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Virally Induced Cancer: Insights into Tumor-Associated Viruses and Emerging Therapeutic Strategies

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Abstract

Cancer remains a major global health challenge, with several human viruses playing a critical role in its development. These "tumor viruses" can integrate into the host genome, disrupting genetic integrity, inhibiting cell death, and promoting uncontrolled cell growth. This report investigates eight key viruses associated with human cancers: Epstein-Barr virus (EBV), Human papillomavirus (HPV), Herpesvirus 8 (HHV-8), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human T-lymphotropic virus 1 (HTLV-1), Merkel cell polyomavirus (MCV), and Human Immunodeficiency virus 1 (HIV-1). Understanding how these viruses contribute to cancer can enhance cancer management strategies. Recent advancements, such as preventive vaccines, oncolytic viruses, and gene therapy, offer promising avenues for reducing cancer risk and improving patient outcomes.

Keywords: Cancer, Virus, Cancer, Disease, tumor viruses

Introduction

Cancer is a significant global health burden. According to GLOBOCAN 2018, cancer is expected to cause 9.6 million deaths this year, excluding non-melanoma skin cancers, and there will be 18.1 million new cancer cases (Bray et al. 2018). Approximately 1.3 million cases, or 15% of all cancers, are attributed to viral infections (Plummer et al., 2016). While viral infection is a significant factor in cancer development, it often requires additional contributing factors. Carcinogenesis is influenced by environmental and lifestyle factors, genetic predispositions, immune responses, chronic inflammation, and metabolic changes (Chang, Y., et al. 2017, Moore, P. S., & Chang, Y. 2010). Viral proteins and immune system responses can disrupt cell homeostasis in chronically infected cells. Cancer is a genetic disease influenced by how cells grow and divide. Mutations can arise from errors during cell division, environmental factors like UV radiation and smoking, and inherited genetic traits (Czene & Hemminki, 2002). Typically, cells with DNA damage are eliminated by the body, but this ability diminishes with age, increasing cancer risk later in life (Hoeijmakers, 2009).

The International Agency for Research on Cancer (IARC) has classified eight human viruses as "carcinogenic to humans," including hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), Epstein-Barr virus (EBV), human T-cell lymphotropic virus type 1 (HTLV-1), Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8), Merkel cell polyomavirus (MCV), and human immunodeficiency virus type 1 (HIV-1) (Javier and Butel, 2008). Viruses, composed of protein coats and genetic material (DNA or RNA), can sometimes cause cancer through genetic mutations, chronic inflammation, disruption of normal cell division control, or immune system

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alterations that hinder the body's ability to combat cancer cells (Camil Castelo-Branco, 2013; Foster J.E., et al., 2018). These mechanisms may lead to cancer by increasing the likelihood of genetic mutations or enhancing tissue injury and inflammation.

Viral carcinogenesis theories

Cancer has been recognized for millennia, with early evidence from ancient fossils and Egyptian mummies. Initially, the Egyptians attributed cancer and other diseases to divine forces, reflecting their limited grasp of disease mechanisms (Kardinal, C. G., & Yarbro, J. W. 1979). The Greek physician Hippocrates (460–370 BCE) proposed the humoral theory, suggesting that an imbalance of bodily fluids caused cancer. This theory dominated over 1,300 years (Grammaticos, P. C., & Diamantis, A. 2008). The 19th century marked a significant shift with the advent of the microscope, leading to the cellular theory of cancer. Rudolf Virchow, a key figure in this period, demonstrated that cancer originates from cells (Kardinal, C. G., & Yarbro, J. W. 1979). Early theories linking cancer to infections were revised as scientific advancements revealed the role of viruses.

In the early 20th century, Vilhelm Ellermann and Olaf Bang discovered the avian leukemia virus. At the same time, Richard Shope and E. Weston Hurst identified that the cottontail rabbit papillomavirus (CRPV) could induce skin cancers (Javier, R. T., & Butel, J. S. 2008; Shope, R. E., & Hurst, E. W. 1933). This period confirmed the significance of viruses in cancer causation. Further research in the 1960s, including the discovery of SV40 in monkey kidney cells, led to establishing the U.S. Special Virus Cancer Program, emphasizing viral contributions to cancer (Sweet, B. H., & Hilleman, M. R. 1960). The 1965 discovery of Epstein-Barr virus (EBV) in Burkitt's lymphoma cemented EBV's role in various human cancers (Butel, 2000). Advancements in viral oncogenesis continued with the discovery of reverse transcriptase in RNA tumor viruses, leading to the provirus hypothesis (Temin, 1964). The Nobel Prize-winning work of Howard Temin and David Baltimore in 1975 highlighted the role of reverse transcriptase, deepening our understanding of viral contributions to cancer (Huebner, R. J., & Todaro, G. J., 1969). Current research continues to explore the complex interactions between viruses and cancer, uncovering new viral oncogenes and mechanisms of tumor formation.

The role of viruses in cancer development

In the early 20th century, high cancer rates in certain professions led to the belief that synthetic substances were the primary cause. However, since the 1980s, research has shown that viruses significantly contribute to cancer development. Viruses cause cancer through both direct and indirect mechanisms. Directly, viral oncoproteins can disrupt tumor suppressor pathways (e.g., pRb, p53) or activate oncogenic pathways (e.g., Ras, Myc), resulting in cancer. Indirectly, viruses may induce immunosuppression or chronic inflammation, altering the tissue environment and promoting cancer progression (Ciccia, A., & Elledge, S. J. 2010; Moore, P. S., & Chang, Y. 2010).

Carcinogenic viruses affect cells in various ways. Direct transformation involves viruses expressing oncogenes that alter infected cells, often leading to monoclonal tumors. Retroviruses integrate into the host's DNA, potentially downregulating cellular oncogenes or tumor suppressor genes through insertional mutagenesis. Conversely, Epstein-Barr Virus (EBV) can transform cells without integration by expressing its oncogenes. Viruses can persist as episomes or integrate into host DNA, as seen with retroviruses and the hepatitis B virus. Indirectly, viruses like HIV contribute to cancer by causing chronic inflammation, attracting immune cells, and causing ongoing tissue damage, which increases susceptibility to EBV-associated lymphomas.

Cancer-causing viruses generally fall into two categories: those causing chronic inflammation (e.g., HBV and HCV, leading to hepatocellular carcinoma) and those causing immunosuppression (e.g., HIV, linked to lymphomas). Cancer development involves initiation through genetic damage, promotion of cell growth, malignant conversion to a cancerous state, and progression involving genetic changes and metastasis (Reddy, A. L., & Fialkow, P. J. 1983; Verma, A. K., & Boutwell, R. K. 1980; Yuspa, S. H., & Poirier, M. C. 1988; Jones, P. A., & Baylin, S. B.

2002; Loeb, L. A., & Cheng, K. C. 1990; Lengauer, C. et al. 1988).

Key viruses linked to cancer

Epstein-Barr Virus (EBV). EBV is the first identified human tumor virus discovered by Tony Epstein and Yvonne Barr in cells from endemic Burkitt's lymphoma. It is linked to Burkitt's lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma (NPC). EBV infects over 90% of people worldwide, primarily through saliva but also through blood, semen, and intimate contact (Dunmire S. K. et al., 2018; Gessese, T., Asrie, F., & Mulatie, Z., 2023). EBV infection raises the risk of several lymphomas, including Burkitt's and HIV-associated lymphomas. There is currently no vaccine for EBV.

Human Papillomavirus (HPV). HPV comprises over a hundred strains, with some causing warts and others linked to genital cancers. Most genital HPV types are benign, but strains like HPV-16 and HPV-18 can lead to cervical dysplasia and cancer if left untreated (Nunes E. M., et al., 2018). HPV is spread through skin-to-skin contact and is responsible for 70% of cervical cancer cases (Soe, N. N., et al., 2018; Araldi, R. P., et al., 2018). The HPV vaccine prevents 70–80% of these cancers and is available up to age 45.

Herpesvirus-8 (HHV-8). HHV-8, also known as Kaposi sarcoma-associated herpesvirus, primarily causes Kaposi sarcoma and is more prevalent in HIV-infected individuals. It spreads through saliva, sexual contact, and blood transfusions. There are ongoing trials for drugs targeting HHV-8-related disorders (Leão, J. C., et al. 2002; Ablashi, D. V., et al. 2002).

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV). Both HBV and HCV can lead to hepatocellular carcinoma (HCC), with HBV causing direct genomic integration and HCV leading to chronic liver damage and cirrhosis. HCV primarily spreads through blood contact and lacks a vaccine, though it can be treated effectively (Chen et al., 2006).

Human T-Lymphotropic Virus-1 (HTLV-1). HTLV-1, a retrovirus, affects 5-10 million people globally and can lead to aggressive T-cell leukemia or lymphoma in 1-5% of infected individuals. It spreads through blood, sexual contact, and from mother to child (Radygina, L. V., & Mochalova, L. V., 2024).

Merkel Cell Polyomavirus (MCV). MCV is linked to Merkel cell carcinoma, a rare but aggressive skin cancer. Transmission likely occurs through skin contact or contaminated surfaces. There are no vaccines for MCV, though Merkel cell carcinoma is treatable if detected early (Liu, W., et al., 2016; Becker, J. C., et al., 2017).

Human Immunodeficiency Virus-1 (HIV). HIV, causing acquired immunodeficiency syndrome (AIDS), attacks T cells, weakening the immune system and increasing the risk of various cancers, including lymphomas, Kaposi's sarcoma, and cancers of the mouth and throat. HIV is spread through body fluids and from mother to child. While there is no cure, it can be managed with medication (German Advisory Committee, 2016).

Emerging approaches in cancer control

Vaccination represents a promising method for cancer prevention by targeting cancer-causing viruses. Preventive vaccines have successfully reduced diseases like smallpox and polio, suggesting similar benefits could be achieved for oncoviruses (Schiller, J. T., & Lowy, D. R. 2010). Although no licensed therapeutic cancer vaccines exist, targeting persistent viral infections and premalignant lesions, especially those expressing viral oncogenes, could be effective (Mesri et al., 2014). Vaccination is particularly impactful in low-resource settings, where infectious agents contribute significantly to cancer rates (De Flora, S., & Bonanni, P., 2011). However, the long latency between viral infection and cancer can delay vaccine benefits (Trovato et al., 2020). Oncolytic viruses, engineered to destroy cancer cells, treat specific cancers, like skin cancer. Recent advancements show that novel oncolytic viruses target cancer cells and enhance immune responses within tumors (Gonzalez et al., 2018). These dual-function viruses have proven more effective in reducing melanoma tumors in mice than standard oncolytic viruses (Kaufman et al., 2015).

Immunotherapy, aimed at boosting the immune system to fight cancer, includes various strategies that enhance the immune system’s ability to identify and destroy cancer cells (Bondhopadhyay

et al., 2020). Emerging immunotherapies are expected to significantly advance cancer treatment. Gene therapy, involving the modification of genes to treat cancer, can enhance the body's ability to target and destroy damaged cells (Das et al., 2015). For oncoviruses, gene therapy may address viral mechanics or genetic susceptibility markers. Preventive measures, including lifestyle changes, regular screening, and vaccinations, can reduce cancer risk by up to 50% and improve early detection and treatment outcomes (Qiang Ma et al., 2022).

Conclusion and recommendations

In conclusion, the global cancer burden remains substantial, with viral infections contributing to approximately 15% of all cancer cases. Historical and modern research has confirmed the role of several key viruses in cancer development, including HPV, HBV, and EBV. While these findings underscore the importance of viral contributions to cancer, they also highlight the complexity of carcinogenesis, which involves a combination of viral, environmental, and genetic factors. Emerging approaches in cancer control offer hope for significant advancements. Preventive vaccines, such as those for HPV and HBV, have shown promise in reducing cancer incidence. Oncolytic viruses and immunotherapies advance cancer treatment by targeting tumor cells and boosting the immune response. Gene therapies also represent a promising frontier, aiming to address viral mechanisms and genetic vulnerabilities. Overall, integrating preventive strategies, cutting-edge treatments, and lifestyle modifications holds the potential to significantly reduce cancer risk and improve patient outcomes globally.

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