International Journal of Biotechnology and Microbiology
www.biotechnologyjournals.com
Online ISSN: 2664-7680, Print ISSN: 2664-7672
Received: 09-11-2025, Accepted: 08-12-2025, Published: 23-12-2025
Volume 7, Issue 4, 2025, Page No. 81-86

Implications of proteins and possibilities of vaccine molecule development for Epstein-Barr Virus (EBV) induced oral carcinomas

Hritik Chaudhary, Vinod Joshi, Bennet Angel, Annette Angel
Department of Life science, Sharda University, Greater Noida, Uttar Pradesh, India

Abstract
Oral cancer is one of the most widespread form of cancer worldwide. It can be caused by various factors including smoking, alcohol consumption and some viral infections. One of the most prevalent viral infection causing oral carcinoma is associated with Epstein-Barr virus (EBV). The aim of this review is **t**o explore the techniques of identification and analysis of different EBV-associated viral factors which can act as antigens and aid in the development of effective immuno-therapies and to explore various possibilities for the development of effective vaccine molecule. After thorough review of published literature various EBV-associated factors have been identified including Latent membrane proteins (LMPs), EBV-associated nuclear antigens (EBNAs), long non-coding RNAs(lncRNAs) and microRNAs, which aid in the viral progression and can be targeted for the development of effective immuno-therapies. And different methods of vaccine molecule development including nanoparticle vaccine, liposome-nanoparticle vaccine and liposome adjuvant conjugated vaccine are also explored. This will further add in our understanding of novel strategies for effective vaccine development which might lead to the global eradication of EBV-associated illnesses.

Keywords: Epstein-Barr Virus (EBV), Oral Squamous Cell Carcinoma (OSCC), ebv-associated antigens, nanoparticle vaccine, liposome-based vaccine

Introduction

Oral cancer is among the most widespread forms of cancer throughout the world and has a high death rate (50%) because of its poor prognosis and delayed clinical identification [1]. Squamous cell carcinomas (SCCs), a form of epithelial tumours in the oro-pharyngeal cavity, account for majority of oral cancers [2]. Consumption of tobacco and alcohol, exposure to certain biotic and abiotic environmental factors, genetic mutations, and immunological inadequacies are among the main causes of oral malignancies [3].

Additionally, viral infections with certain oncoviruses such as Epstein-Barr virus (EBV) and Human papillomavirus (HPV) also play a key role in the progression of oral cancer [4]. EBV is a type of human gamma herpesvirus that affects majority of world's population [5]. The diameter of EBV is around 122–180 nm and it posesses 172 kbps(killo-basepairs) of DNA which encodes for 80 genes expressing themselves at different phases in the viral lifecycle (Fig. 1). The viral DNA is enclosed by a nucleocapsid surrounded by the tegument protein, which is further enveloped by a layer of lipid and surface glycoproteins [6].

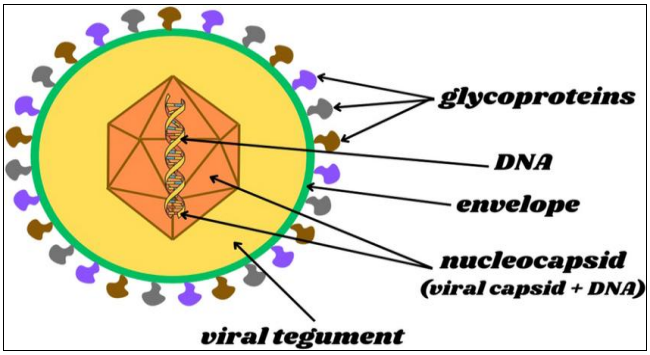

Fig 1: Structure of Epstein-Barr virus (EBV) [Courtesy: https://www.researchgate.net/publication/378283113_Antiviral_Nanomedicine-Based_Approaches_against_Epstein-Barr_Virus_Infection]

Since it's discovery in 1964 by Sir Anthony Epstein and Dr. Yvonne Barr, Epstein-Barr virus (EBV) has been related with different types of human cancers by various studies, recently it's association with oral squamous cell carcinoma (OSCC) has been discovered, which is a common type of oral cancer [7].

In cancer cells a common phenomenon is observed, where glucose metabolism leads to lactate production even in the abundance of oxygen, referred to as Warburg's effect which leads to increased glucose uptake by cancer cells and accumulation of lactate in the microenvironment which in turn promotes cancer progression through various metabolic pathways [8].

EBV has two distinct stages in its life cycle, referred to as latent and lytic phases. After the primary infection, it remains latent at different locations in the body mainly B-cells and epithelial cells of oro-pharynx as well as salivary glands, here it divides and increase in number thereby entering into saliva but without reflecting any major symptoms. There are certain viral genes and their products which may participate in carcinogenesis through various molecular mechanisms [9, 10]. These include some subtypes of Latent membrane proteins (LMP) such as LMP-1 and LMP-2A, 2B, some of which act as active receptors and disrupt B-cell activation and differentiation which provides an immune escape for EBV, thereby promoting long-term latency of EBV in epithelial cells [11].

EBNAs (Epstein-Barr virus nuclear antigens) are also crucial EBV-expressed proteins which play a role in carcinogenesis. There are different subtypes of EBNA such as EBNA-1, 2, 3A, 3B, 3C, and EBNA-5/LP. EBNA-1 is necessary for cell immortalisation and is in charge of viral genome persistence, segregation, and EBV DNA episome replication. Soon after EBV infection, EBNA-2 is co-expressed and plays a crucial role in cell transformation that results in cancer development [12].

BamHI-A rightward frame 1 (BARF-1) is also crucial gene of EBV, its expression in EBV infected cells promote its latency and prolonged cell survival leading to the development of oral carcinomas [13]. It also regulates micro-vessel density (MVD) and micro-lymphatic vessel density (MLVD), which are associated with metastasis of oral carcinomas [14].

There are certain long non-coding RNAs (lncRNAs), when associated with EBV infection they are seen to influence the development and progression of OSCC. LINC00944 is one such lncRNA which is associated with different malignancies and plays a role in their progression but it's role in OSCC is not yet fully determined [15].

Additionally, few MicroRNAs such as MicroRNA-155 (miR-155) when associated with EBV infection, play a crucial part in development of naso-pharyngeal carcinoma (NPC). It has been noted that the control of miR-155 expression brought on by EBV infection plays a significant role in the development of NPC tumours [16].

Development of effective Immunotherapies for Epstein Barr virus is the need of the hour as it continues to infect majority of population worldwide and has been linked to causing various ailments in human body including different types of malignancies such as oral cancer. Currently there is no fully tested and approved vaccine for EBV in the market but different approaches including the usage of viral proteins mentioned earlier, as antigens are being used to develop an effective vaccine [17].

Some of these include subunit vaccines which uses a unique viral factor in the form of a vaccine, viral-vector based vaccines which transfers the required viral component with the help of a viral vector formed by recombinant DNA techniques, mRNA vaccine using viral mRNA to confer immunity in host and nanoparticle based vaccines which uses viral factors in the form of nanoparticles and attach them to liposomes mimicking viral structures sometimes conjugated with adjuvants to confer improved immunisation [18]. Some of these approaches are summarised in figure 2.

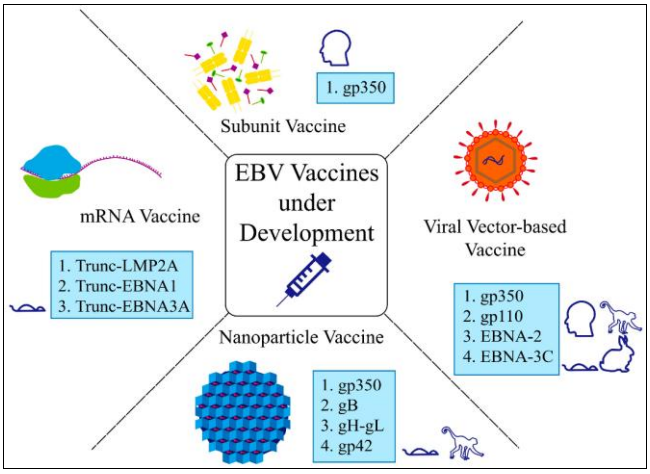

Fig 2: Different types of EBV vaccines under development [courtesy: https://www.researchgate.net/publication/393326302_Recent_Progress_in_the_Vaccine_Development_Against_Epstein-Barr_Virus]

In this review, we explored some crucial approaches to assist the development of effective targeted immunotherapies including usage of different bioinformatics tools for the identification and development of such viral factors which can be used to evoke an effective immune response in humans without causing cross-reactivity with human peptides [19]. We also explored the development of adjuvant-conjugated nanoparticle-based vaccines for EBV using specific adjuvants such as Sigma Adjuvant System (SAS) and a saponin/mono-phosphoryl lipid A nanoparticle (SMNP) [20].

Different methods for vaccine molecule designing are also explored which helps in enhancing the immunogenicity of nanoparticle vaccine molecules in the host cells, therefore it is a crucial step for the development of effective EBV vaccines in the long term. Also, multiple target vaccine molecules can be designed where several specific glycoprotein nanoparticles can be conjugated onto the liposome surface thereby further improving the immune response [21]. This review further highlights the future scope in this niche of research.

1. Implications of Proteins for Epstein-Barr virus (EBV) associated oral carcinomas:

Different types of EBV-associated genes, gene products and other factors aid in the progression of different types of oral carcinomas, including EBV-induced oral carcinomas. Identification and analysis of these factors is crucial for the development of effective immuno-therapies against EBV. In a recent study done by Heawchaiyaphum et al., in 2023 [7, 22], a correlation between EBV infection and oral squamous cell carcinoma (OSCC) have been established. But the underlying metabolic processes are not yet completely understood. They tried to investigate the metabolic processes by which Warburg effect supports EBV-linked oral carcinoma, by establishing a link between EBV infection and up-regulation of genes associated with Warburg effect and whether this up-regulation is linked with tumour progression, which might help in identifying the target molecules associated with EBV-linked OSCC for the development of effective immunotherapies. It was revealed that EBV infection leads to the reduction of mitochondrial DNA (mtDNA) copies which induces a mitochondrial stress. Altered expression of some glycolytic genes especially the up-regulation of genes related to Warburg effect observed through microarray data, which also enhanced lactate production in infected cells. It established a link between EBV infection and up-regulation of genes associated with Warburg effect and revealed that this up-regulation is linked with tumour progression [22].

In another study, investigators attempted to establish a correlation between EBV-infection, expression of EBV-associated Latent membrane protein; LMP-1 and oral malignancies such as oral squamous cell carcinoma (OSCC). They also examined the sub-cellular localisation of this protein in oral mucosa infected by EBV, in comparison with OSCC cells. A large number of biopsy samples detected with OSCC were analysed along with some normal oral mucosa which was infected by EBV using immuno-histochemistry, for finding out the comparative expression levels of LMP-1. And the cellular localisation of LMP-1 was also done using standardised staining procedures, based on which the cells were classified as nuclear, cytoplasmic and nuclear plus cytoplasmic [23].

The role of Latent membrane protein-1 in causing oral cancer is well established by the courtesy of various studies but its correlation with micro-vessel density (MVD) and micro-lymphatic vessel density (MLVD), is not very clear. In a recent study done by Wang et al., in 2016 [24], they analysed the expression of LMP-1 and BARF-1 proteins of EBV in naso-pharyngeal carcinoma (NPC) and also tried to determine their correlation with MVD and MLVD. The

expression of LMP-1 and BARF-1 was determined through immunohistochemistry and the levels of MVD and MLVD were determined with the help of standardised immuno-staining procedures. Out of analysed nasopharyngeal cancer (NPC) tissue samples, 81% were found to be EBV-positive among which around 62% tested positive for LMP-1 expression whereas only around 13% were found positive for BARF-1 expression. Among the LMP-1 positive samples MLVD was found to be significantly higher as compared to LMP-1 negative samples, same trend was seen in case of BARF-1. But no significant correlation of LMP-1 and BARF-1 was seen with MVD, which suggests a correlation between the expression of EBV associated LMP-1 and BARF-1 proteins with MLVD and not MVD [24].

In a study based on similar context Lao et al., in 2019 [16] used tumour and non-tumour tissues from NPC patients and aimed to investigate the connections between the level of expression of microRNA miR-155, and EBV associated membrane proteins LMP-1 and LMP-2. By suppressing or reactivating miRNAs, knowledge of their function enabled the identification of molecular target for developing an effective immunotherapy. Results of this study strongly linked the expression of these potential genes and NPC as different levels of expression of these proteins were observed in all the NPC samples, whereas no positive expression was detected in healthy samples. In another study conducted by the same group they used polymerase chain reaction (PCR) to detect potential genes, such as EBNA-1, EBNA-2, LMP-1, and LMP-2, to investigate EBV infection in nasopharyngeal cancer (NPC). Here they took hundred non-cancerous swab specimens and ninety-three NPC biopsy samples from patients and subjected them to qRT-PCR analysis which revealed similar results where NPC samples showed significantly higher levels of LMP-1, LMP2, and miR-155, while the control group showed lower levels of expression [16, 25].

There are certain long non-coding RNAs (lncRNAs), when associated with EBV infection they are seen to influence the development and progression of OSCC. In a paper published earlier this year, the role of one such EBV-induced lncRNA - LINC00944 in the development and progression of OSCC is explored. Researchers concluded that there is an up-regulation of LINC00944 in cases of EBV-infected oral squamous epithelial tissue, which hints towards its role in carcinogenesis and it also signifies the influence of EBV infection in enhancing its gene expression. Gene expression of LINC00944 was observed in both EBV positive and negative cells in OSCC cell lines with the help of qRT-PCR. LINC00944 was over-expressed in OSCC cell lines and its impact on migration and invasion was analysed to find out its role in cancer development. It was observed that its over-expression in these cell lines greatly increased the motility and invasiveness of cells. Along with this the effect of its over-expression on macrophage differentiation was also analysed and it was observed that macrophage differentiation into M1 subtype is increased. LncRNA-miRNA-mRNA interactions were also analysed in the cell lines which suggested that the up-regulation of LNC00944 expression might regulate RELA gene and NFKB1(Nuclear factor kappa B) which leads to a cascade of reactions which ultimately results in expression of pro-inflammatory genes which aids in cancer progression. So LINC00944 is shown to enhance migration, invasion and metastasis in EBV infected cells which promotes oral squamous cell carcinoma (OSCC) progression [15]. Researchers also investigated how EBNA1 affects the expression of some specific cellular genes such as Derlin1, ZEB1, CNN3, and PSMD10 in HeLa cells for trying to establish its role in oral carcinomas [26].

2. Possibilities of vaccine molecule development for Epstein-Barr virus (EBV) associated oral carcinomas:

Investigators are exploring a number of different approaches for the development of an effective EBV vaccine and in order to do so, we need to identify and analyse some unique viral peptides/antigens and develop novel approaches by which they can be modified to develop targeted immunotherapeutics or vaccine. To support the ongoing efforts Capone et al., in 2015 [19], provided some useful insights as a result of their study, they tried to investigate and analyze some unique Epstein Barr virus (EBV) associated EBNA1 peptides which are only associated with the virus and not found in the human host. Identification and further analysis of such sequences might help in the designing and development of specific peptide based EBV vaccines, which will specifically target and neutralise the viral proteins and show very little or no cross-reactivity with the host proteins [19]. They analysed the primary amino acid sequence of Epstein Barr virus associated EBNA1 protein from GD1 strain of EBV, using different bioinformatics tools such as GenBank and UniProt/SwissProt. The Amino acid sequence of GP350 (Glycoprotein350) associated with EBV was also analysed as a control sequence [27].

Apart from this, similarity of amino acid sequence of EBV associated EBNA1 protein was checked among the human proteome. To achieve this the viral EBNA1 amino acid sequence was divided into 5-mers (penta-peptide residues) in such a way that sequential overlapping of four amino acid residues is present (i.e., MSDEG, SDEGP, DEGPG, EGPGT, etc.). Then all these penta-peptide viral residues were searched against the human proteome using a bioinformatics tool called as PIR (Protein Information Resource), using this all the viral residues which were identical to the amino acid residues in the human proteome were identified [28]. Any identical residue in the human proteome was considered a match and then the cross-reactivity potential for each viral residue was identified using Immune Epitope Database and Analysis Resources (IEDB), to detect any EBNA1 derived B-cell or T-cell epitopes which have been proven to be immunopositive in humans during any prior experimental studies [29]. The information gathered with the help of this study will be useful in determining the potential peptides associated with EBV which are unique to the virus and not found in the human host proteome, so that they can be used as antigens for the development of potential vaccines for EBV.

There are many such proteins associated with EBV which are responsible for the development of various diseases in the human body including different cancers such as oro-pharyngeal cancer. The identification and analysis of there proteins is essential for the development of an effective EBV vaccine. In a recent study conducted by Edwards et al., in 2024 [20] one such viral glycoprotein of EBV referred to as gH/gL glycoprotein complex which is essential for causing infection in human host is explored experimentally as an attractive target for vaccine molecule development. They immunised Rhesus macaques with a newly formulated vaccine molecule which primarily comprises of two components including EBV associated gH/gH conjugated with either of these two adjuvants; Sigma Adjuvant System (SAS) or a saponin/mono-phosphoryl lipid A nanoparticle (SMNP). This provides us with two different systems which

can be compared and analysed for their extent of immunogenicity in the macaques.

After immunisation with these adjuvant conjugated vaccines, the animals were infected with the rhesus lymphocryptovirus (rhLCV) which is an ortholog of Epstein Barr virus and then the plasma of both categories of animals were observed. And even though the plasma of macaques shows very less reactivity for EBV associated gH/gL which were used in the formulation of these vaccines, in comparison to rhLCV associated gH/gL, still prevention of rhLCV infection was observed to some extent in most of the cases. Among the two adjuvants which were used in this study saponin/mono-phosphoryl lipid A nanoparticle (SMNP) showed a stronger immunogenic response as compared to the Sigma Adjuvant System (SAS) based vaccine. The results of this study support the use of EBV associated gH/gL glycoprotein for the formulation of adjuvant conjugated nanoparticle-based vaccines for EBV [20].

There are certain specific EBV glycoproteins identified by different experimental approaches which can be used as antigenic target molecules of the virus for the development of EBV vaccine. Some examples of such EBV associated glycoproteins are gp350, gH, gL, gp42 and gB, all these glycoproteins have a unique crucial role in the entry of virus inside the host cell. Some investigators are designing nanoparticle vaccines displaying these viral molecules, so that they can evoke an effective immune response when given to humans and help in the elimination of EBV [21].

A recent study by Li et al., in 2025 [21] explores one such strategy where the tried to use liposomes mimicking the viral structure for displaying nanoparticles/viral glycoproteins. They synthesised viral structure mimicking liposomes which are used to display an EBV glycoprotein, gp350D123 which is well identified on their surface, via the formation of a stable amide bond between N-hydroxysuccinimide (NHS) group on liposome surface and amine group of glycoproteins. Then this nanoparticle referred to as Lipo-gp350D123 was used as a vaccine for the immunisation of mice along with control groups where only monomer gp350D123 glycoprotein was given to compare the strength of immune responses evoked by both the groups for better understanding the role of liposome in enhancing the cross reactivity.

The results of this study showed that the liposome nanoparticle-based molecules provoked an enhanced immune response via antigen-specific antibody development as compared to the control group. Also, a higher proportion of CD8+ IFN-γ+ T cells is observed in spleen cells along with enhanced secretion of IFN-γ in these isolated cells, when compared to the control group. And no histo-pathological alterations are seen in vaccinated mice. These results support the use of liposomes for displaying viral glycoproteins in the form of vaccines for evoking a stronger immune response against EBV in host cells [21].

Conclusions

In conclusion, this review strengthened the knowledge about different types of EBV-associated genes, gene products and other factors (enlisted in Table 1) which are carcinogenic or assist in some way in the progression of different types of oral carcinomas. We explored the role of EBV-induced factors in the progression of Oral cancer. As EBV infection is shown to reduce the mtDNA number in infected cells, which alters the cellular metabolism by up-regulation of Warburg effect related glycolytic genes which also leads to the upregulation of cancer stem cell markers, thereby promoting stemness and tumorigenesis in infected cells. A link between EBV-infection, EBV-associated LMP-1expression and OSCC is established. As when it's expression in normal oral mucosa was compared to OSCC cells, a clear trend was observed where it showed over-expression in OSCC cells.

A correlation is established between the expression of EBV associated LMP-1 and BARF-1 proteins with MLVD and not MVD in NPC patients. EBV-EBNA1 is seen to promote the survival of cancer cells and aid the progression of cancer by upregulating the genetic expression of Derlin1 and PSMD10, which suggests the role of EBNA-1 in cancer progression. But more research is necessary in order to definitively relate EBV-EBNA1 to the advancement of oral carcinoma. And a strong correlation between miR-155 expression and LMP-1 and LMP-2 expression is established, which might make it easier to create promising biomarkers based on LMPs and miR-155 expression for the diagnosis and treatment of Naso-pharyngeal carcinomas.

The up-regulation of LINC00944 in cases of Epstein-Barr virus (EBV) infected oral squamous epithelial tissue is observed, which hints towards its role in cancer development. EBV induced LINC00944 enhances OSCC progression by increasing migration and invasion in cancer cells as well as macrophage differentiation. This information will further assist the future work involving discovery of novel factors involved in EBV-induced oral carcinomas for the development of effective immunotherapies.

Table 1: EBV-associated factors which are carcinogenic or assist in some way in the progression of oral carcinomas and their functions.

S. No.	EBV-induced Factor	Subtypes	Role in Oral carcinoma
1.	LMPs (Latent membrane protein)	LMP-1	Act as an activated receptor to transform B-cells and epithelial cells leading to inhibition of apoptosis as well as cancer cell growth and proliferation.
		LMP-2A, 2B	Promotes cancer cell survival via different metabolic pathways.
2.	EBNAs (Epstein-Barr virus nuclear antigens)	EBNA-1	Maintain the viral genome as an episome in epithelial cells during cell division.
		EBNA-2	B-cell transformation, leading to proliferation.
		EBNA-3A, 3C	Both works together in suppressing tumor suppressor genes and prevent apoptosis.
		EBNA-3B	Have tumor-suppressive functions and can limit EBNA-3A, 3C effect.
		EBNA-LP/5	Work with EBNA-2 in B-cell transformation.
3.	BARF-1 (BamHI-A rightward frame 1)		Promote latency and prolonged cell survival in infected cells, leading to the development of oral carcinomas.
4.	Long non-coding RNAs (lncRNAs)	LINC00944	Associated with different malignancies and plays a role in their progression but it's role in OSCC is not yet fully determined.
5.	MicroRNAs	MicroRNA-155 (miR-155)	Promotes can cell progression by enhancing migration, cell proliferation and invasion.

This review also explored various approaches which can be employed in the identification of such unique viral factors/proteins, which can be used as antigens with necessary additional modifications for the development of effective vaccine molecules to eliminate EBV. Such as sequential i*n-silico approach which can be implied in order to identify unique viral peptides or antigens of EBV* which can be effectively used for the development of vaccine which are less prone to causing cross-reactions in the human host.

The development of *adjuvant conjugated nanoparticle-based vaccines for EBV* using two specific adjuvants including a Sigma Adjuvant System (SAS) and a saponin/mono-phosphoryl lipid A nanoparticle (SMNP). Both of these vaccines are found to be effective but the SMNP adjuvant-based vaccine is seen to be more effective against the rhLCV infection in macaques, even with less reactivity for EBV associated gH/gL which were used in the formulation of these vaccines, in comparison to rhLCV associated gH/gL. This supported the use of EBV associated gH/gL glycoprotein for the formulation of adjuvant conjugated nanoparticle-based vaccines for EBV.

This study highlighted the importance of identification and analyses of unique viral factors which can be used for the development of effective vaccine molecules and use of liposomes for displaying these viral factors in the form of nanoparticles sometimes conjugated with appropriate adjuvants to form effective vaccines for evoking a stronger immune response against EBV in host cells. Also, multiple target vaccine molecules can be designed in the future where several specific glycoprotein nanoparticles can be conjugated onto the liposome surface thereby further improving the immune response.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA A Cancer Journal for Clinicians,2013:63(1):11–30. doi:10.3322/caac.21166.
2. Tahir A, Nagi AH, Ullah E, Janjua OS. The role of mast cells and angiogenesis in well-differentiated oral squamous cell carcinoma. Journal of Cancer Research and Therapeutics,2013:9(3):387–391. doi:10.4103/0973-1482.119311.
3. D'Souza S, Addepalli V. Preventive measures in oral cancer: An overview. Biomedicine and Pharmacotherapy,2018:107:72–80. doi: 10.1016/j.biopha.2018.07.114.
4. Jalouli MM, Jalouli J, Hasséus B, Öhman J, Hirsch JM, Sand L. Nested PCR for detection of HSV-1 in oral mucosa. Medicina Oral Patologia Oral y Cirugia Bucal,2015:20(6):e664–e669. doi:10.4317/medoral.20630.
5. Young LS, Yap LF, Murray PG. Epstein–Barr virus: More than 50 years old and still providing surprises. Nature Reviews Cancer,2016:16(12):789–802. doi:10.1038/nrc.2016.92.
6. Odumade OA, Hogquist KA, Balfour HH Jr. Progress and problems in understanding and managing primary Epstein–Barr virus infections. Clinical Microbiology Reviews,2011:24(1):193–209. doi:10.1128/CMR.00044-10.
7. Heawchaiyaphum C, Yoshiyama H, Iizasa H, Burassakarn A, Tumurgan Z, Ekalaksananan T, *et al*. Epstein–Barr virus promotes oral squamous cell carcinoma stemness through the Warburg effect. International Journal of Molecular Sciences,2023:24(18):14072. doi:10.3390/ijms241814072.
8. Warburg O. On the origin of cancer cells. Science,1956:123(3191):309–314. doi:10.1126/science.123.3191.309.
9. Bornkamm GW, Hammerschmidt W. Molecular virology of Epstein–Barr virus. Philosophical Transactions of the Royal Society of London Series B Biological Sciences,2001:356(1408):437–459.
10. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell,2011:144(5):646–674.
11. Gires O, Zimber-Strobl U, Gonnella R, Ueffing M, Marschall G, Zeidler R, *et al*. Latent membrane protein 1 of Epstein–Barr virus mimics a constitutively active receptor molecule. The EMBO Journal,1997:16(20):6131–6140.
12. Sivachandran N, Wang X, Frappier L. Functions of the Epstein–Barr virus EBNA1 protein in viral reactivation and lytic infection. Journal of Virology,2012:86(11):6146–6158.
13. Pfitzner AJ, Tsai EC, Strominger JL, Speck SH. Isolation and characterization of cDNA clones corresponding to transcripts from the BamHI H and F regions of the Epstein–Barr virus genome. Journal of Virology,1987:61(9):2902–2909.
14. Lee KM, Danuser R, Stein JV, Graham D, Nibbs RJ, Graham GJ, *et al*. The chemokine receptors ACKR2 and CCR2 reciprocally regulate lymphatic vessel density. The EMBO Journal,2014:33(21):2564–2580.
15. Srisathaporn S, Ekalaksananan T, Heawchaiyaphum C, Aromseree S, Maranon DG, Altina NH, *et al*. EBV-induced LINC00944: A driver of oral cancer progression and influencer of macrophage differentiation. Cancers,2025:17(3):491. doi:10.3390/cancers17030491.
16. Lao TD, Le TAH. Association between LMP-1, LMP-2, and miR-155 expression as potential biomarkers in nasopharyngeal carcinoma patients: A case/control study in Vietnam. Genetic Testing and Molecular Biomarkers,2019:23(11):815–822. doi:10.1089/gtmb.2019.0089.
17. Kanduc D. Immunogenicity in peptide-immunotherapy: From self/nonself to similar/dissimilar sequences. Advances in Experimental Medicine and Biology,2008:640:198–207.
18. Dai Y, Zhang B, Yang L, Tao S, Yu Y, Li C. Recent progress in the vaccine development against Epstein–Barr virus. Viruses,2025:17(7):936. https://doi.org/10.3390/v17070936.
19. Capone G, Fasano C, Lucchese G, Calabrò M, Kanduc D. EBV-associated cancer and autoimmunity: Searching for therapies. Vaccines,2015:3(1):74–89. doi:10.3390/vaccines3010074.
20. Edwards KR, Schmidt K, Homad LJ, Kher GM, Xu G, Rodrigues KA, *et al*. Vaccination with nanoparticles displaying gH/gL from Epstein–Barr virus elicits limited cross-protection against rhesus lymphocryptovirus. Cell Reports Medicine,2024:5(6):101587. doi: 10.1016/j.xcrm.2024.101587.
21. Li P, Yu Z, Jiang Z, Jiang Y, Shi J, Han S, *et al*. A liposome-based nanoparticle vaccine induces effective

immunity against EBV infection. Vaccines,2025:13(4):360. doi:10.3390/vaccines13040360.
22. Heawchaiyaphum C, Yoshiyama H, Iizasa H, Burassakarn A, Tumurgan Z, Ekalaksananan T, *et al*. Epstein–Barr virus promotes oral squamous cell carcinoma stemness through the Warburg effect. International Journal of Molecular Sciences,2023:24(18):14072. doi:10.3390/ijms241814072.
23. Rahman R, Poomsawat S, Juengsomjit R, Buajeeb W. Overexpression of Epstein–Barr virus-encoded latent membrane protein-1 in oral squamous cell carcinoma. BMC Oral Health,2019:19(1):142. doi:10.1186/s12903-019-0832-3.
24. Wang A, Zhang W, Jin M, Zhang J, Li S, Tong F, *et al*. Differential expression of EBV proteins LMP1 and BHFR1 in EBV-associated gastric and nasopharyngeal cancer tissues. Molecular Medicine Reports,2016:13(5):4151–4158. doi:10.3892/mmr.2016.5087.
25. Lao T, Hoang A, Nguyen T, Dung L, Thuy. Pattern of EBNA-1, EBNA-2, LMP-1 and LMP-2 in nasopharyngeal carcinoma in Vietnamese patients. Genetic Testing and Molecular Biomarkers,2018:22(4):243–247. doi:10.1007/978-981-10-4361-1_40.
26. Alipour AH, Hashemi SMA, Gharahkhani F, Katanchi A, Farhadi A, Sarvari J. Epstein–Barr virus nuclear antigen 1 upregulates Derlin1 and PSMD10 expression in HeLa cells. Genes and Cancer,2025:16:26–33. doi:10.18632/genesandcancer.242.
27. Zeng MS, Li DJ, Liu QL, Song LB, Li MZ, Zhang RH, *et al*. Genomic sequence analysis of Epstein–Barr virus strain GD1 from a nasopharyngeal carcinoma patient. Journal of Virology,2005:79(24):15323–15330.
28. Wu CH, Yeh LS, Huang H, Arminski L, Castro-Alvear J, Chen Y, *et al*. The protein information resource. Nucleic Acids Research,2003:31(1):345–347.
29. Vita R, Zarebski L, Greenbaum JA, Emami H, Hoof I, Salimi N, *et al*. The immune epitope database 2.0. Nucleic Acids Research,2010:38:D854–D862.