Cervical cancer immune microenvironment: Mechanisms of HPV-mediated immune evasion and advances in immunotherapy (Review)

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Abstract. Cervical cancer, strongly associated with persistent infection by high-risk human papillomaviruses 16/18 (HPV 16/18), remains a major global health burden. The tumor immune microenvironment (TIME) of cervical cancer plays a decisive role in tumor progression and therapeutic outcomes, where HPV oncoproteins E5, E6 and E7 disrupt antigen presentation, interfere with interferon signaling, activate immune checkpoints and induce metabolic reprogramming, thereby establishing an immunosuppressive TIME. Therapeutic advances, including immune checkpoint inhibitors (e.g., pembrolizumab in KEYNOTE-826, nivolumab in CheckMate 358), therapeutic vaccines and adoptive cell therapies, have shown promise but face challenges such as low response rates, resistance, stromal barriers and microbiome-related influences. The aim of the present review is to summarize the current understanding of the cervical cancer TIME, elucidate HPV-mediated immune evasion mechanisms, and to highlight recent advances and ongoing challenges in immunotherapy. Future directions include combination strategies, novel immune targets, and precision approaches integrating spatial multi-omics and microbiota modulation, which may improve immunotherapy efficacy and support personalized treatments for cervical cancer.

Contents

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1. Introduction

Cervical cancer, a major global health burden, is primarily driven by persistent high-risk human papillomavirus (HPV) infection, with HPV 16 and HPV 18 as key oncogenic drivers. According to the latest GLOBOCAN 2022 global cancer statistics, there were an estimated 662,301 new cases and 348,874 deaths from cervical cancer worldwide (1). Recent epidemiological reports have shown an increasing incidence among younger women, particularly those aged 30-44 years, with an annual rise of ~1-2% in certain populations (2,3). Although HPV infection is common, only a minority progress to malignancy, highlighting the crucial role of the tumor immune microenvironment (TIME), in determining disease outcome.

The TIME, comprising immune cells, cytokines, stromal elements and tumor cells (4,5), orchestrates tumor progression, immune evasion and therapeutic response. Although the TIME is influenced by stromal remodeling, cytokine signaling and microbial interactions, the present review primarily emphasizes HPV-mediated immune evasion and its implications for immunotherapy, while briefly covering secondary mechanisms. Recent advances, including spatial multi-omics and microbiome studies, have revealed novel insights into TIME heterogeneity and HPV-driven immunosuppression, offering novel therapeutic avenues (6,7).

Accordingly, the present review focused on three main objectives: i) To collate current knowledge of the cervical cancer TIME; ii) to clarify HPV-driven immune evasion mechanisms; and iii) to highlight progress, challenges and future prospects of immunotherapy. By prioritizing HPV-related immune dysregulation, the present study aimed to provide a focused and clinically relevant overview that may inform the development of personalized treatment strategies. In summary, the present review is organized into three major sections: First, an overview of the cervical

cancer TIME; second, the mechanisms by which HPV oncoproteins mediate immune evasion; and third, recent advances and remaining challenges in immunotherapeutic strategies. The novelty of this article lies in its comprehensive synthesis of HPV etiology, immune microenvironment remodeling and biomarker interactions, offering an updated perspective that bridges molecular mechanisms with therapeutic innovation.

2. Cervical cancer TIME: Architectural and functional features

Overview of the TIME. The cervical cancer TIME is a dynamic network of immune cells [such as T lymphocytes, tumor-associated macrophages (TAMs), natural killer (NK) cells and myeloid-derived suppressor cells (MDSCs)] (8), cytokines (such as IL-10 and TGF-β), chemokines and stromal components [such as cancer-associated fibroblasts (CAFs)] and tumor vasculature composed of endothelial cells and newly formed vessels. Recent advances in spatial multi-omics have revealed the heterogeneity of immune cell clusters and their spatial relationships with tumor and stromal cells, uncovering mechanisms of immune evasion and therapy resistance, including in cervical cancer (9-12).

Immune cell dynamics in the tumor microenvironment. The TIME hosts diverse immune cell populations with distinct antitumor or protumor functions, thereby shaping disease progression and clinical outcomes (13,14). Cytotoxic $CD8^+$ T cells and NK cells mediate direct tumor elimination (15,16), whereas regulatory T cells (Tregs), TAMs and MDSCs promote immune evasion and tumor progression (13,16). Understanding the balance between these opposing forces provides the foundation for subsequent discussion on HPV-mediated immune escape and immunotherapeutic interventions.

T lymphocytes. $CD8^+$ T cells are cytotoxic effectors, but often display functional exhaustion characterized by programmed death-1 (PD-1) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) upregulation, resulting in impaired antitumor activity (17,18). $CD4^+$ subsets play dual roles: T helper (Th)1 cells enhance IFN-γ, Th2 cells promote immunosuppression and Th17 cells exert context-dependent effects through angiogenesis or T-cell recruitment (19). Tregs are elevated in cervical cancer and promote immune suppression through cytokines such as IL-10 and TGF-β, contributing to disease progression (20-22).

TAMs. Derived from circulating monocytes, TAMs polarize into M1 (antitumor) or M2 (protumor) subsets. In cervical cancer, tumor-derived cytokines favor M2 polarization, which supports angiogenesis, invasion and metastasis, and is linked to poor outcomes (23-26).

NK cells. NK cells contribute to immune surveillance, but their activity is impaired in cervical cancer through mechanisms such as indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan depletion, leading to reduced proliferation and cytotoxicity (27-29). Increased NK infiltration post-chemotherapy has been associated with improved prognosis.

MDSCs. Elevated levels of granulocytic and monocytic MDSCs correlate with tumor burden, recurrence and immune suppression, positioning them as potential biomarkers of progression (30-33).

Immunosuppressive mediators. Key cytokines and checkpoints reinforce immunosuppression within the TIME. IL-10 impairs antigen-presenting cell (APC) maturation and promotes M2 polarization (26,34). TGF-β suppresses the cytotoxic activity of $CD8^+$ T cells and NK cells, drives Treg differentiation, and contributes to stromal fibrosis, thereby restricting immune infiltration (35-39). VEGF facilitates aberrant angiogenesis and recruits Tregs and M2 TAMs, generating a hypoxic, tumor-promoting environment (40,41). PD-1 and its ligand, programmed death-ligand 1 (PD-L1), are overexpressed on T cells and tumor cells, respectively, leading to T-cell exhaustion and disease progression (42,43). These cytokines and checkpoint pathways collectively amplify the immunosuppressive network initiated by Tregs and exhausted T cells, further shaping the cervical cancer TIME. Additionally, stromal elements such as CAFs contribute to immune evasion by remodeling the extracellular matrix, secreting TGF-β and VEGF, which further enhance angiogenesis and immune suppression (44-46). Collectively, both cellular and stromal mediators cooperate to establish an immunosuppressive microenvironment that favors HPV persistence and cervical carcinogenesis.

3. HPV-mediated immune evasion mechanisms

Persistent infection with high-risk HPV relies on a coordinated set of immune evasion strategies orchestrated by the viral oncoproteins E5, E6 and E7. These proteins target multiple components of both innate and adaptive immunity, enabling viral persistence and promoting malignant transformation (47-49).

E5-mediated antigen presentation suppression. HPV E5 downregulates surface expression of major histocompatibility complex class I (MHC-I) molecules on infected keratinocytes, thereby limiting recognition by $CD8^+$ T cells while selectively preserving human leukocyte antigen (HLA)-C and HLA-E to avoid elimination by NK cells (47,50). Through these actions, E5 impairs immune surveillance during the early stages of HPV infection.

E6 and E7 interference with antiviral signaling. E6 and E7 disrupt innate immune recognition pathways that normally trigger antiviral responses. E6 promotes degradation of p53 and inhibits interferon regulatory factor (IRF)-3 and STAT1 signaling, thereby suppressing type I interferon production (49,51,52). E7 inactivates the retinoblastoma protein and downregulates the activity of interferon regulatory factors IRFs (IRF1 and IRF3), thereby suppressing antiviral gene transcription and impairing dendritic cell maturation (49,51,52). In addition, E7 blocks the stimulator of interferon genes (STING)-cyclic GMP-AMP synthase (cGAS) pathway, impairing cytosolic DNA sensing and further attenuating interferon-β production (51,52).

Cytokine and immune checkpoint modulation. HPV infection reshapes the local immune milieu toward an immunosuppressive phenotype. E6 and E7 upregulate the immunosuppressive

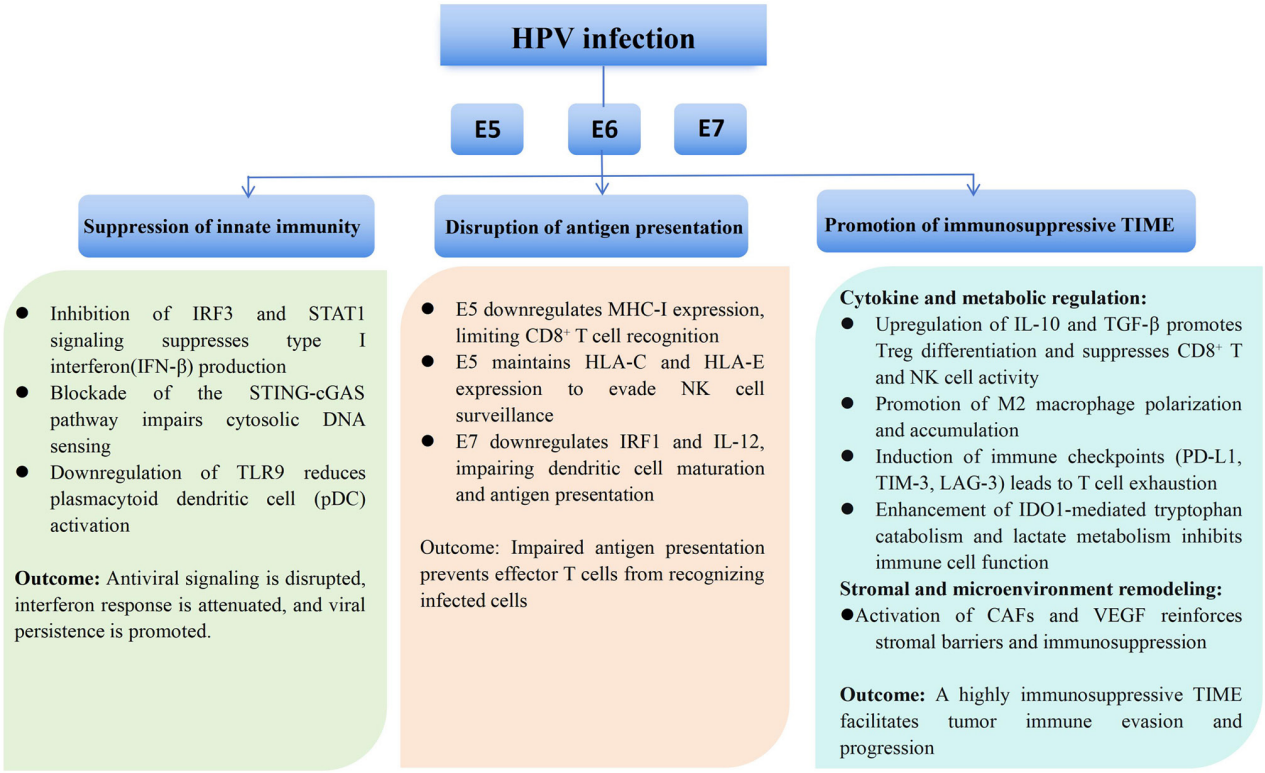

Figure 1. Mechanisms of HPV-mediated immune evasion in cervical cancer. HPV oncoproteins E5, E6 and E7 orchestrate multi-level immune evasion. E6 and E7 inhibit the IRF3, STAT1 and the STING-cGAS signaling pathways, suppressing type I interferon signaling. E5 downregulates MHC-I while maintaining HLA-C/E to avoid NK cells. E6 and E7 impair DC maturation and antigen presentation. Together, these oncoproteins remodel the TIME by upregulating IL-10, TGF-β and PD-L1, inducing Treg and M2 macrophage accumulation, enhancing IDO1-mediated tryptophan catabolism and promoting immune tolerance. Collectively, these processes establish an immunosuppressive TIME that facilitates viral persistence and tumor progression (38-49,64). IDO, indoleamine 2,3-dioxygenase; STING, stimulator of interferon genes; HPV, human papillomavirus; IRF3, interferon regulatory factor-3; cGAS, cyclic GMP-AMP synthase; MHC-1, major histocompatibility complex class I; HLA, human leukocyte antigen; NK, natural killer; PD-L1, programmed death-ligand 1; Treg, regulatory T cell; TIME, tumor immune microenvironment; pDC, plasmacytoid dendritic cell.

cytokines IL-10 and TGF-β, enhancing Treg differentiation and suppressing cytotoxic lymphocyte activity (53,54). E6 and E7 also induce PD-L1 expression on cervical epithelial and tumor cells, leading to T-cell exhaustion (55,56). These events synergize with the pre-existing immunosuppressive tumor microenvironment to sustain HPV persistence and drive immune escape.

To visualize these interrelated mechanisms, Fig. 1 provides an overview of HPV-mediated suppression of innate immunity, disruption of antigen presentation and promotion of an immunosuppressive tumor microenvironment.

Epigenetic and metabolic reprogramming. HPV infection induces widespread epigenetic alterations that contribute to immune evasion. Viral oncoproteins E6 and E7 interact with host chromatin modifiers, leading to DNA methylation and histone modification of key immune regulatory genes such as Toll-like receptor-9, cGAS and STING (57,58). These changes silence antiviral signaling and antigen presentation pathways, thereby reducing innate immune detection. In addition, HPV-driven methylation of the promoter regions of HLA and interferon-stimulated genes further impairs adaptive immune activation (59,60).

HPV also reprograms cellular metabolism to create a microenvironment that supports immune suppression and tumor growth. E6 and E7 upregulate glycolytic enzymes and enhance lactate production, leading to local acidification and inhibition of cytotoxic T lymphocytes and NK cells (61-63). Metabolic byproducts such as adenosine and kynurenine accumulate, engaging adenosine A2A and aryl hydrocarbon receptors on immune cells, which suppress effector T-cell function and promote Treg expansion (59,64). These metabolic shifts cooperate with cytokine and checkpoint-mediated pathways to reinforce an immunosuppressive milieu conducive to viral persistence and tumor progression.

In summary, HPV exploits multiple, interconnected mechanisms-including impaired antigen presentation, disrupted interferon signaling, epigenetic silencing and metabolic rewiring- to escape host immune surveillance and establish a chronically immunosuppressive tumor microenvironment.

4. Advances and challenges in immunotherapy

Immunotherapy has emerged as a promising approach to overcome HPV-driven immune evasion in cervical cancer. Building on advances in other malignancies, various strategies-including immune checkpoint inhibitors, therapeutic vaccines and adoptive cell therapies-have been investigated in cervical cancer, with encouraging but heterogeneous results (61,65,66). Despite notable progress, major challenges such as primary and acquired resistance, lack of robust predictive biomarkers, and the profound influence of the TIME

Table I. Current immunotherapy strategies for cervical cancer and key clinical outcomes.

Modality	Representative agent/strategy	Mechanism of action	Key trials	Clinical outcomes	(Refs.)
PD-1 inhibitor	Pembrolizumab	Blocks PD-1/PD-L1 interaction, restores T-cell activity	KEYNOTE-826 (NCT03635567, phase III)	ORR 80 vs. 68%; PFS 10.4 vs. 8.2 months; OS 28.6 vs. 16.5 months (pembrolizumab + chemotherapy ± bevacizumab vs. placebo + chemotherapy ± bevacizumab)	(67)
	Nivolumab	Blocks PD-1 signaling	CheckMate 358 (NCT02488759, phase I/II)	ORR 26% in pretreated patients; durable response in PD-L1-positive tumors (single-arm study, no control group)	(68)
	Cemiplimab	PD-L1 blockade	EMPOWER-Cervical 1 (NCT03257267, phase III)	OS 12.0 vs. 8.5 months; HR 0.69; ORR 16.4 vs. 6.3% (cemiplimab vs. investigator's-choice chemotherapy)	(69)
Therapeutic vaccine	VGX-3100 (DNA vaccine)	Plasmid DNA vaccine encoding HPV16/18 E6/E7 antigens; induces HPV-specific $CD8^+$ and $CD4^+$ T-cell responses	Phase II	Histological regression in CIN2/3; limited efficacy in advanced cancer	(64)
	GX-188E (DNA vaccine)	DNA vaccine encoding HPV E6/E7 fusion antigens to induce HPV-specific $CD8^+$ cytotoxic and $CD4^+$ helper T-cell responses via MHC-I/II pathways	Phase II	ORR 18%; enhanced with pembrolizumab	(60)
Adoptive cell therapy	LN-145 (TIL therapy)	Expansion of patient-derived TILs	Single-arm phase II (C-145-04, NCT03108495)	ORR 44% in heavily pretreated recurrent/metastatic cervical cancer; durable complete responses; median DOR not reached	(70)
	CAR-T/TCR-T cells	Redirects T cells against HPV antigens	Early-phase trials	Preliminary safety and immune activation; further efficacy validation required	(71,72)

HPV, human papillomavirus; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; CIN2/3, cervical intraepithelial neoplasia; TIL, tumor-infiltrating lymphocyte; CAR, chimeric antigen receptor; TCR, T cell receptor.

remain unresolved. The following section summarizes recent advances, highlights key clinical data, and discusses ongoing challenges and future perspectives.

Immune checkpoints inhibitors (ICIs). PD-1/PD-L1 inhibitors represent the most advanced immunotherapy for cervical cancer. The phase III KEYNOTE-826 trial (ClinicalTrials.

Table II. Predictive biomarkers for cervical cancer immunotherapy.

Biomarker	Mechanism/role	Clinical evidence	Limitations	(Refs.)
PD-L1 CPS	Indicates T cell inflamed TIME, predicts ICI benefit	KEYNOTE-826: Higher CPS improved ORR/OS	Heterogeneous expression; not fully predictive	(67,74)
TMB	High mutation load increases neoantigen presentation	FDA approval of pembrolizumab for TMB-high tumors	Rare in cervical cancer; cut-off values debated	(75)
MSI-H/dMMR	dMMR leads to the accumulation of neoantigens	Pembrolizumab active in MSI-H tumors (pan-cancer)	Very low prevalence in cervical cancer (<3%)	(76,77)
HPV genotype	Viral oncoproteins are immunogenic targets	Basis for vaccine/TCR therapy	Not all genotypes equally immunogenic	(75-77)
TIL density	Reflects host antitumor immunity	High $CD8^+$ TILs improved prognosis, improved ICI response	Variable assessment methods	(79)
Microbiome composition	Influences mucosal immunity and ICI response	Emerging evidence in gynecological cancers	Limited cervical-specific data	(73)

CPS, combined positive score; TMB, tumor mutational burden; MSI, microsatellite instability; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TIME, tumor immune microenvironment; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; FDA, US Food and Drug Administration; dMMR, defective mismatch repair; HPV, human papillomavirus; TIL, tumor-infiltrating lymphocyte; TCR, T cell receptor.

gov, NCT03635567) enrolled patients with persistent, recurrent or metastatic disease. In the PD-L1 combined positive score (CPS) ≥1 population, pembrolizumab combined with chemotherapy ± bevacizumab significantly improved clinical outcomes compared with placebo plus chemotherapy. Median progression-free survival (PFS) was 10.4 vs. 8.2 months (hazard ratio, 0.62), median overall survival (OS) was 28.6 vs. 16.5 months (hazard ratio, 0.60), and the objective response rates (ORR) were 80 vs. 68%, respectively (67). Similarly, the phase I/II CheckMate 358 trial (ClinicalTrials.gov, NCT02488759) evaluated nivolumab monotherapy in patients with recurrent or metastatic cervical cancer previously treated with platinum-based chemotherapy. In this single-arm study, nivolumab achieved an ORR of 26%, with durable responses observed in PD-L1-positive tumors (68). In addition, the phase III EMPOWER-Cervical1/GOG-3016/ENGOT-cx9 trial (ClinicalTrials.gov, NCT03257267) evaluated cemiplimab vs. investigator's-choice chemotherapy in patients with recurrent or metastatic cervical cancer who had progressed after platinum-based therapy. Cemiplimab significantly improved OS (12.0 vs. 8.5 months; HR 0.69, 95% CI 0.56-0.84; P=0.00011) and achieved a higher ORR (16.4 vs. 6.3%) compared with chemotherapy, representing another effective second-line immunotherapeutic option (69). While ICIs represent a major step forward, the ORR remains modest, and most patients eventually experience disease progression.

Therapeutic vaccines. Therapeutic vaccines targeting HPV E6 and E7 oncoproteins aim to induce tumor-specific T-cell immunity. DNA vaccines such as VGX-3100 and GX-188E have shown safety, immunogenicity and HPV-specific T cell activation in clinical studies, with VGX-3100 showing efficacy in HPV-related precancerous lesions (59,64). However, their effectiveness in advanced cervical cancer remains limited, highlighting the immune-suppressive TIME as a major barrier. Ongoing trials are exploring vaccine-ICI combinations to enhance antitumor activity (NCT04287868, NCT03946358, NCT06686043).

Adoptive cell therapy (ACT). ACT strategies, including tumor-infiltrating lymphocytes (TILs) and engineered T cells, have demonstrated encouraging activity in cervical cancer. In the phase II single-arm C-145-04 trial (NCT03108495), the TIL product LN-145 achieved an ORR of 44% in heavily pretreated patients with recurrent or metastatic disease, with durable complete responses and median duration of response not reached at 12 months (70). An early-phase trial of T cell receptor-engineered T cells targeting HPV16 E6/E7 antigens (NCT03356795) is underway, though efficacy and safety require further validation (71,72). ACT represents a promising option for refractory cases but faces challenges in manufacturing, cost and scalability.

A summary of key immunotherapeutic modalities, including checkpoint inhibitors, therapeutic vaccines and adoptive cell therapies, is provided in Table I to highlight their mechanisms of action, clinical trial status and efficacy outcomes.

Challenges and biomarkers. Resistance to immunotherapy arises from multiple mechanisms, including upregulation of alternative checkpoints (e.g., TIM-3 and lymphocyte-activation gene-3), stromal barriers formed by CAFs and dense extracellular matrix that limit immune cell infiltration, metabolic reprogramming (e.g., IDO1 and adenosine) and the immunomodulatory role of the vaginal microbiome (73). Predictive biomarkers for immunotherapy resistance, such as PD-L1 CPS (67,74), tumor mutational burden (TMB) (75), microsatellite instability and HPV genotype (75-77), have been studied, but none alone is able to sufficiently stratify patients. Emerging evidence suggests that integrated biomarker approaches-combining PD-L1, TMB and immune cell infiltration profiles-may improve prediction of patient responses and, therefore, guide precision immunotherapy (66,78-80).

HPV etiology and immunotherapy efficacy. HPV status strongly influences the tumor immune landscape and clinical response to immunotherapy. HPV-positive cervical cancers exhibit higher neoantigen load, increased $CD8^+$ T-cell infiltration and elevated PD-L1 expression compared with HPV-negative counterparts, features associated with improved responsiveness to ICIs (61,78). However, HPV genotype-specific differences exist: Tumors driven by HPV16 tend to show stronger cytotoxic immune activation and improved immunotherapy outcomes, whereas HPV18 and mixed infections are linked to a more immunosuppressive milieu characterized by abundant Tregs and M2 macrophages (65,81). Moreover, persistent HPV E6/E7 oncoprotein expression maintains chronic antigenic stimulation, which can both prime immune recognition and promote T-cell exhaustion (66). Therefore, integrating HPV genotype and viral gene-expression profiles into biomarker evaluation may refine patient selection and optimize immunotherapeutic efficacy.

To provide an overview of currently available and emerging biomarkers for immunotherapy response in cervical cancer, Table II summarizes their biological basis, detection methods and clinical implications.

Future directions. Future research should prioritize biomarker-driven precision immunotherapy. Rational combination regimens-including ICIs with therapeutic vaccines, ACT or oncolytic viruses- are under active investigation and may overcome resistance. Novel approaches such as bispecific antibodies, microbiome modulation and metabolic checkpoint inhibitors hold additional promise (82-84). The integration of spatial multi-omics technologies with immune monitoring will deepen understanding of TIME heterogeneity and inform the design of next-generation immunotherapies. Ultimately, translating these insights into rational, biomarker-guided strategies is key to improving durable benefit for patients with cervical cancer.

5. Conclusion and future perspectives

The present review highlights the central role of the cervical cancer TIME in modulating disease progression, with HPV oncoproteins E5, E6 and E7 orchestrating a multifaceted immune escape strategy. Advances in immunotherapy, particularly ICIs, therapeutic vaccines and adoptive cell therapies, have significantly reshaped the therapeutic landscape, yet their clinical efficacy remains limited to a subset of patients.

Key challenges include primary and acquired resistance, heterogeneous biomarker expression, stromal and metabolic barriers, and the influence of the vaginal microbiome. Future efforts should prioritize biomarker-driven precision approaches, combining PD-L1, TMB and immune infiltration profiles with emerging markers such as microbiome signatures and spatial transcriptomics. Integration of multi-omics technologies will allow for a more comprehensive understanding of the TIME and identification of novel targets.

Furthermore, rational design of combination regimens-including checkpoint inhibitor combinations, oncolytic viruses, bispecific antibodies and vaccines-represents a promising direction to overcome resistance. By emphasizing HPV-mediated immune evasion as a unifying framework, the present review provides a focused perspective that not only synthesizes existing knowledge but also highlights opportunities for innovation in personalized immunotherapy for cervical cancer. In conclusion, a deeper understanding of HPV-mediated immune evasion and the cervical cancer TIME will be essential to guide the development of next-generation, personalized immunotherapeutic strategies.

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Competing interests

The authors declare that they have no competing interests.

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