Oncogenic Viruses in Amazonas: Occurrence, Carcinogenic Mechanisms, and the Therapeutic Potential of Regional Biodiversity.

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1. Introduction

The development of the group of pathologies collectively referred to as "cancer" has been linked to multiple environmental factors, such as solar radiation and soot, occupational exposures like coal tar and asbestos, the use of certain drugs including cyclosporine and tamoxifen, as well as lifestyle and dietary habits such as alcohol consumption, obesity, and physical inactivity. In addition, infectious agents, including parasites, fungi, bacteria, and viruses, have also been implicated in carcinogenesis[1]. In this context, at least 12% of human cancer cases worldwide are attributed to infectious agents, with viruses accounting for the majority[2].

Referred to as oncogenic viruses, or simply oncoviruses, this group of pathogens currently includes: (1) Human papillomavirus (HPV), (2) Hepatitis B virus (HBV), (3) Hepatitis C virus (HCV), (4) Epstein–Barr virus (EBV or HHV-4), (5) Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), (6) Human T-cell lymphotropic virus type 1 (HTLV-1), and (7) Merkel cell polyomavirus (MCPyV). Additionally, (8) Human immunodeficiency virus type 1 (HIV-1) has also been considered, not for a direct carcinogenic role, but for its capacity to increase cancer risk through immunosuppression in people living with HIV (PLWHIV). These eight viruses are classified in Group 1 of biological carcinogenic agents in humans by the International Agency for Research on Cancer (IARC)[2].

The state of Amazonas, Brazil, is characterized by a vast territorial extension, a geographically dispersed population, and transportation that is predominantly fluvial and subject to seasonal river fluctuations. These factors impose unique challenges on the healthcare system, including long travel distances, high operational costs, and inequities in access to medical services[3]. Within this complex scenario, the occurrence of several oncogenic viruses has already been reported, although the available data are mostly derived from isolated epidemiological studies, which limits the construction of a comprehensive overview of the situation in the state.

The compilation of epidemiological data can provide critical insights into the occurrence of oncogenic viruses in Amazonas and support the design of context-specific management strategies. Complementarily, understanding the oncogenic mechanisms of these viruses can highlight natural products already reported in the region that may serve as a basis for therapeutic innovation, while also valuing regional and traditional knowledge

2. Methodology

This integrative review was conducted in two complementary stages. First, to assess the occurrence of oncogenic viruses in Amazonas, a search was performed in Google Scholar, ScienceDirect, Scopus, LILACS, and PubMed using the combination of each virus name (HPV, HBV, HCV, EBV/HHV-4, HHV-8/KSHV, HTLV-1, MCPyV, HIV) with "Amazonas". The most recent original epidemiological studies published in the last five years were included, focusing on general and heterogeneous populations, such as random community samples or blood donors. Review articles and book chapters were excluded. In the second stage, the carcinogenic mechanisms of the viruses reported in Amazonas were reviewed in the literature, along with the potential of natural products from the region to exhibit antiviral activity against them.

3. Results and Discussion

The epidemiological profile of oncogenic viruses in Amazonas highlights significant public health challenges. In this context, HPV is the leading cause of cervical cancer, the second most common cancer in the State of Amazonas (31.7/100,000) [4] and epidemiological studies in the Northern region of Brazil indicate a wide genotypic diversity, with types 16, 18, 31, 33, 45, and 58 being the most prevalent [5]. HBV and HCV, major risk factors for hepatocellular carcinoma, were reported in Amazonas between 2010 and 2020, with nine municipalities accounting for the majority of hepatitis B cases: Manaus (2,173; 58.4%), Coari (229; 4.9%), Eirunepé (227; 4.8%), Tefé (172; 3.7%), Fonte Boa (126; 2.7%), Manacapuru (114; 2.4%), Lábrea (103; 2.2%), Boca do Acre (92;1.9%), and Atalaia do Norte (84;1.8%) [6].

EBV, which can cause lymphoma and infectious mononucleosis in immunocompromised individuals, shows high prevalence in Amazonas, with 95.9% in Presidente Figueiredo and 97% in Manaus[7]. HTLV, associated with adult T-cell leukemia/lymphoma (ATLL), was detected in 0.15% of blood donors in the state between 2018 and 2022[8]. As for HIV, which can increase cancer risk, the state of Amazonas reported the highest AIDS detection rate in Brazil in 2021–2022, with Manaus showing the greatest incidence. The state-wide AIDS rate was 52.2/100,000 inhabitants, more than double the national average of 21.3/100,000[9]. Supporting this concern, a study at the HEMOAM Foundation identified recent HIV infections in 30.3% (43/142) of donor samples through serological and molecular analyses [10].

In summary, among the eight currently recognized oncoviruses, six (75%) have been reported in the state of Amazonas, with KSHV and MCPyV remaining without recent epidemiological studies, which may reflect either the absence of cases or a lack of reporting and surveillance. The available data draw particular attention to EBV, HPV, and HIV, which have shown high prevalence in recent studies. Despite that, HBV, HCV, and HTLV, although less frequent, should not be overlooked due to their significant clinical relevance.

With respect to the mechanisms, oncoviruses drive carcinogenesis through diverse and multifaceted processes (Figure 2). Most of them encode oncoproteins that disrupt key tumor-suppressive pathways, such as p53 and pRB, thereby promoting uncontrolled proliferation, sustaining viral persistence, and ultimately inducing genomic instability[2,11,12]. In this context, viruses such as HPV rely on a limited set of multifunctional oncoproteins to promote tumorigenesis, whereas EBV, which possesses a larger genome, employs a broader arsenal that includes not only multiple viral proteins but also microRNAs[11,12].

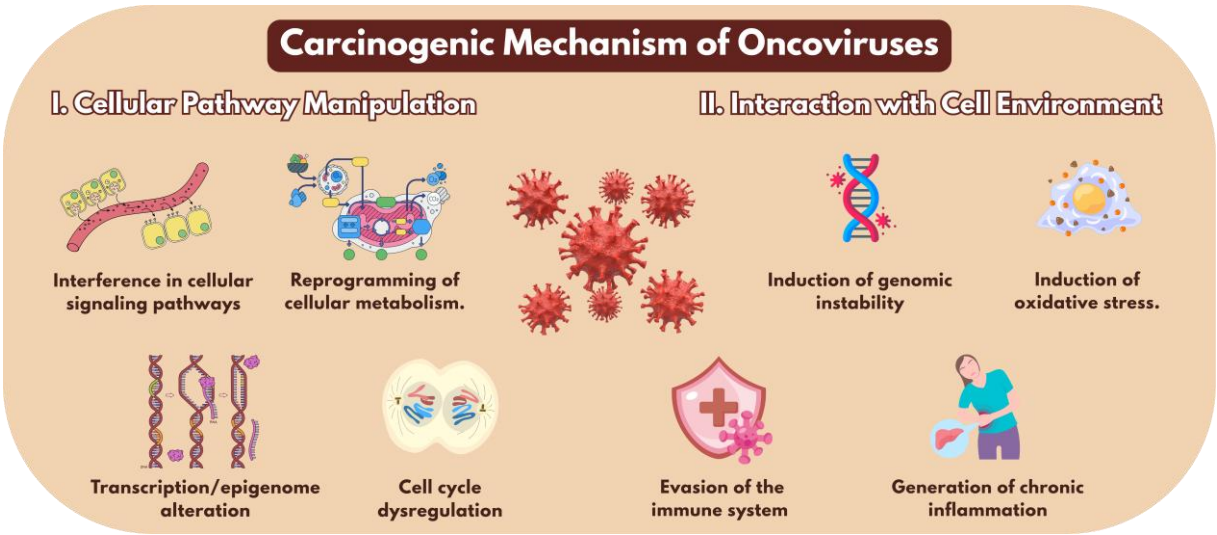

Figure 1. Main mechanisms of virus-induced carcinogenesis. The infographic illustrates viral strategies divided into two categories. On the left (I), manipulation of cellular pathways involving direct interference with cellular machinery. On the right (II), interaction with the cellular environment affecting both cellular and tissue contexts.

The PI3K-AKT-mTOR, MAPK, and NF-κB pathways are among the main signaling cascades targeted by oncoviruses[2,11]. HPV, EBV, and HTLV-1 activate PI3K-AKT-mTOR even under nutrient limitation, promoting proliferation and tumor cell survival. MAPK, regulating genes for proliferation and immune response, is hijacked by HCV and HPV to enhance viral production and, in some cases, cell motility and metastasis. NF-κB is hyperactivated by EBV (via LMP1), contributing to cancer progression[14]. Notch and WNT-β-catenin signaling are also modulated by HPV, EBV, and HBV, affecting proliferation, differentiation, and invasiveness[11].

In addition to the direct manipulation of cellular signaling pathways, oncoviruses employ indirect and shared mechanisms to promote carcinogenesis. These include the establishment of chronic and persistent infections, often asymptomatic for years, which allows gradual adaptation to cellular processes. In this context, infection by these viruses induces genomic instability, impairs DNA damage response (DDR), facilitates immune evasion, modulates microRNAs (miRNAs), and reprograms cellular metabolism[2,11,12].

Genomic instability is promoted by several oncoviruses: HPV induces chromosomal instability[13], EBV increases reactive oxygen species causing DNA damage[11,12], and HBV often triggers insertional mutagenesis[13]. These viruses can also evade immune detection by disabling antiviral defenses such as the cGAS-STING pathway, manipulate host or viral miRNAs to regulate survival and proliferation (as seen in EBV), and reprogram cellular metabolism, exemplified by the "Warburg effect" in HPV and EBV, supporting infected cell growth and proliferation[11,12].

Although HIV-1 is not a classical oncovirus, it contributes to carcinogenesis mainly through immunosuppression, increasing the risk of co-infections with oncogenic viruses such as HPV and EBV, thereby facilitating virus-associated cancers. Recent evidence also shows that HIV-1 proteins (gp120, Nef, p17, Tat, and RT) exert direct oncogenic effects, inducing oxidative stress and ROS production, damaging DNA, proteins, and lipids in both infected and neighboring "bystander" cells. Tat, for example, promotes oxidative stress via NADPH oxidases and mitochondrial dysfunction, while released HIV-1 proteins can enhance malignant transformation or tumorigenicity of surrounding cells, including upregulation of HPV E6 and E7, favoring epithelial-mesenchymal transition[14].

Understanding these mechanisms plays a key role in therapeutic strategies, as virus-associated cancers may offer unique opportunities for both prevention and treatment. Vaccines against HBV and HPV have significantly reduced HBV-related hepatitis, hepatocellular carcinoma, and high-grade cervical intraepithelial neoplasia. Additionally, antiviral therapy in infected individuals, such as HCV treatment with ribavirin, interferon, and protease inhibitors, has decreased hepatocellular carcinoma incidence, especially when viral clearance occurs before cirrhosis[15].

Therapeutic strategies for other oncoviruses can vary and target distinct mechanisms. In the case of EBV, preclinical studies suggest that inhibition of glutaminases GLS1 and GAC may represent a potential approach for EBV-associated cancers[16]. Additionally, the combination of PD-1 inhibitors with radiotherapy has resulted in complete remission in a patient with EBV-positive intrahepatic cholangiocarcinoma[17]. Regarding HTLV-1, treatment of adult T-cell leukemia/lymphoma (ATLL) has focused on therapies targeting surface molecules, monoclonal antibodies, interferon-based therapy, chemotherapy, and hematopoietic stem cell transplantation[18]. In the case of HIV-1, there is no therapy specifically directed at associated cancers; however, controlling the infection with antiretroviral therapy helps preserve immune function in people living with HIV[16].

The vast Amazonian biodiversity holds considerable potential for the discovery of novel antiviral agents, including compounds active against oncoviruses. Traditional medicine in the region has long employed natural products for the treatment of various diseases, and although some studies are beginning to validate these practices, this remains a largely underexplored

field and a critical gap in knowledge[19]. In Amazonas, in particular, research specifically addressing this potential is still scarce.

Nevertheless, Amazonian plants with traditional antiviral uses, such as jucá (Libidibia ferrea (Mart. ex Tul.) L.P. Queiroz) and vindicá (*Alpinia zerumbet* L.), have shown documented activity against herpesvirus and HIV, respectively[19]. Other species with hepatoprotective activity, including quebra-pedra (Phyllanthus niruri L.) and erva-botão (Eclipta prostrata (L.) L.), have been reported to exhibit potential inhibitory effects on HBV replication and anti-HCV activity[20]. Edible and medicinal mushrooms from the Amazon region also represent a promising source of novel antiviral agents. Several studies have demonstrated their ability to produce bioactive molecules with antiviral properties, including lectins, protease inhibitors, oxidative enzymes, and phenolic compounds, in species such as Lentinus strigosus, Pleurotus ostreatus, and Ganoderma spp., underscoring this group as a valuable target for bioprospecting[21-23].

4. Conclusion

The state of Amazonas exhibits a high occurrence and clinical relevance of oncovirus infections, representing a serious challenge for regional public health. In contrast, research focused on developing therapeutic alternatives from its vast and unique biodiversity remains remarkably scarce. Given the clinical and epidemiological significance of these diseases, pharmacological exploration of the local flora and funga constitutes a strategic field that urgently requires greater attention and investment, aiming at the development of novel and effective therapies.

Keywords: Oncoviruses, Amazonian, Natural-antiviruses

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Divulgation

The authors and reviewers have not reported any conflicts of interest during the evaluation. Therefore, the Pan-Amazonian Oncology Congress holds the copyright and has the approval and permission from the authors for dissemination of this abstract via electronic means.

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