated number of new ovarian cancer patients in 2020 was 21,750, and the death toll was estimated to be 13,940 [2]. Currently, treatment options for ovarian cancer are limited to surgery, radiotherapy, and chemotherapy. Due to the difficulty of achieving an early diagnosis, postoperative tumor recurrence, and late chemotherapy resistance, the 5-year survival rate of advanced ovarian cancer is less than 30% [3]. There is an urgent need for new treatment methods to prolong survival for these reasons.

Tumor immunotherapy restores normal antitumor immune responses by restarting and maintaining the tumor-immune cycle, thereby controlling and eliminating tumors [4]. Cancer vaccines rely on tumor antigens and use human-specific immune cells to recognize malignant cells with tumor antigens [5]. Immunotherapy targeting tumor antigens has emerged as an ideal option for immunotherapy in ovarian cancer. The effect of immunotherapy targeting tumor antigens depends on the high expression of these antigens and the specific responses of T lymphocytes to tumor antigens; suitable tumor antigens need to have these two characteristics [6]. Among the tumor antigens, the cancer-testis antigen (CTA) has significant immunogenicity and unique expression patterns in humans [4]. CTA is typically expressed in normal human testes, and a small amount of expression is also present in early developing embryos, placenta, and ovaries [7]. Several studies showed that CTA is overexpressed in various tumor types and is associated with tumor progression [7]. Because the testis is an immune-exempt area with low expression of human leukocyte antigen molecules, the specific expression patterns of CTAs suggest that they are ideal targets for tumor immunotherapy [8]. The development of CTA-based cancer-specific immunotherapy has been going on for many years, and some classic targets have

Table 1. Summary of clinical trials involving CTA that are completed or active

NCT NUMBER	INTERVENTION	PHASE	LAST UPDATE POSTED	SPONSORS
NCT03159585	NY-ESO-1-specific TCR Affinity Enhancing Specific T Cell Therapy	I	2020	Zhujiang Hospital Xiangxue Pharmaceutical (and more)
NCT01536054	ALVAC(2)-NY-ESO-1(M)/TRICOM vaccine	I	2020	Roswell Park Cancer Institute
NCT02650986	Autologous NY-ESO-1 TCR/dnTGFbetaRII transgenic T cells	I/II	2020	Roswell Park Cancer Institute
NCT03691376	Autologous NY-ESO-1-specific CD8-positive T Lymphocytes	I	2020	Roswell Park Cancer Institute, Buffalo, New York, United States
NCT02166905	DEC-205/NY-ESO-1 Fusion Protein	I/II	2020	Roswell Park Cancer Institute
NCT03017131	Genetically Engineered NY-ESO-1-specific T Lymphocytes	I	2020	Roswell Park Cancer Institute
NCT02042430	Epacadostat + cancer-testis antigen 1B	Early I	2020	National Cancer Institute (NCI)
NCT01567891	gene-modified T cells	I/II	2019	Adaptimmune
NCT00803569	ALVAC(2)-NY-ESO-1(M)/TRICOM vaccine	I	2019	Ludwig Institute for Cancer Research
NCT00112957	Recombinant Vaccinia-NY-ESO-1 and Recombinant Fowlpox-NY-ESO-1	II	2018	Ludwig Institute for Cancer Research
NCT00616941	NY-ESO-1 OLP4 peptide vaccine	I	2018	Ludwig Institute for Cancer Research
NCT03132922	Autologous genetically modified MAGE-A4^{c1g32}T cells	I	2017	Adaptimmune
NCT02015416	recombinant NY-ESO-1 antigen and the adjuvant GLA-SE	I	2017	Immune Design
NCT00623831	Mixed bacteria vaccine	I	2017	Ludwig Institute for Cancer Research
NCT00373217	MAGE-A1, Her-2/neu, FBP peptides ovarian cancer vaccine	II	2016	Craig L Slingluff, Jr National Cancer Institute (NCI)
NCT01522820	DEC-205/NY-ESO-1 Fusion Protein CDX-1401	I	2016	Roswell Park Cancer Institute
NCT01673217	NY-ESO-1 peptide vaccine	I	2014	Roswell Park Cancer Institute
NCT00066729	NY-ESO-1 peptide vaccine	I	2011	Memorial Sloan Kettering Cancer Center

been studied in-depth, including melanoma antigen family A (MAGE-A) [9], New York esophageal squamous cell carcinoma 1 (NY-ESO-1) [10], CT45 [11], and human sperm protein 17 (Sp17) [12]. In recent years, some CTAs associated with ovarian cancer have been reported, including TEX19 [13], POTE [14, 15], and HSP70-2 [16]. Many medications based on these targets are studied in clinical trials (**Table 1**). Effector T cells that specifically respond to CTA have been detected in patients with significantly improved survival [17, 18]. These results suggest the effectiveness of CTA-based tumor immunotherapy. This review aims to summarize the characteristics of the classic CTAs and discuss their expression in ovarian cancer, their prognostic value, and research progress in immunotherapy strategies.

Expression of classic CTA in ovarian cancer and research progress

The classical CTAs induce a robust immune response in several cancers. Their robust potential in the diagnosis, treatment, and outcome of ovarian cancer has garnered substantial attention. As a result, they have become the most widely studied classical CTAs.

MAGE-A

The MAGE-A subfamily of the MAGE gene family was the first classical protein identified as a CTA. It is encoded by genes located on the X chromosome (MAGE-A1 to MAGE-A12) [19, 20]. Similar to other CTA family members, MAGE-A is rarely expressed in normal tissues but is highly expressed in bladder cancer [21, 22], lung cancer [23], skin cancer [24], and other tumor tissues. These proteins show significantly high expression and strong immunogenicity in epithelial ovarian cancer (EOC) [20, 25, 26]. Schooten et al. reported that antigen peptides encoded by MAGE-A family genes are presented to T cells by MHC-I molecules of tumor cells through dendritic cells (DC) to activate effector T cells then exert specific anti-tumor activity [27]. These findings suggest that immunotherapy with MAGE-A is a promising therapy.

The expression of MAGE-A in ovarian cancer: Expression levels of MAGE in ovarian cancer have been studied. Daudi et al. used the reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry to measure the expression of MAGE-A in 400 EOC tissues and found that at least five MAGE-A

family members (MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A10, and MAGE-C1) are expressed in approximately 78% of EOC patients [28]. In particular, MAGE-A4 shows relatively high expression frequency and plays a central role in the co-expression of other MAGE-A antigens [29]. Another study showed that, compared with patients with benign diseases, serum levels of MAGE-A4 in ovarian cancer patients were significantly higher, and MAGE-A4 protein was expressed in nearly 22% of primary patients [30]. Yamada et al. reported that the frequency of MAGE-A1 mRNA expression in 58 ovarian cancer tissues was 20.7% [28]. Szajnik et al. reported that MAGE-A3/6 protein was present in all plasma-derived exosomes of ovarian cancer patients but not in benign tumors or healthy controls [31]. Hofmann et al. used multiplex RT-PCR analysis to measure BAGE, MAGE-A1, MAGE-A3, and GAGE1/2 mRNA in peritoneal fluid in patients with ovarian cancer. The combination of the four markers showed a 94% increase in diagnostic sensitivity for ovarian cancer compared to cell morphology alone [32]. Analysis of the Oncomine dataset revealed that MAGE-A is also co-expressed with other genes in EOC, including CT45 [33].

In summary, the expression of MAGE-A is tumor-specific. Compared with benign disease or healthy controls, MAGE-A is highly expressed in tissues and serum of patients. MAGE family members can be used as combined markers for early diagnosis. The high levels of MAGE-A expression in ovarian cancer allow researchers to investigate its value as an outcome predictor in ovarian cancer.

Correlation between MAGE-A and outcomes in ovarian cancer: Many studies reported significant correlations between CTAs and tumor progression and outcome, including for members of the MAGE-A family. Zhang et al. reported that the expression of MAGE-A1 and MAGE-A3 is related to the degree of tumor differentiation and clinical stage of ovarian cancer [34]. Daudi et al. found that, in EOC, the expression of MAGE-A1 and MAGE-A10 was significantly correlated with shorter progression-free survival [29]. Yakirevich et al. demonstrated that MAGE-A4 expression was present in 57% of high-grade serous ovarian cancer, and no staining was detected in serous cystadenoma or normal ovary. MAGE-A4 expression was negatively correlated with survival. Multivariate analysis showed that the expression of MAGE-A4 is an independent risk factor for outcomes; the authors believe that MAGE-A4 may be a reliable prognostic indicator for patients with serous ovarian cancer [35]. The expression of MAGE-A9 is closely related to the high histopathological grade, International Federation of Gynaecology and Obstetrics (FIGO) stage, CA-125 level, and metastasis of ovarian cancer. Patients with MAGE-A9 expression showed poor overall survival [36]. A study examined the prognostic significance of MAGE-A expression in patients with EOC and found that MAGE-A expression is related to the pathological type, FIGO stage, and preoperative serum CA125 levels. Compared with patients with EOC that are MAGE-A-negative, the overall survival of EOC with expression of the MAGE-A family was significantly shorter, consistent with previous findings [20]. Coincidentally, Sang et al. showed that the expression levels of each MAGE-A gene in the peripheral blood of ovarian cancer patients are associated with lower overall survival [26]. Consistently, Daudi et al. used enzyme-linked immunosorbent assay for MAGE-A antigen-specific antibody and found that the presence of humoral immune response against any MAGE antigen signals poor outcome [29].

These studies suggest that MAGE-A is highly expressed in EOC and affects the occurrence, progression, and outcome of epithelial ovarian cancer; for these reasons, MAGE-A has the potential to be a specific target for immunotherapy against ovarian cancer.

Research into MAGE-A in immunotherapy of ovarian cancer: Therapeutic tumor vaccines may be used to exploit CTAs to inhibit or delay tumor growth. After years of research, many therapeutic tumor vaccines have been developed and used, including protein or peptide vaccines, cell-based vaccines, DNA or RNA vaccines, and vector-based vaccines [27]. The MAGE-A protein family has attracted extensive attention in exploring CTA-based immunotherapy because of its expression characteristics. These antigens belong to a highly conserved proteome and share a common MAGE domain that is widely expressed in several tumors [37, 38]. A pre-clinical study showed that, among 15 genetically diverse and unrelated mice

immunized with the MAGE-A vaccine, 14 were induced to respond and develop a cross-reactive immune response. The MAGE-A DNA therapeutic vaccine significantly slowed the growth of tumors and doubled the median survival rate in mice. These findings support the clinical application of several MAGE-A family members to avoid tumor immune escape [39]. Because DCs are the primary antigen-presenting cells, and antigens presented by them activate T cells, many studies focused on peptide-incubated DC vaccines [40]. This therapeutic strategy has been used in clinical trials of the MAGE-A vaccine in melanoma [41-46] and some clinical trials of lung cancer [46-49], colon cancer [50], and myeloma [51]. However, there are few reports on clinical trials of targeted MAGE-A vaccines directly against ovarian cancer. As one of the most immunogenic MAGE-A proteins, the CTA vaccine targeted by MAGE-A4 is being evaluated in a clinical trial, and it targets a broad spectrum of cancers [52]. Batchu et al. used DCs transduced with rAAV-6 capsid mutation vector Y445F to induce MAGE-A3-specific anti-tumor cytotoxic T lymphocyte responses in vitro. This form of rAAV-based DC immunotherapy targeting MAGE-A3, whether used alone or in combination with other immune enhancement programs, may prove effective in treating EOC [53].

The DNA therapeutic vaccine and DC cell vaccine showed promising results. In recent years, clinical trials of MAGE-A targeted tumor immunotherapy has been widely carried out. There are ongoing clinical safety evaluations of T cell therapy in HLA-A2+ subjects with high MAGE-A4 expression and efficacy evaluations experiment of MAGE-A4 T cell therapy combined with low-dose radiation, including in patients with ovarian cancer [54]. In the future, MAGE-A will provide promising new opportunities to treat ovarian cancer.

NY-ESO-1

NY-ESO-1, also known as cancer-testis antigen 1B, is one of the members of the CTA gene family and is encoded by a gene from the Xq28 chromosome located in the coding region of other CTA (MAGE family members) [55, 56]. Chen et al. first described the significance of NY-ESO-1 as a tumor-associated antigen. In 1997, the authors used the cDNA of a patient with esophageal squamous cell carcinoma as an antigen in the patient's serum, then measured the humoral response and identified the corresponding antibody. They also measured the humoral reaction of the antigen in various tumors and found positive reactions in melanoma, ovarian cancer, breast cancer, and bladder cancer [10, 57]. Similar to MAGE-A4 [58], NY-ESO-1 can be identified in testicular germ cells at 18 weeks of gestation. In developing spermatogonia, NY-ESO-1 was identified as one of the nine genes upregulated during differentiation, suggesting its role in the clonal proliferation of spermatogonia [59].

The expression of NY-ESO-1 in ovarian cancer: The characteristics of NY-ESO-1 are like those of other CTAs. It is not expressed in normal tissues but is selectively expressed in testis and many malignant tumors [55], including melanoma [60, 61], lung cancer [62, 63], esophageal cancer [10], and ovarian cancer [64]. Odunsi et al. reported that about 50% of 107 EOC tissue samples expressed NY-ESO-1 or LAGE-1. NY-ESO-1 and LAGE-1 were co-expressed in 11% epithelial ovarian tumor tissue samples and SKOV3 cells [64]. Subsequent studies reported CTA analyses in many ovarian cancer patients and found that NY-ESO-1 was expressed in 41% of tumors [65]. Hurley et al. found that the combination of TRIM21 and NY-ESO-1 provided 67% sensitivity and 94% specificity; that is, TRIM21 and NY-ESO-1 can complement one another for screening women with genetic risk for ovarian cancer or for achieving an early diagnosis of ovarian cancer [66]. These results suggest that NY-ESO-1 is expressed in ovarian cancer patients and lays a foundation for studying the correlation between NY-ESO-1 expression and the occurrence, progression, and outcomes in ovarian cancer.

The correlation between NY-ESO-1 and outcomes in ovarian cancer: Szender et al. were the first to demonstrate the association between NY-ESO-1 expression and the malignant phenotype of invasive ovarian cancer. They reported that patients with positive NY-ESO-1 expression had more serous ovarian cancer tissue types and histopathological grade three tumor patients and higher stage and were less likely to achieve good responses to standard treatment. In patients with positive NY-ESO-1 expression, progression-free survival tended to be shorter, while OS was significantly shortened [65]. Although these data show that

the expression of NY-ESO-1 is related to malignant degree, the specifically related factors still have substantial research value: for example, it is unknown whether there is a correlation between the high expression of NY-ESO-1 and the age and gender of patients with ovarian cancer; it is also unknown whether there is co-expression of NY-ESO-1 with confirmed indicators of poor outcome; finally, it is unclear whether there is expression of NY-ESO-1 in patients with ovarian cancer before and after traditional treatment (surgery, radiotherapy, and chemotherapy).

Research progress of NY-ESO-1 in immunotherapy of ovarian cancer: Clinical trials of treatment strategies targeting NY-ESO-1 have been carried out in patients with ovarian cancer, and NY-ESO-1-specific immunotherapy has evident clinical benefits [67]. As expected, the NY-ESO-1-specific therapeutic vaccine-induced specific cellular and humoral immune responses in most NY-ESO-1-positive patients. Odunsi et al. reported that NY-ESO-1 with HLA-I and II dual-specificity can induce immune responses of complete antibody, HLA-DP4 restricted $CD4^+$ T cells, and HLA-A2/A24 restricted $CD8^+$ T cells in patients with ovarian cancer [68]. After seven years of clinical trials, these researchers reported encouraging results. The combined treatment strategy of decitabine and NY-ESO-1 vaccine stabilized the disease in patients with recurrent EOC or achieved partial clinical responses [69]. Decitabine may enhance the immune response to the NY-ESO-1 vaccine by promoting demethylation of the CTA promoter and enhancing immunity [70, 71]. The success of this regimen may supplement the standard second-line treatment strategy for EOC. Based on the mechanism of demethylation enhancing vaccine effect, Griffiths et al. reported that SGI-110 treatment-induced hypomethylation and CTA gene expression in a dose-dependent manner in vivo and in vitro was generally better than azacytidine or decitabine. There was enhanced expression of MHC-I and ICAM-1 and enhanced recognition of EOC cells by NY-ESO-1-specific $CD8^+$ T cells [72]. These findings suggest that SGI-110 is a candidate for combination with the NY-ESO-1-specific vaccine in EOC treatment.

NY-ESO-1 is an excellent tumor-associated antigen for immunotherapy (cancer vaccine) in clinical trials of immunotherapy for ovarian cancer. In addition to immunotherapy targeting NY-ESO-1, there is synergistic anti-cancer efficacy of NY-ESO-1 with known anti-cancer medications, and this has been confirmed in several medical institutions. There are promising results of NY-ESO-1 in phase I/II clinical trials, especially in ovarian cancer.

CT45

The cancer-testis antigen-45 family (CT45) is not expressed in normal tissues (except for the testis) but is abnormally expressed in many cancers [11]. Large-scale parallel signature sequencing and RT-PCR methods were used for screening and evaluation, and six genes with high similarity (>98% cDNA consistency) were obtained, including the CT45 family (CT45A1, CT45A2, CT45A3, CT45A4, CT45A5, and CT45A6) that is clustered in series in the 125 kb region of xq26.3 [73]. There are many reports of CT45A1. For example, when breast cancer was used as a research model, it was found that the overexpression of CT45A1 positively correlated with tumor invasion and metastasis [11]. Yang et al. reported that MAGE-D4B, CAGE, and CT45A1 promoted epithelial-mesenchymal transition (EMT) and metastasis via upregulation of EMT and metastatic genes [74]. These findings suggest that CT45 has a high research value as a potential cancer target.

The expression of CT45 in ovarian cancer: Chen et al. found that the expression of CT45 protein in tumors correlated with mRNA level detected by quantitative RT-PCR. The evaluation of CT45 protein expression on a variety of cancer tissue microarrays (376 cases of lung cancer, 219 cases of ovarian cancer, and 155 cases of breast cancer) showed that CT45 was expressed most frequently in ovarian cancer (37%), followed by lung cancer (13%), the lowest in breast cancer (<5%) [75]. Zhang et al. identified the co-expression of CT45 and other CTAs through analysis of the Oncomine data set; these genes include MAGE and GAGE [33].

The correlation between CT45 and outcomes in ovarian cancer: Koop et al. studied the biological functions of CT45 cells and found that the increased activity of CT45-positive cells was significantly associated with the progression of the disease [76]. Although the expression mechanism of CT45 in cancer has not yet been elucidated, the relationship between the

expression of CT45 and the development of ovarian cancer and survival has been studied by DNA methylation. After Zhang et al. determined the expression of CT45 in EOC, they defined the epigenetic regulation of CT45 through DNA methylation. Subsequent studies confirmed that, in EOC, CT45 promoter hypomethylation was associated with reduced OS, suggesting that CT45 expression and promoter hypomethylation may indicate poor outcomes in patients with ovarian cancer [33]. Coscia et al. used mass spectrometry-based proteomics and found that CT45 can be used as a marker for long-term survival in advanced metastatic advanced serous ovarian cancer after chemotherapy [77]. There remains controversy regarding the correlation between CT45 and outcomes in ovarian cancer, possibly related to disease state and other treatments.

Research on CT45 in immunotherapy of ovarian cancer: To improve long-term survival and outcomes in immunogenic tumors such as EOC, various anti-tumor vaccines are being developed. Chen et al. showed that the frequency and characteristics of CT45 expression are similar to other CTA cancer vaccine targets in clinical trials (i.e., NY-ESO-1 and MAGE-A) [75]. Other studies showed that decitabine treatment induces the expression of CT45 mRNA and protein in EOC cells, and promoter transgenic analysis showed that DNA methylation directly inhibits the activity of the CT45 promoter. These results suggest that decitabine or other epigenetic regulators might provide effective immune targeting for CT45 [33]. Coscia et al. found that CT45-derived HLA-I peptides using immunopeptideomics activated patient-derived cytotoxic T cells and promoted tumor cell killing [77].

Thus far, our summary suggests that cancer vaccines alone and in combination with anti-tumor medications can improve anti-tumor efficacy. Clinical research on NY-ESO-1 is currently relatively extensive. We can use this as a reference to expand the study of CT45 antigen as a tumor immunotherapy target and explore prospects for its clinical application.

Sp17

Sp17 is a highly conserved protein composed of 151 amino acids. It was initially isolated from rabbit epididymal sperm and testicular membrane sediments, and it has high interspecies homology [78-80]. It was initially thought that Sp17 was only expressed in the testis, and its primary function was to bind to the extracellular matrix of oocytes, allowing sperm to interact with the zona pellucida [81]. Some reports suggested that Sp17 participates in heparin sulfate-mediated cell adhesion or migration in transformed lymphocytes and heme cells [82]. Sp17 is highly expressed in ovarian cancer [83], head and neck squamous cell carcinoma [84], breast cancer [17], non-small cell lung cancer [85], multiple myeloma [86, 87], and other hematological malignancies [88]. These findings suggest that Sp17 may be a highly immunogenic autoantigen in humans and can be used as a target for anti-tumor immunotherapy.

The expression of Sp17 in ovarian cancer: Sp17 was first found to be highly specifically expressed in multiple myeloma. As research extended, Sp17 expression characteristics in ovarian cancer became more apparent [87]. Straughn et al. detected Sp17 transcripts in 15 of 18 cases of primary ovarian cancer (83%), while Sp17 transcripts were not detected in normal cervix or cervix. Sp17 protein was detected in eight of 19 normal sperm and 19 ovarian cancer tissue samples, primarily located in the nucleus with a small amount of cytoplasmic staining [89]. Li et al. showed that Sp17 was abnormally expressed in 43% (30/70) of patients with primary EOC and eight patients with cancer cell-containing ascites. Sp17 expression was also detected in metastatic lesions. In addition, the authors found that overexpression of HSp17 increased the ability of ovarian cancer cells to migrate [90]. These studies suggest that the expression of Sp17 in EOC tissues is increased and suggest that Sp17 is a potential biomarker of EOC.

The correlation between Sp17 and outcomes in ovarian cancer: Brunette et al. showed that Sp17 is not significantly related to the staging of ovarian cancer, it has a higher expression in benign and borderline serous tumors, and its expression further decreases as the cancer level increases [83]. The authors also analyzed the failure free survival and overall survival of 336 EOC patients and found no significant correlation between Sp17 expression and failure free survival or overall survival [83]. However,

small studies found that high expression of Sp17 reduced the chemosensitivity of EOC cells to carboplatin and cisplatin [90]. Sp17 is defined as a candidate gene related to chemotherapy resistance for clear cell adenocarcinoma. Downregulation of Sp17 significantly increased the sensitivity of ovarian cancer cells to paclitaxel [91, 92]. Although the overall outcome of borderline serous and low-grade malignant tumors is better than that of high-grade malignant tumors, they are also chemotherapy-resistant tumors, and it is difficult to treat them if they are not treated with complete surgical resection. Therefore, if there is an effective targeted therapy for Sp17, patients with positive expression of this protein may experience improved outcomes.

Sp17 in immunotherapy of ovarian cancer: Considering the characteristics and expression limitations of Sp17 protein itself, strategies for anti-ovarian cancer immunotherapy against Sp17 are also emerging. Gao et al. found that, compared with Sp17low (PD-L1^{-}MHCII^{+}) EOC cells, the Sp17high (PD-L1^{+}MHCII^{-}) EOC cell population showed significantly enhanced resistance to paclitaxel-induced cell death in vitro. This finding suggests that Sp17 can become a target of immunotherapy [92]. Chiriva-Internati et al. successfully produced HLA-I restricted CTLs from the peripheral blood of three patients with ovarian cancer that target and recognize Sp17. This specific CTL can cleave Sp17 positive autologous tumor cells by modulating the perforin pathway and secreting INF-γ and a small amount of IL-4 [12]. Sp17-conjugated CpG as a therapeutic and preventive vaccine can activate T cells in vivo and redirect inhibitory T-regs to the activated Th-17 phenotype. This vaccine strategy may achieve tumor control and increased survival in ovarian cancer patients [93]. Researchers constructed an antibody-drug conjugate (Sp17-doxorubicin) and found that it inhibited the activity of cancer cells and induced the regression of established SKOV-3 xenograft tumors in mice [94].

In the study of Sp17 immunotherapy, the application of tumor antigen epitope peptides received the most attention. Vermeij et al. used tissue microarrays to determine MHC class I and tumor antigens (including p53, Sp17, survivin, WT1, and NY-ESO-1) in 270 primary tumors tissue samples. In 74.3% of these primary tumors, the co-expression of MHC-I and at least one tumor antigen was observed. These results provide a research basis for multi-epitope anti-ovarian cancer immunotherapy [95].

In recent years, there have also been reports on methods for obtaining potential epitope peptides through big data analysis and screening with software such as the Pir Peptide Match program [96]. Xiang et al. confirmed the immunogenicity of six epitope peptides from Sp17 under the mode of epitope peptide-conjugated CpG and found that the epitope peptide from the 111-142aa sequence of hSp17 induced high levels of antibodies and T cells expressing IFN-γ. One tumor-bearing transgenic mouse treated with the corresponding drug experienced a significantly prolonged lifespan [97]. Mattila et al. optimized the dosage form and incorporated Sp17-derived antigen peptides and CpG oligonucleotides into spray-dried microparticles, administered in oral form. Analysis of spleen cells harvested from vaccinated tumor-bearing mice showed that the immune system responds to SP17 antigen re-stimulation, IFN-γ^{+}/CD8^{+} lymphocytes show strong activation. Four weeks after the tumor challenge, the administration group showed significant ascites/tumor volume reduction [98].

These studies demonstrate that immunotherapy based on Sp17 antigen focus on increasing immunogenicity, enhancing broad-spectrum, and increasing effectiveness. We focused on practical problems encountered in clinical application to optimize preparation and administration modes. Although no anti-ovarian cancer drug targeting Sp17 has entered the clinical trial stage, it can be expected that Sp17 will soon emerge as a target with excellent expression and immunological properties.

The relationships among these CTAs

Based on these four classic CTAs expressed in ovarian cancer, we conclude that expression of the four classic CTAs differ in expression patterns between patients with cancer and normal controls. Second, CTAs can be divided into X-CTA and non-X-CTA depending on whether CTA is located on the X chromosome. The four CTAs referenced above are all located on the X chromosome. It is unknown whether different

Table 2. The relationships between these CTAs

Species	Expression pattern	Positioning	Composition	Immune correlation
MAGE-A NY-ESO-1 CT45 Sp17	It is not expressed in normal tissues, but only in normal testis and a variety of tumor tissues	X chromosome	Often in the form of multiple family members	Cause cellular and humoral immune response

CTA localizations play different roles in ovarian cancer or predict different outcomes; however, the question is worthy of further study. Next, the four CTAs exist as multiple family members, and analysis shows that the frequency of expression differs among family members. Finally, the four CTAs induce cellular and humoral immune responses. Taken together, the evidence suggests that these CTAs can be used as tumor markers in ovarian cancer and may serve as targets for cancer vaccines (**Table 2**).

Relationship between newly discovered CTAs and ovarian cancer

With the development of cancer vaccine research, several new tumor antigens have been identified, including several kinds of CTA. Xu et al. found that knocking down TEX19 inhibited the proliferation, migration, and invasion of ovarian cancer cells. A peptide derived from the dominant epitope of TEX19 may serve as a target for an anti-tumor vaccine [13]. Gupta et al. showed that HSP70-2 promotes the proliferation, migration, and invasion of ovarian cancer cells. For the first time, it was found that ovarian cancer cells lacking HSP70-2 reduced cell motility due to low expression of EMT molecules [16].

The POTE family genes are divided into three phylogenetic groups, Group I (POTEA), Group II (POTEB1, B2, B3, C, and D), and Group III (POTE, F, I, J, KP, and M) [15]. Barger et al. found that POTE family genes (especially group III POTE members) are highly expressed in ovarian cancer tissues and are related to poor outcomes [14]. As new CTAs are identified as potential targets and biomarkers for cancer treatment, the means and methods for cancer treatment will be enriched. Regardless of whether it is used as a single-gene tumor antigen for cancer vaccines or as a combination therapy with other cancer treatments, CTA plays an essential role in treating ovarian cancer.

Discussion

Because ovarian cancer is usually diagnosed at advanced stages and has relatively high postoperative recurrence and metastasis rates, it is difficult to achieve satisfactory results using conventional therapy alone. In ovarian cancer, control of tumor cell growth and removal of residual tumor cells after surgery or chemotherapy remain critical subjects of future study. We urgently need effective treatment strategies (particularly tumor immunotherapy) to resolve this problem. Clinical trials have shown that tumor immunotherapy is effective for ovarian cancer, suggesting a direction for developing ovarian cancer treatment strategies in the future.

Although tumor immunotherapy is an excellent modality for treating ovarian cancer, there remain some problems for individual patients. MAGE-A, NY-ESO-1, CT45, and Sp17 are not expressed in all ovarian cancers. Furthermore, it remains unknown whether the expression of these antigens in ovarian cancer patients can trigger effective immune responses to eliminate tumor cells; it is also unknown whether there are more effective epitope peptides of MAGE-A NY-ESO-1, CT45, and Sp17 that can stimulate sufficient immune responses. To resolve these problems, we should continue to screen and develop other members of the CTA family with high expression in ovarian cancer to cover more ovarian cancer patients. We should develop highly efficient and low-toxicity epigenetic modifiers to enhance the immune effect of CTA vaccines. Improved use of big data and bioinformatics technology will result in the design of optimal candidate epitopes of MAGE-A, NY-ESO-1, CT45, Sp17, and other CTAs to significantly enhance the tumor-killing ability of CTL cells.

The role of cancer/testicular antigens in the development and etiology of ovarian cancer is

not yet clear. An in-depth study and explanation of the biological functions of these CTAs and the interaction between their mechanisms will lay a solid foundation for ovarian cancer immunotherapy with CTA as the target. At present, many research institutions are engaged in this research. Although the results are not completely satisfactory, we believe that immunotherapy will become an essential strategy for treating ovarian cancer in the future.

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Disclosure of conflict of interest

None.

Address correspondence to: Ying Jin, Liaoning Research Institute of Family Planning (Reproductive Hospital Affiliated to China Medical University), Key Laboratory of Reproductive Health and Genetic Medicine, National Health Commission of China, No. 10, Puhe Road, Huanggu District, Shenyang, Liaoning, China. Tel: +86-24-26112885; E-mail: 13998830123@139.com

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