Journal Homepage: https://sayamjournal.com/

Article

# Human Oncoviruses: A Journey from Epstein Barr virus (EBV) to Acquired Immunodeficiency Syndrome (AIDS) through Cancer

Kanchan Karmakar

Assistant Professor, Department of Biochemistry, Asutosh College (Affiliated to University of Calcutta), 92 S.P Mukherjee Road, Kolkata 700026

Corresponding author Email: kanchan.karmakar@asutoshcollege.in

ARTICLE INFO

*Keywords:*

Epstein Barr virus (EBV), Acquired Immunodeficiency Syndrome (AIDS), Human oncovirus, Pathogenesis, Cancer

Received : 06/08/2023
Accepted : 20/02/2024
Date of Publication: 02/06/2024

ABSTRACT

A major breakthrough in oncology and a major contribution to our understanding of human oncoviruses has been made with the discovery of the Epstein Barr virus (EBV), the first virus known to cause cancer. This trip has shown a complex link between viral infections and oncogenesis, spanning from EBV to the complexity of Acquired Immunodeficiency Syndrome (AIDS). Since EBV has been linked to Burkitt's lymphoma, researchers have been investigating the viral processes behind cellular transformation. The Human T-cell Leukaemia Virus (HTLV-1) and Human Papillomavirus (HPV) have yielded additional discoveries that have broadened our understanding of immune evasion, viral oncogenes, and the role chronic inflammation plays in vehicle development. A paradigm shift emphasizing the interaction between immunodeficiency and cancer was brought about by the emergence of AIDS.

## Introduction

An important area of research in the history of medicine is the study of human oncoviruses, which traces a lineage from the identification of the Epstein-Barr virus (EBV) to the current fight against the diseases that cause AIDS and related cancers. This journey began with the discovery that EBV is the first human virus that can cause cancer, specifically Burkitt's lymphoma. This finding also provided an impulse for the advancement of the field of cancer virology. Cancer is not frequently caused by oncovirus infections, despite their prevalence (Zur Hausen, 2009). Cancer development requires one or more additional insults, such as immunosuppression, environmental mutagens, or persistent inflammation (Bouvard et al., 2009; Moore & Chang, 2010). Although there is considerable overlap between the two classifications, oncoviruses are categorized as either direct or indirect carcinogens (Moore & Chang, 2010). While indirect carcinogens generate persistent inflammation, which might result in oncogenic transformation, direct carcinogenic viruses have viral oncogenes that directly contribute to neoplastic cellular transformation (Parsonnet, 1999; zur Hausen, 2001). EBV, hepatitis B virus (HBV), human papillomavirus (HPV), human herpesvirus-8 (HHV-8), and Merkel cell polyomavirus (MCPyV) are examples of oncogenic DNA viruses. Hepatitis C virus (HCV) and human T-cell lymphotropic virus-1 (HTLV-1) are examples of oncogenic RNA viruses. The spectrum of oncoviruses expanded with research, including diseases such as the human papillomavirus (HPV), the hepatitis B and C viruses (HCV and HBV), and the human T-cell leukaemia virus (HTLV-1). Each of these agents made a distinct contribution to our comprehension of viral oncogenesis. The emergence of AIDS provided a fresh perspective on this investigation, exposing how

immunodeficiency could precipitate a diverse array of cancers, and thus, interlinking the narratives of virology, immunology, and oncology. In addition to illuminating the processes by which viruses can change healthy cells into cancerous ones, this scientific journey highlights the vital role that vaccinations and other preventative measures play in the fight against these insidious diseases.

## The history and impact of EBV as the first human oncovirus

Some observations in the 19th century led to the theory that some cancers could be caused by an infectious agent, raising the prospect that cancer could be spread from mother to child or between spouses. However, it wasn't until the middle of the 1900s that the first human cancer virus was identified. In 1964, Epstein and Barr identified this virus, which they named EBV, in the tumor cells of Burkitt's lymphoma patients (Mundo et al., 2023). Subsequent studies showed that EBV could create immortal cell lines from healthy white blood cells. A wide range of additional cancers derived from lymphoid or epithelial cells are also linked to EBV, such as lymphomas related to HIV and post-transplantation, Hodgkin's lymphoma, T-cell lymphoma, nasal-type NK/T-cell lymphoma, nasopharyngeal carcinoma, and several gastric cancers (McLaughlin-Drubin & Munger, 2008). Approximately 200,000 cases of EBV are reported each year, accounting for 1.5% of all cancer cases globally (Esau, 2017). Nonetheless, most of the healthy individuals who contain the EBV virus do not go on to develop cancer, indicating that there may be the involvement of other genetic and environmental factors. This idea is corroborated by the regional distribution of certain EBV-related diseases, such as nasopharyngeal carcinoma in Asia and Burkitt's lymphoma in Africa. Before EBV, there have been various attempts to identify viruses that can cause cancers in humans. An Italian physician named Guiseppe Ciuffo conducted an experiment in 1907 in which he injected himself with a filtered extract of warts (Ciuffo, 1907). Warts, he said, were contagious, and he was searching for the "invisible virus" that created them. This was the initial test that appeared to support the viral source of human tumours, but it was largely ignored, probably because warts are not malignant and Ciuffo's article was in Italian (Ciuffo, 1907). Early in the 20th century, there were other discoveries on animal cancer viruses, such as the ability of cell-free extracts to spread sarcoma and leukaemia in birds. However, the concept that viruses might cause cancer was met with scepticism by many scientists. (Ciuffo, 1907; Rous, 1983). It was only in the 1950s, when several reports showed the transmission of mouse cancers by cell-free extracts, that the theory of oncoviruses gained acceptance (Fulghieri & Bloom, 2014). Another significant achievement took place in 1949 when virus-like particles later named HPV were isolated from skin papillomaviruses, indicating that warts may have a viral origin (Fulghieri& Bloom, 2014; Strauss et al., 1949). However, it took until 1976 for a proposal that some types of HPV also contribute to cervical cancer (Zur Hausen, 1976).

The identification of the oncovirus EBV came about as a consequence of a cooperative effort involving multiple foreign researchers. A medical officer in Uganda named Denis Burkitt made the first observation of a unique lymphoma syndrome in African infants in 1957 when he saw two cases of deadly jaw tumors and went on to gather further information about the illness (Wright, 2012). The lymphoma had a particular geographic distribution, being more common in hot, humid, tropical regions of central Africa and less common in cold, dry, high-altitude locations. When it was found that saliva distributes the EBV virus, his notion that the lymphoma was caused by an insect-transmitted virus was refuted. Subsequently it was proposed that malaria and the mosquitoes that transmit it might work in concert with EBV to promote the growth of lymphoma (Klein, 2009). Since the relationship between EBV and malaria is complicated and poorly understood, research on this theory is still ongoing.

The isolation of EBV from the lymphoma cells was achieved by Anthony Epstein, a medical virologist who attended a lecture by Burkitt in 1961 and became interested in the disease. He obtained the tumor samples from Burkitt and detected viral particles in the cultured cells, which he named after himself and his colleague Yvonne Barr (Epstein & Eastwood, 1995). However, he could not demonstrate that the virus was responsible for the lymphoma, as more evidence was needed for that conclusion. Several experiments to describe EBV and its carcinogenic potential were conducted by two American virologists named Werner and Gertrude Henle, who contributed some of this evidence (Henle, 1968). They demonstrated that EBV DNA was present in lymphoma cells and that EBV may cause blood cell growth when combined with healthy leukocytes. They also explored the EBVrole in infectious mononucleosis, a different disease that also involved the virus, after a lab technician working with them contracted the illness (Henle et al., 1979). It was observed that EBV antibodies were produced during the infection, and that EBV could cause various clinical manifestations (Henle et al., 1979). By the late 1970s, the accumulated data from the Henles and other researchers confirmed that EBV was a human carcinogen, and the first of its kind.

## Different genes of EBV

The herpes virus, EBV that infects human immune cells primarily B and T cells and causes various diseases, including cancers. EBV has two types, EBV-1 and EBV-2, which differ in their genetic variations of the EBNA2 and EBNA3A, 3B, and 3C genes. These differences affect EBV's capacity to infect T cells and produce lymphoblastoid cell lines (LCLs) from B cells (Fig 1). While EBV-2 has a greater affinity for T cells, EBV-1 is more effective at transforming B cells. EBV remains a latent infection in the host cells, which is capable of reactivating in specific circumstances. The limited expression of viral genes that EBV expresses during latency is represented by four patterns: 0–I, II–III. There are differences in the latency pattern based on the kind of cell, duration after infection, and cellular environment. For instance, peripheral blood or the germinal centre. The immediate early genes BZLF1 and BRLF1, which are activated by EBV upon entering the lytic cycle, cause the expression of numerous viral proteins, including BILF1, BMRF1, and BNLF2A. Non-coding RNAs (ncRNAs), such as viral microRNAs, are also produced by EBV and play a variety of roles in both sustaining viral latency and advancing the development of cancer (Mundo et al., 2023). The non-immune, immune, and malignant cells that make up the tumour microenvironment (TME) can all be altered by EBV. These cells interact to provide a distinct immunological profile that represents the immune response. By fostering an environment that suppresses the immune system, EBV can manipulate the TME to its benefit, which promotes the development and spread of cancers linked to the virus. The role of BILF1, a G protein-coupled receptor (GPCR), in EBV pathogenesis and medication development has been extensively researched (Knerr et al., 2021). Viral persistence, cancer, and immune evasion are all facilitated by BILF1's interference with several cellular pathways and activities. BILF1 also affects the epidemiology, treatment, and prevention of EBV-related cancers. Zanella, L. et al. analysed over a thousand EBNA3A sequences from different EBV variants, clinical manifestations, and geographic regions. They identified nuclear localization signals (NLSs), six peptide motifs that varied between EBV-1 and EBV-2(Zanella et al., 2021). They found that EBNA3A from EBV-2 had two non-canonical NLSs (NLS3 and NLS4) compared to EBNA3A from EBV-1. They proposed that these variances could influence the cell-type specificity of EBV. A recent review by Wang, L. et al. about the recent advances in understanding LMP1, a key viral protein that regulates multiple cellular pathways. Wang and Ning (2021) concentrated on the unique elements of the LMP1 signalosome, including LUBAC, p62, and LIMD1. They argued that in order to modify particular cellular processes, LMP1 recruits various components. For instance, LMP1 inhibits the anti-oncogenic Hippo pathway by using LIMD1, disrupts cellular selective autophagy and antioxidative stress by using p62, and regulates the Wnt/β-Catenin/TCF proliferation pathway by using UCHL1. The immunomodulatory characteristics of BARF1, a virus protein that inhibits macrophage activation and differentiation, were investigated by Lo, A.K.F. et al. (Fig. 2). They also explained how BARF1 stimulates genes linked to cell cycle regulation and the NF-κB pathway, which improves immortalization and malignant transformation. They talked about the possible approaches to using BARF1 as a novel therapeutic target for epithelial malignancies caused by EBV.

## The3dentifycation, description, and connection of HTLV-1 to ATL

In 1979, Robert Gallo and others at the National Cancer Institute discovered the first human retrovirus through its extraction from a cutaneous T-cell lymphoma patient. In 1980, they named it human cutaneous T-cell lymphoma virus (HTLV) after they detected it and published their findings (Rho et al., 1981). Later, scientists identified another related retrovirus as HTLV-1 and HTLV-2 after discovering it in a patient with T-cell variant hairy cell leukaemia (Kalyanaraman et al., 1982). These patients, however, most likely had a distinct illness called ATL, which was identified in Japan, and were misdiagnosed. ATL is a rare and aggressive T-cell cancer characterized by skin lesions, lymphadenopathy, hepatosplenomegaly, leucocytosis, and aberrant lymphoid cells with lobulated or indented nuclei. It primarily affects the southern island of Kyushu. Kiyoshi Takatsuki and associates initially reported ATL in 1977, both at the International Congress of Haematology in Kyoto and in Blood (Uchiyama et al., 1977). The discovery of an antibody against viral antigens in the serum of ATL patients, but not in healthy individuals, was made in 1981 by Yorio Hinuma and his colleagues in Kyoto, confirming this (Hinuma et al., 1981). Additionally, a retrovirus known as the ATL virus (ATLV) was identified from ATL cells. The earlier identification of BL, another lymphoma condition, and the virus that was linked to it, EBV—the first virus that was shown to cause cancer in humans—had an impact on the discovery of ATL and ATLV (Yoshida et al., 1982). Despite the discovery of other animal leukaemia viruses in the 1970s and mammalian retroviruses in the 1950s, research on human oncoviruses had been mainly unpopular and ineffective until the isolation of EBV and ATLV. Concurrently, US researchers isolated human retrovirus (HTLV-1) from cutaneous T-cell lymphoma patients. In 1983, they found that ATLV and HTLV-1 were the same

virus, leading to the popular term HTLV-1 (Watanabe et al., 1984). Following HTLV-1's isolation, numerous investigations conducted by collaborative American and Japanese researchers demonstrated that HTLV-1 was the cause of ATL, establishing HTLV-1 as the first human retrovirus with the ability to cause illness.

## The role of EBV and HTLV-1 in AIDS research

HTLV-1 was shown to cause ATL through a series of investigations conducted by collaborative American and Japanese researchers after it was isolated, establishing HTLV-1 as the first human retrovirus with the ability to cause disease. The rare and severe malignancy known as adult T-cell leukaemia (ATL) has been linked to HTLV-1. The discovery of HTLV-1 also made it possible to identify HTLV-2, another human retrovirus linked to neurological illnesses and hairy cell leukaemia. Both HTLV-1 and HTLV-2 belong to the same family as HIV, the causative agent of AIDS. The identification of HTLV-1 and HTLV-2 has profound effects on the study of AIDS, a pandemic that first surfaced in the early 1980s. The earliest indication of AIDS was the development of Kaposi sarcoma and pneumocystis pneumonia in young gay males. Both licensed antiviral medications and skilled infectious disease experts were scarce in the United States at that time. The majority of viral illnesses were either vaccine-preventable or self-limiting (Mayer & Pizer, 2004). Patients with AIDS had a dismal outlook because the only treatment available for their opportunistic infections and cancers was palliative care. However, the scientific community responded swiftly to the challenge of AIDS. Within 2 years of its clinical recognition, a retrovirus was isolated and identified as the cause of AIDS by Montagnier and Barré-Sinoussi (Barre-Sinoussi et al., 2004). This virus was initially known as HTLV-III, but later retitled HIV (Broder & Gallo, 1984). The techniques and protocols developed by Gallo's lab for the characterization of HTLV-1 and HTLV-2 facilitated the isolation and confirmation of HIV. In 1986, the FDA authorized zidovudine, the first antiretroviral medication (Łagocka et al., 2021). Although it was not very effective, it marked the beginning of a new phase of treatment for HIV infection. The earlier understanding and expertise from the HTLV-1 and HTLV-2 study was a major factor in the quick advancement of AIDS research. Furthermore, HTLV-1 and HTLV-2 have a direct influence on the pathophysiology and epidemiology of AIDS. It has been discovered that homosexual males living with AIDS are more likely to develop several cancers, including non-Hodgkin lymphoma (NHL). One of the first types of NHL to be linked to AIDS was Burkitt-like lymphoma, which resembled the endemic form of BL that occurs in Africa. EBV, the oncogenic virus identified in 1964, is the cause of BL (Doll & List, 1982). Nasopharyngeal cancer and infectious mononucleosis are also brought on by EBV. Many NHL cases connected to AIDS are EBV positive. The experience with endemic BL initially led to the treatment of AIDS-related NHL, but it quickly became clear that chemotherapy was less effective in treating AIDS-related BL. The identification of HTLV-1 and EBV provided crucial new knowledge and tools for the understanding and management of HIV and AIDS. They have had a profound and long-lasting influence on the study of virology and cancer.

## Conclusion

The investigation of human oncoviruses, ranging from AIDS to EBV, has clarified the intricate relationship between viral infections and cancer development. As the first virus to be demonstrated to cause cancer in humans, EBV has been crucial in our understanding of oncogenesis processes. From EBV to AIDS, a range of viruses have been associated with different types of cancer, emphasizing the part that viral oncogenes, immune evasion tactics, and persistent inflammation play in cancer development. The study of cancers associated with AIDS provides more evidence of the impact of immunosuppression on cancer prevalence and progression. This area of study not only clarifies the pathophysiology and genesis of cancers linked to viruses, but it also opens doors for specialized therapies and vaccination-based prophylactics. Thus, the field of virology and oncology remains ripe for scientific advancement and has great promise for bringing about a major reduction in the worldwide cancer burden.

**Acknowledgements:** I would like to express my deepest appreciation to Mr. Neelabh Dutta for his helpful discussion regarding this commentary.

## REFERENCES


1. Barre-Sinoussi, F., Chermann, J., Rey, F., Nugeyre, M., Chamaret, S., Gruest, J., &Dauguet, C. (2004). Isolation of T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Revista de investigaciónclínica*, *56*(2), 126-129. https://doi.org/10.1126/science.6189183
2. Broder, S., & Gallo, R. C. (1984). A pathogenic retrovirus (HTLV-III) linked to AIDS. *New England Journal of Medicine*, *311*(20), 1292-1297. https://doi.org/10.1056/NEJM198411153112006.
3. Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Freeman, C., & Galichet, L. (2009). A review of human carcinogens—Part B: biological agents. The lancet oncology, 10(4), 321-322. doi: 10.1016/S1470-2045(09)70096-8.
4. Ciuffo, G. (1907). Innestopositivo con filtrato di verruca volgare. *Giorn Ital Mal Venereol*, *48*(1), 12-17.
5. Doll, D., & List, A. (1982). Burkitt's lymphoma in a homosexual. *Burkitt's lymphoma in a homosexual.*, *1*, 1026-1027. https://doi.org/10.1016/s0140-6736(82)92031-1
6. Epstein, M. A., & Eastwood, M. A. (1995). Denis Parsons Burkitt, 28 February 1911-23 March 1993. In: The Royal Society London.
7. Esau, D. (2017). Viral causes of lymphoma: the history of Epstein-Barr virus and human T-lymphotropic virus 1. *Virology: research and treatment*, *8*, 1178122X17731772.
8. Fulghieri, C., & Bloom, S. (2014). Sarah elizabethstewart. *Emerging Infectious Diseases*, *20*(5), 893. https://doi.org/10.3201/eid2005.131876
9. Henle, W. (1968). Evidence for viruses in acute leukemia and Burkitt's tumor. *Cancer*, *21*(4), 580-586 https://doi.org/10.1002/1097-0142(196804)21
10. Henle, W., Henle, G., & Lennette, E. T. (1979). The Epstein-Barr virus. *Scientific American*, *241*(1), 48-59.
11. Hinuma, Y., Nagata, K., Hanaoka, M., Nakai, M., Matsumoto, T., Kinoshita, K.-I., Shirakawa, S., & Miyoshi, I. (1981). Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proceedings of the National Academy of Sciences*, *78*(10), 6476-6480. https://doi.org/10.1073/pnas.78.10.6476
12. Kalyanaraman, V., Sarngadharan, M., Robert-Guroff, M., Miyoshi, I., Blayney, D., Golde, D., & Gallo, R. C. (1982). A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. *Science*, *218*(4572), 571-573. https://doi.org/10.1126/science.6981847
13. Kitsou, K., Iliopoulou, M., Spoulou, V., Lagiou, P., &Magiorkinis, G. (2021). Viral causality of human cancer and potential roles of human endogenous retroviruses in the multi-omics era: An evolutionary epidemiology review. *Frontiers in Oncology*, *11*, 687631. https://doi.org/10.3389/fonc.2021.687631
14. Klein, G. (2009). Burkitt lymphoma—A stalking horse for cancer research? Seminars in cancer biology, https://doi.org/10.1016/j.semcancer.2009.07.001
15. Knerr, J. M., Kledal, T. N., & Rosenkilde, M. M. (2021). Molecular properties and therapeutic targeting of the EBV-encoded receptor BILF1. *Cancers*, *13*(16), 4079. https://doi.org/10.3390/cancers13164079
16. Łagocka, R., Dziedziejko, V., Kłos, P., & Pawlik, A. (2021). Favipiravir in therapy of viral infections. *Journal of clinical medicine*, *10*(2), 273.
17. Lo, A. K.-F., Dawson, C. W., Lung, H. L., Wong, K.-L., & Young, L. S. (2020). The therapeutic potential of targeting BARF1 in EBV-associated malignancies. *Cancers*, *12*(7), 1940. https://doi.org/10.3390/cancers12071940
18. Mayer, K. H., & Pizer, H. F. (2004). *The AIDS pandemic: Impact on science and society*. Elsevier.
19. McLaughlin-Drubin, M. E., & Munger, K. (2008). Viruses associated with human cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1782*(3), 127-150.https://doi.org/10.1016/j.bbadis.2007.12.005
20. Moore, P. S., & Chang, Y. (2010). Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nature reviews cancer, 10(12), 878-889. doi: 10.1038/nrc2961.
21. Mundo, L., Leoncini, L., & Accardi-Gheit, R. (2023). Epstein–Barr Virus Infection in Cancer. In (Vol. 15, pp. 4659): MDPI. https://doi.org/10.3390/cancers15184659.
22. Parsonnet, J. (1999). Microbes and malignancy: infection as a cause of human cancers. (No Title).
23. Rho, H. M., Poiesz, B., Ruscetti, F. W., & Gallo, R. C. (1981). Characterization of the reverse transcriptase from a new retrovirus (HTLV) produced by a human cutaneous T-cell lymphoma cell line. *Virology*, *112*(1), 355-360. https://doi.org/10.1016/0042-6822(81)90642-5
24. Rous, P. (1983). Transmission of a malignant new growth by means of a cell-free filtrate. *Jama*, *250*(11), 1445-1446.
25. Strauss, M. J., Shaw, E. W., Bunting, H., & Melnick, J. L. (1949). "Crystalline" Virus-Like Particles from Skin Papillomas Characterized by Intranuclear Inclusion Bodies. *Proceedings of the Society for Experimental Biology and Medicine*, *72*(1), 46-50. https://doi.org/10.3181/00379727-72-17328
26. Uchiyama, T., Yodoi, J., Sagawa, K., Takatsuki, K., & Uchino, H. (1977). Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood*, *50*(3), 481-492.
27. Wang, L., & Ning, S. (2021). New look of EBV LMP1 signaling landscape. *Cancers*, *13*(21), 5451. https://doi.org/10.3390/cancers13215451
28. Watanabe, T., Seiki, M., & Yoshida, M. (1984). HTLV type I (US isolate) and ATLV (Japanese isolate) are the same species of human retrovirus. *Virology*, *133*(1), 238-241. https://doi.org/10.1016/0042-6822(84)90446-x
29. Wright, D. (2012). Nailing Burkitt lymphoma. *British journal of haematology*, *156*(6). https://doi.org/10.1111/j.1365-2141.2012.09055.x
30. Yoshida, M., Miyoshi, I., &Hinuma, Y. (1982). Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the

disease. *Proceedings of the National Academy of Sciences*, *79*(6), 2031-2035. https://doi.org/10.1073/pnas.79.6.2031

31. Zanella, L., Reyes, M. E., Riquelme, I., Abanto, M., León, D., Viscarra, T., Ili, C., &Brebi, P. (2021). Genetic patterns found in the nuclear localization signals (Nlss) associated with ebv-1 and ebv-2 provide new insights into their contribution to different cell-typespecificities. *Cancers*, *13*(11), 2569. https://doi.org/10.3390/cancers13112569
32. Zur Hausen, H. (1976). Condylomata acuminata and human genital cancer. *Cancer research*, *36*(2_Part_2), 794-794.
33. Zur Hausen, H. (2001). Oncogenic DNA viruses. *Oncogene*, *20*(54), 7820-7823. doi: 10.1038/sj.onc.1204958.
34. Zur Hausen, H. (2009). The search for infectious causes of human cancers: where and why. *Virology*, *392*(1), 1-10. doi: 10.1016/j.virol.2009.06.001

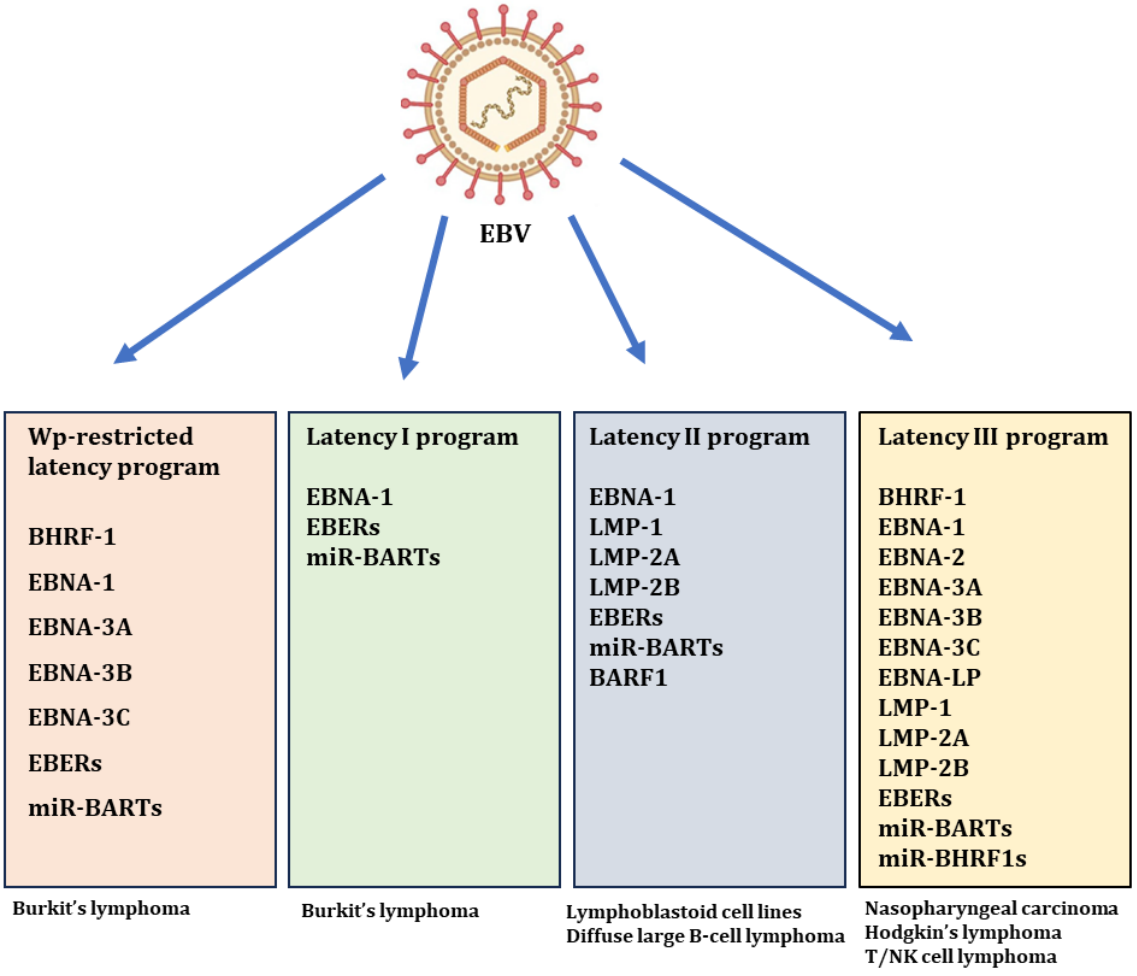


Figure 1 Various EBV-associated illnesses and different forms of EBV latency: Differential expression programs. (Wyżewski, Z et al. 2022)

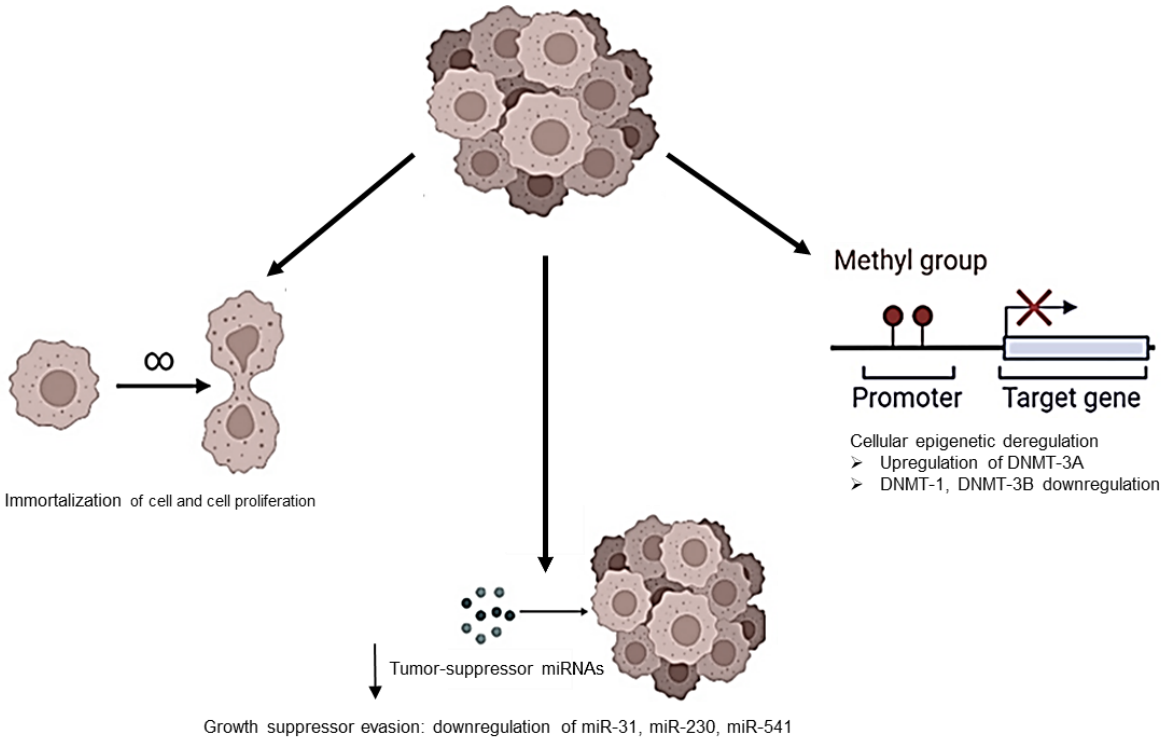


Figure 2 A visual representation of EBV induced viral mechanisms in cancer progression The image depicts the mechanisms by which EBV contributes to the development of cancer. Initially, the virus facilitates cellular immortalization and proliferation by downregu