Review

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Beyond Viral Infections: The Multifaceted Roles of Human Papillomavirus and Epstein-Barr Virus in Shaping the Tumor Microenvironment

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The tumor microenvironment (TME) exerts a profound influence on the oncogenesis and progression of various cancers, notably those instigated by the human papillomavirus (HPV) and the Epstein-Barr virus (EBV). The etiology of HPV and EBV-associated malignancies is rooted in intricate interactions that intertwine viral infections, genetic predispositions, and distinct TME dynamics. These interactions foster a milieu that can either support or hinder tumorigenic progression. Gaining in-depth knowledge of the TME's unique features, including its cellular composition, cytokine profiles, and metabolic alterations specific to HPV and EBV-associated cancers, is fundamental to innovating more efficacious therapeutic strategies. This review delineates the intricate roles of HPV and EBV in shaping the TME and expounds upon the unique TME characteristics specific to HPV and EBV-driven cancers. Additionally, we spotlight innovative approaches to remodel the TME, aiming to augment therapeutic efficacy in combatting HPV and EBV-associated neoplasms.

Keywords: tumor microenvironment; human papillomavirus; Epstein-Barr virus; oncogenic interactions; therapeutic strategies; immune cell infiltration

Introduction

Infectious agents cause a certain fraction of human cancers. Indeed, viruses are estimated to be etiologic agents for nearly 12% of all human cancers reported [1]. The human papillomavirus (HPV) and the Epstein-Barr virus (EBV) are the most commonly identified viral types associated with malignant pathogenesis [2]. HPVs are small, double-stranded DNA viruses generally linked to epithelial and sexually transmitted cancers [3,4]. HPVs are broadly classified into low and high-risk groups depending on their oncogenic potential [5]. While the low-risk groups are linked to benign papillomas and warts [6], high-risk HPVs include nearly 17 HPV subtypes [7] and are associated with several malignancies [8,9]. Low-risk human papillomaviruses (LR HPVs) are responsible for developing anogenital or cutaneous warts, recurrent respiratory papillomatosis, and Heck's disease. On the other hand, high-risk human papillomaviruses (HR HPVs) are recognized for their capacity to promote the formation of tumors in the cervix, anogenital tract, and the mucosa of the head and neck [5,10].

Similarly, EBV belongs to a group of gamma-herpes viruses and is identified as one of the first oncoviruses to draw links with human carcinogenesis [11]. EBV infection is increasingly associated with several cancers [12–14]. Interestingly, in recent years, the co-infection of HPV and EBV has also been reported [15,16], implying their utilization of cooperative mechanisms in inflicting oncogenesis. Various prophylactic and therapeutic vaccines exist to tackle HPV/EBV-related disease [17]. However, such cancers' persistence indicates a poor understanding of the oncogenic mechanisms employed by these oncoviruses.

The E6/E7 oncoproteins and EBV-induced nuclear antigen 1 (EBNA1) protein and latent membrane proteins (LMP1/LMP2A/LMP2B) of HPV and EBV, respectively, are capable of modulating key molecular and cellular processes such as proliferation, migration, invasion and in-

flammation via the tumor microenvironment (TME) [2]. The TME comprises immune and stromal cells, blood vessels, and an extracellular matrix (ECM) that specifically regulates tumor progression, cellular migration and invasion, and metastatic spread [18]. The TME has been strongly implied in the prognosis of cancers and is significantly related to the patient's response to therapy and survival [19].

In oncology, delving deeper into the nuanced and complex mechanisms orchestrated by viruses such as HPV and EBV within the TME is critical in fostering the evolution of potent therapeutic strategies. These viruses function as powerful catalysts, instigating a myriad of alterations within the TME, thereby influencing the pathogenesis and progression of associated malignancies [20,21]. Thus, it is paramount to unravel the intricate interplay between these viral entities and the TME to facilitate the development of targeted and effective therapies.

In this review, we undertake a comprehensive exploration to accentuate the pivotal role and substantial impact of TME in the context of HPV and EBV-induced carcinogenesis. Through meticulous analysis, we seek to delineate the multifaceted mechanisms these viruses employ to modulate the TME, further highlighting their status as potent modulators with significant influences on tumor biology.

Furthermore, this review endeavors to illuminate the promising avenues in TME remodeling to optimize the therapeutic landscape for cancers associated with HPV and EBV. By focusing on the innovative approaches and potential strategies that can be employed to manipulate the TME beneficially, we aspire to pave the way for breakthroughs that could revolutionize the management and treatment of such malignancies.

HPV and Tumor Microenvironment

Role of HPV in Modulating Tumor Microenvironment

The TME has been divided into two general categories as a result of the use of cutting-edge "-omics" technology [22–25]. The first category is known as the cold non-T-cell-inflamed category [26,27]. In the tumor core of this type, there are no cytotoxic T lymphocytes (CTLs) or pro-inflammatory mediators. Instead, there are tumor-associated macrophages (TAMs), which are thought to impede CTL infiltration along the tumor margins [26,28]. Tumors of the second category are thought to be immunologically "hot" or T-cell-inflamed [26,27]. Large amounts of immune-damaging T-cell exhaustion markers, T-cell activation markers, and pro-inflammatory mediators are expressed by CTLs in this condition [26,29].

Depending on the virus, the TME in virus-associated cancer cases may be considerably changed [30]. For instance, some viruses can produce an inflammatory condition and have a long-lasting association with their host, which makes them highly important [31]. Persistent inflammation can activate a carcinogenic backdrop and cause tumor development [32]. It is important to note that viruses incorporating their genetic material into the human genome might lead to oncogene dysregulation and/or tumor suppressor gene inactivation [33].

Human papillomaviruses have been established as a pivotal etiological factor not only for all cervical cancers but also for a substantial fraction of other human malignancies [34–37]. While the majority of HPV infections are transient and resolve asymptomatically, with the immune system usually eradicating the virus, persistent infections with HPV pose a significant risk. Such chronic infections can induce dysplasia in epithelial cells, which may evolve into malignancies if left unchecked [38,39]. In the event of an HPV infection, a complex interplay ensues within the stratified epithelium. This communication begins with the virus's interaction with heparan sulfate proteoglycans, which are present on the cell membranes during the initial stages of keratinocyte infection. This interaction is crucial as it promotes the virus's engagement with components of the extracellular matrix. This engagement is not trivial; it facilitates the infected epithelial cells' ability to navigate through the stromal barrier, which can be thought of as the body's second line of defense [40,41]. Recent discoveries have shed light on the essential roles that matricellular proteins play. These proteins are more than mere structural elements of the TME; they are actively involved in the HPV life cycle and the progression of HPV-induced diseases [42]. Previously, the stroma's role was underestimated, regarded merely as a scaffold for epithelial cells, without recognizing its profound influence on cancer development. Modern research has shifted this view, acknowledging the crucial interactions between the stroma and HPV-infected epithelial cells in the process of oncogenesis [43]. One particularly promising research direction involves exploring the influence of stromal fibroblasts. These cells, fundamental to the connective tissue architecture, are often found near HPV-related lesions. They are instrumental in relaying critical signals that drive the development and progression of cancer, warranting further investigation [44]. Indeed, the interplay of signaling pathways between the stroma and epithelial cells is intricate and critical, highlighting the integral role of the microenvironment in the oncogenic narrative [45].

In the context of head and neck squamous cell carcinomas (HNSCC), smoking and binge drinking were once thought to be the primary risk factors. Yet, the paradigm shifted with the seminal work of Gillison *et al*. [46], which first linked HPV infections to the emergence of HNSCC. Current estimations attribute approximately 25% of all HNSCC cases to oncogenic HPV infections [47]. Furthermore, the tumor microenvironments of HPV-positive HNSCC are markedly different from those that are HPV-negative, a distinction that manifests in their respective molecular and cellular compositions [47,48]. This variance further under-

scores the significant role of HPV in the pathology of HNSCC and suggests that the TME could be integral to understanding the divergent prognoses and responses to therapy observed in HPV-related oncogenesis.

Compared to the more immunologically "cold" HPV TME, the HPV-positive HNSCC subtype exhibits a distinct immune phenotype diagnostic of the infiltrated-inflamed class of TME. This immune phenotype includes more significant immune infiltration, higher T-cell activation levels, and greater immunoregulatory effects [49–51]. The ongoing production of the E6 and E7 cancer-causing proteins in HPV-positive HNSCC may contribute to this distinct immunological phenotype [52]. It has been demonstrated that B-cells inside the TME of HPV-positive HNSCC develop antibodies particular for the E2, E6, and E7 HPV proteins [53,54]. Additionally, several studies have found that individuals with HPV-positive HNSCC possess $CD8^+$ T-cells with epitopes specific to the E2, E5, and E6 HPV proteins [55–57]. Increased immune cell activity against viral antigens in the TME may help tumor cells be recognized as foreign, boosting immune infiltration in HPV-positive HNSCC malignancies.

The TME of cancers infected with HPV is immunologically active. According to Atipas K. and colleagues, higher overall survival was associated with p16 expression and $CD8^+$ tumor-infiltrating lymphocytes (TILs) density in oropharyngeal squamous cell carcinoma patients [58]. However, another study reported that HPV-negative HNSCC patients have a stronger correlation between the ferroptosis signature and inflammation/immune activation than HPV-positive HNSCC patients [59]. The research identified a subset of ferroptotic HNSCCs with immune-active characteristics, suggesting the possibility of priming HNSCC with ferroptosis inducers to boost the anticancer efficacy of immune checkpoint inhibitors [59].

The development of anal squamous cell carcinomas (ASCC) is highly correlated with human papillomavirus infections, which affects between 70 and 90 percent of patients [60]. Gilbert *et al.* [61] found that HPV-positive patients may be further categorized for recurrence-free survival in ASCC using a TIL score, and they discovered a linear association between HPV-positivity and TIL infiltration. A substantial relationship was observed between programmed death-1 positive ($PD\text{-}1^+$) $CD8^+$ TILs in the tumor and the level of HPV-16 DNA was associated with a better prognosis [62]. Together, these findings support the idea that standard chemoradiotherapy (CRT) improves response and long-term outcomes in patients with HPV-positive ASCC and a high density of TILs. Thus, it appears that HPV infection causes an immunological reaction affecting primary CRT effectiveness.

It has gained widespread acceptance over the past 20 years that HPV-positive tumors are probably more amenable to chemoradiation regimens than HPV-negative tumors. While many patient-related factors, such as the tendency of HPV-oropharyngeal cancers to affect younger and healthier adults [63], can be correlated with increased patient survival, the biological pathways underlying HPV cancers also make tumor cells susceptible to DNA-damaging agents.

The efficiency of radiation is increased by reoxygenating the hypoxic TME during treatment. Compared to HPV-negative malignancies, it has been shown that hypoxic subpopulations are less common in HPV-positive tumors [64]. HPV oncogenes, which are necessary but insufficient for HPV carcinogenesis, may favor a less hypoxic phenotype [65]. In addition, hypoxia is known to suppress the expression of E6 and E7 in several cervical cancer cell lines. It is plausible that HPV-positive cancers have evolved to avoid severely hypoxic TMEs because viral oncogenes most likely need oxygen to maintain functioning levels [66].

Characteristics of the Tumor Microenvironment in HPV-Associated Cancers

A particular study [67] analyzed samples from ten different types of cancers to evaluate the characteristics of the TME in HPV-associated cancers. The study focused primarily on the immune-cell infiltration and the metabolic activity occurring within the TME of HPV-positive tumors. Accordingly, the study reported that differences in the TME mainly appeared in tumors expressing the highest levels of HPV oncoproteins (E6/E7) [67]. More specifically, the TME of HPV-positive tumors showed higher infiltration of B-cells and $CD8^+$ T-cells, particularly in head, neck, and cervical squamous cell carcinomas [68]. The elevated levels of immune cell infiltration in the TME of HPV-positive tumors may be a valid and interesting reason for a better prognosis of HPV-associated cancers compared to HPV-negative cancers.

Interestingly, this study [67] also reported a decrease in the stromal cells of HPV-positive tumors that have previously been linked to an improved prognosis of cancer patients [69,70]. Further, this report noted a marked decrease in the nucleotide, carbohydrate, vitamin and co-factor metabolism within the TME. Moreover, since these metabolic pathways have been previously linked [71] to a worse prognosis of cancers, this may be another reason for improved patient survival in HPV-associated cancers. Further, there is evidence that the TME of HPV-associated tumors may be rich in inflammatory infiltrate [72] (Fig. 1). Accordingly, tumors may be infiltrated by myeloid cells with a suppressor phenotype [37]. Interestingly, a particular study aimed to assess the pro-inflammatory characteristics of the TME and its ability to promote leukocytosis in HPV-associated cervical cancer [73]. Accordingly, clear differences were noted in the inflammatory infiltrate and cytokine expression profile among HPV-positive and HPV-negative cervical cancer [72]. Moreover, HPV-associated cancer cells showed higher expression levels of interleukin

6 (IL-6) and interleukin 8 (IL-8), as compared to HPV-negative cancer cells, which showed higher levels of interleukin 16 (IL-16) and interleukin 17 (IL-17). Moreover, the TME in HPV-associated cancer was shown to have a higher recruitment of leukocytes, accompanied by an increase in the myeloid cell proliferation within the bone marrow and spleen [73].

Furthermore, the TME in HPV-positive tumors is largely immuno-suppressive. In particular, HPV infection does not lead to cell lysis; instead, it promotes the release of new virions into the TME, thus preventing the presentation of viral antigens that would otherwise trigger immune responses [74]. In addition, the immuno-suppressed characteristics of the TME in HPV-positive cancers are also linked to the downregulation of the nuclear factor kappa B (NF-κB) pathway. Inhibition of this pathway permits evasion of the immune system facilitated by the binding of E6/E7 with the co-activators of NF-κB in the nucleus, thus also leading to persistent HPV infection [75]. In addition, processes like epithelial-mesenchymal transition (EMT) are largely known to influence the characteristics of the TME, regardless of HPV status [76]. EMT may be defined as the transformation of the tumor, whereby cells undergo a decrease in the epithelial phenotype and an increase in the mesenchymal phenotype [77]. To date, HPVs and EMT are known to share a dynamic relationship depending on the choice of biomarkers and molecules utilized to evaluate EMT [77].

Interestingly, flooding the TME with circulating tumor cells may also imply EMT. These cells are shed from the tumor into the TME and subsequently enter circulation, thus providing valuable assessments of cancer prognosis [78]. In line with this, a recent study [79] reported that EMT biomarkers like *SNAI1*, *SNAI2*, *CDH1*, *TWIST1*, and *ZEB1* were found to be downregulated in the circulating tumor cells of HPV-positive patients of head and neck squamous cell carcinoma as compared to HPV-negative patients. Finally, extracellular vesicles are also an essential component of the TME, where they serve as a carrier of nucleic acids, proteins and lipids [80]. Interestingly, the E6/E7 oncoproteins of HPV have been identified in extracellular vesicles regardless of the integration of the viral DNA into the host genome [81]. Other studies have stated that extracellular vesicles from HPV-positive tumors contain altered molecular cargo as compared to HPV-negative tumors [81,82]. In particular, the purpose of such cargo may be to equip tumor cells to evade the immune system and promote HPV infection through the diffusion of viral components to naïve cells [83]. Therefore, extracellular vesicles from HPV-infected cells permit the stealth transport of viral cargo to neighboring non-malignant cells via the TME.

EBV and Tumor Microenvironment

Role of EBV in Modulating the Tumor Microenvironment

EBV has a diameter of between 150 and 170 nm and is made up of roughly 170 kb of double-stranded DNA that contains more than 85 genes [84]. The viral genome regulates EBV infectious processes and plays a role in developing and manifesting EBV-related human illnesses [85]. The immuno-suppressed TME can be altered by EBV to facilitate cancer development [86,87]. Growing evidence shows that the microenvironment is crucial for the emergence of EBV-related cancers, and the intricate interactions between EBV and the TME are critical for maintaining the delicate EBV-host balance and developing EBV-driven tumors [88,89].

Recent single-cell sequencing identified complicated TME and cell-to-cell communication in nasopharyngeal carcinoma [90]. Chronic EBV infection affects the TME and reduces the immune-modulating properties of cancer cells [91–94] (Fig. 2). The host's immunity cannot identify and destroy EBV-positive tumor cells; thus, avoiding immune detection and T lymphocyte destruction promotes the host's immunological tolerance to EBV-positive tumor cells [95]. There are more $CD8^+$ T lymphocytes in EBV-positive malignancies than in EBV-negative tumors. EBV generates products that independently disrupt antigen presentation on human leukocyte antigen class I (HLA I) by inhibiting the production of HLA I molecules, preventing EBV-specific $CD8^+$ T lymphocytes from recognizing infected cells [96]. EBV-positive malignancies' peripheral blood and TME have shown significant accumulations of worn-out $CD8^+$ T-cells [97]. Similarly, $CD4^+$ $CD25^+$ regulatory T cells (Tregs) are attracted to and encouraged to infiltrate EBV-positive malignancies via EBNA1 and LMP1 [95,98,99]. LMP1 is a significant carcinogenic protein produced by EBV [100]. It has also been discovered that EBNA1 affects proteins in cells and pathways in various ways that could be crucial for viral persistence [101]. According to increasing evidence, myeloid-derived suppressor cell expansions caused by viruses that persist and initiate cancer may influence the immune microenvironment [102]. LMP1 increases and induces these cells in EBV-positive malignancies with potent immunosuppressive properties [103]. Even though natural killer (NK) cells are heavily recruited in EBV-positive malignancies, when EBV-infected cells reach the latency phase, their functions can be compromised to varying degrees [104]. In EBV-positive malignancies, EBV impairs NK cells' ability to fight tumors and subsequently promotes immune evasion [105]. B-cells are frequently present in EBV-positive malignancies, albeit less frequently than T-cells [106]. LMP1 can prevent B-cells from differentiating into cells that secrete antibodies, reducing immunological responses [107].

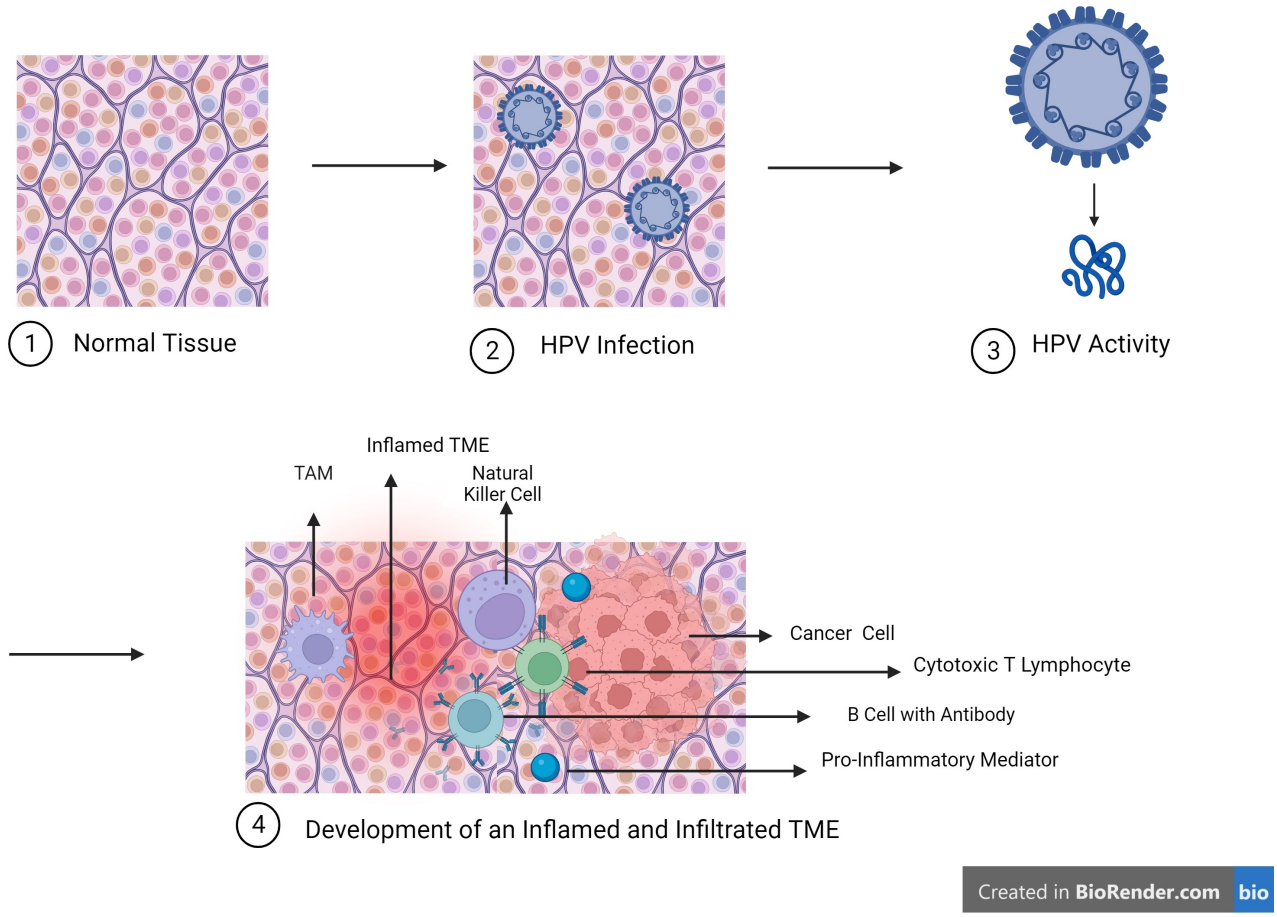

Fig. 1. Showing inflamed and infiltrated tumor microenvironment (TME) in human papillomavirus (HPV)-positive tumor. TAM, tumor-associated macrophage.

In addition to modulating the immune cells in TME, EBV also causes the local release of cytokines and chemokines that promote inflammation and depress the immune system [95]. The function of immune cells is also impacted by these abnormal soluble components, which creates a TME in which cells infected with EBV can multiply, avoid apoptosis, and survive the host's anti-tumor defense [108]. For example, IL-1β is reported to be overexpressed in EBV-positive malignancies [109]. Moreover, in EBV-infected cells, LMP1 can lead to increased tumor necrosis factor alpha (TNF-α) levels TNF receptor-associated factor 2, 5 (TRAF2,5) and the NF-κB pathway [110].

The interaction within the TME is enhanced by EBV's capacity to change the composition of extracellular vesicles, impact their release, and help to avoid the immune system [111,112]. A recent study showed that stromal interaction molecule 1 (STIM1) controls exosomal EBV-LMP1 distribution to endothelial cells in Nasopharyngeal carcinoma (NPC) TME to regulate tumor angiogenesis [113]. NPC pathogenesis and EBV infection are closely related, and the coexistence of EBV-infected NPC cells and TILs constitutes a unique, quite diverse TME that facilitates immune escape and encourages tumorigenesis [114]. Unique multicellular environments of EBV DNA Sero-negative and Sero-positive NPCs have been described from a single-cell perspective. Understanding the changed TME of NPCs linked to EBV DNA seropositivity will help develop logical immunotherapy strategies.

Characteristics of the Tumor Microenvironment in EBV-Associated Cancers

The anti-viral immunity induced by $CD4^+$ or helper T-cell activity is strongly implied within the TME of EBV-associated tumors, mainly when infected tumor cells express a high level of HLA class II (HLA II) molecules [115]. However, certain molecules like Gp42, an entry receptor by which EBV binds to HLA II on B-cells [116], acts as immuno-suppressive molecule by blocking the function of T-cell receptors, thereby inhibiting the activation of helper T-cells [117]. In addition, studies have also identified increased numbers of Tregs within the TME of EBV-associated tumors [118]. This increase may occur because EBV oncoproteins EBNA1 and LMP1 are known to recruit and promote Tregs infiltration, further confirming the immuno-suppressive nature of the TME in EBV-associated cancer [119].

Beyond T-cells, tumor-associated macrophages significantly shape the TME, particularly influencing tumor progression dynamics. There is a notable disparity in the TME of EBV-associated cancers, which exhibit a heightened presence of M2-polarized tumor-associated macrophages compared to EBV-negative tumors [120]. This distinct infiltration is not an arbitrary event; it is orchestrated through the targeted recruitment of macrophages by specific chemokines.

Among the chemotactic signals, the monocyte chemoattractant protein-1 (CCL2) and C-C Motif Chemokine Ligand 5 (CCL5) are prominent; they are secreted in response to the EBV-encoded LMP1 [121]. LMP1, a constitutively active oncogenic protein expressed in EBV-infected cells, has been implicated in modifying the TME to favor tumor progression. The chemoattraction mediated by these chemokines draws macrophages into the TME, where they assume a phenotype that typically correlates with immunosuppression and tissue repair, characteristics conducive to tumor growth and spread. Macrophages are instrumental in the immune response to cancer, straddling the line between innate and adaptive immunity. They are not mere passive inhabitants of the TME but are active participants in the inflammatory response. This duality equips them with the ability to modulate the immune landscape—either bolstering defenses against tumor cells or, paradoxically, contributing to tumor growth and metastasis.

The role of macrophages in cancer is multifaceted and complex. As part of the innate immune response, they are among the first to encounter and respond to cancerous cells, often determining the subsequent quality and type of the adaptive immune response. Their influence extends to shaping the TME through the release of cytokines, growth factors, and proteases, which can remodel extracellular matrices, promote angiogenesis, and support tumor cell survival and proliferation. The significance of TAMs in the pathology of EBV-associated and other cancers has paved the way for innovative therapeutic strategies aiming to modulate or re-educate these macrophages, converting them from tumor-promoting to tumor-suppressing actors within the TME.

Dendritic cells (DCs) are well recognized as the most efficacious antigen-presenting cells in activating anti-viral immune responses. Tumor areas in EBV-associated malignancies have been shown to have significant infiltration of DCs [95]. Moreover, the TME in EBV-associated malignancies is also known to be infiltrated with high numbers of DCs [122]. However, to evade the host's immune system, the activity of DCs is often suppressed within the exosomes of infected tumor cells [123]. In addition, DCs within the TME can infiltrate tumors, subsequently leading to the expression of programmed death-ligand 1 and 2 (PD-L1/L2) that interact with PD-1 on the cell surface of cytotoxic T-cells, thereby promoting T-cell exhaustion [124]. In addition, the activity of other immune cells like NK cells and B-cells is also known to be hampered within the TME of EBV-associated tumors, thereby worsening the immuno-suppressive characteristics of the TME. For example, EBV encodes miRNA-BARTs capable of impeding immune recognition and cytotoxic activity of the NK cells [125]. LMP1 has garnered significant attention due to its oncogenic characteristics *in vivo* and *in vitro* [126,127]. LMP1 hinders B-cell differentiation into antibody-secreting cells in the TME, consequently inhibiting their function [107].

Apart from immune cells, various other components are also known to define the characteristics of the TME in EBV-associated cancers. For example, pro-inflammatory soluble molecules like IP-10, a member of the CXC chemokine family, regulate cell cycle and apoptosis in the TME [128]. In particular, LMP1 may be capable of mediating the expression of IP-10 via post-transcriptional mechanisms [95]. Moreover, interleukin 1 (IL-1) is found to be overexpressed in the TME of EBV-infected tumors [129], where it may display anti-tumor effects; thus, it is linked to the improved survival of patients with EBV-associated cancer [129]. Tumor necrosis factor alpha, originally identified as an anticancer protein, has been demonstrated to play a crucial role as a pro-inflammatory cytokine in various disease pathologies, including cancer [130]. TNF-α is known to alter functional activity implicated within the TME of EBV-positive tumors. The expression of TNF-α is upregulated by LMP1 via the NF-κB pathway [110], causing it to bind to its receptor, tumor necrosis factor receptor-1 (TNFR1), thereby triggering apoptosis [131]. However, LMP1-expressing tumor cells are known to downregulate the expression of TNFR1 and inhibit the downstream effect of the caspase proteins involved in apoptosis [110], thereby rendering them resistant to TNF-α-induced apoptosis.

Moreover, certain immuno-suppressive cytokines are commonly found in EBV-positive tumors but not in EBV-negative tumors. For example, interleukin 10 (IL-10) is an immuno-suppressor molecule that induces Tregs expression and hinders cytotoxic and helper T-cell expression [132]. Consequently, the LMP2A-induced expression of IL-10 [133] is elevated in EBV-associated cancers [134]. In addition, LMP1 may stimulate the expression of other immuno-suppressive cytokines like IL-6 and IL-8 via the NF-κB pathway [95].

Finally, other characteristic components of the TME, like extracellular vesicles, are also strongly involved in mediating EBV-induced pathogenesis. EBV is known to be intricately involved in modifying the contents of extracellular vesicles [112] that help evade the immune system, thereby reforming the TME to support tumor progression [111]. In addition, various other studies have also outlined the immuno-suppressive effects of extracellular vesicles generated post-EBV infection, thereby confirming their crucial role within the TME [135–138].

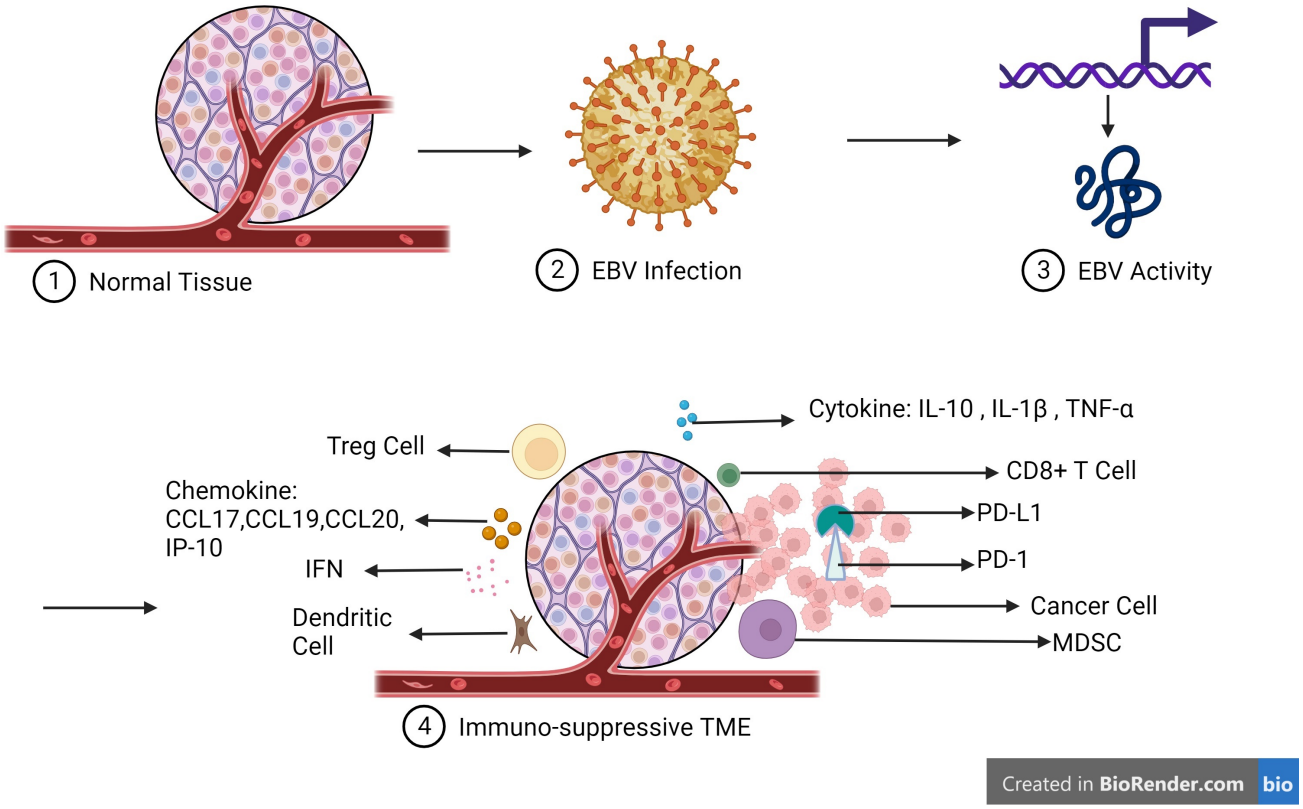

Fig. 2. Showing TME of Epstein-Barr virus (EBV)-infected tumor characterized by the coexistence of Pro-inflammatory and immuno-suppressive variables, including immune cells, cytokines, chemokines, programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1). Tregs, regulatory T cells; IL-10, interleukin 10; TNF-α, tumor necrosis factor alpha; MDSC, myeloid-derived suppressor cells; IFN, interferon; CCL17, C-C Motif Chemokine Ligand 17; IP-10, interferon gamma-induced protein.

In summary, both HPV and EBV interact with the TME through unique mechanisms to cause cancer (Table 1, Ref. [67,73,79,81–83,95,96,107,110–112,117,128,129]). These involve cellular change, immune evasion tactics, and the creation of an immunosuppressive milieu. Through different cellular and molecular dynamics, HPV and EBV impact cellular constituents and molecular processes inside the TME. For example, cellular proliferation, apoptosis evasion, and immunological modulation are directly impacted by the production of latent membrane proteins in EBV and viral oncoproteins E6 and E7 in HPV. Remarkably, anomalies in TME in HPV- and EBV-associated malignancies may also serve as targets for treatment. Investigating the TME unique to these viruses can provide valuable knowledge, which could result in more advanced and successful therapeutic approaches.

Remodeling of the Tumor Microenvironment for the Therapeutic Benefit of HPV and EBV-Associated Cancers

The introduction of sequencing technologies and analytical bioinformatics has allowed for the analysis of individual cells, revealing the extensive complexity of the TME. Contrary to previous beliefs, it is now recognized that the TME can either support or suppress tumor growth, depending on the specific stage and type of cancer [139–141]. TME harbors essential components that can impact tumor progression, invasion, and metastasis, as well as tumor regression and response to therapy. Therefore, TME may be exploited as a platform to direct the course of the cancer through effective remodeling toward the goal of therapeutic benefit. However, it is paramount to consider the intricacy of TME and utilize the unique characteristics of each tumor to achieve the ideal balance between treatment effectiveness and failure. Due to the complexity and ongoing evolution of TME, massive research is still needed to understand anomalies in various tumor phenotypes. Such therapeutic methods may be invalidated by incomplete knowledge of the TME and the immune landscape in certain cancers. Therefore, enhancing knowledge of cancer heterogeneity, implementing more pertinent animal models and testing procedures, and pre-selecting patients who are most likely to react to corresponding therapies are all useful strategies [142]. It has been reported that changes in the composition of components in the extracellular matrix can influence the prognosis of certain cancers [143]. For instance, glucose degradation in the TME makes it more acidic and subse-

Table 1. A broad classification of the characteristics of the altered TME in HPV/EBV-associated cancers.

Characteristics of the TME	Type of Viral cancer	Implication
Secretion of inflammatory mediators	HPV	Higher expression levels of pro-inflammatory cytokines IL-6 and IL-8 were noted in HPV-associated cancer [73].
	EBV	Pro-inflammatory soluble molecule IP-10 is implicated in regulating the cell cycle and apoptosis [128] in the TME. IL-1 and TNF-α are pro-inflammatory cytokines upregulated in EBV-associated cancers [110,129]. Expression of pro-inflammatory cytokines IL-6 and IL-8 is stimulated by LMP1 [95].
Modified components of the extracellular matrix	HPV	Circulating tumor cells showed the downregulation of EMT markers [79]. Extracellular vesicles from HPV-positive tumors contain altered molecular cargo [81,82] to equip tumor cells to evade the immune system and promote HPV infection by diffusion of viral components [83] to naive cells.
	EBV	EBV can modify the contents of the extracellular vesicles [112] to help evade the immune system and better equip the TME to support tumor progression [111]. LMP1 in exosomes can modulate tumor progression and prevent B-cell differentiation [107].
The interplay between tumor and stroma cells	HPV	Decrease in stromal cells of HPV-positive tumors [67].
	EBV	EBV hinders recognition by EBV-specific $CD8^+$ T-Cells in the TME, thereby promoting immune escape [96]. EBV inhibits the activation of helper T-cells [117]. LMP1 also hinders the differentiation of B-cells into antibody-secreting cells [107].

HPV, human papillomavirus; EBV, Epstein-Barr virus; IL-6, interleukin 6; IP-10, interferon gamma-induced protein; TNF-α, tumor necrosis factor alpha; LMP1, latent membrane protein 1; EMT, epithelial-mesenchymal transition; TME, tumor microenvironment.

quently activates enzymes like metalloproteinases involved in the deterioration of the extracellular matrix, which is often a requisite for tumor invasion and motility leading to metastasis [144]. Therefore, inhibiting such changes in the TME may pose beneficial outcomes in suitable therapeutics.

Interestingly, the TME's dendritic cells are considered promising targets for therapeutic benefit in HPV/EBV-positive tumors. Accordingly, dendritic cells within the TME may be stimulated to enhance their maturation, recognition, internalization, and antigen presentation properties [145]. The broad goal of modulating dendritic cells is to enhance the tumor specificity of cytotoxic T-cells to recognize and target E6/E7 expressing cells in HPV-associated cancers. In this regard, therapies for benign and malignant HPV-related diseases target the E6 and E7 antigens widely expressed during tumor development [146]. In addition, exosomes secreted by immune cells like dendritic or NK cells may also depict efficient anti-tumor activity [147,148]. For example, exosomes from phosphor-antigen-expanded Vδ2-T-cells eliminated EBV-positive tumor cells with enhanced efficiency [149].

As previously stated, macrophages are identified as a critical component of the TME. Therefore, remodeling of the TME may also be achieved through the modulation of macrophages dedicated to immuno-suppression. Specific immunotherapies can eliminate suppressive molecules released by tumor-associated macrophages like IL-10, IL-6, and transforming growth factor-α (TGF-α) [150,151]. Accordingly, a particular study has evaluated the utilization of RNAi silencing to inhibit the expression of such mediators in Papilloma disease [152]. Thus, decreasing the expression of such immuno-suppressive molecules will eventually favor the functioning of dendritic cells and macrophages, enabling them to trigger cytotoxic and helper T-cell responses and develop a pro-inflammatory condition [150]. Moreover, monocytic myeloid-derived suppressor cells resembling M2 macrophages, known to play an immunosuppressive role, are found in the TME. A particular report has also described the modulation of mononocytic myeloid-derived suppressor cells as targets of suitable immunotherapy [153].

Further, immuno-modulatory molecules like cytokines and receptor agonists are likewise being exploited to reshape the TME. For example, TGF-β signaling is a critical moderator within the external stroma of the tumor. Therefore, clinical trials are investigatingTGF-β resistant T-cells in patients with EBV-associated nasopharyngeal carcinoma (NCT02065362). Further, remodeling of the TME may be specifically executed by receptor agonists that trigger the activation of helper T-cells. Such approaches have been assessed in treating HPV-associated head and neck squamous cell carcinoma [154]. In most cases, such molecules are delivered through nano-systems like nano-emulsions and nanoparticles [155]. A particular study reported the development of a nano vaccine for EBV-associated tumors [156]. This nano vaccine was encapsu-

lated with a Toll-like receptor 9 agonist and demonstrated to target lymph nodes, triggering a robust immune response and enhancing tumor elimination. Interestingly, this study proved that combining the EBV nano vaccine with anti-PD-L1 molecules was further effective in tumor reduction and prolonged survival [156]. These results vividly suggest that such nano vaccines may reverse immune checkpoint inhibitor resistance via remodeling of the TME.

The exploration of immune cell modulation within the TME is a promising frontier for improving therapeutic outcomes in cancer treatment. Cell therapy, representing an innovative paradigm in oncology, harnesses the power of immune cells to selectively target and eradicate cancer cells. This approach involves the strategic remodeling of the TME, achieved by introducing immune cells with intrinsic anti-tumor capabilities. These cells are either naturally occurring or genetically engineered to repair tissue damage and inhibit malignant growths [157]. The strategies for T-cell therapy, particularly in relation to HPV-associated cancers, can be divided into intrinsic and extrinsic methods. Intrinsic therapy pertains to the manipulation of T-cells already present within the TME, aiming to boost their native tumor-fighting abilities. Extrinsic therapy, such as adoptive cell transfer, involves the external administration of engineered T-cells that are specifically tailored to target tumor cells [158]. Advances in gene-editing technology have led to the development of T-cells engineered to exhibit heightened activity against the E6 and E7 oncogenic antigens of HPV. These modified T-cells can identify and attack HPV-infected cells with increased efficiency [159–161]. Notably, particular research has yielded compelling results; for instance, one study demonstrated that the cleavage of E6 and E7 mRNA significantly halted cellular proliferation in both *in vitro* and *in vivo* settings [162]. Another innovative approach utilized gene-editing encapsulated in liposomes to amplify the immune response of cytotoxic T-cells against HPV-positive tumors [163]. Further breakthroughs have been made with T-cells engineered to express receptors that target the E7 oncoprotein of HPV. These T-cells have been shown to possess the ability to selectively engage with and destroy cells of cervical and oropharyngeal cancers that are HPV-positive. Such targeted action has been effective in causing tumor regression in mouse models, providing a promising glimpse into the potential of T-cell therapies to confer specific, potent, and durable anti-tumor responses [164]. The advancements in cell therapy and genetic engineering not only underscore the vast potential of T-cells as a therapeutic tool but also indicate a shift towards personalized and precision medicine in oncology. As this field evolves, it holds the promise of revolutionizing the treatment landscape for HPV-associated and other types of cancers, offering patients tailored and potentially more effective therapeutic options.

Further, chimeric antigen receptor T-cells (CAR-T) therapy has demonstrated reliable results in preliminary clinical trials for HPV-associated cancers [165,166]. Finally, adoptive transfer techniques to introduce tumor-infiltrating lymphocytes and HPV-targeted T-cells directly into the TME have shown promising results in treating HPV-related cancers. These studies have demonstrated the potential of the adoptive transfer of tumor-infiltrating lymphocytes, leading to the regression of HPV-positive tumors in cervical and epithelial cancers [166, 167]. Similarly, ongoing clinical trials are being conducted for adoptive cell transfer of EBV-tumor cell receptor T-cells (NCT03648697) capable of directing robust anti-tumor activity within the TME. Adoptive transfer therapy is also being attempted for cytotoxic T-cells targeting other EBV oncoproteins like EBNA1, LMP, and BARF1 (NCT022873110). Interestingly, the adoptive transfer of EBV-specific T-cells generated towards EBV-positive tumors is being evaluated as a treatment option in combination with chemotherapies like carboplatin and gemcitabine in nasopharyngeal carcinoma patients [168].

Finally, anti-HPV/EBV therapeutic vaccines are also based on remodeling the TME by delivering tumor-specific antigens through antigen-presenting cells or other vector systems to boost immune recognition. Further, therapeutic vaccines based on the utilization of dendritic cells in HPV-associated cervical cancer have been developed and reported to show superior outcomes in terms of targeted immune responses and regression of HPV-associated tumors [169]. Similarly, other dendritic cell-based vaccines have been assessed in treating patients with early stages of HPV-associated cervical cancer. These showed an enhanced expansion of HPV-specific T-cells, improving clinical responses [170]. Yet another study used a vaccine comprising dendritic cells transfected with ribonucleic acid coding for the E6 and E7 oncoproteins of HPV to stimulate the generation of HPV-specific T-cells [171]. This vaccine has proven highly effective in targeting and eliminating tumor cells in a cervical cancer model [171]. Similarly, dendritic cells expressing LMP2 coupled with the modified vaccinia Ankara have shown exceptional results in safety and tolerance in EBV-associated cancer [172].

Conclusion

In conclusion, as we venture beyond the immediate ramifications of viral infections, it becomes evident that the multifaceted roles of HPV and EBV in sculpting the TME are critical facets in the escalating burden of virus-associated cancers. The limitations of existing prophylactic and therapeutic vaccines are pronounced in the current landscape, mainly due to the sophisticated immune evasion strategies devised by the viral oncoproteins within the TME's confines. These strategies manifest in complex and intricate interactions that influence the tumor's development and progression, emphasizing the need for a more profound understanding of tumor-TME communication.

Indeed, the oncoproteins of HPV and EBV alone cannot drive the full spectrum of oncogenesis and malignant transformation. This underscores the pivotal role played by the TME, functioning as an active participant in fostering a conducive environment where the oncovirus can potentiate tumor development and advancement. This active engagement is characterized by a dynamic exchange involving the secretion of inflammatory mediators, alterations in the components of the extracellular matrix, and a finely tuned interplay between tumor and stromal cells, which collectively define the signature traits of the TME in HPV and EBV-associated cancers.

Furthermore, the TME serves as a double-edged sword in the context of viral cancers, harboring the capacity to either promote tumor progression or facilitate regression, hinging on its selective modulation and remodeling. This duality underscores the complexity of the interactions within the TME, pointing towards a labyrinthine network of regulatory pathways that dictate the fate of the tumor.

Looking ahead, future research endeavors must pivot towards an enriched comprehension of the underlying mechanisms fostering the tumor-TME dialogue. As we stand at the cusp of potential breakthroughs, a concerted effort to delineate the pathogenesis of these viral cancers can pave the way for innovative therapeutic modalities. By dissecting the complex orchestra of interactions within the TME, we aspire to unlock novel avenues for clinical intervention, fostering a future where managing viral cancers is proactive and effective, minimizing their impact on global health.

Abbreviations

HPV, human papillomavirus; HPVs, human papillomaviruses; EBV, Epstein-Barr virus; LR HPVs, Low-risk human papillomaviruses; HR HPVs, high-risk human papillomaviruses; EBNA1, EBV-induced nuclear antigen 1; LMPs, latent membrane proteins; TME, tumor microenvironment; ECM, extracellular matrix; CTLs, cytotoxic T lymphocytes; TAMs, tumor-associated macrophages; HNSCC, head and neck squamous cell carcinomas; TIL, tumor-infiltrating lymphocyte; ASCC, anal squamous cell carcinomas; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CRT, chemoradiotherapy; IL, interleukin; NF-κB, nuclear factor kappa B; EMT, epithelial-mesenchymal transition; HLA I, human leukocyte antigen class I; Tregs, regulatory T cells; NK, natural killer; TNF-α, tumor necrosis factor alpha; STIM1, stromal interaction molecule 1; NPC, Nasopharyngeal carcinoma; CCL2, monocyte chemoattractant protein-1; CCL5, C-C Motif Chemokine Ligand 5; DCs, Dendritic cells; TNFR1, tumor necrosis factor receptor-1; CAR-T, chimeric antigen receptor T-cells; MDSC, myeloid-derived suppressor cells; IFN, interferon; CCL17, C-C Motif Chemokine Ligand 17; IP-10, interferon gamma-induced protein.

Availability of Data and Materials

Not applicable.

Author Contributions

QF & GS: writing and reviewing original draft, conception, designing and figure preparation; KSP, SK: conception and designing, writing and reviewing; SD, MM, KJ & AAB: conception and designing, critical reviewing and editing; SU: supervision, conception and designing, critical reviewing and editing the manuscript. All authors approved the manuscript. All authors agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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