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TRABAJO FIN DE GRADO

VIRUS EPSTEIN-BARR Y CÁNCER

EPSTEIN-BARR VIRUS AND CANCER

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1. ABSTRACT

The Epstein–Barr virus (EBV) is a gamma herpesvirus which is associated with different diseases including multiple sclerosis, infectious mononucleosis, and several types of cancer such as Burkitt and Hodgkin lymphoma, nasopharyngeal, lymphoepithelium-like or gastric carcinoma. EBV infection can be latent or replicative, corresponding to different expression patterns of viral genes. EBV infection can be detected utilizing antibodies used in the different EBV-associated illnesses. EBV infection has been associated with malignancies such as Burkitt and Hodgkin lymphoma, nasopharyngeal, lymphoepithelium-like, or gastric carcinoma. The most prevalent tumor associated with EBV is Burkitt lymphoma, and nasopharingeal carcinoma is the most common in absolute number of cases. EBV infection is common in the population; however, the impact of Burkitt lymphoma is higher in sub-saharian African. EBV induces B-cell transformation by activating key cell signaling pathways and persists in memory B cells of healthy individuals. Classical karyotyping and advanced transcriptomics show that all Burkitt lymphomas carry a MYC/IgG translocation, but there are other molecular changes, such as mutations in p53 which are also important. Burkitt lymphoma is classified in three groups: endemic, sporadic and immunodeficiency-associated lymphoma. The association of EBV is much higher in the endemic form (approximately 95% of the cases), typical of regions where malaria is also prevalent.

KEY WORDS: Epstein-Barr virus (EBV), Burkitt lymphoma (BL), B cell lymphoma, c-MYC.

2. SUMMARY IN SPANISH

El virus de Epstein-Barr (VEB) es un herpesvirus gamma asociado a distintas enfermedades, entre ellas la esclerosis múltiple, la mononucleosis infecciosa y varios tipos de cáncer, como el linfoma de Burkitt y Hodgkin, el carcinoma nasofaríngeo, el linfoepitelial o el gástrico. La infección por VEB puede ser latente o replicativa, lo que corresponde a diferentes patrones de expresión de los genes virales. La infección por VEB puede detectarse utilizando anticuerpos utilizados en las diferentes enfermedades asociadas al VEB. La infección por VEB se ha asociado a neoplasias malignas como el linfoma de Burkitt y de Hodgkin, el carcinoma nasofaríngeo, el linfoepitelial o el gástrico. El tumor más prevalente asociado al VEB es el linfoma de Burkitt, y el carcinoma

nasofaríngeo es el más frecuente en número absoluto de casos. La infección por VEB es común en la población; sin embargo, el impacto del linfoma de Burkitt es mayor en el África subsahariana. El VEB induce la transformación de las células B mediante la activación de vías clave de señalización celular y persiste en las células B de memoria de individuos sanos. El cariotipo clásico y la transcriptómica avanzada muestran que todos los linfomas de Burkitt portan una translocación MYC/IgG, pero hay otros cambios moleculares, como mutaciones en p53 que son también importantes. El linfoma de Burkitt se clasifica en tres grupos: endémico, esporádico y linfoma asociado a inmunodeficiencia. La asociación del VEB es mucho mayor en la forma endémica (aproximadamente el 95% de los casos), típica de las regiones en las que también prevalece la malaria.

PALABRAS CLAVE: Virus Epstein-Barr, linfoma de Burkitt, linfoma células B, C-MYC.

3. ACKNOWLEDGEMENTS

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4. ABREVIATIONS

- **AICDA:** activation-induced cytidine deaminase
- **BCR:** B cell receptor
- **BL:** Burkitt lymphoma
- **DLBCL:** Difuse large B cell lymphoma
- **EBER:** Epstein-Barr encoded RNA
- **EBNA:** Epstein-Barr nuclear antigen
- **EBV:** Epstein-Barr virus
- **FISH:** Fluorescent *in situ* hybridization
- **GC:** Germinal center
- **HSCs:** Hematopoietic stem cells
- **LCLs:** Lymphoblastoid cell lines

- **LMP:** Latent membrane proteins
- **MA:** Membrane antigen
- **MHC:** Major histocompatibility complex
- **MS:** Multiple sclerosis
- **NK:** Natural killer
- **NPC:** Nasopharyngeal carcinoma
- **PCs:** Plasma cells
- **PTLD:** Post-transplant lymphoproliferative disease
- **PTLs:** Post-transplant lymphomas
- **TCL:** T cell lymphocytes
- **VCA:** Viral capsid antigen
- **WHO:** World Health Organization

5. INTRODUCTION

Epstein-Barr Virus (EBV) is a gamma herpesvirus with the ability to infect B cells, transforming them into Lymphoblastoid Cell Lines (LCLs) *in vitro*. It was discovered in 1964 in samples of Burkitt lymphoma in African children (see below)[1]. Humans are the only natural EBV hosts, and EBV has a high incidence worldwide. Over 95% of the adult population is known to be infected by EBV, but only a low percentage develops EBV-associated diseases. EBV infection can be latent or replicative. However, a lytic replication cycle can also occur. Infectious mononucleosis is the fundamental clinical manifestation of EBV infection. EBV is also associated with other cancers and non-cancerous diseases. This virus is associated with Burkitt lymphoma, immunosuppression-related lymphoma, extranodal NK/T-cell lymphoma, Hodgkin lymphoma, gastric, lymphoepithelial cancer, and nasopharynx cancer.

This bibliographic review aims to study the role of the Epstein Barr virus in the development of cancer. Among the different EBV-associated cancers, Burkitt lymphoma is the most recognized, which is associated with deregulation of c-MYC gene. Hence, this TFG will more extensively cover EBV-associated Burkitt lymphoma.

Burkitt Lymphoma (BL) is an aggressive form of B-cell lymphoma that can be classified as sporadic, endemic, or immunodeficient. More recent classifications tend to divide BL simply into EBV-associated and non-associated lymphomas. BL produced by EBV carries chromosomal translocations that activate the oncogene MYC, which is expressed during B lymphocyte development, thereby blocking the differentiation process.

While there is a clear correlation between MYC translocation and EBV infection in the endemic BL, there are questions still unsolved such as the role of EBV in BL initiation or maintenance and the mechanistic relationship between EBV infection and MYC.

In this TFG, I will also review the role of MYC in the pathogenesis of EBV, the importance of MYC deregulation for the treatment of cancer, and the variations in MYC expression within the different types of cancer that carry EBV infections.

6. METHODOLOGY

This final degree project consists of a bibliography review based on the information found in databases such as Pubmed and Medline. A total of 170 references including research articles, reviews and book chapters have been included in the reference list and they have been searched in English language.

The PubMed database (http://pubmed.ncbi.nlm.nih.govor) was mainly used. PubMed is a public database that contains more than 33 million citations and abstracts of biomedical and chemical literature. The words asked to Pubmed were EBV and cancer, EBV and lymphoma, EBV and EBV and MYC, EBV and sclerosis.

The Mendeley Reference Manager was used as a tool for the organization of bibliographical references.

7. THE EPSTEIN BARR VIRUS

The Epstein-Barr Virus (EBV) is a human herpesvirus (HHV-4) which belongs to the gamma herpesvirus subfamily from the Lymphocryptoviral gender. Humans are the only natural EBV hosts [2]. There are two types of EBV: EBV1 and EBV2. The main difference

between them consists of the sequence of the genes that encode for their nuclear antigens (EBNA-2, EBNA-3A/3, EBNA-3B/4, and EBNA-3C/6).

EBV virion has a diameter of 100-200 nm and consists of a toroid-shaped protein core wrapped with DNA, a nucleocapsid with 162 capsomers, a protein tegument between the nucleocapsid and the envelope, and an outer envelope with external virus-encoded glycoprotein spikes[3] *(Figure 1).* Among these, gp350/220 is the most abundant glycoprotein complex and plays an important role for virions attachment to the cell host.

EBV genome is made of a linear, double-stranded DNA of approximately 172 kb, and it encodes 86 proteins and 44 non-coding RNAs. EBV proteins can be divided into four different types corresponding to EBV's different infective programs: 1) latent phase proteins, 2) immediate early replicative phase proteins, 3) early replicative phase proteins and 4) late phase proteins [4,5]. Accordingly, EBV genome can be divided into latent and lytic genes.

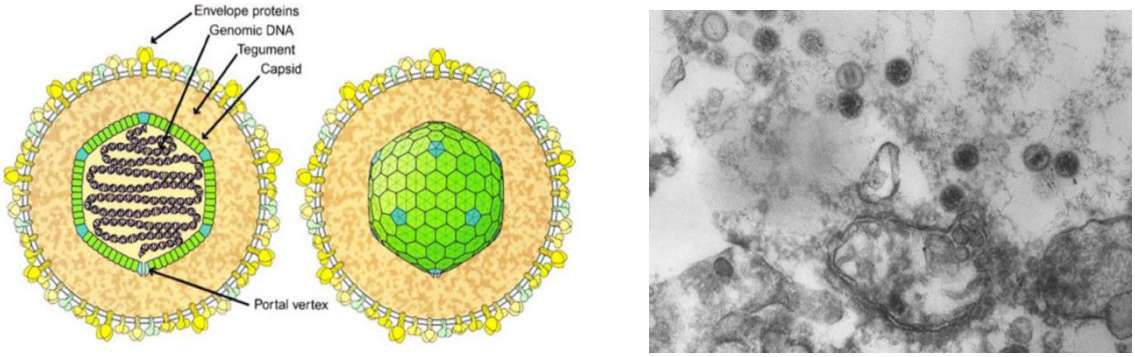


FIGURE 1: Left: Structure of Epstein-Barr virus [6] *Right: Epstein-Barr virus (EBV) virions in a transmission electron microscopic (TEM) image* [7].

EBV can induce a latent or lytic infection. Upon the latent phase, resting B cells are transformed into permanent, latently infected Lymphoblastoid Cell Lines (LCLs). In this case, EBV1 seems to be more effective than EBV2 [2,8].

During the latent infection, EBNA genes are transcribed from the two viral promoters, termed Cp and Wp, allowing the transcription of all EBNA isoforms. Wp is only activated in the initial stages of the infection of B lymphocytes, followed by the activation of Cp *(Figure 2)* [9]. In EBV infection, there can be a deletion of the promoter that stimulates the tumorigenesis of EBV lymphomas [10].

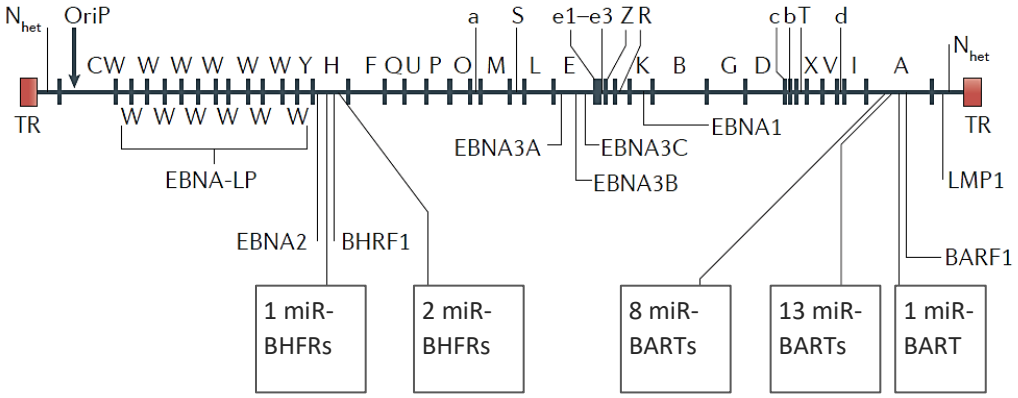


FIGURE 2: Location of ORF for EBV latent proteins in BamHI restriction fragment of EBV B95-8 genome and miRNAs. Modified from Young, L. S. [11]

When the virus starts the replication phase upon lytic infection, EBV proteins like the early antigen (EA), the viral capsid antigen (VCA) and the glycoproteins of the membrane antigen (MA) are produced. These proteins activate the host immune response. On the contrary, upon latent infection, episomes (about 10 per cell) replicate during cell division allowing the synthesis of EBNA 1, 2, 3A, 3B and 3C and latent membrane proteins like LMP1, LMP2 [5].

7.1. VIRAL LIFE CYCLE

EBV usually infects B lymphocytes through the binding of gp350/220 to the C3d complement component CR2 (also called CD21)[12,13]. The interaction of EBV with its host cell receptors is followed by EBV internalization into cytoplasmatic vesicles and a second interaction between EBV gp42, which is a product of BZLF2 gene[14], and B1 domain of HLA class II molecule *(Figure 3, left).* EBV also can infect T-lymphocytes or epithelial cells producing nasopharyngeal and gastric carcinomas and oral hairy leukoplasia [15].

EBV also can infect epithelial cells, which lack CR2/CD21 expression. In this case, the infection process is not well known yet, but it has been suggested that several integrins could be involved in such process [16]. These cells without HLA class II do not need complexes with gp42. EBV has a gH-gL complex that binds ephrin receptor A2 leading to the activation of the EBV fusion protein gB allowing the union of the membranes. This

infection also involves the viral protein BMRF2 that interacts with some integrins *(Figure 3, right).*

Finally, the genetic material enters the nucleus of the cell, and the DNA circularizes turning into a circular episome [17].

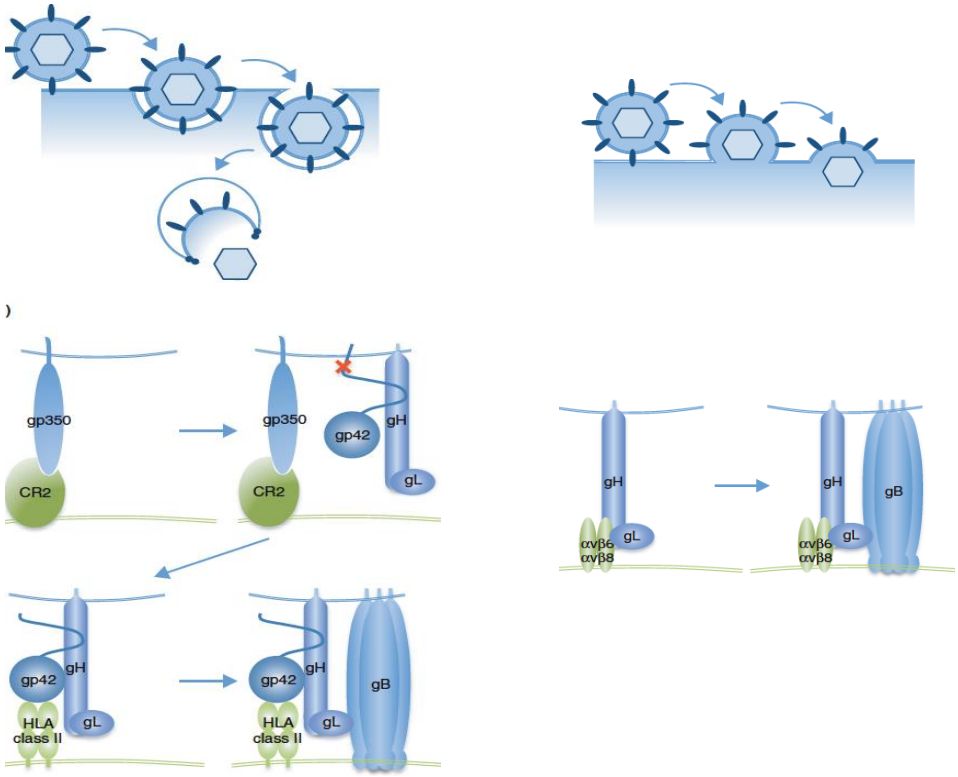


FIGURE 3: Left: B cell infection by EBV, mediated by CR2/CD21. Right: Epithelial cell infection by EBV. Molecules from the EBV are represented in blue while molecules from the host cell can be seen in green [18].

Around 90-95% of the adult population is infected by EBV[19]. The main reservoir of EBV infected cells is the lymphoid tissue. The primary contact with the EBV usually happens during childhood and its first form of presentation is the infectious mononucleosis (see below). It can be transmitted not only via oral but also by transplants or blood transfusions [54].

EBV has two infection cycles: lytic and latent. The latent cycle comprises four latency programs (0, I, II, and III) which are classified according to the differential expression of the EBV latent genes that will be explained in the following section.

During the primary infection, the main way of replication is the lytic one. It starts with the entrance of EBV in the epithelium of the oropharynx followed by its spreading to the lymphoid tissues. The immediate stages after the EBV entrance into a B-cell are still poorly understood. EBV has been suggested to be able to turn B cells into memory cells in the germinal center by somatic Ig-gene hypermutation. However, patients with infectious mononucleosis have no hypermutation in their B cells in the extrafollicular areas.

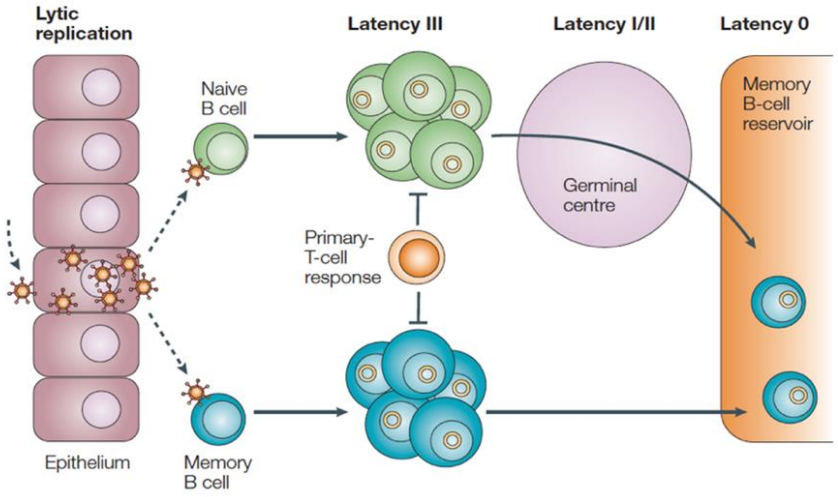


FIGURE 4: Primary infection by EBV. The virus promotes lytic replication in the epithelium, and it spreads throughout the lymphoid tissues [16].

After the first lytic replication, most of the infected cells are eliminated by T cells but some of them escape from the immune system surveillance by the downregulation of antigen expression levels (latency programs) and the development of a reservoir (Latency 0) *(Figure 4)*, leading to a persistent latent infection.

For the persistent infection in the latent cycle *(Figure 5),* EBV infects memory B-cells that are occasionally recruited to the germinal center. These cells can turn back to the reservoir as memory cells or to mucosal sites for plasma cell differentiation activating the lytic cycle. Latent infection has also been detected in naïve B-cells.

If the cells remain latent, there can be an activation of the Latency III program of naïve B and memory cells replenishing the B-cell reservoir in the germinal center [16,19] . In this location, there is a downregulation of EBNA2 and the EBNA3s of B cells. The survival of B cells is achieved by the constant expression of LMPs in Latency II program. For

example, it has been described that LMP2a might mimic signaling through the B-cell receptor and LMP1 might provide signals similar to those induced by CD40 engagement [20–22] *(Figure 6).*

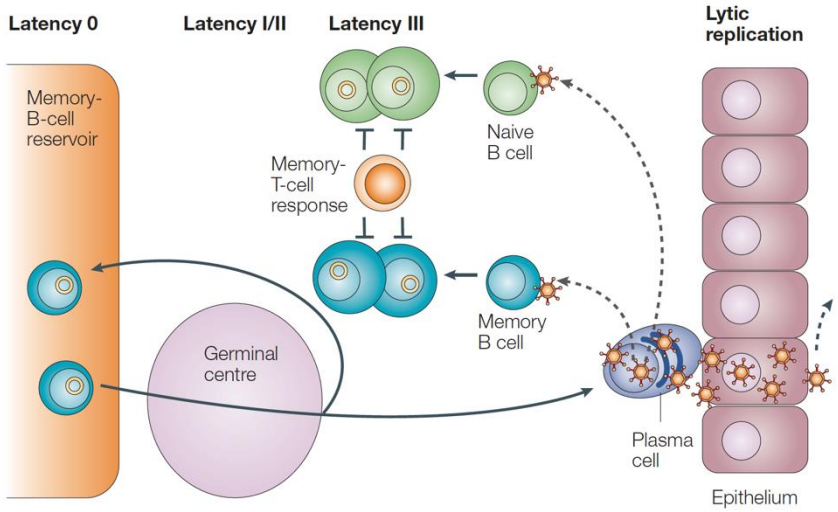


FIGURE 5: Persistent infection of EBV. EBV-infected B-cells are recruited to the germinal center leading to the activation of latency programs [16].

Infected B cells downregulate the expression of viral proteins when they leave the germinal center. EBV remains in the host memory B cells and during cell division, and it is transmitted to the daughter cells by the activation of EBNA1 during the latent I program[23].

7.2. VIRAL GENE PRODUCTS ASSOCIATED TO EBV INFECTION

The main EBV genes expressed during EBV infection are:

- **EBNA-1:** It is a DNA binding protein that activates viral replication. It activates the transcription of latency genes and destabilizes p53 protecting cells from apoptosis[24]. B cells that only express EBNA-1 are poorly recognized by CTLs[25].
- **EBNA 2 and 3:** They are transcriptional regulators. EBNA genes can be transcribed by either Cp or Wp promoter. EBNA2 activates viral and cellular promoters[26].

  There are three different EBNA-3 proteins, which repress EBNA2-mediated transactivation, LMP-2A, and LMP-1 promoters[27]. EBNA3 acts as a tumor suppressor in diffuse large B cell lymphoma (DLBCL)[28].

- **LMP-1:** It is an integral membrane protein, similar to an active CD40 receptor, which induces many gene expression changes. It activates major cell signaling pathways like NF-κB, JNK-kinase and JAK/STAT[29]. It is the principal oncogenic protein leading to lymphomagenesis. LMP-1 is essential for the transformation of B lymphocytes into lymphoblastoid cell lines[30]
- **LMP-2A:** It is another integral membrane protein that activates cellular signaling pathways such as PI3K/Akt. LMP2A attenuates activation through B-cell receptors[31]. Furthermore, EBV can immortalize BCR GC B cells thanks to this protein [32].
- **LMP-2B:** It is a transmembrane protein that modulates the activity of LMP-2A.
- **EBER 1 y 2:** They are non-coding RNA which regulate signaling pathways and transcription factors that regulate the production of interferons and cytokines [33]. EBERs main role takes place within the pathogenesis of Burkitt lymphoma[34].
- **Micro-RNAs:** EBV encodes 44 micro-RNAs divided in two clusters (BHFR1 and BART1/2) that downregulate the expression of mRNA [35]. They seem to target several genes like PUMA in the p53 pathway having a central role in the EBV tumorigenesis [36].

The major activities of these genes are summarized in *Figure 6.*

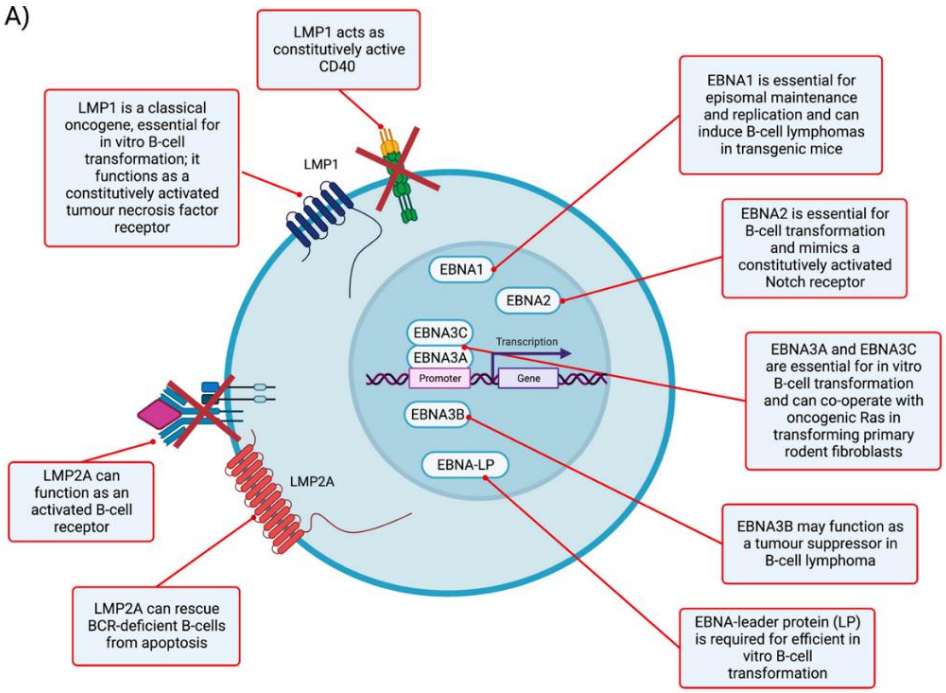


FIGURE 6: EBV latent proteins in the pathogenesis of EBV-associated B-cell malignancies [37] .

7.3. EBV LATENCY PROGRAMS

There are different patterns of genetic expression of the EBV depending on its type of cycle. The latent phases have different genetic transcriptional programs *(Table 1, Figure 7).*

Latency III. Also known as growth program. The different types of EBNA3 proteins negatively autoregulate the growth program allowing the cell to migrate into the follicle to initiate a germinal center reaction. Most of the viral proteins are expressed in this program *(Table 3).*

Latency II: In this phase, all the EBNA genes are transcribed from Cp or Wp promoter. Its function is the differentiation of activated B cells to memory cells. This latent phase is mainly found in Hodgkin disease and nasopharyngeal carcinoma (NPC).

Latency I: B cells infected by EBV that only express EBNA1. There is a transference of the EBV genome to the successive cells. Latent cells are transformed into plasma cells. This program is typical of Burkitt lymphoma.

Latency 0: The virus remains in memory B lymphocytes with its genetic expression turned off. In this phase, the only expressed genes are EBERs [16]. This latency program is also known as the "germinal center model of EBV persistence" due to the downregulation of most latent proteins.

	LATENCY 0	**LATENCY I (BL)**	**LATENCY II (Hodgkin, NPC)**	**LATENCY III (PTLD)**
EBERs	+	+	+	+
LMP1	-	-	+	+
LPM2A	-	-	+	+
LMP2B	-	-	+	+
EBNA1	-	+	+	+
EBNA2	-	-	-	+
EBNA3A	-	-	-	+
EBNA3B	-	-	-	+
EBNA3C	-	-	-	+
EBNA-LP	-	-	-	+

TABLE 1: Summary of EBV genes expressed in the different latency programs and their major associated diseases [37]

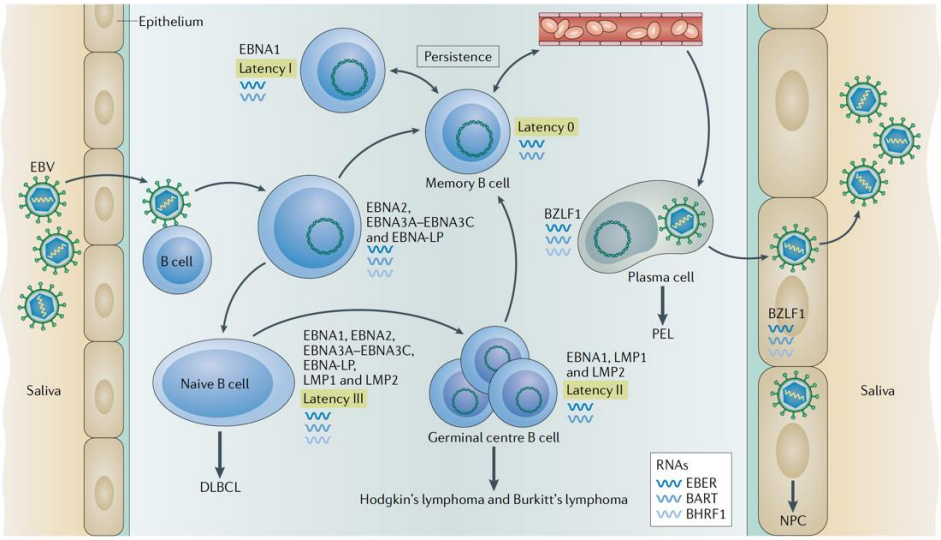


*FIGURE 7: Models of latent Epstein-Barr virus infection to reach viral persistence. Latency and lytic replication in Epstein–Barr virus-associated oncogenesis. Diffuse large B cell lymphoma (DLBCL), Primary effusion lymphoma (*PEL*) and nasopharyngeal carcinoma (NPC)* [38]

Upon primary infection, the affectation starts with the lytic replication in the host cells as already mentioned. It is divided into four stages:

1. Early gene expression: Early transcription factors like BZLF1 or BRLF are expressed, which induce the expression of BMRF1, BALF2 and BHRF1 genes. BZLF1 activates the transcription factor NFAT which influences the microenvironment for increased EBV- associated tumor formation[39,40].
2. DNA replication
3. Late gene expression: it includes viral structural proteins like gp350.
4. Assembly and secretion [41]

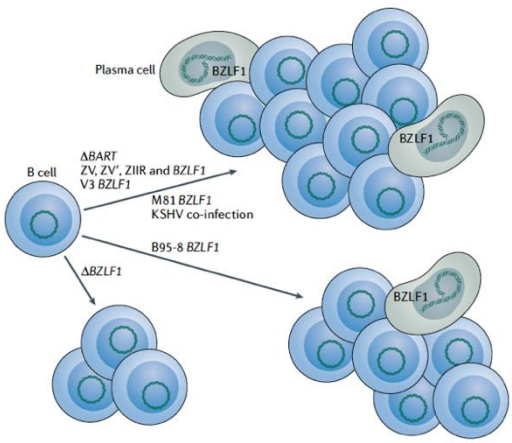


FIGURE 8: Latency and lytic replication in Epstein–Barr virus-associated oncogenesis [38]

Altogether, EBV has a total of five genetic programs which are summarized in table 1.

TRANSCRIPTION PROGRAM	GENE PRODUCTS EXPRESSED	INFECTED B-CELL TYPE	MALIGNANCIES
Growth (Latency III)	EBNA1, 2, 3A, 3B, 3C, LP, LMP-1, LMP2A and LMP2B, EBERs	Naive	AIDS- associated lymphomas Post-transplant lymphoproliferative disorders
Default (Latency II)	EBNA1, EBERs, LMP1, LMP2A, BAR0	Peripheral memory	Hodgkin disease Nasopharyngeal carcinoma Peripheral T/NK lymphoma
True latency (Latency 0)	EBERs	Peripheral memory	None
EBNA-1 only (Latency I)	EBNA-1, EBERs	Dividing peripheral memory	Burkitt lymphoma Gastric carcinoma
Lytic	BZLF1, BRLF1, BILF4	Plasma cell	None. Initial of infection

TABLE 2: EBV genetic programs. Modified from Thorley-Lawson, D. A [42].

7.4. EBV INFECTION DETECTION

EBV is detected in tissues using PCR or *in-situ* hybridization assays. The BamH1 internal fragment is used for diagnostic PCR, while the small nuclear EBV encoded RNAs, EBER-1 and EBER-2, which are highly expressed in all forms of EBV infection, are used as probes in the *in-situ* RNA hybridization assays [34].

Different markers can be used for the detection of EBV infection *(Figure 9).* They are useful to determine if a person is either a healthy carrier or undergoing an EBV-related disease. High EBV DNA levels in serum are predictors for the development of post-transplantation lymphoproliferative disease[43].

Different patterns of antibody response have been found in primary or latent infection, healthy carriers, viral reactivation, and EBV-associated cancers. Upon EBV infection, antibodies (IgG, IgM and IgA) are raised against EBNAs, early antigens (EAs) and VCAs [44]

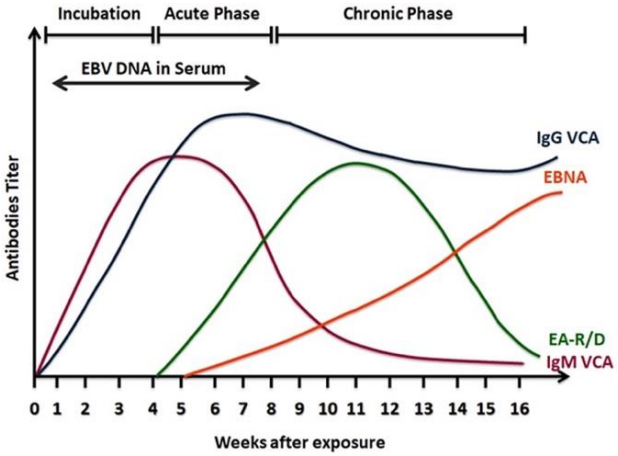


FIGURE 9. Serological response to Epstein–Barr virus (EBV) infection. VCA (Viral capsid antigen) EBNA (Epstein-Barr nuclear antigens) EA (Early antigen) [45].

Around 90-95% of the adult population is infected by EBV, as evidenced by the presence of serum antibodies. However, some factors impinge on the infection rate:

- **Socioeconomical position**. The prototype infected person usually belongs to low-income family [46].
- **Immunosuppression**. Immunosuppressed people are more susceptible of EBV infection [47] .
- **Geographical distribution**. The EBV is worldwide spread causing asymptomatic infection, but the cancers associated with EBV show a marked geographical distribution as discussed below.
- **Age**. It is common to get the virus at a young age. In these cases, they usually are asymptomatic, or the symptoms are like in other respiratory illnesses. Infectious mononucleosis is typical of young adults.

When normal B cells become infected, they usually undergo apoptosis upon the activity of cytotoxic T cells. However, this does not happen if the virus enters a latency phase. Within malaria-endemic regions, the response of cytotoxic T cells with EBV were diminished in children at peak age of Burkitt lymphoma incidence[48].

Stable quantities of IgG antibodies against viral proteins such as VCA, gp350 and EBNA-1 are commonly found in healthy human serum[49]. Antibodies against EA are not always detected in healthy carriers. Having anti-EBNA-1 and anti-VCA does not seem to protect from EBV infection as much as expected[50].

A relationship between serum anti-VCA IgA and nasopharyngeal carcinomas was also found [51].

Whereas cell-free EBV DNA cannot be detected in healthy individuals, plasma EBV DNA was found to be an accurate marker for diagnosis, disease monitoring, and prediction of outcome of EBV-associated diseases. Thus, it is found in diseases such as Hodgkin disease, post-transplant lymphoproliferative diseases, NK/T-cells lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma, and EBER-positive gastric carcinoma[5253]. It is mainly used in the detection of EBV in Hodgkin disease [54]. The presence of EBV DNA is used for the diagnosis of nasopharyngeal carcinoma[55].

8. EBV-ASSOCIATED DISEASES

There is a range of diseases associated with EBV infection, both non-malignant diseases and cancer.

8.1. NON-MALIGNANT DISEASES

A. INFECTIOUS MONONUCLEOSIS

The infection of EBV can produce a syndrome called infectious mononucleosis. It usually affects people between 15-25 years old who are infected through saliva (in fact, it receives the nickname of “kissing disease”). The common symptoms are fever, fatigue, sore throat, petechiae and pharyngeal inflammation. The diagnosis of the infectious mononucleosis is based on the detection of a heterophile antibody test, but the gold standard remains in the detection of EBV IgM[56].

EBV-infected B-lymphocytes evade the immune activity of T-lymphocytes. Proliferation of B cells infected with EBV is mainly controlled by $CD8^+$ cytotoxic T cells. These lymphocytes are called “Downey cells”, which are found at high levels during the second week of infection. These cells are lymphocytes presented in peripheral blood that try to eliminate EBV infected B lymphocytes [57].

Soon after EBV infection, IgM antibodies against VCA are detected, followed by rising titers of IgG to EA, and to VCA. IgA antibodies to these antigens may also appear.

Neutralizing antibodies to gp350 are detected during the acute phase of infectious mononucleosis [58]. Also, patients show an IgG response to EBNA-2 (and probably to EBNA-3A, -3B, and -3C), thus anti-EBNA-2 is the first one to be detected[59]. On the contrary, IgG response to EBNA-1 is not usually detected until convalescence.

B. MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system. Its cause is unknown but one of the possible causes is latent EBV infection which, when activated, triggers a secondary autoimmune response *(Figure 10)*. The highest incidence occurs in young women with HLADR2 [60,61].

EBV is associated to MS since elevated antibodies against EBNA1 were found in serum of 85% of patients from a study [62]. Due to the high prevalence of EBV and the low prevalence of MS, cohort studies are difficult to carry out [63].

There is scientific evidence that EBV infection and the expression of the histocompatibility antigen HLA-DR15 could act synergistically in the origin of MS[64].

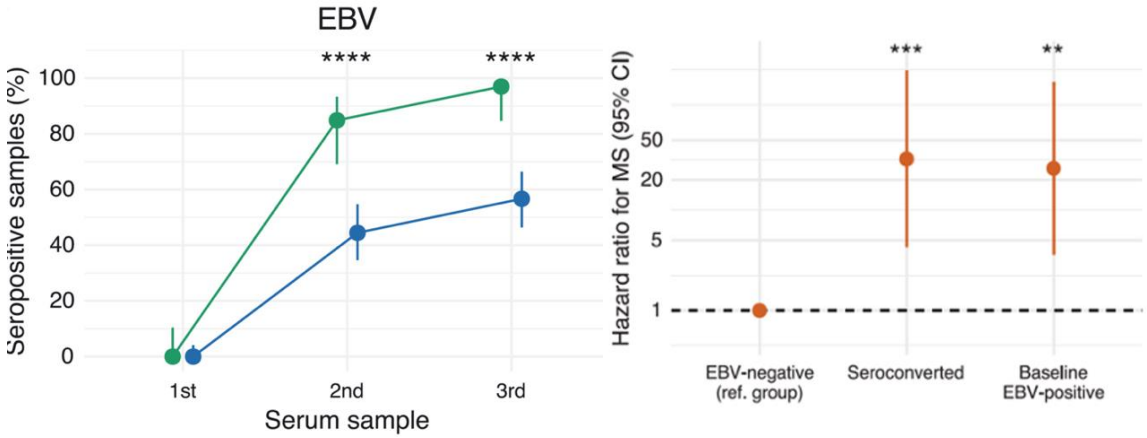


FIGURE 10: EBV infection precedes MS onset. Green: MS positive. Blue: Non-MS. Left: Proportion of individuals who were EBV-positive at the time of the first, second, and third sample. Right: Risk ratio for MS according to EBV status. EBV seropositivity in the first sample and seroconversion in the third sample were associated to higher risk for the development of MS. Modified from Bjornevik, K. *et al* [65].

8.2. MALIGNANT DISEASES

EBV infection is associated with non-lymphoma neoplasias such as nasopharyngeal, gastric and lymphoepithelium like cancer and lymphomas like T cell and NK, Hodgkin or Burkitt.

8.2.1. NON-LYMPHOMA CANCER ASSOCIATED WITH EBV

A. NASOPHARYNGEAL CANCER

Nasopharyngeal cancer (NPC) is an uncommon cancer type. Most of the cases are described in the southeast of Asia, with less than one case for every 100000 people each year. EBV infection is associated to almost 100% of non-keratinizing NPCs. The relationship between EBV and NPC was established when high titers of serum antibodies against lytic cycle proteins like VCA Ig A and EA [66,67].

In situ hybridization allowed the discovery of EBV genome in high-grade pre-invasive lesions while it is absent in the low-grade disease. NPC tumor cells have clonal EBV genomes in Latency II program[68] expressing EBNA-1, LMP-1, LMP-2A, LMP-2B, the EBERS, and micro-RNAs [69]. This type of cancer expresses LMP-1 which may contribute to its faster growth rate, compared to other cancers. LMP-2A induces migration and invasion of epithelial cells. This carcinoma expresses EBERs and EBV micro-RNAs[70] although their respective role in tumorigenesis has not been addressed yet [71].

The lack of detection of EBV in normal nasopharyngeal cells, which is in contrast with the viral presence in immunosuppressed individuals, argues against a pre-existing normal reservoir of epithelial cells from which EBV can infect.

Nasopharyngeal carcinoma comprises three types: NPC class I (keratinizing squamous cell carcinoma), which represents less than 20% of the cases, NPC class II (differentiated non keratinized squamous cell carcinoma) and class III (undifferentiated carcinoma). The highest incidence of patients with EBV infection and this type of carcinoma has been found in the regions with more cases of undifferentiated carcinoma (class III). The lytic program is the predominant one in this type of cancer. NPC class II and III EBV's main genetic program is the Latent I [72].

NPC develops from the monoclonal expansion of an EBV-infected cell, meaning that the infection happened before the expansion of the tumor cell [73]. There can be a predisposition for EBV infection associated to the loss of heterozygosity (LOH) at chromosomes 3p and 9p due to environmental cofactors[74]. There are other genetic changes such as the deletion of 11q, 13q and 14q or the hypermethylation of the promoter region of genes on 3p and 9p [16] *(Figure 11).*

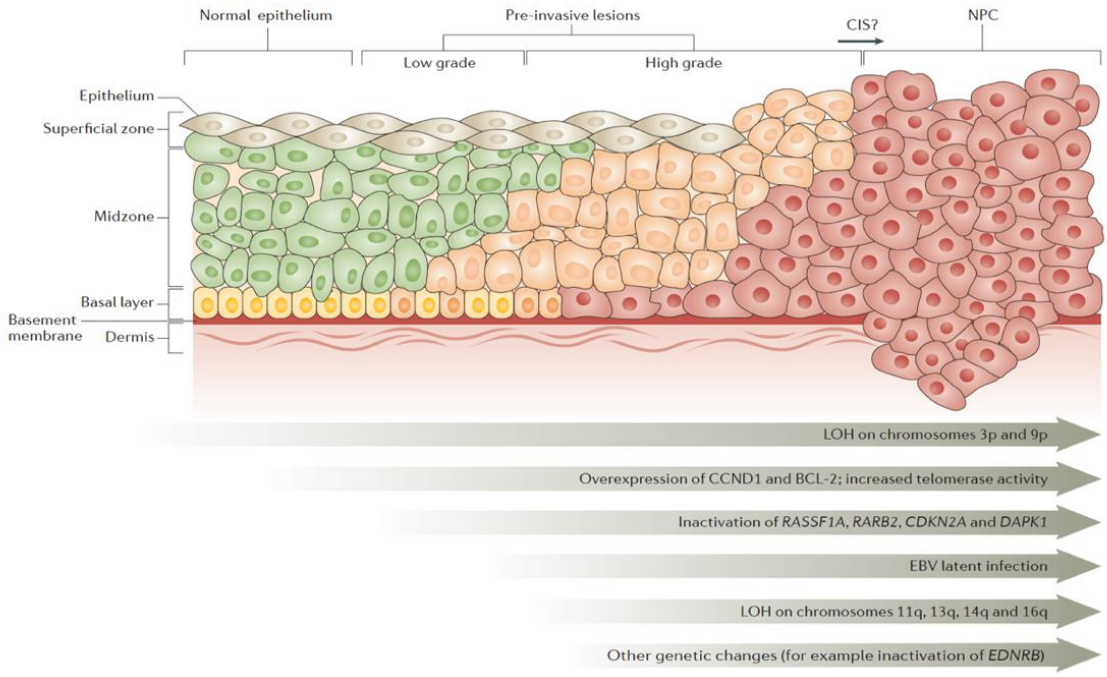


FIGURE 11: Epstein–Barr virus in the pathogenesis of nasopharyngeal carcinoma. The detection of EBV and the expression of different oncogene and tumor suppressor genes along the development of NPC are indicated below [75].

B. GASTRIC CANCER

EBV-associated gastric cancer represents 5-10% of total gastric carcinoma[76]. Therefore, it can be considered the most common EBV-associated malignancy in view of its absolute numbers [77,78], given the worldwide prevalence of gastric cancer (952,000 cases in 2012) [44,79]

There are differences such as the phenotype and clinic in gastric cancer depending on the presence or absence of EBV. There are EBV-related molecular alterations such as the loss of cyclin-dependent kinase (CDK) inhibitor $p16^{INK4A}$ expression, high CpG island

methylator phenotype (CIMP), the presence of wild-type p53, driver mutations in the subunit-α of *PI3K* and *ARID1A* genes[80–83] .

As in NPC, gastric cancer displays Latency I/II programs (expressing EBNA-1, EBERs, BARF-0, LMP2A, and microRNAs). Lytic infection genes like BAR-1 and BHRF-1 and EBERs are also expressed, while expression of LMP-2A and the lytic genes are variable[80,84].

The pathogenic mechanisms by which EBV contributes to gastric cancer are unclear, but it has been shown that in gastric cells, EBV uses LMP-2 to activate the NF-κB-survival pathway, which confers resistance to apoptosis induced by serum deprivation[85].

C. LYMPHOEPITHELIUM – LIKE CANCER

Lymphoepithelium-like cancer is histologically similar to NPC, and it can be found in salivary glands and in the stomach. There are not many cases of this type of cancer. The prevalence of the EBV infection depends on the tumor localization. In a study comprising 102 lymphoepithelial cancers of the salivary glands, 90 of them had EBV while another case-control study showed 100% of association[44].

8.2.2. EBV-ASSOCIATED LYMPHOMAS

A. T CELL AND NK LYMPHOMAS

EBV is associated with NK/ T-cell lymphoma which was known as angiocentric T-cell lymphoma[44]. NK/T cell lymphomas are more common in central and south America and in east Asian countries. It represents less than 2% of T-cell lymphomas and around 40% of these lymphomas have EBV infected cells which express EBER and LMP1 [86]. .

In a case control study of anti-EBV antigens as VCA, EA, and EBNA, there was found a correlation between the increase of anti EBV VCA IgG and EA IgG and a higher risk of having the disease [87].

These lymphomas express the Latency II pattern with LMP1 expression. This protein induces the production of pro-inflammatory cytokines which are common in NK/T cell

lymphomas [88]. Recent studies show that EBV2 strains prefer to infect primary T cells allowing the expression of latent genes and activation of T cells [89].

Other T-cell lymphoproliferative disorders that seem to be associated with EBV are peripheral T-cell lymphomas like angioimmunoblastic T-cell lymphoma[90,91], enteropathy-type T-cell lymphomas, γδ T-cell lymphomas, T-cell lymphoproliferative disorders after chronic EBV infection, EBV-associated cutaneous T-cell lymphoproliferative disorders and aggressive NK-cell leukemias/lymphomas [44]

B. CLASSICAL HODGKIN LYMPHOMA

In this cancer, B-lymphocytes multiply in an irregular way accumulating in specific parts of the lymphatic system. The most common symptom of this lymphoma is a painless swelling in the neck.

There are two types of Hodgkin lymphoma (HL): classical and non-classical. The main difference is the type of lymphocyte that is transformed. Classical HL is composed of the so-called Hodgkin Reed-Sternberg (HRS) cells, whereas these cells are not present in the non-classical HL. HRS derive from germinal center B cells that lack a functional BCR and have escaped apoptosis[92]. These cells lack the expression of immunoglobulins and lose the expression of HLA [93].

Classical HL is more frequently associated with EBV than the non-classical form. It has a bimodal age distribution in developed countries: first peak between 15 and 34 years old and second peak in people older than 50 years old[94]. EBV appears in around 30-50% of classical HLs. HL cells have a mutated IgV sequence as well as EBV-positive post-transplant lymphomas (see below) that carry inactivated Ig genes or non-antigen selected mutations [95,96]. It allows the transformation of B cells in the germinal center and some markers like BCL6, MUM1 or CD138 allow the distinction from PTLD [97].

The risk factors associated with this lymphoma are elevated antibody levels to the EBV VCA and EA proteins, immunosuppression, and prior history of infectious mononucleosis. Also, NF-κB deregulation is common among HRS cells producing 50% of classical HL [98,99].

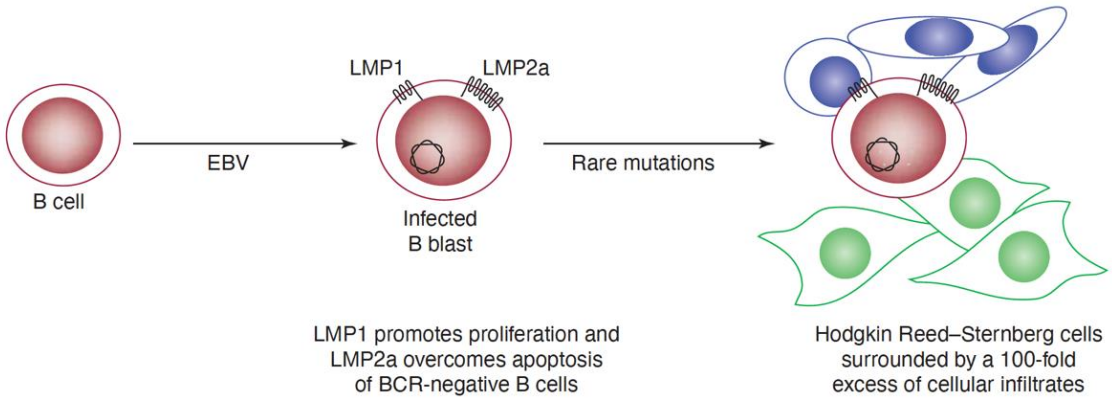


FIGURE 12: Molecular evidence of a pathogenic role for EBV in classical HL [100].

HL cells which are infected by EBV1 are different from those with EBV2. EBV2 classical HL has low levels of HLA class I while EBV1 cHL shows elevated levels of HLA containing cytotoxic T lymphocytes [101,102].

The immune evasion of EBV1 can be explained by the induction of PD-L1 which suppresses cytotoxic T cell response from LMP1 [103]. LMP1 drives proliferation and LMP2A alters B-cell gene expression. These molecules, together with EBERs and EBNA1, inhibit apoptosis[104].

Hodgkin lymphoma treatment consists of chemotherapy and radiotherapy. Elderly people infected by EBV1 have worse prognosis and therefore immune checkpoint inhibitors can be used. They can be combined with EBV therapies like EBNA1 inhibitors although they are still in preclinic research phase or *ex-vivo* manufactured donor T cells[105,106].

C. DIFFUSE LARGE B-CELL LYMPHOMA (DCBCL)

DLBCL is the most prevalent subtype of HL, an aggressive B cell lymphoma, which is associated with EBV in 8-15% of Asian population while in Western countries it only represents less than 5% [107,108]. DLBCL typically affects lungs, gastrointestinal tract, skin and bone marrow of elderly people who have worse prognosis [109]. DLBCL treatment is based on chemotherapy [107].

Primary effusion lymphoma (PEL) is a rare subtype of DCBCL which can appear in immunocompromised individuals infected by Kaposi Herpes virus and EBV. It is found together in about 80% of these lymphomas and is not related to disorders in c-MYC. The main characteristic of PEL is neoplastic effusions in body cavities without detectable tumor masses [110].

D. LYMPHOMAS IN IMMUNOSUPPRESSED INDIVIDUALS

Post-transplant lymphoproliferative disease (PTLD) is a term used to name those diseases that appear during the first-year post-transplant in immunosuppressed individuals, which happen to be EBV positive in 30-40% cases. Furthermore, it can be the first form of manifestation of HIV in infected individuals[111].

B-cell lymphoma easily develops in T-cell immunocompromised patients. There is an activation of the latency program response like latency III producing the growth of B cells [112]. In the late onset post-transplant lymphomas, tumors are either EBNA2- and LMP1- or EBNA2- and LMP1 positive [95,96].

E. BURKITT LYMPHOMA

The association between EBV and Burkitt lymphoma was discovered in African children by Dennis Burkitt in 1958. He described its clinical and pathologic characteristics. A few years later, Epstein, Achong and Barr found EBV particles in samples of these tumors [5].

They thought about the possible relationship between Burkitt lymphoma and its geographical distribution with certain rainfall and temperature patterns. It seems to have a similar spreading to malaria. EBV was the first virus associated with a human malignancy [15]

Burkitt lymphoma (BL) is a type of lymphoma that affects B cells and is characterized by its rapid growth rates. Abdominal and extranodal affections are found. In most cases, BL shows a translocation (8,14) with a juxtaposition of the MYC gene. The rest of the cases it occurs between chromosomes 2 and 8. For its diagnosis, a biopsy or puncture of the affected node is necessary.

The hypothesis of a relationship between EBV and Burkitt lymphoma originated in the disease of young children in underdeveloped countries. They show high antibody titers to the virus prior to Burkitt lymphoma development. The discovery of EBV's ability to transform B cells, i.e., the same type of cells affected in Burkitt lymphoma, supports this relationship [113,114].

Malaria increases the risk of BL [115]. However, the mechanism of this association is unclear. One hypothesis is that the parasite has a ligand for toll-like receptor 9 (TLR9) inducing the enzyme activation-induced cytidine deaminase (AICDA) in human B cells. The overexpression of this enzyme would produce the translocation of MYC [116,117].

BL originates from the germinal center of the lymph nodes. The node has medulla and cortex. In this last structure there are germinal centers and parafollicular or T zones. The maturation process of B-cells or centroblasts occurs in the germinal centers, during the primary response.

The germinal center is divided in dark and light zone. The dark zone is where centroblasts proliferate and undergo somatic mutations of the variable regions of their antibody genes. On the other hand, the light zone is where the segregation into plasma cells and memory B cells takes place [118] *(Figure 13).*

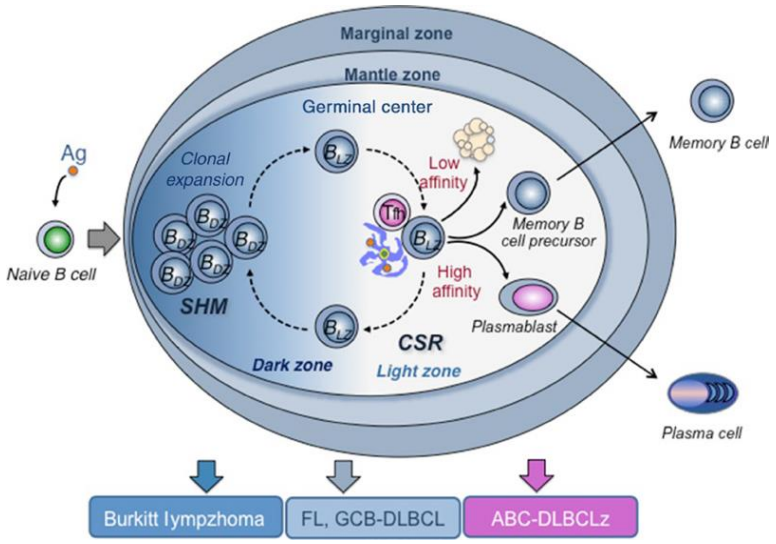


FIGURE 13: Germinal center of a lymph node representing the proliferation and development stages of a B cell in Burkitt lymphoma (BL), follicular lymphoma (FL), and diffuse large B cell lymphoma (DLBCL) in germinal-center B cell (GCB) or activated B cells (ABC) are the lymphomas derived from the indicated areas of the node [116,119].

The molecular hallmark present in virtually all BL is the chromosomal translocations involving the MYC oncogene. The possible mechanism by which EBV and MYC induce BL development will be discussed further below, but it involves the protection against apoptosis and immune surveillance *(Figure 14).*

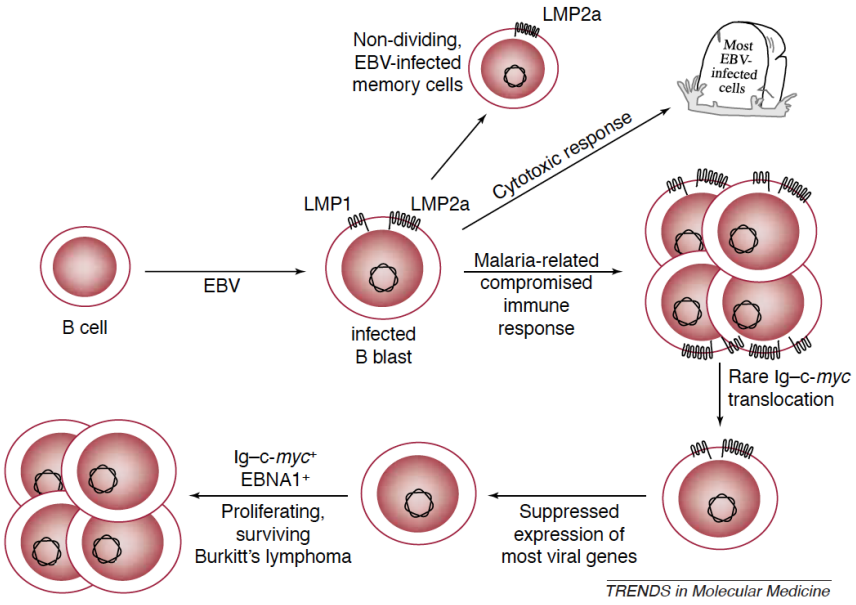


FIGURE 14: A model for the evolution of Burkitt lymphoma [100].

Burkitt lymphoma was first described in African children, leading to its original classification by its geographical localization:

Endemic lymphoma (eBL). It is common in equatorial Africa and Papua Nueva Guinea regions which are endemic for malaria. The annual incidence is 4-10 for age 3-12/100,000. In the high-risk areas, BL means roughly 50% of total childhood cancer and 90% of total lymphoma diagnoses [117] . The majority is associated with EBV infection, and there has been seen a correlation between a rise in the titer of antibodies against EBV and the risk of eBL, as discussed below.

Plasmodium falciparum, which is the malarial parasite, acts as a coadjuvant with EBV leading to the stimulation of polyclonal B-cell proliferation and reduction of T-lymphocyte response[57].

Sporadic lymphoma (sBL). It is the main type in non-malarial areas. It is more rarely associated to EBV. Sporadic Burkitt lymphoma represents 1-2% of adult lymphomas and

30-40% of chilhood non-Hodgkin lymphomas. People with inmunodificiency like HIV are related to this type of BL. About 30% of the cases present EBV infection [120].

Immunodeficiency-associated Burkitt lymphoma (like PTLD) **or HIV-BL.** It is spread worldwide, and its incidence is lower compared with e-BL. It is related to EBV in 15-85 % of the cases.

Infection by HIV produces acquired immunodeficiency syndrome (AIDS). Infected people show a higher incidence of developing BL or DLBCL. BL in AIDS expresses the most common translocations of MYC[121], with relatively normal titers of T-CD4 cells due to expansion of the germinal center activity [122,123]. HIV stimulates the reservoir of B cells producing translocations.

The major differences between the three variants of BL are summarized in Table 3. However, it must be noted that the last WHO classification removes the distinction between endemic and sporadic to classify BL between EBV-associated and non-associated BL.

BURKITT LYMPHOMA	EBV- POSITIVE BL (most of the eBL)	EBV- NEGATIVE BL (majority of eBL and HIV-associated BL)
Fraction of EBV positive lymphomas	95%	25-40%[124]
Distribution and age	Equatorial belt of Africa and Papua Nueva Guinea	Worldwide (>North America, northern Europe and east Asia)
Site	Jaw, eye, abdomen, kidneys and ovaries	Abdomen, lymph nodes and bone marrow
Annual incidence	40-50 per million children younger than 18 years. 50% of all childhood cancers and up to 90% of lymphoma. Median of 6 years Boys > Girls (twice)	2-3 per million Age 3-12 years Boys > Girls (3-5 times more)[117]
Cofactors	EBV, malaria infection	HIV infection in HIV association
Class of breakpoint	Class II	Class I
Ig breakpoint	VDJ region, switch (s)μ in some cases	Sμ, Sα or J region in sBL Sμ in HIV-associated BL
Main MYC breakpoint	>100 bp upstream of first exon	Between exons 1 and 2
Location of Ig heavy intron enhancer	On the same chromosome than the translocated MYC	On the opposite chromosome of the translocation Heavy chain and kappa light chain genes are always located on the same chromosome
Somatic hypermutations	Yes	No
Surface phenotype	Germinal center B cell	Germinal center B cell
Likely precursor	Memory B cell	Germinal center B cell

TABLE 3: Characteristics features of the different Burkitt lymphoma. Epstein–Barr virus and Burkitt lymphoma. Modified from Brady et al., Thorley-Lawson [75] [119].

BL represents less than 5% of non-Hodgkin Lymphomas (NHL) worldwide. There are 2.5 cases of the total BL/1,000,000 habitants/year. In endemic BL, its association to EBV is about 95%. However, sporadic BL has 10-20% relation to EBV. BL also represents 30-40% of NHL in HIV patients[125].

- **CLINICAL AND HISTOLOGICAL FEATURES**

The most recognizable symptom of EBV-positive BL is the jaw tumor. This cancer is localized in the alveolar process of the maxillary or mandible zone. It starts with the loss of molars and the growth of tissue around it. There is also chemosis of the conjunctive and edema in the eyelids *(Figure 15).*

Despite the marked face change, the tumor does not cause a lot of pain in the patient. Furthermore, the repercussion in blood analysis is only mild anemia and it cannot be found in urine the Bence-Jones protein (produced by plasmatic cells and typical in multiple myeloma).

The second most relevant symptom consists of an abdominal swelling tumor. This way of presentation is common in Africa. In fact, both jaw and abdominal swelling tumors show similar incidences.

Paraplegia is another symptom of BL. There are also urinary and fecal incontinence problems (tumor accumulation in the vertebral canal) due to the eventual paralysis of the lower limbs and weakness. This happens because of the compression of nerve roots and spinal cord.

Apart from skin affectation, other organs like kidneys, liver or adrenals are involved. It is also common to see deposits in thyroid, testis, pancreas, stomach, femur, salivary glands, cranium but not in lymph nodes or spleen.

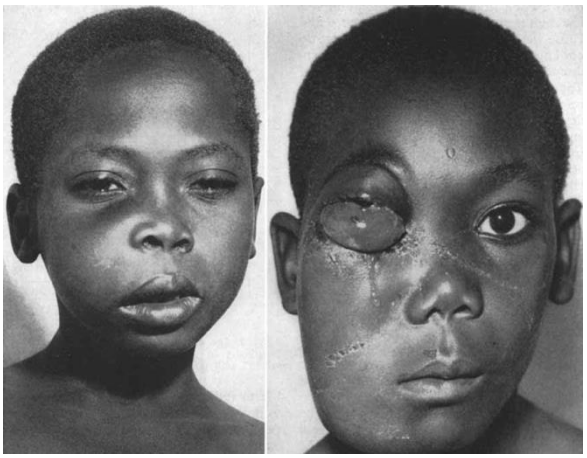


FIGURA 15: Left: Malignant lymphoma in the right maxilla of a 6-year-old boy. Right: Malignant lymphoma in the orbit with deposits in the maxilla and mandible in a 6-year-old boy [126] .

On the other hand, EBV negative-BL major affectation is found in the abdomen. The typical pattern of Burkitt lymphoma in stained biopsies is "starry sky" made by scattered macrophages among monomorphic lymphoma B cells. Malignant cells are rounded or polyhedral with a vesicular nucleus with two nucleoli. The cytoplasm is eosinophilic [126,127]

There is a huge proliferation indicated by Ki67>95% *(Figure 16)* and markers like BCL6+, CD10+, CD38+ in germinal center B cells. The histologic appearances of Burkitt lymphoma (BL) and large B cell lymphoma (DLBCL) are similar.

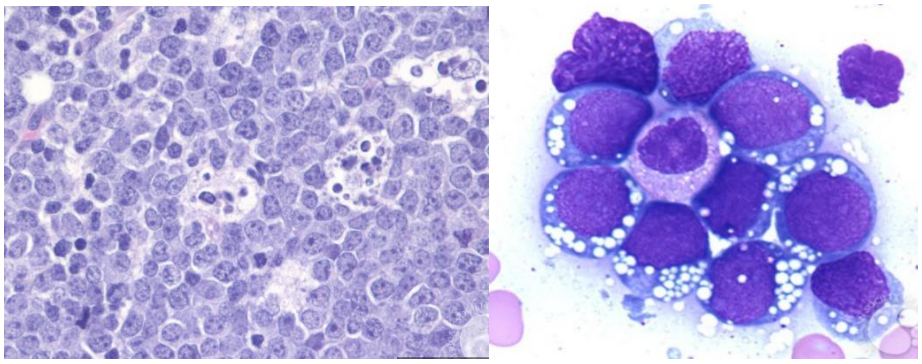


FIGURE 16. Left: Starry sky pattern in Burkitt lymphoma due to the presence of macrophages surrounded by B cells. Right: Burkitt cells in BL [128].

- **MYC ONCOPROTEIN**

MYC proteins consist of a family of transcription factors that regulate growth and cell cycle entry by the induction of the genes involved in such processes.

The MYC family includes three genes: MYC (or c-MYC), MYCN (or N-MYC) and MYCL1 (or L-MYC). MYC acts as a protooncogene involved in plenty of cancers such as leukemia and lymphoma being expressed during B lymphocyte development. MYC overexpression in cancers happens mainly through gene amplification, chromosomal translocations, and aberrant regulation of its transcription.

MYC belongs to the helix-loop-helix- leucine zipper (b-HLH-LZ) family of proteins and forms a dimer with another b-HLH-LZ protein, MAX. MYC-MAX heterodimers bind through their basic domain to E-boxes of DNA, and it determines the transcriptional regulation of MYC. They recruit chromatin remodeling proteins like histone acetyltransferases P300 and CBP [129–131].

MYC N-terminal region or transactivation domain (TAD) contains conserved sequences among the MYC family, and the phylogenetic scale called MYC boxes (MB): MBI, and MBII. MBII recruits coactivators of MYC like CBP/P300 or SKP2. MBIII is located within the middle regions of MYC and is important for transcriptional repression [132,133].MBIV is related with transcription and apoptosis[134].

The C-terminal region of MYC contains a b-HLH-LZ domain (basic region-helix-loop-helix-leucine zipper). The LZ domain allows the dimerization with MAX. MYC-MAX binds DNA thanks to the basic domain and first helix [129,135].

The activity of MYC depends on the proteins that interacts with it. MYC controls RNA polymerase II and ribosomal RNA [136]. It is also important for B cell regulation and DNA binding sites in promoter and noncoding regions [137,138] *(Figure 18).*

The role of MYC as global transcriptional amplifier is believed to be based on the RNA polymerase II complex pause release thought the interaction of it to P-TEFb (positive transcription elongation factor b) [139]. However, it is also demonstrated that MYC acts as specific transcription factor of a broad number of target genes [140,141].

N-MYC expression is tissue restricted and it has a similar function to MYC. Both N-MYC and MYC are expressed in lymphocyte progenitors but only MYC remains during the rest of the differentiation process.

L-MYC function is less known although it seems to have a role in lung cancer development.

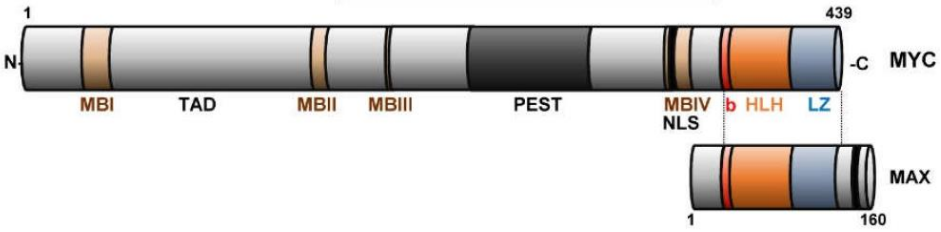


FIGURE 17: MYC and MAX proteins structure and MYC-MAX interaction [142].

MYC sequence comprises three exons:

- Exon 1: Non-coding but there are two promoters and regulatory sequences.
- Exons 2 and 3: They contain the protein-coding sequence beginning on nucleotide 16 of exon 2[143].

MYC is involved in different functions such as cell-cycle progression energetic metabolism, lipid and nucleotide biosynthesis, energy metabolism, protein synthesis, ribosome genesis, genome instability, immortalization and telomere maintenance or block of differentiation [144].

- **MYC IN LYMPHOMA**

MYC is one of the most frequently activated oncogenes in human cancer, being dysregulated in about 50% of human malignancies[145,146].

There are different mechanisms that account for MYC dysregulation in cancer: chromosomal translocation, gene amplification, hyperactivation of MYC transcription and missense mutations that lead to a more stable protein. MYC is associated with a variety of lymphomas such as neoplasms of T-cell or B-cell precursors. The incidence of MYC dysregulation in lymphoma is summarized in Table 4.

TYPE OF LEUKEMIA OR LYMPHOMA	INCIDENCE OF MYC TRANSLOCATIONS
Lymphoblastic leukemia of T- cell precursors	6%
Lymphoblastic leukemia of B-cell precursors	2-5%
Mantle cell lymphoma and chronic lymphocytic leukemia	<20%
Diffuse large B-cell lymphoma	70%
Burkitt lymphoma	100%
Multiple myeloma	15-50%

TABLE 4. Incidence of MYC deregulations the different lymphoid cells and lymphomas where is involved [147]

- **MYC IN B CELL DIFFERENTIATION**

Mature B cells develops from ematopoietic stem cewlls (HSC) that differentiates into pro-B and then to pre-B cells before circularizing into the blood system. Their introduction into the germinal center of secondary lymphoid tissues starts with the antigen recognition. In this location, there is a clonal expansion and somatic hypermutation in the dark zone (DZ). B cells start the class switch recombination, and they are transformed into memory B cells *(Figure 18).*

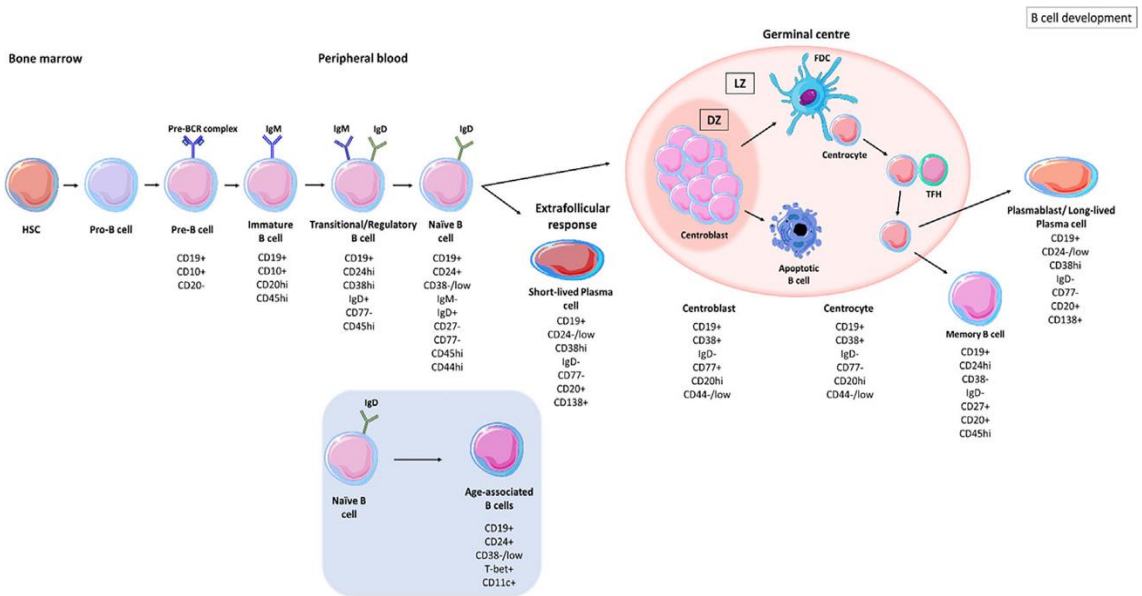


FIGURE 18. The development stages of B cells. Each precursor is defined by several markers identified by flow cytometry which are indicated below each form [120].

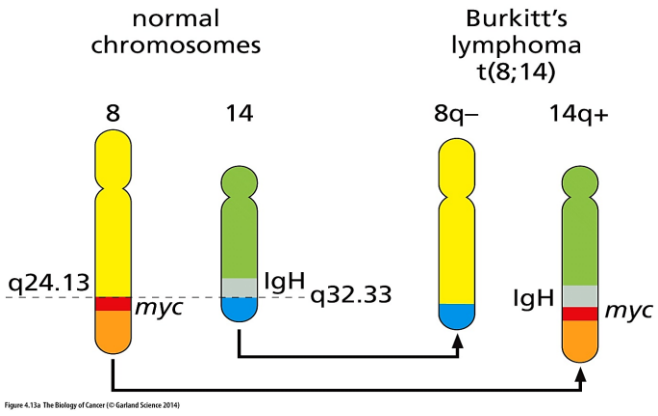
c-MYC levels are high in pro-B cell stage, and they decrease during differentiation. The presence of c-MYC is necessary in all stages, except in mature spleen B lymphocytes [148]. MYC expression in mature B cells is rapidly induced by mitogenic activation mediated by the inhibition of cell cycle inhibitor p27 [149]. There is a correlation between the apoptosis through the B cell receptor and inhibition of c-MYC expression [150].

B cells differentiate into plasma cells (the antibody secreting cells) and memory cells. They are fundamental for humoral immunity. However, the transcription programs that control B cell and plasma cell differentiation are mutually exclusive. MYC role in this process is not well known yet [151].

- **MYC DEREGULATION IN BURKITT LYMPHOMA**

The currently accepted mechanism for Burkitt lymphoma development is by EBV causing MYC translocation. BL is believed to originate in the germinal center, where somatic hypermutation and class-switch recombination of the immunoglobulin heavy chain genes take place [152], mediated by the activation-induced cytidine deaminase (AICDA). It has been proposed that AICDA can also induce Ig/MYC translocation [153,154].

The most frequent translocation occurs into the immunoglobulin heavy chain [t (8;14) (q24;q32)] but it could also be found in the light chain loci [t(2;8) (p11;q24) and t(8;22)(q24;q11)]. Besides translocations, MYC gene carries missense mutations in about 40-60% of BL cases [155–157]. The translocations breakpoints of the two types of BL are indicated in Figure 19.



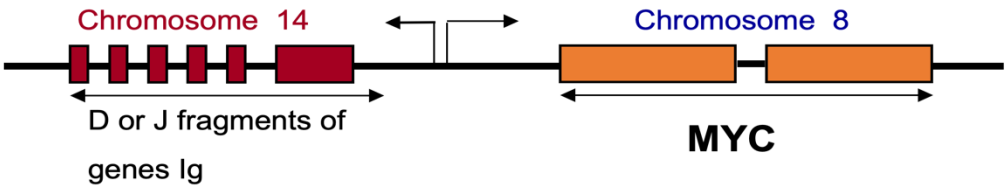


FIGURE 19: Translocation t(8;14)(q24;q32) producing the activation of myc [158]

In sBL and HIV-BL, the breakpoint in *MYC* is usually between exons 1 and 2 (being exon 1 non-coding), and the breakpoint in IgH occurs in the switch region[119]. These differences are important in relation to the timing of the translocation during B-cell development [159]. It seems that eBL originates from a GC or memory B cell[160] and the MYC breakpoint is often more than 1 kb upstream from first coding exon [57].

Although MYC deregulation is the most important genetic alteration for BL, there are other molecular changes found in BL. For instance, it has been reported that 30% of endemic BL tumors and up to 70% of long-established BL lines have mutations in p53 [161]. Other genes frequently mutated in BL are ID3 (an inhibitor of the transcription factor TCF3) mutated in 35-65% of BL [162].

BCR signaling, an important process in BL, is promoted by ID3 inactivating mutations and TCF3- activating mutations. MYC increases the expression of ID3, a gene induced upon BCR activation. Therefore, in B cells there is a positive loop between BCR, ID3 and MYC regulation.

BL expresses latency I program which includes EBNA1, involved in episomal replication, various miRNA and EBER 1 and 2 [11,163]. The intervention of growth program proteins such as EBNA-1 inhibits apoptosis. EBERs induce apoptosis through the production of IL10 [33]. These alterations lead to the development of Burkitt lymphoma. EBNA2 and EBNA3C induce AICDA that can produce changes in the involvement of MYC in BL [164]. MYC represses the EBV transforming LMP1 gene and inhibits the viral lytic cycle [165].

- **IS EBV THE CAUSATIVE AGENT OF MYC TRANSLOCATION AND BL?**

The role of EBV in BL pathogenesis has been matter of debate, but the general consensus supported by the WHO consists of the declaration of EBV as the causative agent of eBL, based on the following data:

1. EBV antibodies in serum precede the onset of BL in African children.
2. EBV protects BL cells from apoptosis. It also happens with the coinfection from malaria and VIH. They cooperate with MYC in the promotion of B cell proliferation and inhibition of programmed cell death.
3. EBV contributes to the scape from immune surveillance of BL cell.
4. EBV induces MYC gene translocation via activation of AID.

However, there is data that argues against the hypothesis that EBV is causing BL:

1. The vast majority of adults and teenagers infected with EBV do not develop BL.
2. MYC is not translocated in other tumors with high prevalence of EBV infections as NPC and Hodgkin, suggesting the EBV per se cannot mediate MYC translocation.
3. The transforming genes of EBV are not expressed in BL.
4. Most sBL and immunodeficiency BL carry MYC translocation without EBV infection.
5. MYC induces the expression of EBV receptor, suggesting that MYC deregulation precedes EBV infection.

The hypothesis which is currently accepted (canonical hypothesis) for development of BL is that EBV leads to an activation and expansion of B cells producing translocation of MYC *(Figure 20).*

However, it has also been recently proposed that MYC induces CR2 expression in infected B cells. This would mean that upregulation of MYC by translocation increases the density of virus receptors in B cells allowing EBV infection. This mechanism does not contradict canonical hypothesis, but it proposes an alternative mechanism in which B

cells with hyperexpression of MYC could have higher density of receptors increasing EBV infection probability [166] *(Figure 20).*

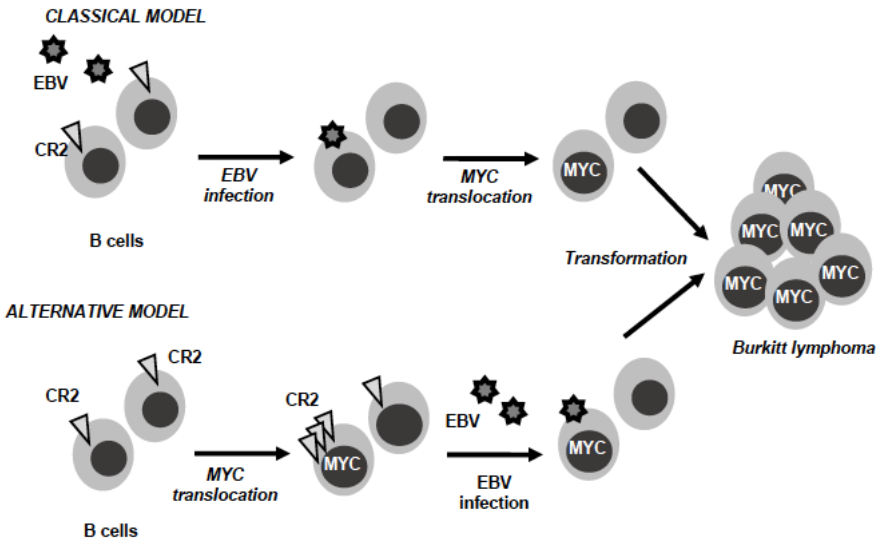


FIGURE 20. Two models for pathogenesis of BL (Garcia-Gutierrez and Leon, unpublished).

8.2.3. TARGETING EBV AS A THERAPEUTIC STRATEGY TO TREAT CANCER

Treatments against EBV-positive lymphoma are not different from EBV-negative lymphomas with the same histology. Thanks to the lytic cycle there is a production of 70 viral proteins which can be potentially utilized for EBV-specific therapies [15,167].

No drugs are approved yet in clinical to be used as MYC antagonists, although several molecules and peptides are in clinical trials. Thus, it might be possible to use MYC downregulation as a potential therapeutic approach in BL not only by decreasing cell proliferating but also by stimulating the lytic cycle and hence killing of the EBV positive BL cells.

One therapy consists of the reactivation of lytic EBV conferring cytotoxicity of antiviral drugs to achieve specific killing effects against EBV-positive cells. So far, the only study that has shown promising results is the combination of gemcitabine and valproic acid with valganciclovir in patients with NPC. It is based on the cytotoxic activity and CD8-T cell immunooncology [165,168].

It has been recently reported that high MYC expression contributes to repressing the EBV lytic cycle and maintains the viral latency [168]. However, current chemotherapy treatments to EBV+ Burkitt lymphoma do not take advantage of the presence of viral genomes in tumor cells.

EBV therapies like lytic inducers are still under research. EBNA1, which is a latent protein that enables tumor proliferation, is being studied as a therapeutic target. An example of its possible use is small-molecule inhibitors against EBNA1-DNA binding or peptide-based inhibitors from EBNA1 DNA biding domain or dimerization domain [169]. Possible problems of this approach could be the low efficiencies in the reactivation of EBV, the reliance on the cellular background of lytic inducers or the concern of promoting viral dissemination in the induction of EBV lytic cycle [165,168].

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