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Review Article

Progress and prospects of the combination of BMI1-targeted therapy and immunotherapy in cervical cancer

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Abstract: Cervical cancer is one of the most prevalent gynecologic malignancies, posing a significant threat to women's health and survival. Despite advancements in early screening and diagnosis, which have led to cervical cancer being termed a "preventable" cancer, treatment options for advanced and recurrent cervical cancer remain limited. Consequently, identifying new therapeutic targets and treatments is crucial for advancing the research and management of cervical cancer. In recent years, targeted therapy and immunotherapy have become focal points in oncology research, offering new avenues and directions for the treatment of cancer. Preclinical studies have demonstrated that targeting BMI1 can inhibit cervical cancer progression, while immunotherapy has advanced to phase III clinical trials, showing promising results. To date, there have been no reports on the combination of BMI1-targeted therapy and immunotherapy in cervical cancer. This review, therefore, elucidates the current state of research and explores the potential and perspectives of combining targeted therapy with immunotherapy for cervical cancer.

Keywords: BMI1, cervical cancer, targeted therapy, immunotherapy, PTC596

Introduction

Cervical cancer, the most common malignant gynaecological cancer, is a major global health problem and a major cause of disability adjusted life years [1]. It mainly affects women in developing countries, and studies have found it to be associated with persistent infections with high-risk human papillomavirus (HPV) types. The prevention and early diagnosis and treatment of cervical cancer has developed rapidly due to the popularity of cervical cancer screening technology and the attention paid to the disease and the use of HPV vaccine nowadays [2]. The stage of cervical cancer at diagnosis strongly influences treatment approaches and outcomes for cervical cancer patients. According to statistics, the 5-year overall survival rate for all stages combined is 67%: 91% for early stage, 60% for locally advanced disease, and 19% for metastatic disease [3]. Therefore, the treatment of advanced cervical cancer and recurrent and metastatic cervical cancer has become a key and difficult issue in the treatment of cervical cancer.

With the recent approval of a PD-1 blocking antibody for recurrent or metastatic disease, immunotherapy offers a new method for cancer treatment. Clinical studies on cervical cancer have been conducted since 2015. The notable KEYNOTE-158 phase II clinical trial investigated the use of pembrolizumab as a monotherapy in cervical cancer [4]. Based on the results of this study, the FDA approved pembrolizumab for the treatment of cervical cancer [4]. With more and more in-depth research on immunotherapy for cervical cancer, immunotherapy has also become a second-line treatment strategy for replaced cervical cancer.

Recent years, more and more researches demonstrated that BMI1 significantly overexpressed in many cancers including cervical cancer. Targeting BMI1 in a variety of ways, including induction of autophagy-mediated necrosis, inhi-

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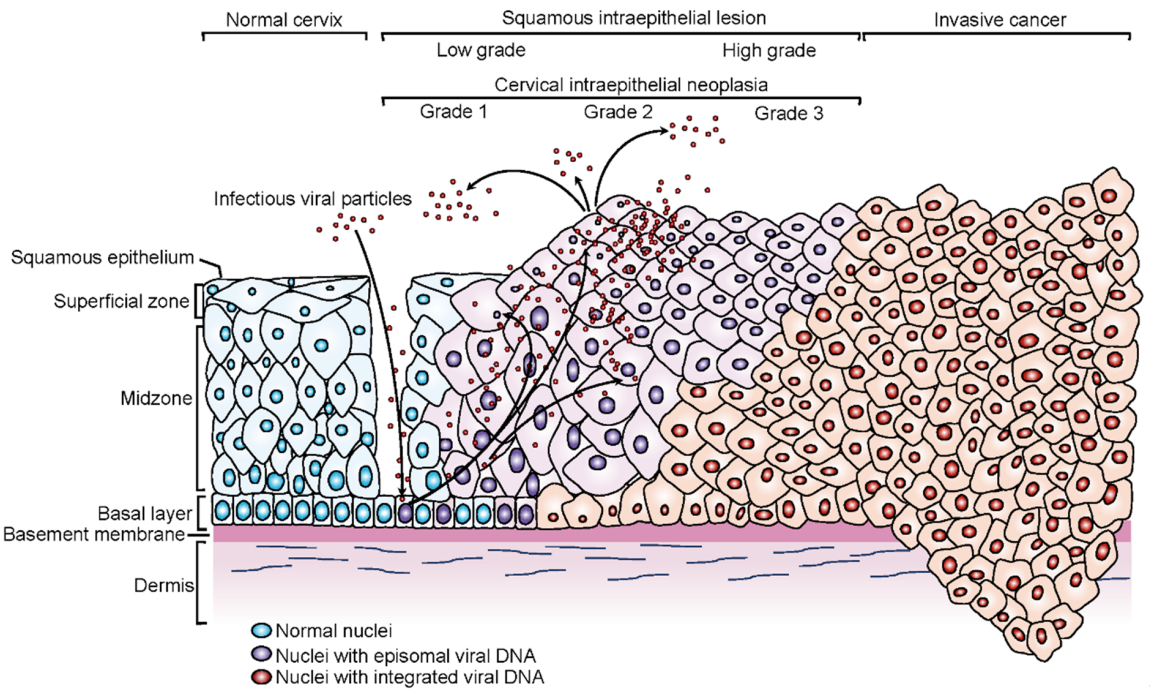

Figure 1. Schematic diagram of the pathogenesis of cervical cancer. Persistent infection of normal cervical epithelium with HPV causes the cervical epithelium to overexpress HPV oncoproteins E6 and E7, gradually leading to malignant transformation of the cervical epithelium.

bition of epithelial-mesenchymal transition and regulation of tumor immunoenvironment, dramatically reduces cancer proliferation and metastasis [5]. BMI1 expression levels are closely correlated with the histological grading of cervical cancer, and the inhibition of cervical cancer cell proliferation, colony formation, and lymph node metastasis [6]. And in other cancer research, BMI1 can enhance the infiltration and activity of CD8+ T cells in the tumor microenvironment, and improve the immunotherapeutic efficacy of PD-1 inhibitors, thereby preventing immune escape [7].

This review explores the potential synergistic effects of BMI1 inhibition and immunotherapy, with the goal of addressing existing therapeutic limitations. Addressing the intricate tumor microenvironment and resistance mechanisms of cervical cancer, this combined approach could provide more effective and sustainable treatment solutions for patients.

Current status of cervical cancer

Cervical cancer is the most prevalent gynecologic malignancy, ranking fourth among all female cancers, posing a significant threat to women's health and lives [8]. Over 500,000 women are diagnosed with cervical cancer annually, with over 300,000 deaths occurring globally each year [9]. Most cervical cancers are linked to persistent infections with high-risk HPV types, such as 16 and 18. HPV screening and vaccination programs have become effective strategies for cervical cancer prevention [10]. Persistent high-risk HPV infection causes cervical epithelial cells to overexpress the oncoproteins E6 and E7, which inhibit the tumor suppressors p53 and Rb, respectively, leading to the malignant transformation of cervical epithelium [11] (**Figure 1**). These oncoproteins also inhibit apoptosis, destabilize the genome, prevent telomere shortening, promote angiogenesis, and facilitate the invasion and metastasis of cervical cancer [12]. Squamous cell carcinoma and adenocarcinoma are the most common histological subtypes of cervical cancer, comprising approximately 70% and 25% of cases, respectively [13]. Despite advances in prevention, screening, diagnosis, and treatment over the past decade, significant regional and global disparities persist in cervical cancer treatment outcomes. These disparities prompted the International Gynecologic Cancer

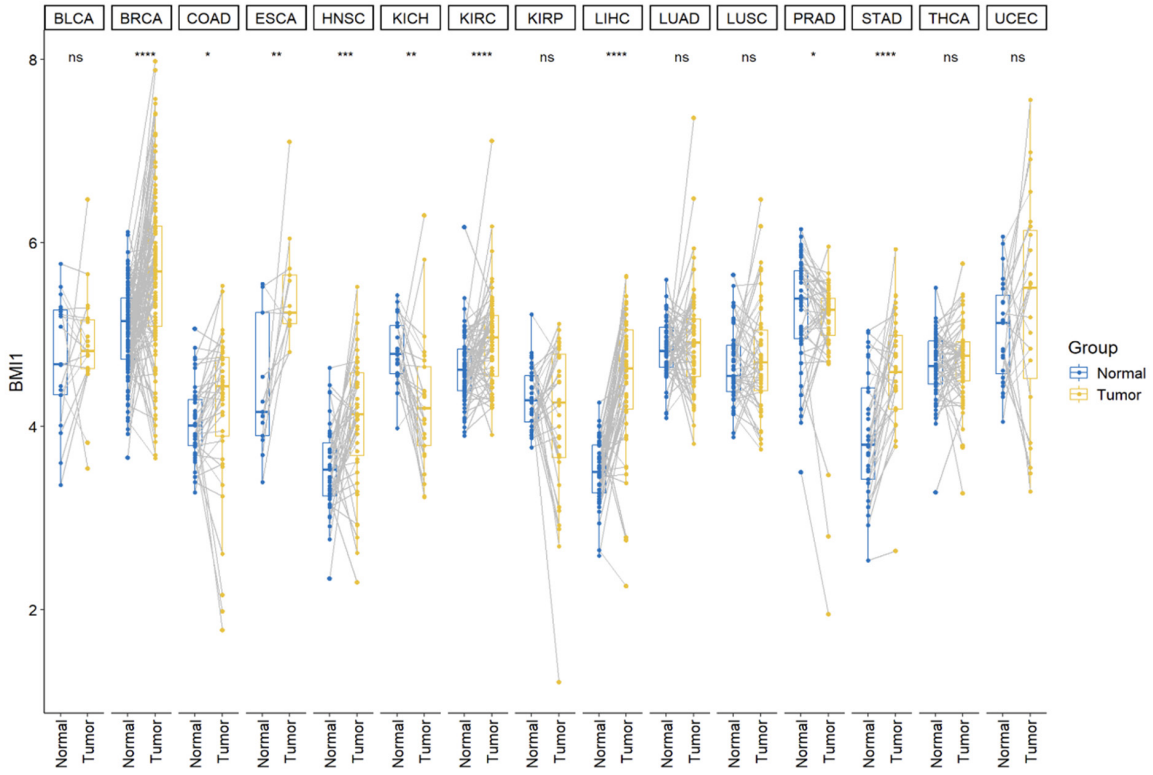

Figure 2. The expression of BMI1 in paired samples of cervical tissue from public databases (TCGA and GTEx).

Society to publish evidence-based management guidelines aimed at improving patient care quality [14]. The treatment of advanced and recurrent cervical cancer remains clinically challenging, prompting researchers to explore new therapeutic approaches.

Association between BMI1 and cervical cancer

Overview of BMI1

The B lymphoma Mo-MLV insertion region 1 homolog (BMI1) gene was first identified in 1991 by the Netherlands Cancer Institute in lymphoma cells. It is a core member of the Polycomb gene family (PcG) with oncogenic properties and is considered a proto-oncogene that collaborates with c-myc to drive cell transformation and tumor formation [15]. Research indicates that PcG proteins are pivotal in the epigenetic modification of chromatin and stem cell self-renewal, governing cell fate decisions, cancer development, and acting as crucial transcriptional repressors [16]. BMI1, a member of the Polycomb repressive complex 1 (PRC1) [17], has recently been recognized as a survival factor for tissue and cancer stem cells [18], influencing the expression of genes involved in cell growth, proliferation, apoptosis, senescence, and DNA repair [19-21].

Relationship between BMI1 and cervical cancer

BMI1 is reported to be highly expressed in various cancers, including glioma [22], head and neck tumors [23], non-small cell lung cancer [24], gastric cancer [25], prostate cancer [26], ovarian cancer [27] and cervical cancer [28]. Analysis of BMI1 expression in paired samples of cervical tissue from public databases (TCGA and GTEx) indicated that BMI1 expression levels were significantly higher in tumor tissue than in normal tissue (**Figure 2**). Although the expression level of BMI1 is not the highest in cervical cancer, it is higher than the most other tumors (**Figure 2**). High levels of BMI1 have been shown to promote cervical cancer development by binding to the E-Box region of the Sox2 promoter, leading to upregulation of Sox2, a tumor stem cell-associated transcription factor [28]. BMI1 expression levels are closely correlated with the histological grading of cervical

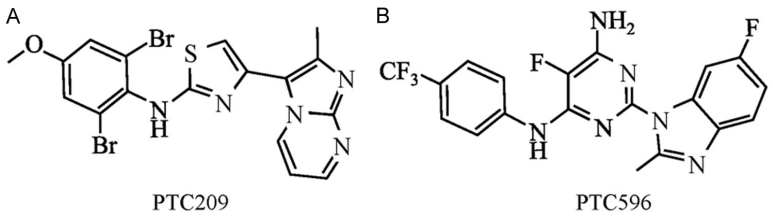

Figure 3. Molecular structure diagrams of BMI1 inhibitors. A. Molecular structure diagram of the first-generation inhibitor PTC209; B. Molecular structure diagram of the second generation inhibitor PTC596.

cancer, and the inhibition of cervical cancer cell proliferation, colony formation, and lymph node metastasis [6]. With the down-regulation of BMI1 expression level, the expression level of STAT3 and pSTAT3 was significantly decreased, which in turn reduced the expression of N-cadherin and Vimentin, leading to a reduction in the occurrence of epithelial mesenchymal transition in cervical cells from the transcriptional level [29]. Targeting BMI1-positive squamous cell carcinoma tumor stem cells has been shown to improve tumor resistance and inhibit tumor growth [23], suggesting that BMI1 could serve as a potential therapeutic target for cervical cancer treatment [30].

BMI1 inhibitor

There are several BMI1 inhibitors used in many rsearches, such as PTC209, PTC-209 HBr, PTC208 and PTC596. PTC-209 is a first-generation BMI1 inhibitor and is widely used in many oncology studies. PTC-209 HBr is the hydrobromide salt of PTC-209, a potent and selective BMI-1 inhibitor [31], and its function is same to PTC209. PTC-028 is a biologically orally active compound capable of reducing BMI1 levels through post-translational modification. Treatment with PTC-028 selectively inhibited cancer cells without affecting normal cells in clonogenic growth assays and cell viability assays. PTC-028 removes intracellular highly phosphorylated BMI-1 and leads to a transient decrease in ATP levels and impaired mitochondrial redox homeostasis, which further strengthens the caspase-dependent apoptotic response [32]. PTC596, also called unesbulin, is a second-generation BMI-1 inhibitor that accelerates the degradation of BMI-1. PTC596 is now in Phase II clinical trials as it is more biologically safe. In this review, we focus on the PTC209 and PTC596.

PTC209

In 2013, a research team developed the first-generation BMI1-selective inhibitor, PTC209, using high-throughput screening through a proprietary drug discovery platform technology called Gene Expression Modulation by Small-Molecules (GEMS) [19] (The molecular structure of PTC209 is shown in **Figure 3A**). PTC-209 inhibits UTR-mediated expression of reporter genes and endogenous BMI-1 in human colorectal HCT116 and human fibrosarcoma HT1080 tumor cells. And PTC-209 reduces the growth of rectal tumor cells dependent on BMI-1. In addition, PTC-209 damages tumor initiating cells by inhibiting their irreversible growth [19]. Subsequent studies have reported that PTC209 was effective in preclinical trials against various tumors, including colorectal cancer [33], breast cancer, bile duct cancer [34], glioma [35], prostate cancer [26], lung cancer [36], head and neck tumors [23], and cervical cancer [37]. Additionally, evidence suggests that PTC209 induces cell cycle arrest and apoptosis in cervical cancer cell lines [37].

PTC596

Compared to PTC209, PTC596, a second-generation BMI1 inhibitor (**Figure 3B**), is cell-permeable and promotes the degradation of BMI1 protein at nanomolar concentrations (as opposed to micromolar concentrations for PTC209) [38]. Furthermore, PTC209 has not yet entered clinical trials due to limited efficacy and poor pharmacokinetic properties, whereas PTC596, with a promising safety profile, has advanced to early clinical trials [39] (ClinicalTrials.gov Identifiers: NCT02404480, NCT03206645, NCT03605550, NCT03761095) (**Table 1**). Therefore, PTC596 shows greater effectiveness than PTC209 in cancer treatment.

PTC596 is a novel small-molecule inhibitor of BMI1, and recent studies have demonstrated its ability to inhibit cancer cell proliferation and promote apoptosis both in vivo and in vitro [40]. PTC596 effectively reduces the function, activity, and quantity of BMI1 through phosphorylation, accelerates BMI1 protein degradation, and subsequently inhibits BMI1-mediated sig-

Table 1. Ongoing clinical trials of PTC596

Clinical Trial Title	ClinicalTrials.gov Identifiers	Study population	Number of participants	Clinical Trial Phase	Treatment options
PTC596 in combination with dacarbazine for advanced smooth muscle sarcoma (LMS) participant study	NCT03761095	Locally recurrent, unresectable, or metastatic recurrent/refractory smooth muscle sarcoma	41	Phase 1B	PTC596 + Dacarbazine
Phase 1b study of PTC596 in children with newly diagnosed diffuse pontine glioma and high-grade glioma	NCT03605550	Diffuse pontine glioma and high-grade glioma	54	Phase 1B	PTC596 + Radiotherapy
Study of PTC596 in patients with advanced smooth muscle sarcoma	NCT05269355	Advanced smooth muscle sarcoma	345	Phase 2/3	PTC596 + Dacarbazine
PTC596 for patients with advanced solid tumors	NCT02404480	Advanced solid tumors	31	Phase 1	PTC596
PTC596 for women with ovarian cancer receiving neoadjuvant chemotherapy	NCT03206645	High-grade plasmacytoid ovarian cancer	27	Phase 1B	PTC596 + Carboplatin + Paclitaxel

naling pathways to reduce tumor growth in vitro, PTC596 preferentially targets chemotherapy-resistant tumor stem cells [38]. Studies on PTC596's inhibition of BMI1 function have so far been limited to lymphoma, acute leukemia, ovarian cancer, and glioma, but it has entered clinical trials for the treatment of advanced solid tumors, including advanced ovarian cancer. In phase I clinical trials, PTC596 was well tolerated by patients, with manageable gastrointestinal side effects (ClinicalTrials.gov Identifiers: NCT03206645). Recent studies report that PTC596 inhibits BMI1 expression in cervical cancer and promotes Mcl-1 degradation and apoptosis in HeLa (cervical cancer) and Caki (kidney cancer) cells by downregulating DUB3 levels, thereby inhibiting tumor progression [41].

BMI1 and tumor microenvironment

Tumor microenvironment

Definition and components of tumor microenvironment: The tumor microenvironment (TME) is a critical component of tumor development. The tumor microenvironment consists of not only the tumor cells but also the surrounding components, such as stromal cells, vascular endothelial cells, and associated immune cells, including tumor-associated fibroblasts, T cells, NK cells, macrophages, and B cells [42] (**Figure 4**).

Despite the complexity of the tumor immune microenvironment, the advent of single-cell sequencing technology has enabled a detailed dissection of its nature [43]. Understanding the fundamental role of the tumor microenvironment in cancer evolution has shifted the perspective from a tumor cell-centered view to the concept of a complex tumor ecosystem that supports tumor growth and metastasis [44].

Immune cells in the tumor microenvironment: Tumor-associated immune cells are generally classified into two categories: anti-tumor immune cells and pro-tumor immune cells, each playing distinct roles at various stages of tumor progression.

Anti-tumor immune cells primarily include effector T cells (CD8+ cytotoxic T cells and CD4+ effector T cells), Natural Killer (NK) cells, Dendritic cells (DCs), M1-polarized macrophages, and N1-polarized neutrophils, while tumor-promoting immune cells mainly comprise regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [45]. This discussion focuses on CD8+ cytotoxic T cells (CTLs). CD8+ CTLs have long been recognized as the primary lymphocyte subpopulation responsible for killing cancer cells presenting Major Histocompatibility Complex Class I (MHC-I) molecules [46]. Upon antigen presentation by DCs, CD8+ T cells can be induced to differentiate into cytotoxic effector CD8+ T cells [47]. Guided by chemokines secreted by DCs, such as CXCL9 and CXCL10, activated CTLs migrate into the inflammatory environment through the expression of CXCR3 [48, 49]. The interaction between ligands on DCs (CD70 and CD80-CD86) and receptors on CD8+ T cells (CD27 and CD28) is considered a critical step in CD8+ T cell activation [47].

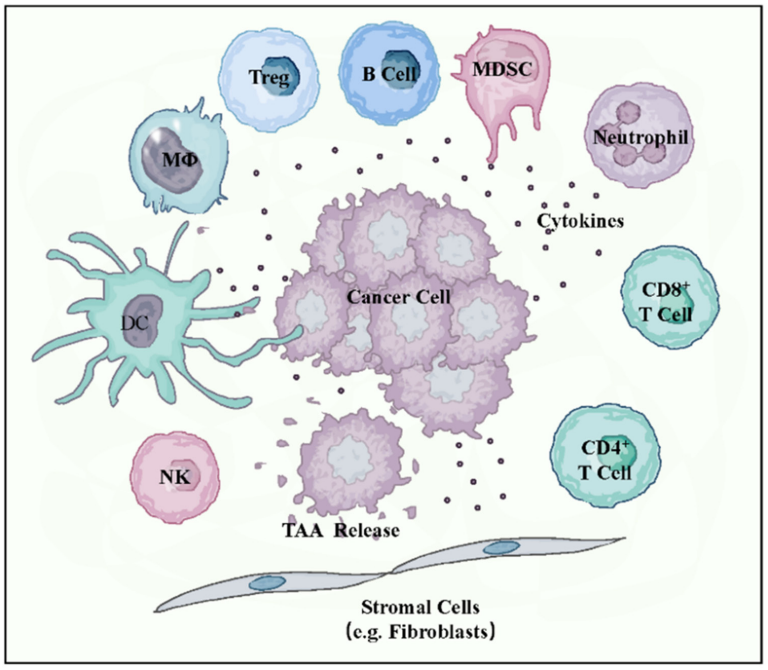

Figure 4. Tumor microenvironment pattern map. TAA: Tumor Associated Antigens; DCs: Dendritic cells; NK: Natural Killer. The tumor microenvironment includes immune cells, stromal cells, endothelial cells, and tumor-associated fibroblasts in addition to tumor cells.

Immune checkpoints: The activation and regulation of CTLs require two signals: one from the T-cell receptor (TCR) and the other from receptors known as immune checkpoints (ICs) [50]. Immune checkpoints are categorized into two types: suppressive checkpoints (e.g., CTLA-4 [51], PD-1 [52], TIM-3 [53], LAG-3 [54], TIGIT [55] and CD96 [56]) and stimulatory immune checkpoints (e.g., ICOS [57], OX-40 [58], 4-1BB [59], GITR [60], CD27 [61], HVEM [62], CD40L [63]).

Further research has revealed that in certain tumors, cancer cells inhibit CTLs by expressing programmed death-ligand 1 (PD-L1), which interacts with the inhibitory checkpoint receptor programmed death receptor 1 (PD-1), a key mechanism of immune escape in cancer [64]. Additionally, within the tumor microenvironment (TME), persistent antigenic and inflammatory responses can drive CTLs into a state of "exhaustion", resulting in T-cell dysfunction and promoting tumor development [65].

Programmed death receptors and programmed death ligands: Programmed cell death protein 1 (PD-1; also known as CD279) is a co-suppressor receptor expressed on the surface of activated T cells following antigen stimulation [66]. PD-1 interacts with two ligands: programmed death-ligand 1 (PD-L1; also known as CD-274) and programmed death-ligand 2 (PD-L2; also known as CD273). PD-L1 is typically found in tumor cells and tumor stroma, where it is highly expressed. Its binding to PD-1 alters T cell activity through multiple pathways, inhibiting T cell proliferation, survival, cytokine production, and other effector functions [67], thereby suppressing antitumor immunity. Currently, antibodies targeting the PD-L1-PD-1 axis are under evaluation in over 1000 clinical trials and have been approved by the Food and Drug Administration (FDA) for the treatment of melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), Hodgkin's lymphoma, bladder cancer, head and neck squamous cell carcinoma (HNSCC), Merkel cell carcinoma, and microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors [68].

BMI1 and tumor immune microenvironment

With in-depth studies of the tumor microenvironment, BMI1 has been found to regulate the immune microenvironment of tumors and play a significant role, and involved in the regulations of many immune cells, such as T cell. In multiple myeloma (MM), BMI1 regulates the pro-myeloma characteristics of tumor-associated macrophages (TAMs) [69]. BMI1 has also been reported to inhibit IL-10 expression in macrophages during the acute phase response induced by lipopolysaccharide (LPS) [70]. In pancreatic cancer, BMI1 inhibits antitumor immunity by reducing NK cell-mediated killing through the suppression of MHC class I chain-related protein A/B (MICA/B) expression. Additionally, the study showed that BMI1 suppresses GATA2 in pancreatic cancer cells, leading to the downregulation of MICA/B expression and ultimately promoting immune escape [71].

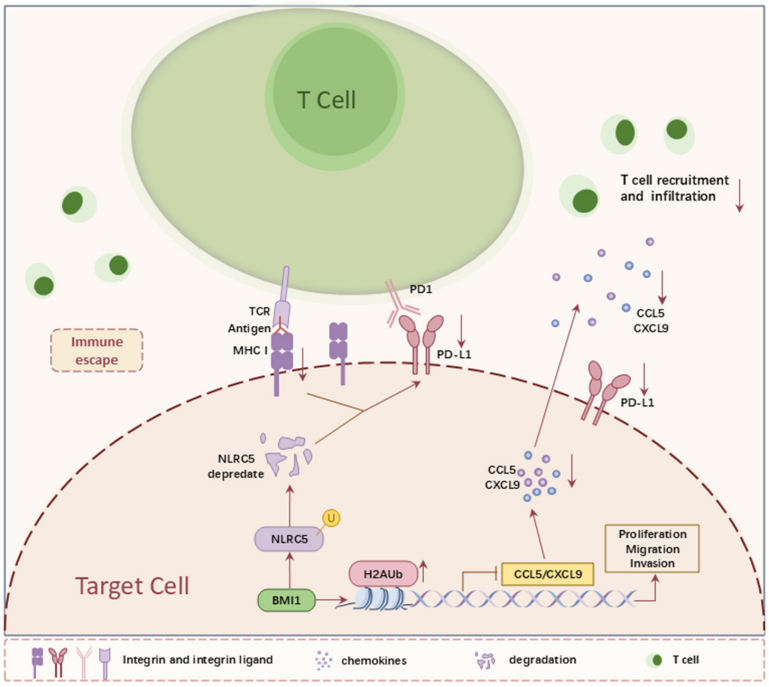

Figure 5. The diagram related to the potential mechanism of BMI1 regulating T cell function.

BMI1 is known to mediate gene silencing via H2AUb and to repress the expression of genes [72]. As the **Figure 5** showed that a research indicated that BMI1 inhibitors reduced the expression of H2AUb, thereby decreasing the transcriptional levels of CCL5 and CXCL9, further reducing the recruitment process of CD8+ T lymphocytes in cholangiocarcinoma (CCA) [73]. Furthermore, BMI1 maintains antigen-specific CD8+ T-cell clonal expansion during chronic viral infection, and BMI1 deficiency promotes senescence [74]. And another research indicated that BMI1 regulates the clonal expansion of T cells in the hepatocellular carcinoma (HCC) microenvironment by proteomic analysis of TIL fractions in two murine HCC models, followed by flow cytometry analysis [75]. In head and neck tumors, BMI1 inhibitors can target cancer stem cells (CSCs), enhance the infiltration and activity of CD8+ T cells in the tumor microenvironment, and improve the immunotherapeutic efficacy of PD-1 inhibitors, thereby preventing immune escape [7]. In addition, BMI1 induces ubiquitination and protein degradation of NLRC5 and suppresses HLA class I expression, and consequently inhibit T cell activation and increased PD-1/PD-L1 levels in the co-culture system, which potentially helps immune escape in non-small cell lung cancer (NSCLC) [76]. Therefore, BMI1 plays a regulatory role in the tumor immune microenvironment and contributes to tumorigenesis.

Current status of immune microenvironment and immunotherapy for cervical cancer

Characteristics of the immune microenvironment in cervical cancer

Cervical cancer cells evade the immune system by inducing an immunosuppressive state within their microenvironment [77, 78]. High-risk subtypes of human papillomavirus (hr-HPV), such as types 16 and 18, are more likely to persist and integrate into the host genome, resulting in the overexpression of oncoproteins E6 and E7 [79]. These oncoproteins downregulate key pathways that disrupt natural immune responses, including interferon production and the cGAS/STING pathway, and inhibit HPV antigen presentation via MHC class I molecules [80]. Additionally, HPV oncoproteins prevent regulatory transcription factor 9 (IRF9) from binding to phosphorylated STAT1 and STAT2, and inhibit STAT1 and STAT2 phosphorylation by interacting with tyrosine kinase 2 (TYK2), which in turn inhibits the IFN-α/β receptor (IFNAR) pathway, disrupting the positive feedback loop in virus-infected cells [81].

Intensive research on the immune system has identified the Jak/STAT signaling pathway as a critical communication hub [82], playing a pivotal role in cancer progression. In June 2018, the US FDA approved pembrolizumab, the first immunotherapy drug for the treatment of advanced and recurrent cervical cancer, based on the findings of the KEYNOTE-158 phase II clinical trial [4], marking significant progress in cervical cancer immunotherapy. In acquired immunity, signaling pathways such as Jak/STAT, PI3K, MAPK, and NF-κB are reported to be involved in the induction of PD-L1 expression by IFN-γ [83, 84]. The Jak/STAT signaling pathway is essential for PD-L1 expression and contributes to drug resistance [85] and as reported, it not only upregulates PD-L1 but also

influences tumor antigen expression [86]. Jak1 is crucial for IFN-γ-mediated immune responses and MHC class I/II expression, while Jak2 promotes IFN-γ-induced STAT5 phosphorylation and PD-L1 expression, thereby suppressing antitumor immunity [86]. In pancreatic cancer, gemcitabine upregulates PD-L1 expression via the Jak/STAT signaling pathway, leading to chemoresistance [87].

Tumor immunotherapy

Tumor immunotherapy treats cancer by enhancing the body's immune capacity to eliminate malignant cells, representing a major breakthrough in tumor research. Currently, immunotherapy is clinically employed to treat various cancers, including melanoma [88], non-small cell lung cancer [89], renal cell carcinoma [90] and triple-negative breast cancer [91], with notable efficacy, though the precise mechanisms remain unclear. Historically, immunotherapy has encompassed lysovirus therapy [92], cancer vaccine therapy [93], cytokine therapy [94], relay immune cell therapy [95] and immune checkpoint inhibitor therapy [96]. Adoptive cell transfer therapy and immune checkpoint inhibitor therapy have gained prominence in immunotherapy due to their superior clinical efficacy [43], with their success demonstrating that immune cells, particularly T cells, can effectively eliminate tumor cells. Immune cells form the cellular foundation of immunotherapy, making the understanding of immune infiltration in the tumor microenvironment crucial for enhancing immunotherapy responsiveness and developing new therapeutic strategies [97]. T cells have emerged as the focus of tumor immunotherapy research due to their potent tumor-killing capabilities [98]. T cell function is initiated by the binding of the T cell receptor (TCR) to major histocompatibility complex (MHC) molecules or human leukocyte antigens (HLAs) presenting tumor antigen peptides [99].

Immune checkpoints are molecules within co-suppressive signaling pathways between immune cells and target cells that maintain immune tolerance, but cancer cells often exploit these pathways to evade immune surveillance [88, 100]. The interaction between PD-1 and PD-L1 is the co-suppressive mechanism most commonly responsible for immune escape [101]. PD-1/PD-L1-based immune checkpoint blockade therapies have demonstrated significant efficacy across various tumors, but the emergence of drug resistance has posed a major challenge in immunotherapy, attributed to T cell dysfunction, impaired antigen recognition, and T cell exhaustion [102]. Consequently, many researchers have proposed combination strategies in immunotherapy to address these challenges. The combined application of radiotherapy and immunotherapy has demonstrated significant advantages in the clinical treatment of tumors. Immunotherapy can reduce radiotherapy resistance in non-small cell tumors, while radiotherapy can enhance immune infiltration and significantly improve patient prognosis [103].

Current status of research on immunotherapy for cervical cancer

Clinical studies on cervical cancer have been conducted since 2015. The notable KEYNOTE-158 phase II clinical trial investigated the use of pembrolizumab as a monotherapy in cervical cancer [4]. Based on the results of this study, the FDA approved pembrolizumab for the treatment of cervical cancer [4]. Another notable study is CheckMate-358, which investigated the use of nivolumab as monotherapy in cervical cancer patients [104]. These studies demonstrated that pembrolizumab and nivolumab exhibit antitumor activity in advanced/recurrent cervical cancer. Pembrolizumab's efficacy may be associated with PD-L1 expression as a potential predictive marker, whereas for nivolumab, positive PD-L1 expression was not a predictor of efficacy. Further studies with larger sample sizes are needed to validate these findings [105].

To expand and advance the indications, the pivotal phase III clinical trial KEYNOTE-826 evaluated the efficacy of pembrolizumab in combination with chemotherapy, with or without bevacizumab, for the first-line treatment of cervical cancer, regardless of PD-L1 expression status [106] (**Table 2**). The results, presented at the European Society of Medical Oncology (ESMO) Congress in 2021, marked the first phase III trial with positive outcomes for both progression-free survival (PFS) and overall survival (OS) as dual endpoints in first-line PD-1/PD-L1 treatment for cervical cancer, indepen-

Table 2. Ongoing phase III clinical trials with immune checkpoint inhibitors for the treatment of cervical cancer

Clinical Trial Title	ClinicalTrials.gov Identifiers	Study population	Number of participants	Clinical Trial Phase	Treatment options
Efficacy and safety of BCD-100 (anti-PD-1) in combination with platinum-based chemotherapy with or without bevacizumab as first-line treatment in subjects with advanced cervical cancer (FERMATA)	NCT03912415	Advanced cervical cancer	316	Phase III	Paclitaxel + cisplatin (or carboplatin)/ bevacizumab/BCD-100 (anti-PD1)
Efficacy and safety study of pablizumab (MK-3475) in combination with chemotherapy versus placebo in the first-line treatment of women with persistent, recurrent or metastatic cervical cancer (MK-3475- 826/KEYNOTE-826)	NCT03635567	Recurrent or metastatic cervical cancer	600	Phase III	Paclitaxel + Cisplatin (or Carboplatin)/ Bevacizumab/Pembrolizumab
Platinum chemotherapy plus paclitaxel with bevacizumab and atezumab for metastatic carcinoma of the cervix	NCT03556839	Recurrent or metastatic cervical cancer	404	Phase III	Paclitaxel + cisplatin/bevacizumab/ atezumab

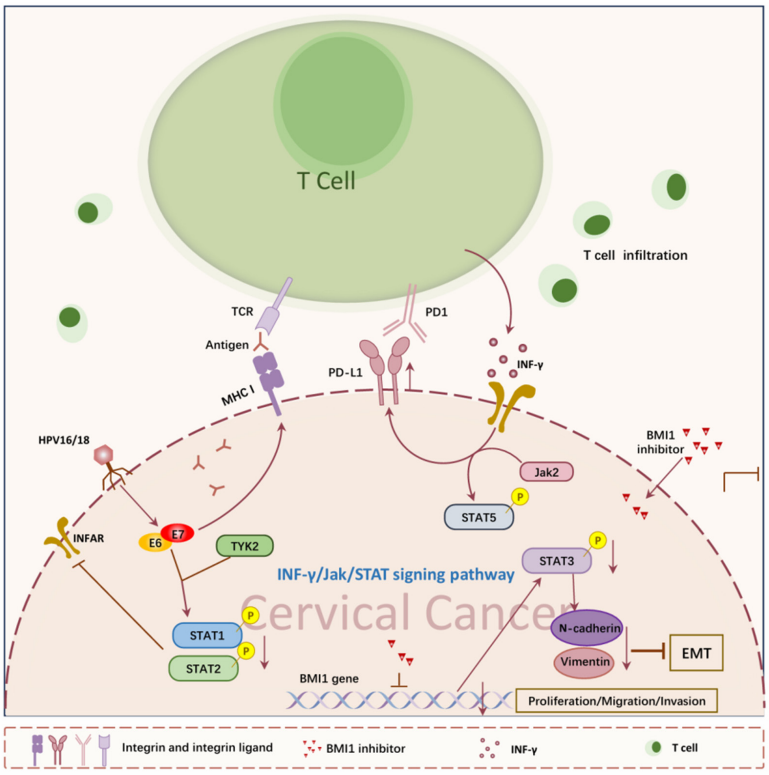

Figure 6. The diagram related to the potential mechanism of BMI1 inhibitor combining immunotherapy in cervical cancer.

dent of PD-L1 expression status [106]. The KEYNOTE-826 study demonstrated that pembrolizumab combined with chemotherapy, with or without bevacizumab, significantly improved OS and PFS in first-line patients with advanced metastatic cervical cancer, offering a reliable safety profile compared to placebo, regardless of PD-L1 status [106]. This regimen is anticipated to become a new standard of care for the first-line treatment of advanced recurrent and metastatic cervical cancer, marking a new chapter in the clinical management of this patient population.

Summary and outlook

Cervical cancer is the most common malignant tumor of the female reproductive system, with an increasing incidence rate, particularly among younger women, posing a significant threat to women's health and life. Clinically, managing advanced and recurrent cervical cancer remains challenging, as conventional treatments like surgery, radiotherapy, and chemotherapy are often ineffective. Thus, exploring new therapeutic targets and treatments for cervical cancer is crucial.

With advancements in molecular biology and genomics, targeted therapies and immunotherapies have become prominent research areas in cervical cancer treatment. Targeted therapy, often referred to as a "biological missile", specifically binds to defined oncogenic sites at the molecular level, killing tumor cells while sparing normal tissues, thereby improving efficacy and reducing toxic side effects [107]. Immunotherapy is a therapeutic approach that stimulates the host's immune system to actively or passively produce anti-tumor immunity through in vitro intervention. It has been used with remarkable success to treat various tumors, including melanoma, non-small cell lung cancer, renal cell carcinoma, ovarian cancer, and cervical cancer [108]. Targeting the BMI1 protein has been shown to inhibit the progression of cervical cancer, and immunotherapy for cervical cancer has also entered phase III clinical trials with promising results. And some researches showed that BMI1 inhibitor can influence the Jak/STAT signing pathway, which is critical pathway in cervical cancer immunoenvironment (**Figure 6**). Therefore, researching targeted therapy and immunotherapy methods can provide valuable data and insights for treating cervical cancer, particularly advanced and recurrent cases, and offer practical opportunities for prolonging patient survival and improving quality of life.

Disclosure of conflict of interest

None.

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