THE TUMOR IMMUNE MICROENVIRONMENT AS A KEY DETERMINANT OF DISEASE PROGRESSION AND THERAPEUTIC RESPONSE IN HPV-ASSOCIATED CERVICAL CANCER

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Abstract. This thesis synthesizes current concepts of HPV-driven immune remodeling across disease stages, highlights TIME features associated with progression and outcome, and discusses actionable translational strategies—including biomarker-guided immunotherapy combinations, microenvironment reprogramming, and multi-omics profiling—to improve responses and durability of control.
Keywords: cervical cancer; HPV; tumor immune microenvironment; immune evasion.

INTRODUCTION

Cervical cancer remains a paradigmatic infection-driven malignancy in which oncogenesis is tightly linked to persistent high-risk human papillomavirus (HPV) infection. In principle, the presence of viral antigens should render transformed cells visible to immune surveillance, making cervical cancer an attractive target for immune-mediated control. In practice, however, progression from cervical intraepithelial neoplasia to invasive carcinoma reflects a gradual, stepwise breakdown of effective anti-viral and anti-tumor immunity. This breakdown does not occur in isolation at the level of malignant epithelial cells; rather, it unfolds within a tissue ecosystem in which immune infiltration, stromal remodeling, vascular function, and metabolic conditions co-evolve with the tumor [1].

MATERIALS AND METHODS

A defining feature of HPV-associated cervical cancer is immune editing driven by chronic viral persistence. Early lesions can be infiltrated by cytotoxic T cells and antigen-presenting cells, yet persistent infection favors a local milieu in which HPV-infected epithelium avoids innate sensing and limits adaptive priming. Mechanistically, HPV oncoproteins (including E5, E6, and E7) can reduce the visibility of infected/transformed cells by interfering with antigen presentation and by dampening interferon-mediated alarm signals, thereby weakening both dendritic cell maturation and T-cell activation cascades. Over time, lesions that progress tend to accumulate

functional hallmarks of immune dysfunction—T-cell exhaustion, impaired antigen processing, skewed myeloid recruitment, and checkpoint dominance—suggesting that the TIME is not merely reactive but actively sculpted by viral and tumor programs [2].

RESULTS AND DISCUSSION

At the cellular level, the balance between effector immunity and suppressive immunity is a major determinant of progression. Tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, are often present but may exhibit exhausted phenotypes characterized by diminished cytotoxicity and reduced proliferative capacity. Meanwhile, regulatory T cells (Tregs) can expand and suppress local effector responses through IL-10, TGF-β, and contact-dependent inhibition. Myeloid populations frequently anchor immunosuppression: tumor-associated macrophages (TAMs) may polarize toward M2-like states that promote angiogenesis, matrix remodeling, and suppression of T-cell activity, while myeloid-derived suppressor cells (MDSCs) can inhibit T-cell function through arginase activity, reactive oxygen species, and immunosuppressive cytokines. A recurring theme in contemporary reviews is that HPV-driven lesions show a trajectory of increasing suppressive myeloid involvement alongside dysfunctional lymphocyte infiltration, aligning immune contexture with histologic and clinical progression [3].

Immune checkpoints represent a molecular “control panel” of the TIME, translating chronic antigen exposure and inflammatory signaling into restrained effector function. PD-1 expression on T cells and PD-L1 expression on tumor cells, macrophages, and other stromal elements can create an inhibitory synapse that reduces cytotoxic killing even when antigen recognition occurs. Beyond PD-1/PD-L1, additional inhibitory axes—such as CTLA-4, LAG-3, TIM-3, and TIGIT—may contribute to layered resistance, especially in settings where PD-1 blockade alone yields limited activity. The TIME also includes soluble mediators that reinforce checkpoint biology: TGF-β can exclude T cells from tumor nests and suppress effector differentiation; IL-10 can impair antigen presentation; and chemokines can selectively recruit suppressive subsets rather than cytotoxic effectors. Contemporary mechanistic syntheses emphasize that HPV oncoprotein activity is intertwined with these pathways, fostering checkpoint upregulation and a tolerogenic cytokine profile.

Future progress will likely hinge on two parallel advances: better measurement of the TIME and more precise intervention in its dominant suppressive circuits. On the measurement side, integrating digital pathology (quantitative TIL mapping), transcriptomic immune signatures, and spatial multi-omics promises a finer-grained classification of cervical tumors into immune-inflamed, immune-excluded, and

immune-desert states with actionable implications. On the intervention side, the priority is not simply "adding another drug," but selecting combinations that make immunologic sense—restoring antigen presentation, improving trafficking, reversing exhaustion, and neutralizing myeloid and metabolic suppression—while maintaining tolerability. In short, the TIME is becoming both the map and the target: it explains why progression occurs despite viral antigens, and it offers a structured way to design therapies that shift the balance toward durable immune control [4].

CONCLUSION

HPV-associated cervical cancer illustrates how oncogenic viruses can coexist with host immunity until the tumor microenvironment is rewired toward tolerance and immune escape. The tumor immune microenvironment determines whether immune cells can recognize tumor antigens, reach malignant niches, remain functional under metabolic and cytokine stress, and sustain cytotoxic pressure over time. As disease progresses, suppressive myeloid compartments, checkpoint dominance, stromal barriers, and interferon/antigen-presentation defects can converge to produce a functionally "cold" tumor even when viral antigens persist.

REFERENCES

1. Colombo N., Dubot C., Lorusso D., et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer // New England Journal of Medicine. – 2021. – Vol. 385, No. 20. – P. 1856–1867. – DOI: 10.1056/NEJMoa2112435. PubMed
2. Tewari K.S., Monk B.J., Vergote I., et al. Survival with Cemiplimab in Recurrent Cervical Cancer // New England Journal of Medicine. – 2022. – Vol. 386, No. 6. – P. 544–555. – DOI: 10.1056/NEJMoa2112187. PubMed
3. Manzo-Merino J., Del-Toro-Arreola S., Rocha-Zavaleta L., et al. Immunology of Cervical Cancer // Revista de Investigacion Clinica. – 2020. – Vol. 72, No. 4. – P. 188–197. – DOI: 10.24875/RIC.20000057. PubMed
4. Zhou X., An R., Li X., et al. Cervical cancer immune microenvironment: Mechanisms of HPV-mediated immune evasion and advances in immunotherapy (Review) // Oncology Letters. – 2026. – Vol. 31, No. 1. – Art. 22. – DOI: 10.3892/ol.2025.15375.