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Review Article

A Comprehensive Review of the Role of Viruses in the Onset and Progression of Lung Cancer

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Abstract

A number of variables may influence the development and spread of lung cancer (LC), one of the most prevalent and fatal cancers in the world. In this context, viruses are important, especially the human papillomavirus (HPV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), influenza virus (IV), and cytomegalovirus (CMV). These viruses can influence the development of LC through metabolic alterations, immune response suppression, and disruption of the tumor microenvironment (TME). Specifically, HPV may contribute to LC through genetic effects, while EBV can induce molecular changes in cells. HIV, by suppressing the immune system and increasing the risk of secondary infections, may create conditions conducive to the development of lung tumors. IV and CMV can also play a role in accelerating tumorigenic processes by impacting the immune system and promoting inflammation. This review article examines the various mechanisms by which viruses are involved in LC and their association with the progression of lung tumors. Additionally, the role of vaccination in preventing LC, particularly in individuals infected with specific viruses, is explored.

1. INTRODUCTION

Lung cancer (LC) is the leading cause of cancer-related death worldwide, with an estimated 2.1 million new cases and 1.8 million deaths reported in 2018(1). With an estimated lifetime risk of 3.8% for men and 1.77% for women, it is the second most prevalent cancer in both sexes (2). In some parts of the world, environmental and occupational risk factors such radon, asbestos, arsenic, and unprocessed biomass fuels can also raise the prevalence of LC (3). Globally, tobacco use remains the primary driver of LC-related mortality, particularly in Asia (4). About 16.1% of cancers are caused by pathogenic microorganisms, making infectious illnesses the third most common cause of cancer

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globally, behind smoking and dietary factors (5). Recently, the role of human papillomavirus (HPV) in the development of LC has garnered significant attention, with HPV types 6 and 11 implicated in the formation of respiratory papillomas, which can occasionally lead to malignant transformation of infected cells (6). By changing cellular metabolism, Epstein-Barr virus (EBV) infection promotes tumor development and has been linked to a number of malignancies, including LC (7). This virus infects both B cells and epithelial cells (8). The chance of getting LC might rise by up to 2.5 times if you have Human immunodeficiency virus (HIV). In reality, LC has become a major cause of mortality for HIV patients in the US because to the development of antiretroviral medication (ART), which stops opportunistic infections linked to Acquired immunodeficiency syndrome (AIDS) (9, 10). Complex clinical symptoms are caused by influenza virus (IV) infection, especially in individuals with LC. By changing the tumor microenvironment (TME), this virus may hasten the progression of LC and hinder the effectiveness of anticancer treatments. Consequently, it is advised that all LC patients get antiviral therapy and influenza vaccine (11). Cytomegalovirus (CMV), a double-stranded DNA virus belonging to the beta-herpesvirus subfamily, is capable of infecting various human cell types and is primarily associated with glandular cell cancers, such as adenocarcinoma. CMV infects approximately 80% of the adult human population and can establish latent and persistent infections following initial exposure (12). Investigating the relationship between LC and other viral infections, such as HPV, EBV, HIV, IV, and CMV, is the goal of this research. This research specifically assesses how these viruses contribute to the development of LC and how they affect TME alterations.

2. ANALYSIS OF LUNG CANCER EPIDEMIOLOGY

LC includes a wide variety of malignancies with distinct histological and genetic characteristics. Small cell lung cancer (SCLC), which accounts for 15% of occurrences, and non-small cell lung cancer (NSCLC), which accounts for 85% of cases, are the two main types of lung cancer, according to histology. Adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma are the subtypes of non-small cell lung cancer (NSCLC) (13). These subtypes are distinguished by unique phenotypic features and driver mutations and often exhibit varying degrees of heterogeneity, invasiveness, and response or resistance to treatment (14). Smoking, the most prevalent risk factor, especially for males, is one of the variables that lead to the development of LC (15). Other contributing factors include air pollution, occupational exposures, genetic predispositions, biological factors, infections (Table 1), and ionizing radiation (16). Patterns of tobacco use are closely linked to the incidence and mortality of LC, with increased smoking rates correlating with higher LC rates. However, tobacco control programs are essential to reducing these statistics (17).

3. HUMAN PAPILLOMAVIRUS

LC is associated with various factors, and some studies suggest that HPV is also prevalent in this type of cancer, although HPV is primarily known as a major cause of cervical cancer (24). The Papillomaviridae family includes HPV, a tiny, non-enveloped virus having a double-stranded circular DNA genome (25, 26). Biopsies of LC have shown a significant prevalence of HPV, particularly HPV16 and HPV18. This virus is active and expresses its oncoproteins, E6 and E7, in lung tumor cells. These findings, by demonstrating transcriptional activity in tumor cells, link HPV to lung carcinogenesis (6). After integrating its genome into the host genome, HPV overexpresses two key oncoproteins in the early stages of its life cycle: E6 and E7. Two tumor suppressor proteins are rendered inactive by these proteins: E6 disrupts p53, while E7 modifies the retinoblastoma protein. These interactions promote transcriptional processes and viral genome replication by upsetting the host cell cycle (27, 28). These oncoproteins can also accelerate tumor growth through the epithelial-mesenchymal transition (EMT) (29). Two molecular changes in HPV-associated LC include integration of the HPV genome and disruption of the E2 open reading frame (ORF), which activates the early promoter p97 in HPV16. Overexpression of E6/E7 oncoproteins and increased activity of the HPV early promoter are caused by the activation of the PI3K/Akt/mTOR signaling pathway in cancer stem cells (CSCs). E6/E7 oncoproteins prevent apoptosis and encourage cell proliferation by degrading p53 and pRb. Additionally, E6 increases B-cell lymphoma 2 (Bcl-2) levels, which leads to resistance to cisplatin. Through the ERK-C/EBPβ-TLR4-NF-κB pathway, it increases the expression of programmed cell death-ligand 1 (PD-L1), which in turn promotes tumor growth and invasion (18).

4. HUMAN IMMUNODEFICIENCY VIRUS

LC, also known as a non-AIDS-defining cancer (NADC), is the leading cause of cancer-related death among people infected with HIV. Increased smoking rates are the primary reason for the elevated risk of LC in HIV-positive

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Table 1. Viruses Associated with LC

Viruses	Immune mechanisms leading to LC	Reference
HPV	Expression of E6/E7 oncogenes and activation of PI3K/Akt/mTOR pathways and ERK-C/EBPβ-TLR4-NF-κB pathway and PD-L1 expression	(6)، (18)
HIV	Reduction in the number of T helper cells (CD4+) and their function, increase in proinflammatory cytokines (RANTES, TNF-b, IFN-g, IL-6, (IP-10)	(19) ، (20)
EBV	Wnt/β-catenin, NF-κB, JNK, JAK/STAT, EGFR/MAPK, and PI3K/AKT are among the cell signaling pathways that are activated in conjunction with the expression of EBV proteins	(21)
IV	Establishment of systemic antitumor immunity based on CD8+ T cells	(22)
CMV	Suppression of activated NK and T cells	(23)

individuals, but growing evidence also implicates immune suppression and inflammatory processes (30). The T-cell response to HIV infection contributes to tumor immune escape and immune checkpoint blockade in HIV-positive patients. HIV infection reduces the number and function of CD4+ T cells, increasing the risk of cancer immune escape by impairing anti-tumor cytotoxic T-cell responses and CD8+ T-cell regulation of inhibitory receptors (19). The inhibitory molecule programmed death-1 (PD-1), which plays a critical role in T-cell regulatory responses, has recently gained attention in HIV research. In chronic infections like HIV, immune dysregulation occurs primarily due to inefficient virus-specific T- and B-cell responses. Both acute and chronic HIV infection are influenced by PD-1, which is expressed on CD4+ T cells, CD8+ T cells, NK T cells, B cells, and monocytes. Cellular fatigue and compromised immune responses result from elevated PD-1 expression on CD4+ T cells, CD8+ T cells, and B cells during infection. According to studies, inhibiting PD-1 helps manage chronic infection, promotes viral antigen clearance, and restores virus-specific CD8+ T-cell activity. Furthermore, upon PD-1 inhibition, B cells dramatically boost the production of virus-specific antibodies, and CD4+ T cells restore their helper role (31, 32). In HIV patients, pulmonary inflammation contributes to immune dysfunction and the persistence of the HIV reservoir. Despite antiretroviral therapy, HIV-positive individuals continue to experience lung diseases. Chronic inflammation and immunological activation are caused by the virus as well as other things including smoking, co-infections, and damage to the mucosal barrier. The buildup of defective CD8+ T cells and elevated levels of pro-inflammatory cytokines (e.g., RANTES, TNF-β, IFN-γ, IL-6, IP-10) worsen immunological impairment and prevent the removal of the HIV reservoir in mucosal CD4+ T cells and alveolar macrophages (AMs) (20).

5. Epstein-Barr Virus

In more than 90% of adult humans worldwide, EBV causes a chronic infection that lasts a lifetime (33). Human herpesvirus 4 (HHV-4) is another name for EBV, which is a member of the gammaherpesvirus subfamily (34). An icosahedral capsid made up of 162 capsomeres encloses the linear double-stranded DNA genome of the EBV core, which is around 172 kilobases in size (21). The primary host cells for EBV are lymphocytes and epithelial cells (35). Several essential viral proteins, such as Epstein-Barr nuclear antigen 1 (EBNA1), latent membrane protein 1 (LMP1), and LMP2, which are normally expressed during latent infection and are essential for host cell transformation and oncogenesis, mediate the oncogenic potential of EBV in lung epithelial cells (7). In lung epithelial cells, LMP1 acts as an oncogenic driver by activating multiple signaling pathways, including NF-κB, PI3K/Akt, EGFR/MAPK, and JAK/STAT (36). Increased cell adhesion, proliferation, migration, and invasion result from the release of LMP1, a key EBV oncoprotein, in extracellular vesicles, which changes their cargo and composition. By upregulating cadherins, fibronectin, integrin-α5, matrix metalloproteinase 9 (MMP9), and MMP2, these LMP1-containing vesicles alter the tumor microenvironment and encourage carcinogenesis or metastasis (37). LMP2A gives lung epithelial cells survival signals that stop apoptosis by activating the PI3K/Akt pathway and imitating B-cell receptor signaling. Early on in the development of LC, this anti-apoptotic action is especially significant because it enables infected cells to resist cell death processes and accumulate genetic abnormalities (7). The latent EBNA1 protein binds as a dimer to the latent origin of replication (oriP). EBNA1 binding to oriP facilitates the segregation and replication of the episome during cell division and plays a critical role in maintaining and transcribing the EBV genome (38). EBNA1 can also induce oxidative stress and contribute to chromosomal instability (39). Oncogenes can be activated and tumor suppressor genes silenced as a result of epigenetic alterations that EBV can cause in host cells, including DNA methylation and histone modifications. These epigenetic modifications are essential for the development and spread of LC and are a major way that EBV AIDS in the development of cancer (40).

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6. INFLUENZA VIRUS

IVs are one of the most frequent reasons why people get respiratory diseases (41). Influenza infection is associated with a 1.09-fold increased risk of LC, and this risk escalates with the frequency of infections. For instance, patients who have contracted influenza more than five times exhibit a 25% higher risk of LC (42). IVs belong to the Orthomyxoviridae family, which includes four genera: influenza A, B, C, and Thogotovirus (43). Annual influenza vaccination can stimulate a T helper 1 (TH1) immune response, enhancing anti-tumor defense. The anti-tumor immunity is dose-dependent and becomes more robust and stable with repeated influenza vaccinations (44). Seasonal influenza vaccination without adjuvants, when administered intratumorally (rather than intramuscularly), induces systemic CD8+ T-cell-mediated anti-tumor immunity (22). The identification of viral peptides by major histocompatibility complex class I (MHC-I) molecules by CD8+ T cells delays viral clearance (45). IV infection can modulate multiple immune features, including increased chemokine secretion (which AIDS immune cell migration), sustained production of interferons (IFNs) and interferon-stimulated genes (ISGs) (leading to treatment resistance), reactive oxygen species (ROS) (contributing to oxidative stress), immunosuppressive molecules (resulting in immune suppression), and inflammatory cytokines (11).

7. CYTOMEGALOVIRUS

CMV is the largest member of the Herpesviridae family, ubiquitously present and capable of infecting nearly all individuals at some point in their lives (46). Because CMV inhibits T cells and natural killer (NK) cells, which are essential for destroying cancer cells, it has been linked to helping tumor cells elude immune responses. Inflammation is linked to a number of tumors infected with CMV. In particular, malignancies of the colon, breast, prostate, and lung overexpress cyclooxygenase-2 (COX-2), and this overexpression is frequently associated with the advancement of the illness and a poor clinical prognosis (23). Upon initiating replication, CMV can exacerbate inflammation by stimulating specific cellular mechanisms. CMV can influence cell cycle regulation by modulating histone acetylation and suppressing certain tumor suppressor genes, potentially leading to increased cellular proliferation and activation of mechanisms that promote both malignant cell growth and viral dissemination. This potential mechanism may explain the association between CMV and certain types of cancer (47). Changes in the expression patterns of surface adhesion molecules induced by CMV infection may affect the migratory ability of various cell types, thereby influencing tumor invasiveness (23). CMV has developed multiple strategies to evade the host immune system. Immune suppression may be caused by the variety of immune regulators that are expressed by distinct CMV gene products. Other CMV genes, such as the IL-10 homolog (UL111a), viral proteins that function as receptors for host inflammatory cytokines (e.g., US28), and CMV genes that disrupt the presentation of major histocompatibility complex (MHC) class I and II antigens, further suppress host immune responses. These processes interfere with NK cell identification, interferon responses, and CD4+ and CD8+ T-cell-mediated immune surveillance (48).

8. DIAGNOSIS

LC is typically diagnosed at advanced stages and has a poor prognosis (49). Despite available treatment options, the overall survival rate for lung cancer has not significantly improved. Therefore, prevention and early detection are crucial to halt tumor growth, eliminate malignant tumors, and ultimately reduce lung cancer mortality (42). Eukaryotic cells secrete various membrane vesicles, which are classified into microvesicles and exosomes. Nevertheless, nothing is known about exosomes' function in NSCLC (50). Exosomes are secreted by dendritic cells (DCs), B lymphocytes, platelets, T cells, and epithelial cells (intestinal epithelial cells and tumor cells) (51) and are used as biological markers for disease identification (52). Exosomes play a key role in LC, participating in various processes such as cell growth, tumor spread, EMT, angiogenesis, and alterations in the tumor microenvironment. Tumor-derived exosomes contain factors that help regulate the immune system. These factors can influence the tumor microenvironment and contribute to the growth and spread of LC (53). The introduction of low-dose computed tomography (LDCT) has transformed lung cancer screening, with research showing its ability to detect many tumors at early stages (31). LDCT scans effectively aid in the early detection of lung tumors at operable stages (54). Detection of viral components in leukocytes, such as antigen testing and identification of prominent nuclear cells through histopathology, are key methods. The principal molecular method for virus detection is viral nucleic acid amplification, usually carried out by polymerase chain reaction (PCR) (55). Additionally, identifying early molecular changes, such as chromosomal gains or losses, can play a crucial role in early lung cancer diagnosis. Methods like DNA methylation, analysis of chromosomal abnormalities in sputum, fluorescence bronchoscopy, and

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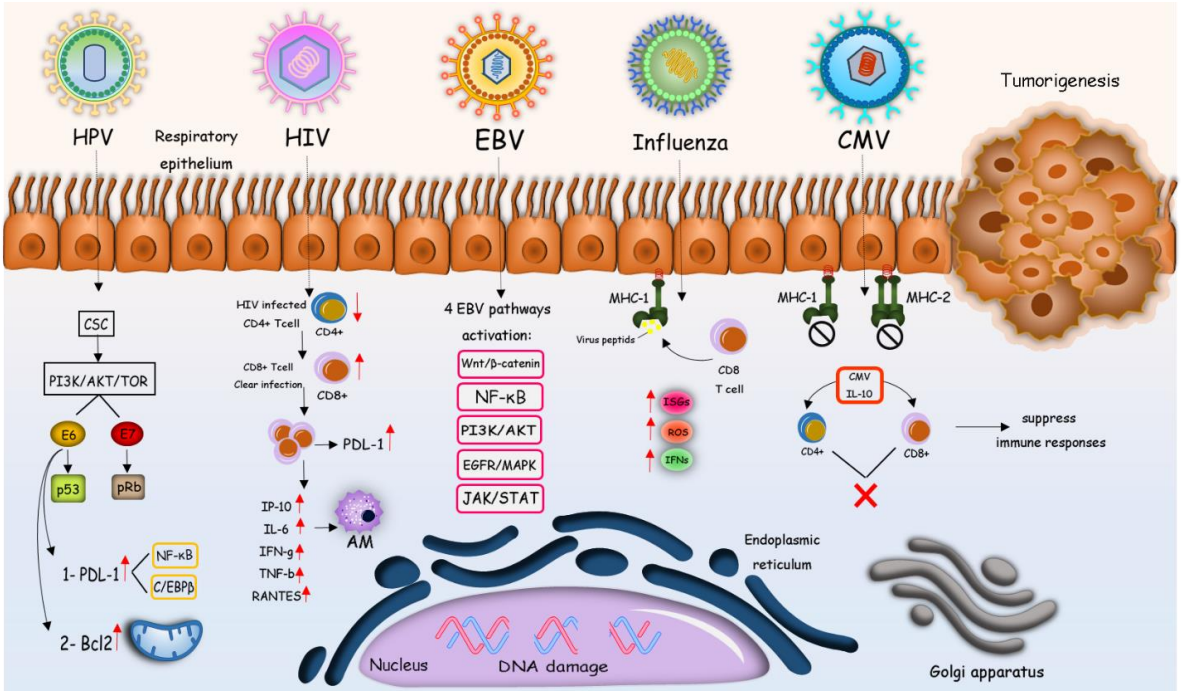

Figure 1. Mechanism of carcinogenesis. 1) The human papillomavirus (HPV) expresses the oncoproteins E6 and E7 in lung tumor cells. E6 interferes with p53, while E7 affects the retinoblastoma protein. Furthermore, E6 promotes tumor development and invasion by raising Bcl-2 levels and improving PD-L1 expression via the ERK-C/EBPβ-TLR4-NF-κB pathway. 2) HIV infection decreases helper T cells' (CD4+) quantity and functionality. This process impairs the adequate response of anti-cancer cytotoxic T cells and CD8+ T cells, leading to an increase in inhibitory tumor receptors. 3) The expression of Epstein-Barr virus (EBV) proteins activates various cellular signaling pathways, including Wnt/β-catenin, NF-κB, JAK/STAT, EGFR/MAPK, and PI3K/AKT. 4) Influenza virus infection increases the secretion of chemokines, enhances the sustained production of type I interferons (IFNs) and interferon-stimulated genes (ISGs), elevates reactive oxygen species (ROS) production, and increases inflammatory cytokines. 5) CMV viral genes disrupt the identification of CD4+ and CD8+ T lymphocytes and the presentation of MHC class I and II antigens. Further suppressing host immune responses are other CMV genes, including the IL-10 homolog (UL111a) and viral proteins that function as receptors for host inflammatory cytokines.

breath condensate analysis can help identify high-risk individuals. Combining national lung cancer screening studies with molecular research can enhance the sensitivity and accuracy of early diagnosis (56).

9. Prevention and Treatment

Smoking patterns are closely linked to the prevalence and mortality of LC, with increased smoking rates correlating with higher LC incidence. Tobacco control programs are essential to reducing these statistics(17). Raising public awareness about LC risk factors encourages individuals to adopt healthier lifestyles and undergo screening, which can reduce the likelihood of developing LC (16). Treatment approaches for LC include radiation therapy, surgery, targeted drug therapies, and chemotherapy (57). Vitamin supplements such as vitamins A and E and selenium have not shown a positive impact on reducing LC mortality, highlighting the need for more precise preclinical models and optimized experimental designs (58). The significant potential of nanoparticles (NPs) as drug carriers in the treatment of cancer, especially lung carcinoma, for detection, imaging, and therapies has been shown by expanding clinical applications in cancer nanotechnology (59). High doses of anticancer drugs often lead to rapid cellular resistance and systemic toxicity. Pharmaceutical formulation is critical in developing effective inhalable drugs. Achieving this goal requires considerations such as pharmacological activity, targeted delivery, and prolonged retention in the lungs for optimal drug efficacy (60). Nanotechnology-based systems, such as liposomes, polymeric nanoparticles, or micelles, are specifically designed to enhance the bioavailability of anticancer drugs and improve their therapeutic index (61). Oral or injectable administration of anticancer drugs exposes the body to toxins, reducing drug concentration in tumor tissues and causing unintended distribution in healthy tissues (62). The role of viral infections in lung cancer has garnered attention, and addressing them through strategies such as vaccination, immune system enhancement, and targeted therapies can

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effectively reduce disease risk. Vaccination against cancer-associated viruses, such as HPV and EBV, can be an effective preventive measure (4). The body's resistance to the carcinogenic effects of certain viruses can also be increased by fortifying the immune system by a healthy lifestyle, appropriate diet, frequent exercise, and avoiding risk factors like tobacco use. Immunotherapy and the use of antiviral medications can also significantly lower the viral load and stop the spread of cancer cells.

10. Conclusion

This study shows that viruses are important in the development and spread of lung cancer. Viruses can cause lung cancer by a number of ways, including immune system suppression, genetic changes, and disturbance of the tumor microenvironment. Early detection of viral infections and preventive measures, including vaccination, immune system enhancement, and targeted therapies, can effectively reduce the risk of lung cancer and improve treatment outcomes. By identifying and addressing viruses involved in lung cancer before malignancy develops, significant strides can be made in preventing this disease.

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Conflict of interest
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Ethical statement
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