International Journal of Research in MEDICAL SCIENCE

ISSN Print: 2664-8733
ISSN Online: 2664-8741
IJRMS 2024; 6(1): 120-129
www.medicalpaper.net
Received: 05-03-2024
Accepted: 04-04-2024

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The role of Epstein-Barr virus in the development of cancers

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DOI: https://doi.org/10.33545/26648733.2024.v6.i1b.88

Abstract
Epstein Barr Virus (EBV), is associate to the *Herpesviridae* family, revealed as a corporate pathogen within human viral infections, in addition representation an important source in the progress of many types of cancers, influencing global health troubles. So, this review searches in association of EBV's with cancer development by probing its molecular mechanisms, epidemiological styles, besides correlated malignancy disorders. Many studies showed that EBV is thoroughly associated to lymphatic tumors such as "Burkitt lymphoma and Hodgkin lymphoma, as well as with epithelial malignant tumors similar to a nasopharyngeal carcinoma in addition to gastric carcinoma". This virus shows a notable capability to modify functions within the host cellular system, by avoiding the immune response recognition, then activate the genomic variability, which give its oncogenic possibility. Furthermore, within distinction in the frequency of EBV correlated cancers through various body sites, this approve the stimulus power of genetic and environmental factors on disease progress. Recently the improvements in cure management, as well as including the immunotherapy and applying of biomarkers for prompt revealing and diagnosis, afford a novel prospects for management of these cancers. Also this review outlines promising capable research guidelines, that fixing the vaccine advance and originally applications of therapeutic methods which directed and targeted at decreasing and prevent the worldwide effect and control of EBV related and connected with malignant tumor.

Keywords: Epstein Barr Virus, cancer, lymphoma, vaccine, malignant tumor

1. Introduction
Epstein Barr Virus (EBV) has DNA of a double-stranded structure shape, firstly revealed in the year1964 by Epstein, Achong, and Barr whereas inspecting derivative cell lines from Burkitt lymphoma tissues [1]. Subsequently the finding, EBV has been known as one of the highest corporate human viruses, that infecting above than (90%) of the worldwide people liveing at some points of frequent infections. Usually the virus diffused through saliva, concluded EBV forms permanent latency within B lymphocytes, after the initial infection [2]. While many primary infections are asymptomatic, some individuals experience infectious mononucleosis, a condition marked by fever, fatigue, pharyngitis, and lymphadenopathy [3].

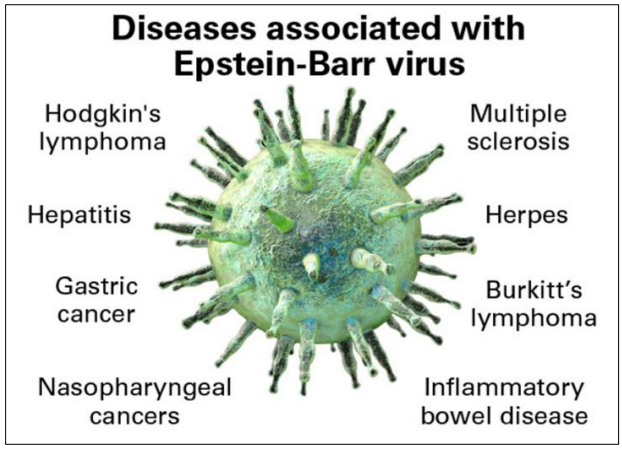


Fig 1: EB virus's inflammatory and oncogenic association.

The ability of EBV to transition between latent and lytic phases enables the virus multitude to persevere within the host and evade immune detection. For the period of latency, also EBV vocalizes a partial range of genes, ensuring its survival and minimizing immune recognition [4, 5]. These genes, including the Epstein-Barr nuclear antigens (EBNAs), besides hidden sheath proteins or latent membrane proteins (LMPs) that show pivotal characters in cellular transformation and immune modulation [6, 7].

EBV involved with the improvement of a number of malignancies sites, including in cooperation epithelial besides lymphoid cancers [8]. The virus's oncogenic potential is primarily linked to its capacity to manipulate host cell pathways, induce genomic instability, and evade immune responses [9, 10]. Although "Burkitt lymphoma and nasopharyngeal carcinoma" have intensely linked with EBV, this virus similarly supports to initiate Hodgkin lymphoma, besides progression a subgroup of gastric carcinomas [11]. These malignancies demonstration the environmental and geographical deviations and variations within predominance, influenced by subjective factors such as co-infections, nutritive habits, and genetic susceptibility [12].

The consequence effectiveness of EBV within worldwide health spreads further than its role in cancer progress. Considerate the mechanisms of EBV's oncogenesis propositions many chances for primary definition [13], with directed targeted therapy besides vaccine advancement and development. So, this review objectives to probe deep into the molecular biology, with epidemiology, and therapeutic inferences of EBV, for finding and providing a complete considerate understanding of its important role in cancer initiation, development and progress as mention in table 1 at summary.

2. EBV Structure and Life Cycle

EBV has a genome of gammaherpesvirus with encrypting above 80 proteins codes. With life cycle alternatives between the latent and lytic phases, and within latency form a crucial and principal to oncogenic probability. During the latency stage, the EBV positions have a regulated and controlled consistent of genes [14], in addition to the Epstein-Barr nuclear antigenic proteins (EBNAs), within the latent proteins membrane (LMPs), and Epstein-Barr programmed the RNAs (EBERs) [15, 16], and these genes yields determination cell proliferation creation, stopping the apoptosis action, and avoid the immune responses. The transition between latency and the lytic phase is regulated by viral genes such as BZLF1 and BRLF1 [17], which are critical for reactivating the virus. Additionally, the latency phase is classified into three types (I, II, and III) based proceeding the expression within specific detailed viral proteins, with each type associated with different cancers [18, 19]. This dual-phase lifecycle ensures the virus's persistence and ability to influence tumor genesis, as mention in table 2 at summary.

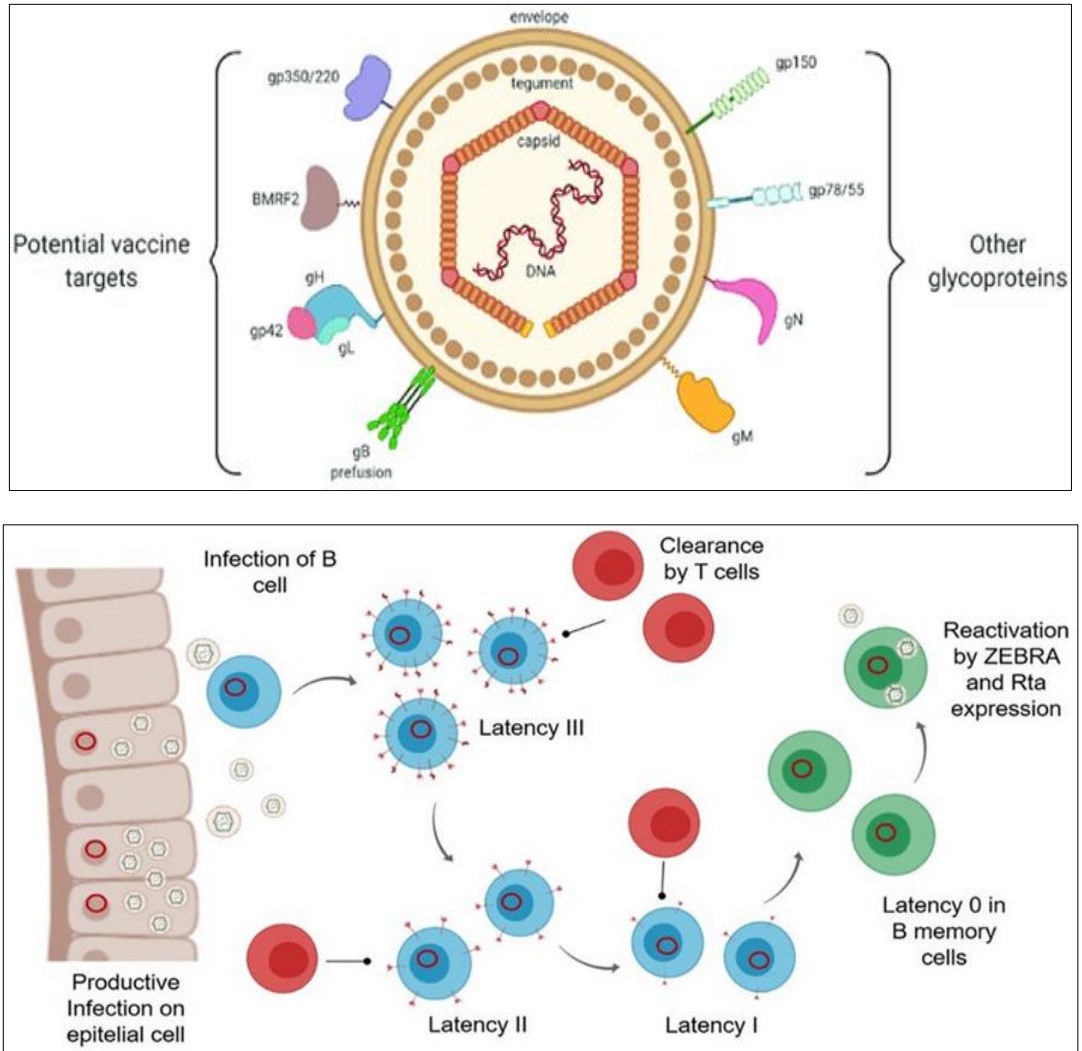


Fig 2: EBV Structure and Life Cycle

3. EBV-Associated Cancers

3.1 Burkitt Lymphoma (BL)

The highly aggressive cancer of B-cell non-Hodgkin lymphoma that refer to Burkitt lymphoma, is a strongly associated with EBV, particularly in endemic regions of Africa [20]. The virus drives on cogenesis through c-MYC translocation, a hallmark genetic abnormality, coupled with viral latency proteins that promote unchecked proliferation [21, 22]. Co-factors such as chronic malaria exacerbate the risk of BL in endemic regions (Epstein & Barr, 1964). EBV's role in endemic Burkitt lymphoma is also linked to the suppression of immune responses due to chronic infections, creating a permissive environment for malignant transformation [23, 24].

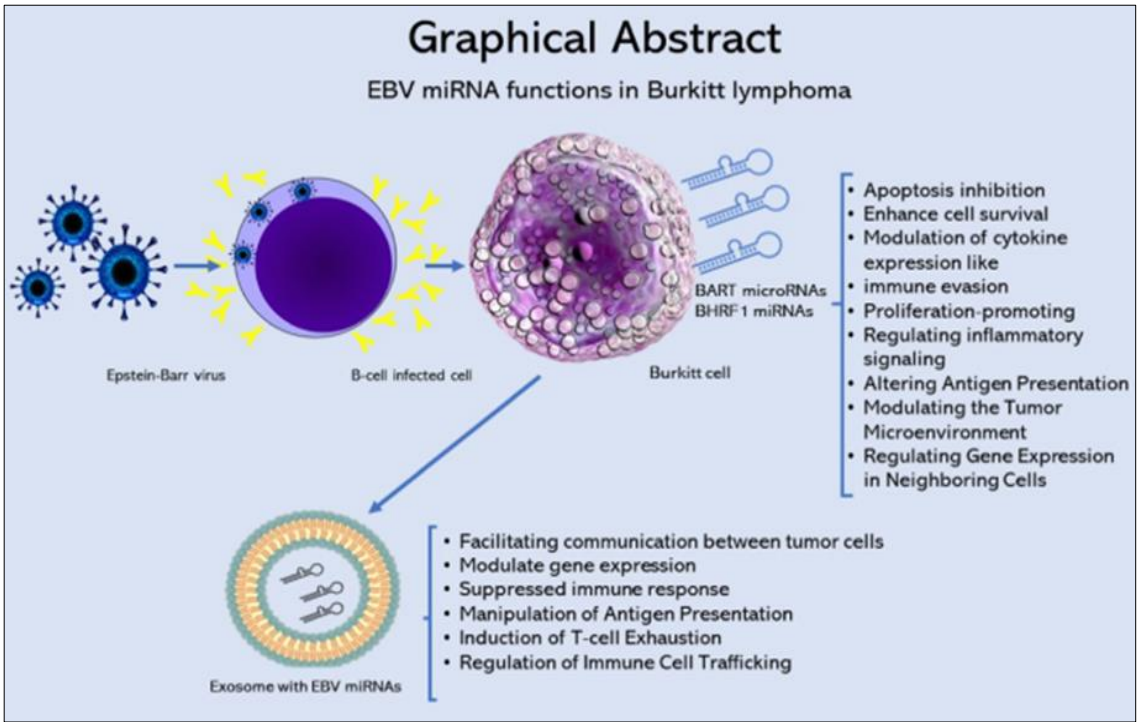


Fig 3: Burkitt Lymphoma (BL) linked to EBV expression

3.2 Hodgkin Lymphoma (HL)

EBV is detected in approximately 40-50% of Hodgkin lymphoma cases. The virus's role in HL involves the expression of LMP1 [25], which mimics CD40 signaling, activating NF-κB and promoting cell survival. LMP1 also induces a pro-inflammatory microenvironment, enhancing tumor progression [26]. EBV-positive HL is often associated with distinct clinical features, including a younger onset age and a more favorable prognosis compared to EBV-negative cases (Shannon-Lowe & Rickinson, 2017) [27, 28]. Recent studies highlight differences in genetic and epigenetic profiles between EBV-positive and EBV-negative HL, providing insights into tailored treatment strategies [29].

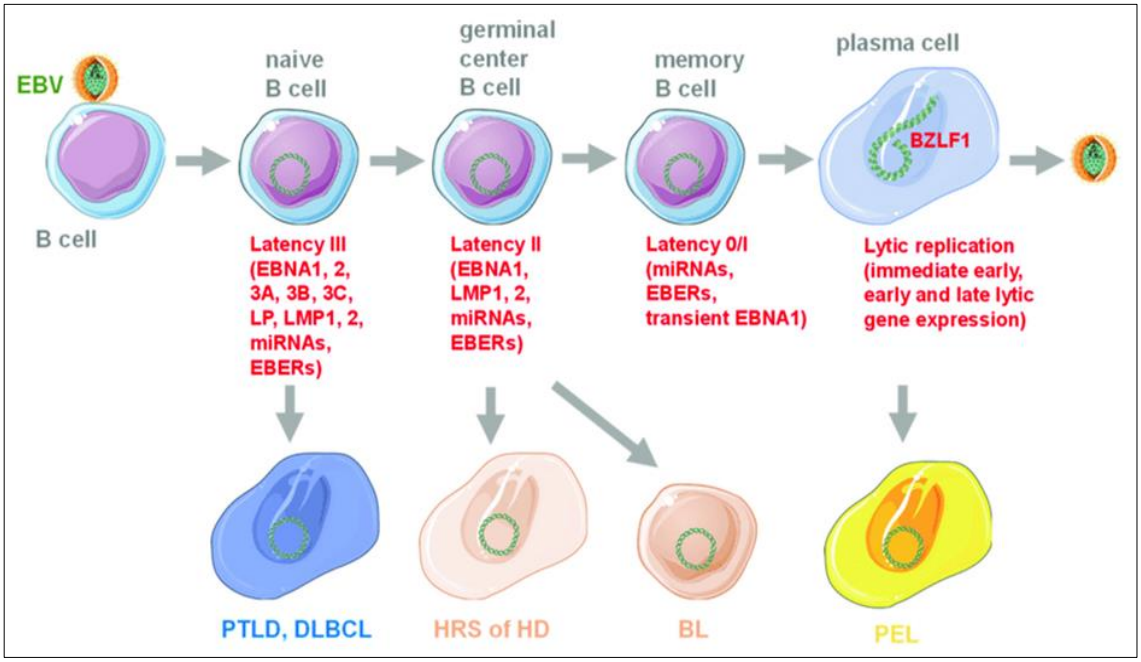


Fig 4: Hodgkin Lymphoma (HL) mechanism linked to EBV

B cell lymphomas non-Hodgkin's lymphomas

Epstein-Barr virus (EBV) is a pervasive herpes-virus, distressing about 90% of the people. Also EBV was major well-known as an oncogenic virus [30], and still consequently initiate a determination within a variation of distortions or malignancies as in diffuse large B-cell lymphoma (DLBCL) [31, 32], besides another lymphoma types. Because of EBV has an affinity to B lymphocytes, also has an exceptional capability to occurring a latent stage, with escaping from the immune response [33]. The diminished cell facilitated immunity within patients with broadminded age, or immune suppression, the progressive virus is capable to increase in an tolerant mode, and articulating in expressing viral antigens that prompt and induce the transformation [34, 35].

3.3 Nasopharyngeal Carcinoma (NPC)

Nasopharyngeal carcinoma, endemic in Southeast Asia, is universally linked to EBV. Viral proteins such as LMP1 and LMP2A promote epithelial cell transformation, while EBERs enhance immune evasion [36]. EBV-induced promoter hyper methylation and genetic mutations, such as those in the TP53 gene, are critical drivers of NPC on cogenesis (Tsao *et al*., 2017). Environmental factors, such as the consumption of nitrosamine-rich salted fish, interact with EBV to increase NPC risk [37, 38]. Additionally, genome-wide association studies have identified susceptibility loci in HLA genes associated with EBV-positive NPC [39].

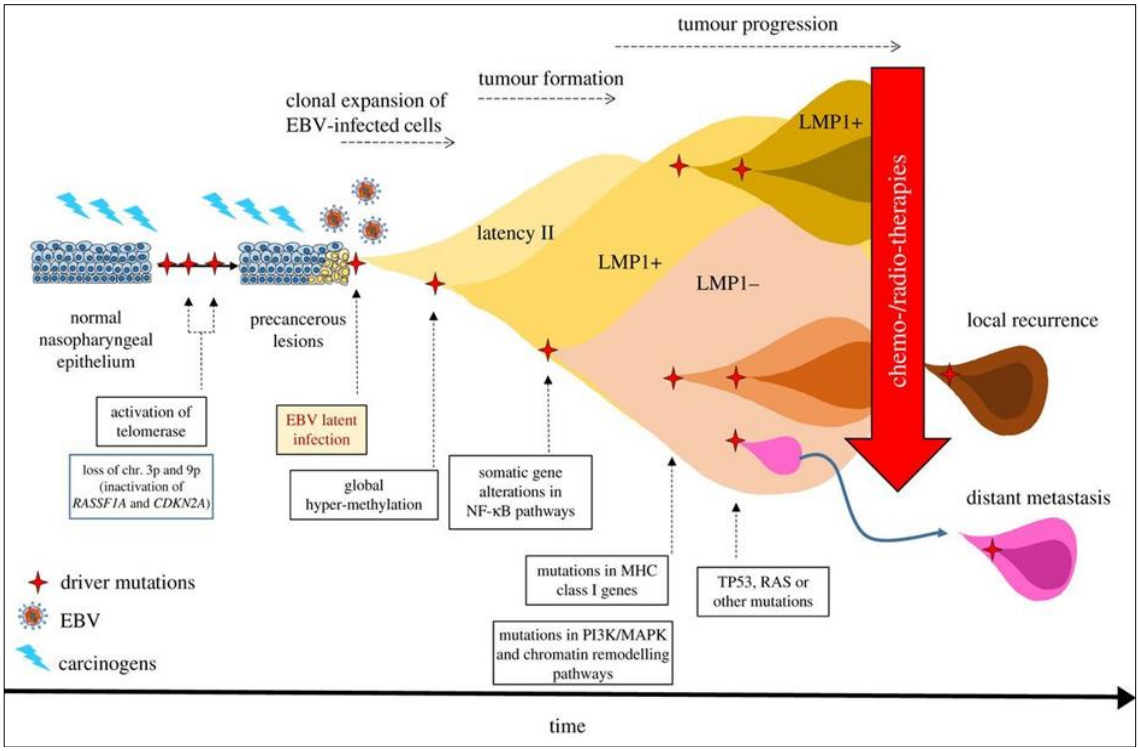
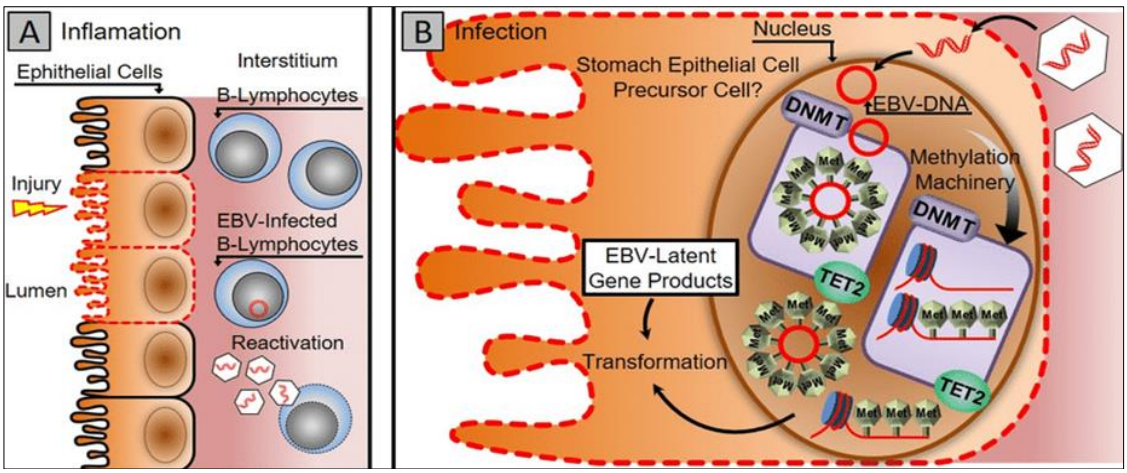


Fig 5: Nasopharyngeal Carcinoma (NPC) linked to EBV. viral proteins

3.4 Gastric Carcinoma (GC)

EBV is associated with approximately 10% of gastric carcinoma cases. EBV-positive GC is characterized by unique molecular features, including PIK3CA mutations and extensive promoter hyper methylation [40, 41]. LMP2A's ability to induce the epithelial progress within mesenchymal transition (EMT) that productions a substantial part within tumor advancement (Thompson & Kurzrock, 2004). Furthermore [42, 43, 71], EBV-positive GC exhibits distinct immunological profiles, such as increased infiltration of cytotoxic T cells, which may have implications for immunotherapy approaches [44].



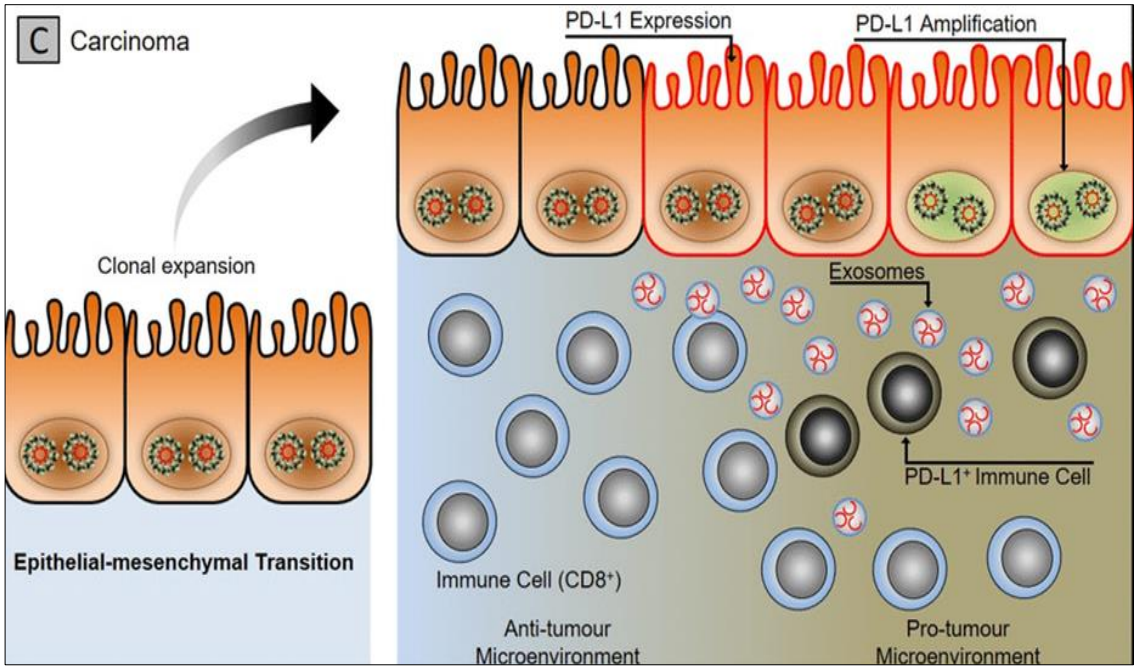


Fig 6: Gastric Carcinoma (GC) associated with EBV

4. Mechanisms of EBV-Induced Oncogenes is EBV employs several molecular strategies to drive cancer development.

Immune Evasion

EBV down regulates MHC class I and class II molecules, preventing recognition by cytotoxic T cells [45, 72]. Viral miRNAs further suppress immune signaling by targeting host mRNA involved in immune responses as mention with Cohen, [46]. These mechanisms allow the progressive virus to establish latency stage besides continue in persist within the host [47, 73].

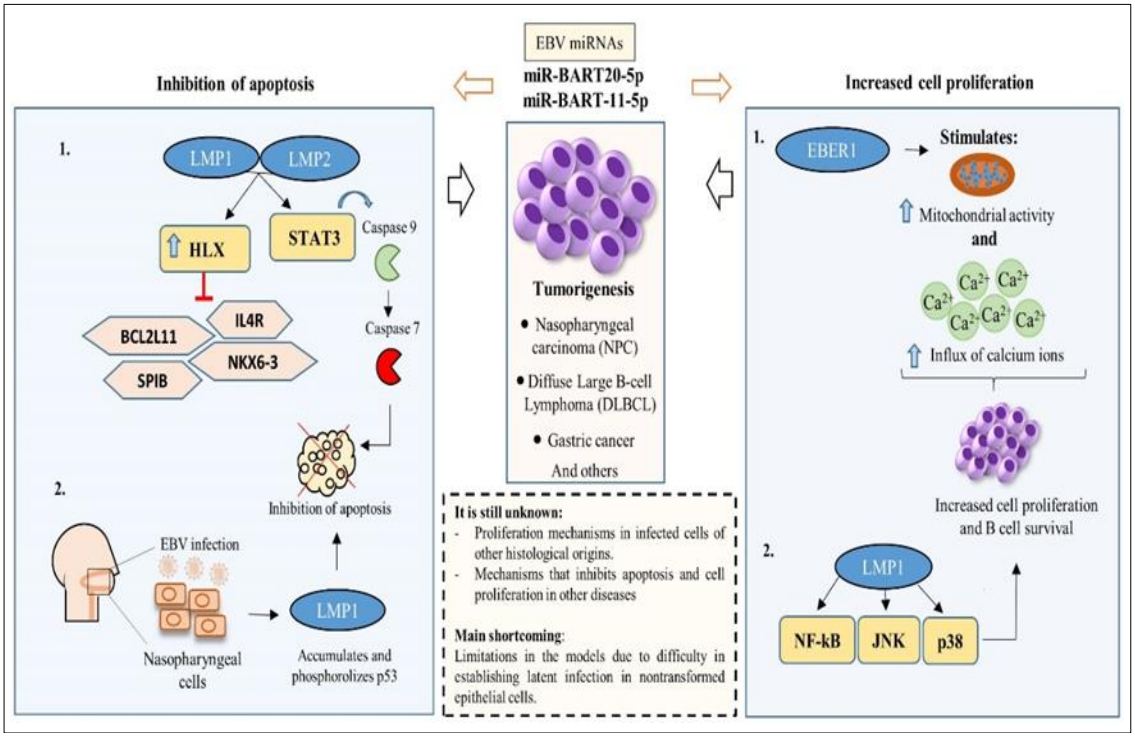


Fig 7: Immune evasion by EBV down-regulates MHC class I and class II molecules, preventing recognition by cytotoxic T-Cells.

Epigenetic Modifications

EBV induces methylation of tumor suppressor gene promoters, altering host cell gene expression and creating a permissive environment for tumor genesis as with Young & Rickinson [48, 49]. Histone modifications mediated by EBV proteins further contribute to the reprogramming of cellular pathways [50].

Genomic Instability

EBV disrupts DNA repair mechanisms, leading to chromosomal abnormalities and mutations [51]. Reactive oxygen species generated during infection exacerbate DNA damage, creating additional genetic aberrations that drive cancer progression [52, 74].

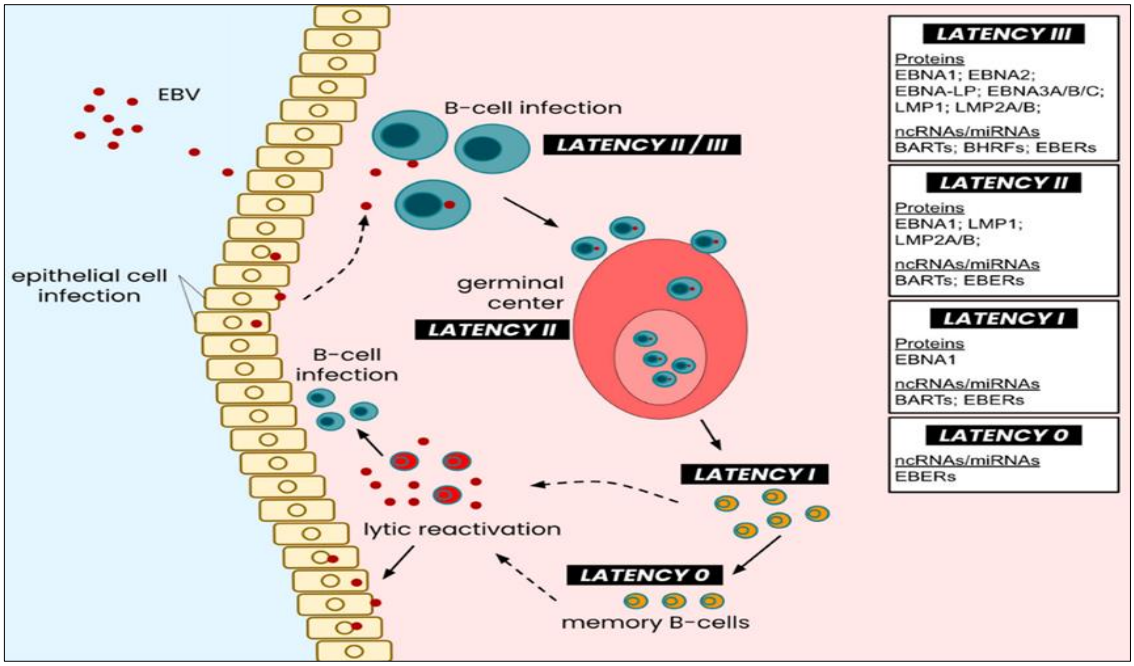


Fig 8: Epigenetic modifications by EBV induces methylation of tumor suppressor gene

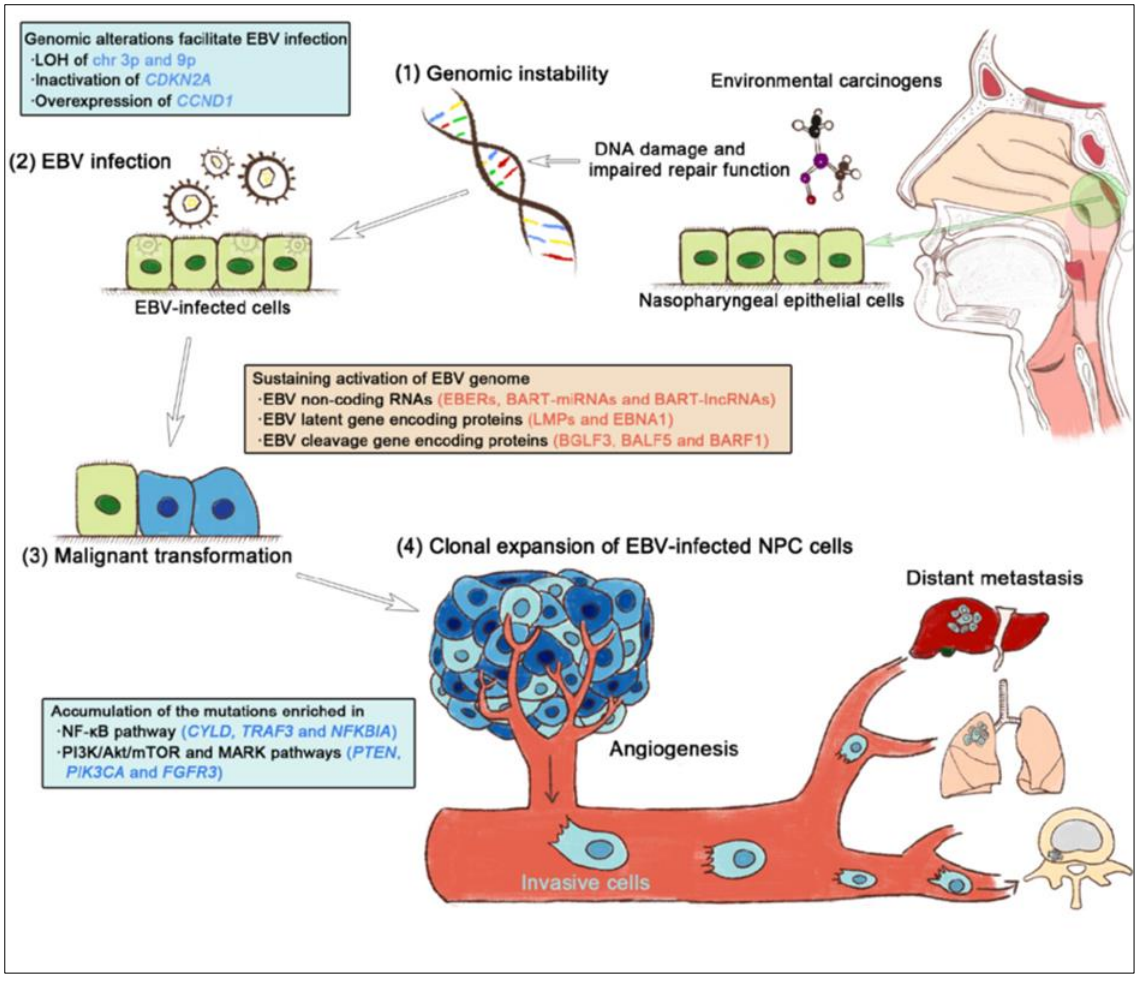


Fig 9: Genomic Instability by EBV disrupts DNA repair mechanisms

Activation of Oncogenic Pathways: Viral proteins, such as LMP1 and LMP2A, activate signaling pathways like PI3K/AKT, JAK/STAT, and NF-κB, promoting survival and proliferation Tsao *et al* mention that in study [53, 75]. These pathways are critical for cellular transformation and the inhibition of apoptosis. The significance action of these modifications in genetic materials is converse an evolution improvement to the cell [54, 55, 76]. The three mechanisms of these genetic changes, stimulate oncogenes within human neoplasms include: (1) mutation events, (2) gene extension, and (3) chromosome reorganizations and rearrangements [56, 78].

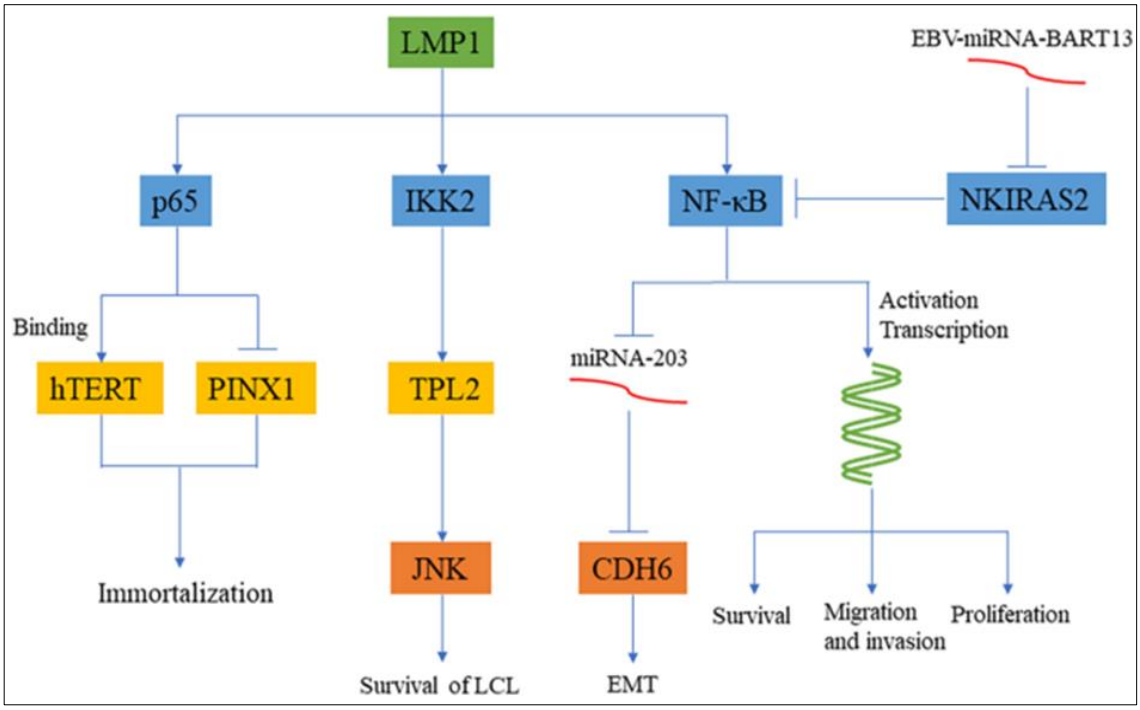


Fig 10: Activation of Oncogenic signaling pathways by viral proteins

5. Therapeutic Implications

Current treatments for EBV-associated cancers include chemotherapy, radiotherapy, and immunotherapy. Targeted approaches, such as adoptive T-cell therapy, focus on EBV-specific antigens, including LMP1 and LMP2 [57, 77]. Advances in genome-editing technologies, such as CRISPR-Cas9, offer new avenues for precise targeting of EBV-infected cells [58, 78]. Additionally, biomarkers such as plasma EBV DNA can aid in early detection and monitoring of EBV-associated malignancies [59, 60, 79]. Immunotherapies, such as checkpoint inhibitors, have shown promise in enhancing the immune response against EBV-positive tumors [61]. Vaccine development efforts, although still in experimental stages, aim to prevent primary EBV infections and reduce the risk of associated cancers [62, 63, 80]. Then within the management of EBV-LPDs, it is frequently comparable to that of EBV-negative lymphoma within the histology identical, including radiotherapy, chemotherapy, and even hematopoietic stem cell transplant (HSCT) [64, 65, 81]. Nevertheless, the difficulties like drug resistance, and severe toxicity are deteriorate and worsen the persistence estimate and prediction in patients, as mention in table 3 at summary [66].

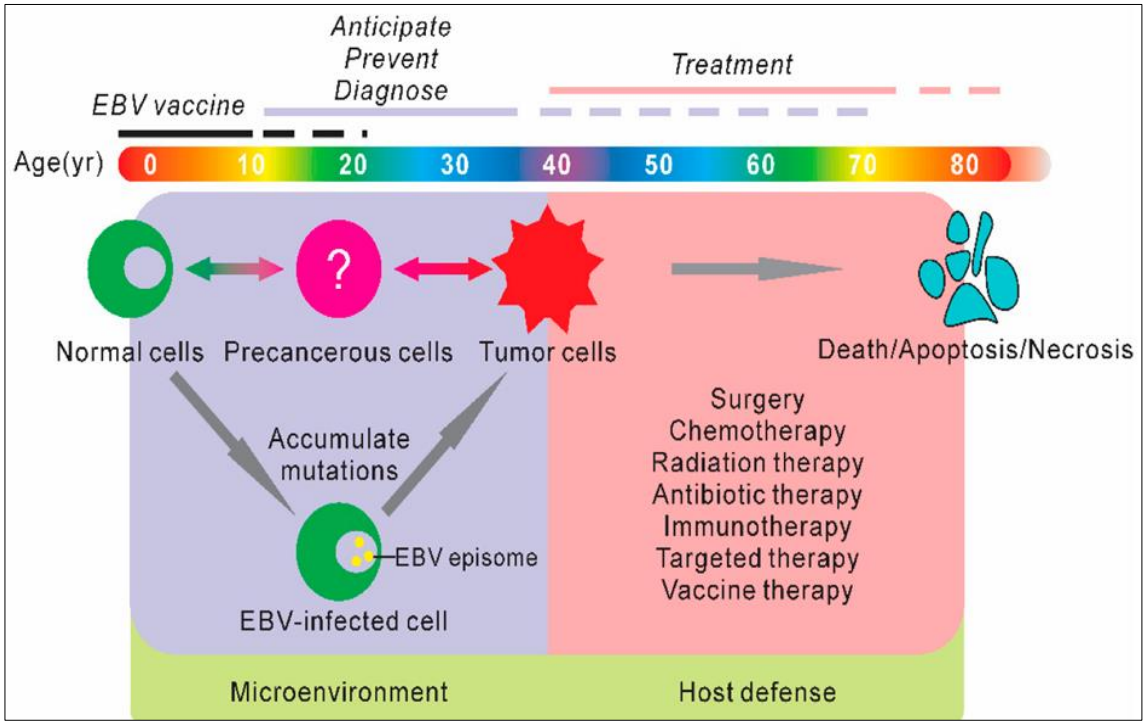


Fig 11: Treatments for EBV-associated cancers include chemotherapy, radiotherapy, and immunotherapy.

Summary of Previous Studies

Table 1: Oppose EBV's Role in Cancer

Study	Findings	Support or Oppose EBV's Role in Cancer	Comments
Cohen (2015) [22]	Highlighted EBV's role in immune evasion mechanisms	Support	Provided molecular insights into how EBV avoids immune detection
Albzreh *et al*. (2020) [51]	Linked EBV latency to lymphoma genesis	Support	Emphasized therapeutic potential in targeting latent phases
Carbone & Gloghini (2019) [36]	EBV-positive HL shows distinct clinical features	Support	Suggested better prognosis for EBV-positive cases
Kaymaz *et al*. (2019) [42]	Identified immune checkpoint expression in EBV-positive GC	Support	Proposed implications for immunotherapy
Tsao *et al*. (2017) [17]	Discussed EBV's contribution to NPC	Support	Showed interaction between environmental and viral factors
Zur Hausen (2001) [46]	Explored viruses' role in human cancers	Support	General commentary on viral on cogenesis
Dolcetti & Boiocchi (2007) [52]	Questioned universal causality of EBV in Burkitt lymphoma	Oppose	Suggested multifactorial etiology

5.1 Epidemiological Data on EBV-Associated Cancers

Table 2: Epidemiological Data on EBV-Associated Cancers

Cancer Type	Prevalence (Global)	Regional Variations	Key Risk Factors
Burkitt Lymphoma	High in sub-Saharan Africa	Endemic in malaria regions	Malaria co-infection, immunosuppression
Nasopharyngeal Carcinoma	High in Southeast Asia	Rare in Western populations	Dietary habits, genetic predisposition
Gastric Carcinoma	~10% of global GC cases	Higher in East Asia	Helicobacter pylori co-infection, dietary factors
Hodgkin Lymphoma	~40-50% EBV-positive cases	Varies by subtype	Immunosuppression, genetic factors

5.2 Therapeutic Developments for EBV-Associated Cancers

Table 3: Therapeutic Developments for EBV-Associated Cancers

Therapy Type	Target	Advantages	Limitations
Adoptive T-cell Therapy	LMP1, LMP2	Targeted immune response	High cost, limited availability
Checkpoint Inhibitors	PD-1/PD-L1	Enhances T-cell activity	Risk of autoimmune side effects
CRISPR-Cas9	EBV genome	Precise targeting	Ethical concerns, off-target effects
Biomarker-Based Monitoring	Plasma EBV DNA	Early detection	Requires robust validation

6. Conclusion and Future Directions

The role of EBV in cancer underscores its significance as both a diagnostic marker and therapeutic target [67]. Continued research into virus-host interactions and the development of EBV-specific vaccines hold promise for reducing the global burden of EBV-associated malignancies [68, 82, 83]. Future directions should focus on integrating genomic and proteomic approaches to better understand EBV's role in tumor heterogeneity. Cooperative determinations among the oncologists, virologists, and immunologists are very essential in explaining these obsessed outcomes to actual and effective cures methods for therapies and prevention strategies [69, 70].

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
Alhasnawi EAF, Diwen IK, Saleh MF. The role of Epstein-Barr virus in the development of cancers. International Journal of Research in Medical Science 2024;6(1):120-129.