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Epstein-Barr Virus in Silico Studies– Brief Review

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***Abstract*:** *One of the widespread herpes viruses that infect most people at some point is the Epstein-Barr virus (EBV). It can cause various diseases, from infectious mononucleosis (mono or glandular fever) to certain types of cancer. It has two primary states: latent infection and lytic replication. EBV expresses lytic proteins, such as BZLF1, BRLF1, and BALF2, which activate the expression of the entire lytic gene cascade, initiate viral DNA replication in replication compartments, and produce infectious virions that can spread to new cells. EBV expresses latent proteins in latent infection, such as EBNA(1-3), EBNA-LP, LMP(1–2), and some miRNAs. These proteins help the virus maintain its genome as circular episomes in the nucleus, evade immune recognition, and modulate host cell proliferation and survival. This mini-review aims to summarise the current knowledge of EBV involving computer-aided studies classified according to its type for the past ten years. Computer-aided or in silico analyses of EBVs are a promising way to investigate these proteins' structure, function, and potential drug targets. These studies could lead to the advancement of new treatments for EBV infection.*

Keywords: *In Silico, EBV, LMP1, Latent Membrane Protein 1, Epstein-Barr Virus*

1. Introduction

One of the most common and well-studied human herpes viruses is the Epstein-Barr virus (EBV). It was first found in 1961 in Uganda, Africa. As a surgeon, Denis Burkitt documented that African children had a high tumour incidence in some geological regions. This illness was later called Burkitt's lymphoma (BL) [1]. Owing to the coincidental geographic location, scientists Epstein, Barr, and Achong started examining tumour samples supplied from Africa for viruses that cause cancer [2]. Using an electron microscope, researchers identified a novel herpes virus in 1964 that is currently referred to as the EBV.

EBV is a virus with double-stranded, linear DNA. In latent form, it seems circular, while in mature virions, it appears linear. EBV is a Herpes Type 4 from the Herpesviridae family. Its dimensions are around 80–100 nm in capsid form and 120–150 nm in enveloped form [3]. Nucleic acid replication of the EBV occurs in the nuclear membrane, where the capsid assembly is assembled. EBV enters the cell by attaching to a protein on the host cell's surface (the C3d complement protein). In the host cell's cytoplasm, the viral DNA encircles itself, penetrates the nucleus, and merges with the genetic material to express the viral proteins [4].

EBV infects 80-90 percent of people globally and remains dormant, or lysogenic, for some time before activating [5]. During this latent stage, the host has no symptoms, antibodies, or virions. EBV does not cause disease, but its constant gene translocations can. EBV antibodies are overproduced; oncogenes will likewise be overproduced if positioned adjacent to a gene involved in antibody synthesis [6]. Two major EBV types, EBV-1 and EBV-2, can cause human diseases and infections. They are also known as EBV types A and B. The two kinds of EBV differ in their genetic sequence and have different biological features. EBV-1 is the most common type of EBV, and it is found worldwide. It converts B cells into lymphoblastoid cell lines and is expected to cause infectious mononucleosis (mono or glandular fever). It can also lead to various other illnesses and

complications. EBV-2 is less common, mainly found in Africa and Asia. For example, EBV-2 is more likely to relate to BL and nasopharyngeal carcinoma (NPC). It is important to note that while these are the known types of EBV, other less common types or strains may still need to be identified or extensively studied [7].

2. Background

EBV encodes various viral proteins involved in multiple stages of the virus lifecycle, such as lytic and latent cycles. This includes entry into host cells, immune evasion, establishment of latency, and replication. Some critical types of viral proteins encoded by EBV are immediate-early proteins, early proteins, late proteins, latent proteins, and microRNAs (miRNAs). These viral proteins play critical roles in the EBV lifecycle and contribute to the virus's ability to persist in the host and cause various diseases, including infectious mononucleosis, NPC, BL, and Hodgkin's lymphoma (HL). Understanding the functions of these viral proteins is essential for developing plans to prevent or treat EBV-associated diseases [8].

Currently, there is no commercially obtainable vaccine explicitly targeting the EBV. However, several research efforts and clinical trials are underway to develop a vaccine against EBV. Developing a vaccine against EBV is challenging, mainly due to the complex life cycle of the virus and its ability to establish lifelong latent infections. One promising vaccine candidate is EBV-001, which EBViously is developing. EBV-001 is a subunit vaccine that is made from a protein called gp350. gp350 is a critical protein that EBV uses to attach to and infect cells [9]. Another promising vaccine candidate is EBVax, which the University of Pennsylvania is developing. EBVax is a live attenuated vaccine made from a weakened version of EBV [10]. Both EBV-001 and EBVax have shown favourable results in animal studies. However, additional research is necessary to determine their safety and efficacy in humans.

Several other vaccine candidates are also in development [11]. These include vaccines that are made from other EBV proteins, as well as vaccines that are made from DNA or RNA. Moreover, novel strategies such as DNA vaccines and viral vectors are being explored to induce a robust immune response against EBV. These approaches involve delivering viral DNA or modified viral vectors into cells to trigger an immune response against EBV antigens. An example is a study by Moin et al. (2023), whereby they designed a multi-epitope vaccine against two different strains of EBV using immunoinformatics. They also found that the predicted binding interactions were stable, which suggests that the developed vaccine is safe and can generate an effective immune response [12].

With the success of developing the COVID-19 vaccine in a relatively short time, mainly contributing to computer-aided studies, other viral-related diseases such as EBV see promising hope to have a vaccine of its own. In silico EBV studies involve using computer-based models, algorithms, and databases to analyse various aspects of the virus. These studies can provide insights into the virus's genetic composition, protein interactions, pathogenesis, and potential drug targets. In silico analyses of EBV include genomic analysis, protein-protein interactions, vaccine design, drug discovery, and epidemiology and evolution. In silico studies of EBV complement experimental approaches and enable researchers to generate hypotheses, design experiments, and guide subsequent investigations. They contribute to a better understanding of EBV and potential strategies for preventing, treating, and controlling EBV-associated diseases. Therefore, this mini-review aims to summarise the current knowledge of EBV computer-aided studies.

3. EBV Lytic Cycle Proteins

EBV lytic cycle products revolved around immediate-early, early, and late proteins. These complexes consist of viral structural proteins, replicative enzymes, and membrane proteins.

3.1. EBV Immediate-Early Proteins

EBV immediate-early proteins are a group of viral proteins expressed at the earliest stage of infection, and the products are trans-activator proteins. They regulate the viral life cycle and the host’s immune response. EBV

immediate-early proteins include BZLF1, BRLF1, BRRF1, and BSLF2, which have diverse functions such as transactivating other viral genes, interacting with cellular factors, and inducing lytic replication [13]. One interesting study by Tiwari et al. suggests a probable role of EBV protein in mediating Alzheimer's disease. Their findings showed possible interactions between the C-terminal domain of apolipoprotein E and EBV proteins, particularly BZLF1 and EBNA1 [14].

3.2. EBV Early Proteins

EBV early proteins are viral proteins translated during the EBV infection lytic cycle. They consist of products triggered by the immediate-early EBV proteins. EBV early proteins are essential in modulating the host immune response, regulating cellular signalling pathways, and facilitating viral DNA replication and transcription. Some of the most studied EBV early proteins include BMRF1, BALF2, BGLF4, and BGLF5. These proteins have diverse functions, such as activating the expression of other viral genes, binding to cellular factors, phosphorylating cellular and viral substrates, and degrading cellular proteins [15]. Althurwi et al. used immunoinformatic and molecular modelling approaches to construct multi-epitope mRNA vaccines from B and T cell epitopes. Among the epitopes was BMRF1, and their predictions affirmed that the chosen proteins could induce an immune response, hence offering a promising choice for a potent EBV vaccine [16].

3.3. EBV Late Proteins

EBV late proteins are a class of viral proteins that are produced late in the lytic phase of EBV infection. Viral DNA replication is the checkpoint between early and late gene expression. These proteins are involved in viral replication, such as DNA synthesis, capsid assembly, nuclear egress, and virion maturation. EBV late proteins also target the host immune response and can modulate the host cell environment to facilitate viral spread and persistence. Some EBV late protein products are glycoproteins, structural proteins and viral interleukin-10 [17].

Glycoprotein, or EBV envelope proteins, mediates the attachment and entry of the EBV into host cells. It comprises two subunits, gp350 and gp220, derived from a single precursor protein. The gp350 component interacts with the B cell complement receptor type 2 (CR2), whereas the gp220 subunit promotes membrane fusion. For EBV cell entry, many envelope proteins are required. Envelope proteins gp350, gH, gL, gB, and gp42 are required for EBV infection of B cells. In contrast, the envelope proteins BMFR2, gH, gL, and gB are essential for EBV infection of epithelial cells [18].

One study by Bingöl et al. used molecular dynamics simulations to study the structural stability of the EBV envelope protein gp350 and CR2. They uncovered novel regions that can modulate gp350 activity [19]. Another study identified EBV envelope proteins gp350, gp42, gB, and gL to create a prophylactic epitope vaccine using a computer-experimental strategy [20].

4. EBV Latent Proteins

The latent phase of EBV infection is when the EBV latent proteins are generated. These proteins are critical in gene expression regulation, viral genome maintenance, host immune response modulation, and cellular transformation induction. EBV latent proteins include six nuclear antigens: EBNA (1 – 2), EBNA (3A – 3C), and EBNA-LP), three latent membrane proteins (LMP1, LMP2A – 2B), and two small non-coding RNAs (EBER1 and EBER2) [21].

4.1. Epstein-Barr Nuclear Antigens (EBNAs)

Epstein-Barr nuclear antigens (EBNAs) are a group of proteins encoded by the EBV. They are essential for the virus's ability to establish latency in B cells. Infected cells contain EBNAs in their nuclei. There are six EBNAs: EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP. Each EBNA has a different function. EBNA-1 is critical for maintaining the viral episome, the circular DNA molecule the virus integrates into the host cell's genome. EBNA-2 is a transactivator protein that causes the expression of other viral genes to

be activated. EBNA (3A-3C) are proteins that regulate cell development and differentiation. EBNA-LP is a leader protein that helps to recruit other proteins to the viral genome. EBNAs in the blood can be used to diagnose EBV infection—antibodies to EBNAs develop 6 to 8 weeks after primary infection and are detectable for life [22].

In silico studies of EBNAs and their target genes provide valuable information about the virus's molecular mechanisms and potential therapeutic targets for EBV-associated diseases. However, most of the EBNA's computer-aided studies focus on targeting EBNA-1; hence, it will be interesting to see if potential inhibitors can also be found for the other EBNAs. For example, research by Mathivadani et al. provides promising evidence that Murraya koengii bio-compounds could be potential inhibitors of EBNA-1. They first identified several conserved residues in the EBNA-1 binding pocket. The authors found that a few Murraya koengii bio-compounds could bind to the EBNA-1 binding pocket with high affinity. These compounds included isomahanine, murrayanol, and mahanimbine [23]. Similarly, Jakhmola et al. demonstrated proof-of-concept research that used molecular docking and molecular dynamics simulations to discover possible EBNA-1 inhibitors. The authors identified siponimod and ozanimod compounds that showed strong interactions with EBNA1, and they were found to be stable in the binding pocket of EBNA-1 [24]. Another novel anti-malaria drug study by Indari et al. to investigate the antiviral potency of antimalarials by targeting the viral proteins of EBV and SARS-CoV-2 found potential inhibitors for EBNA-1 [25]. Meanwhile, in an interesting protein-protein interaction study, Mei and Zhang found EBNA-LP, EBNA-1 and EBNA-3, among other EBV proteins that targeted the Notch and Hedgehog signalling pathway involved in several cancer-related diseases [26].

4.2. Latent Membrane Protein (LMP)

EBV encodes various viral proteins to establish and preserve a latent infection in human B lymphocytes. One significant viral protein in this activity is the latent membrane protein (LMP), specifically LMP1 and LMP2. LMP1 is a multi-functional protein crucial in transforming infected cells and is associated with developing certain EBV-associated cancers, such as HL and NPC. It acts as a constitutively active mimic of CD40, a surface receptor found on B cells, and stimulates signalling pathways usually activated by CD40 ligand binding. This activation promotes B cell survival and proliferation and modulates the immune response. LMP1 also interacts with various intracellular signalling molecules, including NF-κB, JAK/STAT, and MAPK pathways, leading to the dysregulation of gene expression, cell growth, and immune evasion. Its expression can also disrupt the normal regulation of cell death, leading to resistance against apoptosis [27]. LMP2, on the other hand, is expressed during latent infection and acts as a negative regulator of the B cell receptor (BCR) signalling pathway. It helps the viral protein to evade immunosurveillance by modulating BCR signalling through binding and inhibiting the Src family kinases required for BCR signalling. LMP2 also assists in maintaining the latency of the virus by suppressing lytic replication [28].

Due to their involvement in EBV-associated cancers and their essential roles in maintaining viral latency, LMP1 and LMP2 are potential targets for vaccine development and therapeutic interventions. However, developing effective vaccines or drugs targeting these proteins is complex due to their multiple functions and interactions with various signalling pathways. Current research efforts are focused on understanding the mechanisms of LMP proteins, particularly LMP1 and their contributions to EBV-related diseases, which may lead to developing novel strategies to prevent or treat these infections.

One example is using molecular docking to design peptides that can bind to LMP1 and inhibit its activity. Wang et al. create a membrane-insertable peptide that impairs the oncogenic LMP1's transmembrane domain 5's strong trimeric self-association. Their study was also the first to show how to build a peptide inhibitor by interrupting the LMP1 homo-trimeric transmembrane helices to control membrane protein assembly [29]. A similar study involving the transmembrane domain 5 of LMP1 showed how pentamidine derivates can disrupt LMP1. Zhang et al. did molecular dynamics simulations to understand the interaction and justify structure-activity relationships. Their proof-of-concept study suggested that the small molecule and lipid membrane interaction should be considered while designing LMP1 inhibitors [30]. Another molecular dynamic study

looked at the effect of gold nanorods on LMP1 binding to TNF receptor-associated factor 3. (TRAF3). When the gold nanorod was heated, the LMP1-TRAF3 combination became unstable, implying a biophysical explanation for using gold nanorods in tumour photothermal therapy [31].

5. miRNAs

MiRNAs are non-coding RNAs that control gene expression by interacting with target messenger RNAs (mRNAs) and either blocking or encouraging translation. EBV encodes at least 44 miRNAs (miRNAs) expressed at various latency stages and tissue types. These miRNAs can be categorised into four clusters based on their genomic locations: BART miRNAs, BHRF1 miRNAs, BART/BHRF1 miRNAs, and EBV-miR-B1-5p. EBV encodes viral miRNAs that have been found to play essential roles in the virus's pathogenesis, including regulating viral gene expression, host immune response, cell proliferation, apoptosis, and tumorigenesis. [32].

The analysis of viral microRNA (miRNA) targets and their potential role in EBV-associated diseases is also fascinating, especially in computer-aided research development. Researchers can utilise computational tools and databases to predict and identify potential target mRNAs for EBV-encoded miRNAs. Among these tools are TargetScan (https://www.targetscan.org/vert_72/), which indicates the target genes of miRNAs based on their sequence homology; miRDB (http://www.mirdb.org/), a database that contains information about miRNAs, including their sequences, target genes, and expression patterns; and miRanda (https://regendbase.org/tools/miranda), which examines the complementarity of sequences between miRNAs and target mRNAs. By combining the predicted miRNA-mRNA interactions with the functional annotations and pathway analysis, researchers can gain insights into the potential mechanisms by which EBV-encoded miRNAs contribute to viral replication, immune evasion, and tumorigenesis. Additionally, this information can guide experimental validation studies to confirm the predicted miRNA-mRNA interactions and investigate their functional consequences in EBV-associated diseases.

Wan et al. employed bioinformatics to look for differences in cellular and EBV miRNA expression patterns in twenty NPC tissue microarrays. They revealed that 19 cancer-associated upregulated miRNAs target the p53 signalling pathway, especially the TGF- and Wnt signalling pathways. In contrast, the downregulated miRNAs regulate cancer-related pathways, particularly involving the MAPK signalling pathway [33]. Similarly, Jasinski-Bergner et al. use bioinformatics instruments to screen EBV-miRNA data sets to identify potential EBV-miRNA target genes. They discover five unique target genes for EBV-miRNAs implicated in tumour immunologic and biologic processes. The statistically significant ($p < 0.05$) microarray data sets revealed deregulated genes when analysed from healthy human B cells and malignant-transformed EBV-positive B cells in BL patients [34].

6. Conclusion

In conclusion, EBV is linked to a variety of disorders, including infectious mononucleosis, some forms of malignancy, and autoimmune diseases. While developing an EBV vaccine is complex, ongoing research and clinical trials hold promise for the future. In silico studies of EBV proteins help understand the complex interplay between EBV proteins and host cellular proteins, facilitating the identification of potential targets for drug discovery and developing therapeutic strategies to combat EBV-associated diseases. A safe and effective EBV vaccine could help prevent EBV infections, decrease associated disease incidence, and improve public health.

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