

The Tri-Viral Synergy of EBV, HPV and HIV in Non-AIDS-Defining Cancers

Hanqing Yang

Shanghai Pinghe School, Shanghai, China

Emillyyang111308@gmail.com

Abstract. Epstein-barr virus (EBV) and human papillomavirus (HPV) are among the highly prevalent oncogenic viruses. Both can dodge host immune surveillance and reprogram cellular signaling to produce malignancy. For PLWH, long - term immune suppression and steady inflammation amplify these effects, leading to an increasing prevalence of non-AIDS-defining cancers (NADCs). This paper looks into the molecular and immunological interactions among EBV, HPV, and HIV that bring about viral-driven oncogenesis. Latent proteins, including LMP1 and EBNA, modify NF- κ B and JAK/STAT pathways to increase the level of proliferation and block apoptosis. Meanwhile, HPV oncoproteins E6 and E7 break p53 down and inactivate pRb to induce genomic instability. CD4+ T-cell depletion stemming from HIV and dysregulated cytokine profiles make viral persistence and co-infection synergy possible. Epidemiological and molecular data imply that EBV-HPV coinfection causes more aggressive tumor behavior and a worse prognostic scenario, especially in immunocompromised hosts. All things considered, this study emphasizes how the interaction of EBV, HPV, and HIV forms a joint oncogenic network that sustains viral persistence, evades the immune system's control, and hastens the transformation into a malignant state. Grasping this triviral synergy is essential for bettering cancer prevention and management strategies among PLWH. Comprehending this three-virus cooperation is essential for bettering cancer prevention and management strategies for PLWH.

Keywords: EBV, HPV, HIV, viral synergy, non-AIDS-defining cancers.

1. Introduction

Viral oncogenesis exhibits a highly involved convergence of infection, immunity, and cancer biology. Around 15% to 20% of global human malignancies are associated with oncogenic viruses, for instance, Epstein-Barr virus (EBV), human papillomavirus (HPV), and human immunodeficiency virus (HIV) [1]. EBV, HPV and HIV are well-regarded for their unique yet linked contributions to cancer advancement. HPV and HIV are well-regarded for their individual but interlinked contributions to cancer progression. It is recognized that EBV and HPV can lead to some forms of cancer: EBV is the factor for B-cell lymphomas and nasopharyngeal carcinoma, whereas high-risk HPV

Genotypes (e.g., HPV-16, HPV-18) are the well-known etiological agents of cervical and oropharyngeal malignancies [2]. However, HIV does not directly bring about cancer. It weakens the immune system so greatly that it facilitates other cancer-causing viruses to stay in the body for a long period [3]. This disruption exerts a notable effect on persons with HIV (PLWH), because a weakened immunity increases the probability of dormant EBV and HPV infections leading to cancer. This has led to a boost in non - AIDS - defining malignancies (NADCs), and they are now a major public health problem. This has led to an upsurge in non-AIDS-defining malignancies (NADCs), which are now a grave public health matter.

In-depth study has revealed the distinct carcinogenic routes of EBV and HPV: EBV generates latent membrane proteins (LMP1, LMP2A) and nuclear antigens (EBNAs) that initiate oncogenic signaling pathways (e.g., NF- κ B, MAPK, JAK/STAT) to avoid apoptosis and promote the continuation of cell proliferation, while HPV employs oncoproteins E6 and E7 to destroy indispensable tumor suppressors (p53, pRb) [4,5]. Recently, the focus has veered towards EBV-HPV coinfection. Findings indicate that when both viruses are present at once, cells are more likely to change, which is associated with more aggressive tumor types and leads to poorer clinical results [6].

This adds one more layer of complexity to viral oncogenesis in persons with a compromised immune system. This places an additional layer of complexity onto viral oncogenesis in individuals with impaired immune systems.

The initiation of combination antiretroviral therapy (ART) has changed cancer morbidity trends in people with HIV (PLWH). It has reduced the incidence of AIDS-defining cancers like Kaposi sarcoma, but it has not halted the increase of non-AIDS-defining cancers (NADCs) [7]. This disparity results from partial immunological reconstitution that isn't potent enough to fully suppress oncogenic viral coinfections. In this context, growing proof of collaborative relationships between EBV, HPV, and HIV highlights the need to understand how HIV - induced immunosuppression modifies viral oncogenesis. Grasping the combined action of these three viruses is essential for formulating strategies to stop and treat NADCs in HIV-positive persons. Figuring out how these three viruses work in tandem is essential for making schemes to prevent and handle NADCs in HIV-infected people.

2. The Oncogenic Mechanisms of Epstein-Barr Virus (EBV)

2.1. Epidemiology and Latency

Epstein-Barr virus (EBV) is a common virus that affects people; more than 90% of individuals across the globe have been infected by it [8]. After the first instance of infection, EBV persists in the body over a lifetime, predominantly in B lymphocytes, by staying in episomal form and being reactivated from time to time. During the latent state, the expression of viral genes is highly restricted, enabling the virus to evade the immune system and allowing cells to survive for an extended period [4]. The latent reservoir stands as a groundwork for eventual oncogenic transformation, particularly in the presence of compromised immune surveillance. The latent reservoir functions as a groundwork for eventual oncogenic transformation, particularly in the face of compromised immune surveillance.

2.2. Oncogenes from Viruses and Signaling Pathways in the Host

In latency, EBV makes a collection of latent proteins that interfere with normal cell function. Latent Membrane Protein 1 (LMP1) acts as a continuously active tumor necrosis factor receptor, which triggers NF- κ B, JAK/STAT, and MAPK signaling to foster cell growth and prevent apoptosis [4]. LMP2A is capable of emulating B-cell receptor (BCR) signaling to deliver survival signals when there's no antigen [9]. EBV nuclear antigens (EBNAs) manage the host's transcription and chromatin structure, facilitating the working of oncogenic gene expression programs [10]. These viral elements collaborate to induce genomic instability, evade growth checkpoints, and facilitate the clonal expansion of infected B-cells. These viral components collaborate to induce genomic instability, evade growth checkpoints, and foster the clonal expansion of infected B-cells.

2.3. Immune Regulation and Advancement to Malignancy

In immunocompetent individuals, EBV-infected B cells are strictly managed by cytotoxic T lymphocytes, in particular CD8⁺ T-cells, and natural killer (NK) cells [11]. But when the immune system becomes weakened (e.g., due to HIV infection or iatrogenic immunosuppression), this immunological control lessens, allowing EBV-infected clones to grow [3]. The persistent spread and aggregation of mutations in B cells might lead to EBV-associated lymphomas, including Burkitt lymphoma, Hodgkin lymphoma, and posttransplant lymphoproliferative diseases (PTLD) [12]. The constant proliferation and gathering of mutations in B cells may bring about EBV-associated lymphomas, which include Burkitt lymphoma, Hodgkin lymphoma, and posttransplant lymphoproliferative diseases (PTLD) [12].

3. The Carcinogenic Potential of Human Papillomavirus (HPV)

3.1. Virology and High-Risk Genotypes

The human papillomavirus (HPV) is a double-stranded DNA virus that doesn't have an envelope and attacks basal epithelial cells [2]. There are more than 200 genotypes of HPV that are known, and high-risk forms like HPV-16 and HPV-18 are strongly connected to cancers of the cervix, anus, penis, and oropharynx [5]. The addition of HPV DNA into the host genome is a significant step towards malignant transformation [13]. The incorporation of HPV DNA into the host genome becomes a key step in the process of malignant transformation [13].

3.2. Molecular Mechanisms of Transformation

The ability of HPV to trigger cancer predominantly comes from the functions of the E6 and E7 proteins. The E6 protein links to p53 and conveys it to the proteasome for destruction. This puts a stop to DNA damage checkpoints and apoptosis [5]. E7 binds to the retinoblastoma protein (pRb) at the same time, releasing E2F transcription factors and pushing cells into S phase, avoiding cell cycle regulation [5]. This imbalance induces genomic instability, the collection of mutations, and the advancement of cancer. This imbalance leads to genomic instability, the collection of genetic mutations, and the spread of cancer.

3.3. Immune Clearance vs Persistence

In those with immunocompetence, most HPV infections are short-term, typically clearing within 1–2 years because of the host's immunological responses, especially cell-mediated immunity [14]. However, for those whose immune systems are compromised, e.g., for PLWH, immune suppression curbs viral clearance, resulting in ongoing high-risk HPV infections that are characterized by elevated viral loads and a higher probability of progressing to precancerous lesions and aggressive malignancies [3]. PLWH, immune suppression slows down viral clearance, resulting in ongoing high-risk HPV infections characterized by increased viral loads and an enhanced risk of advancing to precancerous lesions and aggressive malignancies [3].

4. HIV as a Cofactor in Viral Oncogenesis

4.1. Immune Suppression and Dysregulation

HIV infection brings about a steady decline in CD4⁺ T cells, messing with both the adaptive and innate immune systems. When immune surveillance is absent, EBV may reactivate or proliferate in an unregulated manner, and the removal of HPV-infected epithelial cells is hampered [3]. Chronic HIV infection leads to persistent inflammation throughout the whole body, oxidative stress, and cytokine irregularities (e.g., high IL-6 and TNF- α concentrations), increasing the likelihood of tumors in the environment [15]. Chronic HIV infection results in long-standing inflammation in the body, oxidative stress, and problems with cytokines (e.g., elevated levels of IL-6 and TNF- α), increasing the likelihood of a tumor-producing environment [15].

4.2. What ART (Antiretroviral Therapy) Does

The introduction of combination ART has considerably strengthened immune reconstitution and decreased the prevalence of numerous AIDS - defining cancers (e.g., Kaposi sarcoma) [7]. However, the rate of non-AIDS-defining malignancies (NADCs), specifically those related to EBV and HPV, remains higher among people living with HIV (PLWH), presumably indicating a lack of efficient immunological recovery and ongoing viral cofactor impacts [7]. However, the rate of non-AIDS-defining malignancies (NADCs), particularly those associated with EBV and HPV, continues to be higher among people with HIV (PLWH), likely suggesting sub-optimal immunological recovery and abiding viral cofactor effects [7].

5. Synergistic Oncogenesis of EBV and HPV Coinfection

Evidence across epidemiological, molecular, immunological, and clinical areas backs up the synergistic oncogenesis of EBV and HPV coinfection. Recent epidemiological research indicates that EBV–HPV coinfections occur in malignancies of the head, neck, cervix, and anogenital areas, particularly among those with HIV. For example, co-infection of EBV and HPV has been detected in samples of oropharyngeal carcinoma and cervical cancer. Tumors infected with multiple viruses often behave more aggressively in clinical practice, return more often, and have a worse prognosis than those infected with a single virus [6]. At the molecular level, EBV and HPV have comparable oncogenic mechanisms—both can activate NF- κ B, suppress apoptosis, and interfere with the functions of p53 and pRb. Experimental co-expression studies show that EBV's LMP1, together with HPV's E6/E7, causes synergistic boosts in cell proliferation that are greater than the combined effects of each virus alone. In terms of the impacts on the immune system and cells, EBV could locally reduce the immune activity in coinfecting tissues by modifying cytokine networks and obstructing antigen presentation, letting HPV persist and multiply. Meanwhile, genomic instability due to HPV may offer a favorable environment for EBV reactivation or clonal expansion. The combined working of EBV and HPV can cause earlier onset, more forceful advancement, and treatment resistance in cancers among PLWH, spotlighting the significance of early detection and coordinated treatment when both viruses are there. The synergistic relationship between EBV and HPV could bring about earlier onset, more aggressive advancement, and treatment resistance in cancers among individuals with PLWH, spotlighting the need for early detection and coordinated treatment when both viruses are present.

6. Reasons for the Increasing Number of NADCs in PLWH

Many factors have a link to the upswing in NADCs in PLWH. Electronic viral persistence is crucial since HIV - related immune regulatory dysfunctions allow infected and altered cells to continuously multiply and build up over time. This unbroken persistence exacerbates inflammation and cytokine imbalance. Where chronic inflammatory conditions and increased amounts of pro-tumorigenic cytokines such as IL-6 and TNF- α foster tumor survival, trigger the creation of new blood vessels, and allow tumors to migrate to remote sites within the body. Genomic and epigenetic instability also contribute to this pattern. HPV integration affects host-related genes, and EBV modifies DNA methylation and chromatin states, both of which raise mutation rates and impede normal transcription. Moreover, strategies for immune system evasion are quite essential: proteins produced by EBV and HPV stop the occurrence of antigen presentation, stop apoptosis, and stop immunological signaling. HIV itself renders it more arduous for the immune system to battle infections. In the end, host and treatment modifiers greatly affect the possibility of PLWH getting NADCs. They comprise age, ART adherence rate, co-infection burden, and the time span of a person's immunosuppression. They encompass age, ART adherence status, co-infection load, and the length of the person's immunosuppression period.

7. Prevention, Management and Comparative Perspectives

Integrated screening programs are extremely pertinent for prevention, management, and comparison. Regular HPV - related cancer screenings, like anal Pap smears, HPV DNA testing, and visual checks of the oropharynx, should be incorporated into HIV care. Besides, keeping tabs on the EBV viral load in high-risk PLWH may aid in detecting early lymphoproliferative disease. Making vaccines and treatments matters a great deal. HPV vaccination is particularly key for HIV patients, even after they've been infected, whereas research on EBV vaccines and therapeutic vaccines against viral antigens is vital. Regarding clinical and public health strategies, commencing ART immediately and adhering strictly to it slows the immune system's downward trend. Having educational programs that teach individuals about safer sex practices and virus spread prevention is also crucial. In the end,

addressing cancers associated with coinfection should involve more than a single discipline. In a comparative scrutiny, people with HIV have greater rates of persistent HPV, increased EBV amounts, and an earlier start of virus-related malignancies compared to HIV-negative counterparts. Although antiretroviral therapy reduces AIDS-related cancers, non-AIDS-defining cancers (NADCs) continue to persist. To conclude, the HIV-EBV-HPV triad creates a formidable carcinogenic network. EBV and HPV employ distinct yet cooperative molecular mechanisms to commandeer host signaling and inhibit immune regulation, and HIV magnifies these effects via immunosuppression, inflammation, and viral protein activity. Future research is supposed to concentrate on formulating safe and efficient EBV vaccines, enhancing the availability of HPV vaccination for those with HIV, developing therapeutic immunotherapies aimed at viral antigens, and introducing screening approaches that combine HIV and cancer treatment. Future research ought to focus on formulating reliable and efficacious EBV vaccines, increasing the availability of HPV vaccination for those suffering from HIV, devising immunotherapies targeting viral antigens, and establishing screening methods that integrate HIV and cancer treatment.

8. Conclusion

This study stresses the vital function of viral synergy in the onset of malignancies among PLWH. EBV and HPV use diverse means to disturb cellular homeostasis, for instance, activating NF- κ B, breaking down p53, and turning off pRb. HIV-related immunosuppression worsens these cancer-causing effects by making it more arduous for the body to eliminate the virus and increasing chronic inflammation. The three viruses build a self - sustaining network of persistent infection, genomic instability, and immune evasion that helps non - AIDS - defining malignancies (NADCs) begin and expand. The inspected epidemiological and molecular data show that EBV–HPV coinfection is not only a chance event but a synergistic state, resulting in cancers that are more aggressive, recurring, and unresponsive to treatment modalities compared to single-infection-related cancers. This emphasizes the essentiality of integrated screening programs in HIV care, with HPV testing and EBV viral load scrutiny, to enable early detection and intervention. Deploying HPV vaccines, advancing EBV-targeted immunotherapies, and improving adherence to antiretroviral medication (ART) are crucial for lessening cancer risk in this group. Adopting HPV vaccines, moving forward with EBV-targeted immunotherapies, and enhancing antiretroviral medication (ART) adherence are essential for reducing cancer risk in this demographic. In closing, the HIV-EBV-HPV trio exemplifies a complex yet clinically relevant model of viral interaction in oncogenesis. This research points out the essential need for interdisciplinary prevention and treatment strategies that merge virology, oncology, and immunology to handle the escalating incidence of virus-related cancers in people with HIV. This study brings to light the essential requirement for interdisciplinary prevention and treatment strategies that blend virology, oncology, and immunology to handle the escalating occurrence of virus-linked cancers in those with HIV.

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