General Introduction

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Epstein-Barr virus (EBV) is a human gamma-1 herpesvius, also named human lymphocryptovirus or human herpesvirus 4 (HHV-4). EBV infects over 90 % of the world population via salivary contact and persists in its host for life, usually without complications. Primary infection frequently goes unnoticed early in life, but may cause infectious mononucleosis (IM) if acquired during adolescence or adulthood. Besides being the etiological agent of IM, EBV has been found to play a diverse and complex role in multiple chronic and malignant diseases occurring worldwide (1,2). EBV was first described in 1964 by Anthony Epstein and Yvonne Barr who discovered herpes virus-like particles in Burkitt lymphoma derived cell lines (3,4). EBV is considered to be a vital component in the pathogenesis of African Burkitt lymphoma in conjunction with Malaria infection and chromosomal defects (5,6). Almost fifty years of research has shown that EBV has developed a complex and intricate relationship with its human host. EBV exists in a tight balance with the human immune system demonstrated by the high incidence of B cell lymphoproliferative diseases that occur in immunocompromised individuals, including transplant recipients, HIV/AIDS patients and elderly (7,8).

The virus initially infects submucosal B cells in the naso-/oropharynx and transforms these into latently infected long lived memory cells, which are essential for virus persistence. EBV has dual tropism *in vivo* infecting B lymphocytes and epithelial cells (9-11). This dual tropism is reflected by its association with several lymphomas and carcinomas, where distinct viral gene products support viral genome maintenance and contribute to the oncogenic process (12-15). The immune system strongly responds to EBV infected cells maintaining a lifelong well-balanced equilibrium, but the virus can evade elimination by restricting the number of expressed genes to a bare minimum, so called latency (15,16). This latent state, which is regulated by a small subset of viral genes, enables the virus to persist lifelong in the human host (12).

Table 1. Expression profiles of viral latent genes in EBV associated disorders

Latency type	Expression profile	Associated disease
Latency I	EBERs, BARTs, EBNA1	Burkitt's Lymphoma
Latency I +	EBERs, BARTs, EBNA1 + BARF1, LMP2A	Gastric Carcinoma
Latency II	EBERs, BARTs, EBNA1, LMP1, LMP2A/B	Hodgkin's Lymphoma Non Hodgkins Lymphoma
Latency II +	EBERs, BARTs, EBNA1, LMP1, LMP2A/B + BARF1	Nasopharyngeal Carcinoma
Latency III	EBERs, BARTs, EBNA1/2/3A/3B/3C/LP, LMP1, LMP2A/B	Post Transplant Lymphoproliferative Disorders AIDS-related Lymphomas Infectious Mononucleosis Lymphoblastoid Cell Line (LCL)

2. Biology of EBV infection

2.1 B lymphocyte infection

Primary EBV infection occurs in the oropharyngeal cavity via salivary contact. Although EBV can infect both epithelial and lymphoid cells, mature B lymphocytes are considered the primary target for infection as the virus is not found in individuals with a B cell deficiency (17). EBV virions cross the epithelial barrier of the tonsil crypt to reach the submucosal naïve B lymphocytes (18,19). B cell infection occurs mainly through interaction of the major viral envelope glycoprotein gp350/220 with complement receptor type 2, named CD21 or CR2, on the B cell surface (20-22). Interaction of the gp42/gp85/gp25 trimolecular complex is necessary for efficient endocytosis and fusion (23,24) after which the capsid travels into the nucleus, degrades and releases the viral linear DNA. The binding of EBV triggers a series of events mimicking the antigen-driven germinal center differentiation program towards memory B cells. Newly EBV infected cells become activated through the CD21 receptor and differentiate into B blasts. From the incoming viral genome, EBNA2 and EBNA leader protein (-LP or EBNA5) are the first proteins expressed, driven from the unmethylated W-promotor (Wp) (25,26). EBNA2 promotes B cell activation as a functional Notch1 homologue (27) and upregulates cMYC and RUNX expression via interaction with CBF1, also named RBP-Jκ (28-30). Subsequently, the EBNA3A,3B,3C proteins counteract the strong EBNA2 effects by competing for RBP-Jk and modify the host genome by defined methylation (e.g. of the Bim promoter), and their own Wp, creating a switch to the adjacent C-promotor for their expression (25), EBNA2 initially drives LMP1 expression which provides strong and crucial growth and survival functions to the infected cell (Blast-stage growth). Subsequently, EBNA1 is expressed from the Cp and the host cell DNA repair enzymes are used for circularization of the viral genome at the terminal repeats (31), a process that is essential for subsequent establishment of viral latency. Upon circularization of the viral genome, LMP2a, is expressed from a coding region crossing the repeats, and provides signals necessary to rescue activated blasts into memory B cells. In addition several non-coding viral RNA molecules, including EBER1, EBER2, BHRF1, BARTs, become expressed that stabilize the newly transformed cell by interfering with the host endogenous homeostasis, but which are not essential for growth transformation. This initial EBV infection is also referred to as the B-cell transformation process and takes 24-48 hours to be established (12). This way EBV effectively turns naïve B-cells with a defined lifespan into immortalized cells, that can be cultured indefinitely and cause tumors in nude mice (oncogenic potential). LMP1, a ligand independent “constant firing” functional homologue of CD40, mimics the growth and activation signals otherwise given by CD40 ligand on activated T helper cells (32-35). LMP2a mimics the B cell receptor survival signal (36,37). LMP1 is the major transforming gene of EBV and has many properties that mediate constitutive, antigen-independent B cell activation, it protects the B cell from apoptosis by Bcl-2 upregulation, and induces immune suppressive IL-10 (38-40). EBNA1 is essential for maintenance of the EBV genome in dividing cells. The B cell now follows the growth program also called latency type III, (Table I). Proteins from the EBNA3 family

continue the transformation process by activating G1 cell cycle progression and downregulating EBNA2, whereas LMP1 ensures survival via Bcl-2 upregulation and LMP2 driven signals upregulate Bcl-6 expression, inducing follicle migration (41). After the B cell has migrated to the follicle it switches to a more restricted expression profile with further Wp/Cp silencing by methylation, allowing Q-promotor driven EBNA1 expression in combination with LMP1 and LMP2a, which is known as the default program or latency type II. As a final step to viral persistence in memory B cells, all EBV latent genes are silenced by promotor methylation and other epigenetic regulatory mechanisms (42,43), except EBNA1 and the non-coding transcripts EBER1,2 and BARTs, driven by non-methylated promotors. The latter stage is known as latency program or latency type I. During latency, the circular EBV genome forms an episome bound by EBNA1 at a genomic region called Ori-P (see for details later) and is tethered by EBNA1 to the host chromosome via AT-rich sequences in host chromosomes, ensuring reliable replication in each cell division. EBNA1 is therefore considered essential for replication and maintenance of the EBV genome in infected dividing cells (44). Only in rare cases EBV is integrated in host cell DNA (45).

2.2 Epithelial cell infection

The mechanism of infection, virion release, and virus spread in epithelial cells is not well understood. Although the mucosal epithelium of the oropharyngeal surface may serve as a portal of entry for EBV during primary infection and as the pathway of exit for progeny virions (18,19), EBV replication can rarely be detected in post-mortem tongue or salivary gland biopsies of immunocompetent EBV carriers (46) and the site of EBV replication causing its abundance in naso-/oropharyngeal mucosal secretions remains to be defined. Productive EBV infection of the oral mucosal epithelium can be found in oral hairy-leukoplakia (OHL), a hyperplasia associated with immunodeficiency in AIDS patients (47,48), and the only clinical syndrome associated with lytic viral replication. In contrast to B cells, EBV does only very inefficiently infect epithelium *in vitro* (49,50) unless specific steps are undertaken to facilitate binding and entry (51-56). Epithelial cells do not or only express limited amounts of CD21 (57), suggesting that the mechanism is CD21 independent (54,58). Tugizov et al. (19) studied EBV infection in polarized tongue and pharyngeal epithelial cells, and suggested three pathways of CD21-independent cell entry i.e. (A) cell-to-cell transmission by direct contact of apical cell membranes with EBV infected B lymphocytes, (B) by entry of cell-free virions through basolateral membranes mediated in part through an interaction between β1 or α5β1 integrins and the EBV-BMRF2 envelope protein containing an RGD motif (59), or (C) after initial infection virus may spread directly across lateral membranes to adjacent epithelial cells (19,51). More recent studies support pathway A; direct transfer from B to epithelial cells (56,60). Another mechanism was suggested by Sixbey and Yao (55) who suggested that EBV virions produced by submucosal B lymphocytes can be internalized via the epithelial polymeric immunoglobulin receptor (pIgR) when in complex with EBV-specific IgA (55,61,62). Other researchers have found that infection of epithelial cells mainly depends

on glycoprotein gp85/gp25 complex, also named gHgL (63). Virus without this complex loses is capability to infect a gastric carcinoma cell line (23,64). The receptor for the gHgL complex is still unknown. Another glycoprotein playing a role in epithelial cell infection is gp42. For B cell infection, gp42 cooperates with gp85 and gp25 in a trimolecular complex (65,66). Borza and Hutt-Fletcher found that virus derived from HLA-class II positive B cells has less gp42 on its surface than virus derived from HLA-class II negative epithelium (65,67). Gp42 is trapped by endogenous MHC class II of the B cells and becomes therefore a target for degradation. Gp42-high virus from epithelial cells was more infectious for B lymphocytes, using MHC-II as co-receptor, while gp42-low virus from B cells was more infectious for epithelial cells. gp42 is not required for infection of epithelial cells, therefore, gp42 could act as a tropism switch (24). gB or gp110 is a protein well conserved among herpesviruses that only recently has been found to be of importance for viral infection. Activated gH/gL is thought to help gB achieve its fusogenic potential (68-70). gp110 seems to determine cellular tropism since it is more important for epithelial cell penetration than for lymphocytes (70,71). It is very well possible that inflammation or damage of epithelial cells in the oropharyngeal cavity or stomach by smoking or dietary habits might affect viral entrance, enabling epithelial cell infection.

3. EBV replication

3.1 Lytic replication

Being a gamma herpesvirus, EBV can be present in cells in either latent, or lytic form. Lytic replication, required for progeny virus production, follows differentiation of B cell into plasma cells but also occurs in epithelial cells (9,72,73). The expression of viral genes during lytic reactivation follows a specific order. First, the immediate early (IE) genes are expressed, followed by the early lytic genes (EA) and the late genes (L) (Figure 1). The switch from latent to lytic Epstein-Barr virus (EBV) infection is mediated by the viral immediate-early (IE) proteins, BZLF1 (Z, Zta, ZEBRA, EB1) and BRLF1 (R, Rta) (74). Z and R are transcription factors which autostimulate their own expression, reciprocally activate each other, and cooperatively induce expression of all early lytic viral proteins, driving the virus to replicate (72,75,76). Lytic replication differs from the latent amplification state and is mediated by the virus encoded DNA polymerase (BAFL5) using the 2 oriLyt sequences as replication origin, and results in the nucleo-cytoplasmic assembly and release of infectious viral particles (72,75).

In most asymptomatic carriers of EBV, the virus is periodically replicated. *In vivo*, replication can be triggered when a memory B cell encounters antigen or receives T cell signaling via CD40 (77,78). Also environmental factors such as chemicals (butyrates, nitrosamines), gamma radiation, inflammation, and cellular factors such as overexpression of p53 (79) are thought to trigger EBV lytic reactivation. *In vitro*, this effect can be mimicked in B lymphocytes and epithelial cells by a variety of treatments such as tetradecanoyl phorbol acetate (TPA), Ca2+ ionophore, sodium butyrate (NaB), transforming growth factor beta 1

(TGF-β1), and hypoxia, or with anti-IgG, the latter being the most natural way of reactivation (80-84). The early genes (EA) encode predominantly proteins involved in nucleotide metabolism and host cell survival, and enzymes needed for viral DNA replication (9,72). Recently, BARF1 has been shown to be expressed as an EA gene, possibly necessary for its immune modulating role (85,86). Following viral DNA synthesis the late (L) gene products are expressed which are mainly consisting of structural capsid and envelope glycoproteins, but also immune modulating and anti-apoptotic factors (9,72). This finally results in the formation of progeny virus.

Viral DNA synthesis and consequently virion production can by blocked by specific antiviral agents such as phosphonoacetic acid (PAA), or phosphonoformic acid, also called Foscarnet, that directly inhibit the virus encoded DNA polymerase BALF5, or acyclic nucleoside analogs such as (val)ganciclovir and (val)acyclovir, that require viral protein kinase (BGLF4) or thymidine kinase (BXLF1) to become tri-phosphorylated in the target cell and then cause host and viral DNA-chain termination leading to apoptotic cell death (87). These agents are widely used to treat diseases linked to lytic virus replication, e.g. oral hairy leukoplakia. However, these drugs have little or no value for treatment in clinical syndromes associated with latent stage replication, such as mononucleosis and cancer.

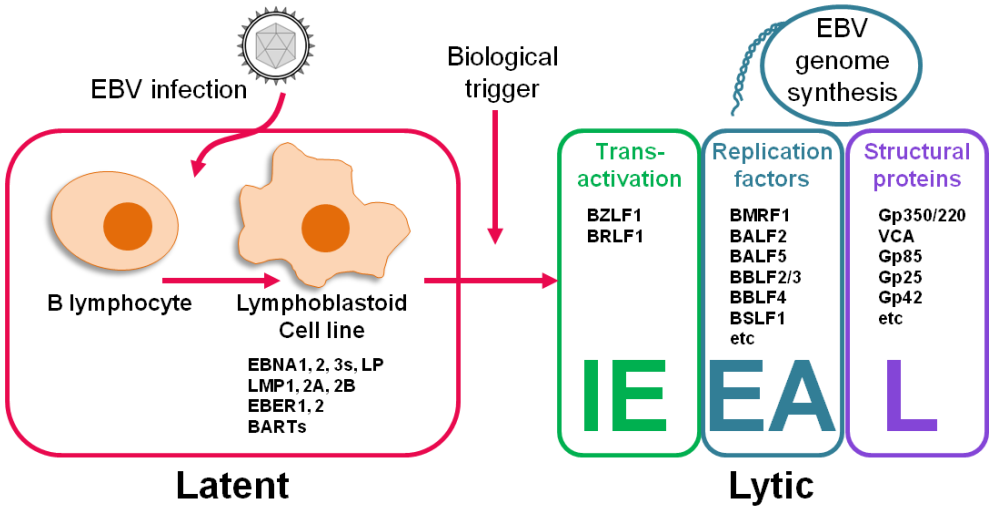

Figure 1. Overview of EBV gene expression patterns. Epstein-Barr virus infection can be latent or lytic. After induction of the lytic cycle, Immediate Early (IE), Early (EA), and Late (L) genes are expressed in sequential order. Adapted from Tsurumi et al. (77).

3.2 Latent replication

In latency, EBV expresses only a few genes necessary for viral genome persistence, altering signal transduction and cell cycle control, causing apoptosis inhibition, and modulation of immune recognition. The latency type of an EBV positive cell is defined by the expression pattern of latent genes (Table 1), while the rest of the viral episome is transcriptionally

silenced via methylation (72,88-91). During cell division the viral episome(s) reliably replicates once per cell cycle, simultaneously with the host chromosomes (44). In latency, no viral enzymes are involved, and viral genome replication solely relies on the cellular replication machinery. The pivotal viral protein during latent infection is EBNA1, which is essential for the maintenance and replication of the EBV genome (92-94). EBNA1 functions as multimeric dimer to bind sequence specific to the origin of latent viral replication on the episome, oriP (95). OriP contains two functional elements, the dyad symmetry element (DS) (96) and the family of repeats (FR)(95). The DS contains four EBNA1 binding sites and is the initiation site of DNA replication. The FR contains twenty 30 bp tandem copies of a palindromic EBNA1 binding site of 18 bp, followed by a 12 bp AT-rich sequence (95,96). The C-terminus of EBNA1 (AA 459-641) interacts with the DS and FR sites of oriP and is responsible for EBNA1 dimerization (97). The interaction of EBNA1 and OriP supports long term reliable EBV replication in dividing cells (92) as well as enhances transcription of other viral latency and host genes (98-100). EBNA1 recruits factors of the cellular replication machinery to oriP, such as origin recognition complex (ORC) and minichromosome maintenance (MCM) complex (101), telomere repeat binding factor 2 (TRF2) (102), replication protein A (RPA) (103) and nuclear import receptor Rch1/importin α (104). For attachment of the viral episome to host chromosomes the repeated Gly-Arg-rich region of EBNA1 (amino acids 33-89 and 325–376), also called AT-hook, is critical (105,106), and functionally resembles host HMGA proteins mediating binding to AT-rich regions in chromosomes (105). Cellular proteins that mediate EBNA1 chromosomal binding are EBP2 (107,108) and p32/TAP (109). DNA is replicated during S phase, after which the episomes tether symmetrically to sister chromatids (110,111).

4. EBV latent gene products

The EBV genome is approximately 170 Kb in size and contains about 80-100 open reading frames (ORF), of which only 50-60 are characterized in some extend. The ORFs are alphabetically named according to the size of the BamHI restriction fragment containing the RNA start site, the largest fragment being BamHI-A, with either rightward or leftward transcriptional orientation, e.g. BARF1 means BamHI-A rightward frame 1. Latency in EBV infected memory B cells, but also in EBV-associated malignancies, is characterized by distinct EBV transcription profiles, so called latency types (table 1). The genes that are expressed in the different latency types are discussed below.

EBV encoded RNAs (EBER1 and 2)

EBERs 1 and 2 are small non-coding RNAs and are expressed in all forms of latency. EBER1 and EBER2 are 167 and 172 nucleotides long, respectively, and are the most abundant viral transcripts reaching 107 copies per cell. Therefore, EBERs are used as a target molecule to detect EBV infected cells in tissues by RNA in situ hybridization (the so called EBER-ISH) (112). Both EBER molecules form strong secondary structures, which comprise many short stem-

loops. The EBER sequences are highly conserved indicating that they are important for the life cycle of the virus, however EBERs are not essential for EBV induced transformation of primary B lymphocytes (113). The location of EBERs is mainly in the nucleus where they interact with the auto-antigen La (114), Ribosomal protein L22 (115), RNA activated protein kinase PKR (116) and Retinoic acid Inducible Gene I (RIG-I) (117). EBERs may suppress the antiviral effects of IFNγ and PKR activation (118), induce IL-10 through RIG-I mediated signaling thereby supporting the growth of Burkitt lymphoma cells (117,119), and inhibit apoptosis (120). EBER1 may be secreted via La protein or through incorporation into exosomes, thereby providing inflammatory triggers via Toll-like receptors TLR3 and TLR7, upon uptake in surrounding cells, such as plasmacytoid dendritic cells (121,122).

Epstein-Barr nuclear antigen 1 (EBNA1)

EBNA1 is a DNA binding protein that is essential for the replication and maintenance of the viral episome in the host cell as described in paragraph 3.2. EBNA1 is necessary for the replication and maintenance of EBV in dividing cells and it can transactivate the expression of other EBV latency genes. In addition to these functions are indications that EBNA1 contributes to cell proliferation and survival (99). When bound to the family of repeats (FR), EBNA1 enhances transcription from Cp, a downstream promoter active during the latent phase of the viral life-cycle (123). Similarly, transcription of the EBV latent membrane protein (LMP1) is enhanced (100). EBNA1 has also been found to act as an oncogene by induction of the cellular recombinase-activating genes RAG1 and RAG2, leading to genetic instability (124) and interfering with DNA repair through disruption of host cell PML-bodies (125). EBNA1 inhibits apoptosis by binding to the cellular ubiquitin-specific protease USP7/HAUSP, thereby causing p53 destabilization (126). Microarray studies performed in EBV negative cells expressing EBNA1 indicate that EBNA1 may also modulate host cell's signaling pathways, such as STAT1 and TGFβ1 pathways (127,128), and induces survivin expression to enhance apoptosis resistance of the host cell (99). Although EBNA1 is a foreign protein to the host, cells expressing EBNA1 are not killed by cytotoxic T cells (CTLs). This is due to a domain consisting of co-polymers of glycine and alanine, called Gly-Ala repeat (AA 95-325), which interferes with proteosomal degradation and antigen processing and thereby evading the immune system (129).

Latent membrane protein 1 (LMP1)

The LMP1 protein is an integral membrane protein of 63 kD and is considered to be the most important transforming gene encoded by EBV (72,130-134). LMP1 protein has three domains: (a) a N-terminal cytoplasmic tail (amino acids 1–23) which tethers and orientates the LMP1 protein to (endoplasmic reticulum) membranes, (b) six hydrophobic transmembrane loops which are involved in self aggregation and oligomerization (amino acids 24–186); (c) a long C-terminal cytoplasmic region (amino acids 187–386) which possesses most of the molecule's signaling activity. While earlier studies show patch-like localization on the plasma membrane (135,136), more recent studies show that LMP1

localizes to late endosomal compartments and is secreted via exosomes (137,138). The biological functions of LMP1 are diverse and are related to its localization and cellular context in which it is expressed. At the early stage of primary B cell infection, LMP1 acts as a constitutive signaling functional CD40 homolog, promoting B cell blast activation and proliferation (32-35). LMP1 activates the NFκB pathway via direct interaction with tumor necrosis factor receptor associated factors (TRAFs) (139), it activates the JAK/STAT (Signal Transducer and Activator of Transcription) pathway (140,141), and the MAP kinase and PI3 kinase pathways (142-144). LMP1 also inhibits apoptosis by upregulation of Bcl-2 and A20 (40,145) and can mediate malignant progression by influencing angiogenesis (146,147) and metastatic ability (148-150). Depending on the cell type and context, LMP1 thus affects growth, cell survival and metastasis and is considered to be the major viral oncogen of EBV. In addition, LMP1 modulates immune responses by upregulation of cytokines (39,142,151) and chemokines (152), influencing antigen processing and presentation (153,154), and antiviral signaling (155). The first transmembrane region of LMP1 contains the LALLFWL sequence that has been shown to suppress T cell activation, either direcly or via exosome association (156-158). LMP1 is not expressed in gastric carcinoma and variably expressed in nasopharyngeal carcinoma, therefore in tumors with an epithelial background LMP1 might have a different role (15,159-161).

Latent membrane protein 2A and B (LMP2A and LMP2B)

LMP2A and LMP2B are membrane proteins with twelve transmembrane domains and a cytoplasmic C-terminal region. Although the proteins are largely transcribed from the same exons, they have separate promoters and start sites, resulting in an additional large cytoplasmic N-terminal domain in LMP2A that contain several ITAM signaling motifs (72). LMP2B is considered to negatively regulate LMP2A activity (162,163). Similar to LMP1, LMP2A and LMP2B localize in patches on the plasma membrane, perinuclear regions and endosomal compartments, and indications are that LMP2A is also secreted via exosomes (164-167). LMP2A and LMP2B are not essential for B cell transformation, but are thought to contribute to EBV persistence (36,168,169). LMP2A blocks B cell receptor signaling, thereby preventing lytic activation, and provides survival signals (36,170,171). LMP2A activates the MAP kinase and PI3 kinase pathways (172-174) inducing anchorage-independent growth, cell adhesion and motility (175-177). Further, LMP2A influences epithelial cell differentiation via ΔNp63α and β-catenin upregulation and stabilisation. β-catenin expression stimulates cell cycle progression and proliferation (178,179). Upregulation of ΔNp63α reduces normal cell differentiation and might act to keep EBV in a latent state, but is also thought to play a role in cancer pathogenesis (180,181).

BamHI-A rightward transcripts (BARTs)

The BARTs encode a number of potential open reading frames (ORFs) including BARF0, RK-BARF0, A73 and RPMS1 (182-184). Whether or not these transcripts are translated into protein is controversial (185,186). BARF0, RK-BARF0 and RPMS1 might have a nuclear and

A73 a cytoplastic localization (186,187). Both RK-BARF0 and RPMS1 might downregulate Notch signaling, thereby reducing EBNA2 transactivating activity (188,189). BARTs also serves as a template for EBV encoded microRNA (see below).

EBV microRNAs

microRNAs (miRNAs) are small single stranded RNA molecules that function as regulators of gene expression. Following transcription, precursor miRNAs is shuttled out of the nucleus, cleaved by Dicer and loaded into the RISC complex (190). EBV is the first human virus reported to encode miRNAs (191) encoded into three clusters; BHRF1, encoding 4 miRNAs, and two clusters of multispliced BART, encoding 23 miRNAs, while miRNA-BART2 is and individual miRNA (192-195) (Figure 2). The role of miRNAs in EBV biology is not fully understood and the targets could be viral or cellular. miRNA-BART2 downregulates BALF5 expression (196), and miRNA-BART22, has been shown to downregulate LMP2 (197). miRNAs from BART cluster 1 have been shown to reduce LMP1 protein expression (198) and miRNA-BART6 silences EBNA2 (199). Cellular genes implicated as targets of miRNAs are apoptosis genes, tumor suppressor genes, and genes involved in immunity (190,200-202). The BHRF1 encoded miRNAs contribute to B cell transformation (203). Recently, EBV miRNAs have been found to be selectively secreted into exosomes after which they can target neighboring cells (204-206).

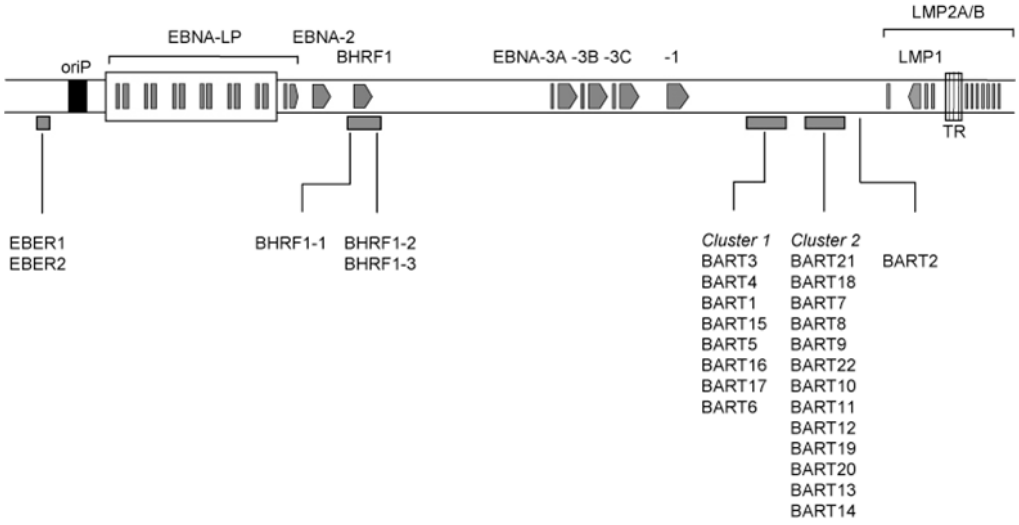

Figure 2. Expression of non-coding EBV RNAs. Schematic illustration of the EBV genome showing the location of the non-coding EBER RNAs, BHRF1 miRNAs and BART miRNAs. Also shown are the location of the latent cycle proteins LMP1, LMP2A/B, EBNA1/2/3A/3B/3C/LP, latent origin of replication (oriP) and terminal repeats (TR) (407).

BamHI-A rightward frame 1

The BamHI-A rightward frame 1 (BARF1) gene encodes a 29-33 kDa protein that is selectively transcribed during latency in carcinomas (207-209). After cleaving off the first 20 amino acids, BARF1 is secreted as a glycosylated hexameric protein (210-212). BARF1 induces

malignant transformation in several cell types and functions as an oncogene (213-217). BARF1 might act as a mitogenic growth factor (218-220), and inhibits apoptosis (216,221). Secreted BARF1 (sBARF1) has immune modulating properties and functions as a decoy receptor for macrophage colony stimulating factor (M-CSF) (86,222-225). A detailed review about the functions and properties of BARF1 is described in chapter 2.

5. Immune responses to EBV and viral immune evasion

Infection with EBV triggers innate, humoral and cellular immune responses to virus-encoded proteins. EBV persists for life in its human host and in immunocompetent individuals the virus is effectively controlled by the immune system. Lifelong viral latency reflects a dynamic balance between virus reproduction and host immune control. To counteract host defenses EBV has developed evasive strategies against both the innate, cellular and humoral immune responses as described here below.

5.1 Innate immune response

The innate immune response is the first line of defense to invading pathogens such as EBV. Antigen presenting cells (APCs) such as monocytes, dendritic cells (DCs), and macrophages secrete cytokines and chemokines following activation of their pattern recognition receptors and thus raise the alarm for the immune system. Especially Toll-like receptors 3, 7 and 9 (TLR-3, -7 and TLR-9), protein kinase R (PKR) and the Retinoic Acid Induced Gene 1 (RIG-1) have been implicated in sensing of EBV. TLR-3, -7, PKR and RIG-1recognize EBERs (121) whereas TLR-9 recognizes non-methylated EBV double stranded DNA (226). Activated APCs can the present viral antigen from infected B cells to CD4 and CD8 T cells in order to develop adaptive immune responses (227,228). There are several indications that also natural killer (NK) cells are involved in EBV innate immune responses. Firstly, elevated levels of NK cells are detected in peripheral blood during primary infection (229-231). Secondly, patients with an immunodeficiency that involves NK cells are extremely susceptible to EBV infection and associated malignancies (232-234), and thirdly, tonsillar NK cells primed *in vitro* by DCs with EBERs produce interferon-gamma in amounts capable of delaying EBV-driven B cell transformation (235).

5.2 Cellular responses

Primary infection is mainly monitored in patients with infectious mononucleosis (IM) who have an unusual strong cell-mediated immune response predominantly consisting of CD8+ T cells with a smaller contribution of CD4+ T cells (16,236,237). The cytotoxic T-lymphocyte (CTL) response is directed largely towards lytic proteins and the magnitude of the response is related by their order of synthesis; the response is the strongest towards immediate early gene products such as BZLF1 (238-240). Unlike in IM, asymptomatic individuals undergoing primary infection show no massive T cell expansions, despite high viral loads in blood (241-243). So the T cell response in IM patients is critical for controlling viral replication but may

also be responsible for the symptoms of infectious mononucleosis. The high occurrence of EBV lymphoproliferation and lymphomagenesis in immunosuppressed patients is evidence that CD8+ T cell responses are essential for the control of EBV and therapeutic infusion of EBV-specific CD8+ T-cells can reverse the disease in these patients (12,244).

CD8+ T cells in IM patients are granzyme-B and perforin-positive and have cytotoxic activity. The markers on these cells show a profile that is evidence of recent antigen stimulation and activation, namely CD38, CD69, CD45RO, Ki-67 and HLA-DR (16,240,245-247). These activated T cells die rapidly by apoptosis *in vitro* unless antigen stimulation is given, because of their low level of anti-apoptotic Bcl-2, Bcl-x and survivin, and high level of pro-apoptotic Bax (237,248). Over time, both the activation and the reactivity to certain EBV antigens will change to a memory CD8+ profile, more potently targeting latency-associated gene products, in particular the EBNA3 family (16).

In contrast to the T cells in acute primary infection (i.c. IM), most memory CD8+ T cells in asymptomatic EBV carriers show a resting phenotype with with expression of the memory maturation marker CD27 and without expression of CD38 and CD69 activation markers. However, a few EBV-specific T cells remain active and control the asymptomatic state (239,247,249). The antigen-specific response is not uniform across all latent EBV proteins. Immunodominant epitopes are derived from the EBNA3A, B, and C family (250,251), and subdominant epitopes are from EBNA1, LMP2 and LMP1 (252). The presentation of these antigens is not equally efficient across all HLA-types which is important for the development of immunotherapy for EBV-associated malignancies (253-256). The proportion of EBV-specific CD8+ T cells remains stable over time and may even rise in elderly (257,258).

In comparison to CD8+ response to EBV, much less is known about the CD4+ response, but recent studies shown that CD4+ T cells are essential for proper persisting immune control of EBV infected cells (259). During acute infection the level of activated CD4+ T cells first rises, and then gradually declines to a smaller population of effector cells to mediate protection during the persistent phase of infection (260). CD4+ T cells predominantly target lytic cycle antigens and EBNA1 (259,261). The kinetics and immunodominance of CD4+ T cells for EBV epitopes is different than in CD8+ T cells, with EBNA1 being most dominant (261-263).

5.3 Humoral responses

Upon antigen-specific triggering of the immunoglobulin surface receptor and with the help of T cells, B lymphocytes will mature into antibody producing plasma cells, and later on into memory B cells. Antibodies can bind to the intact virions, and various structural and non-structural (glyco-)proteins expressed in/on or released by virus-infected cells. This will lead to neutralization of infectious viral particles, death of infected cells and clearance of viral antigens via immune complex formation. In case of EBV, viral antigens exposed on the surface of the host cells can be targeted by antibodies, after which either complement components C1q/C3 or phagocytic cells, such as NK cells or macrophages, recognize the distorted Fc part of the bound antibody and eliminate the infected cell via antibody

dependent complement or cell-mediated cytotoxicity (ADCC). Antibody responses to EBV are dependent on the time after exposure in healthy individuals and can be used as a diagnostic tool for EBV-associated disease (9). Knowledge of antibody responses to EBV antigens can also be applied to develop a prophylactic vaccine or for immunotherapy strategies in EBV associated cancers (264-268).

Early studies to EBV antibody response used immunofluorence and immunoblot methods, but nowadays involve less laborious and highly reproducible enzyme-linked immunosorbent assays (ELISA) (269,270). After primary infection most infected individuals develop EBV-specific IgM, IgA and IgG antibodies against viral capsid antigens (VCAs), early antigens (EAs) and EBNAs (271). VCA–IgM is detected at the initial stage of EBV primary infection, while VCA–IgG indicates EBV carriership (272). Antibodies to EA genes are indicative of lytic replication and are good markers for active EBV infection (273). EBNA2 IgG antibodies are only temporarily detected in IM patients, while IgG to EBNA1 persists for life and is indicative for EBV seropositivity (273,274). Detailed analysis of peptide-epitopes on EBV proteins, has allowed development of more simple and accurate serodiagnostic tests (275-277). Elevated levels of IgA to VCA, EBNA1 and EA genes are characteristically found in EBV-associated carcinomas such as NPC. Elevated levels of VCA-IgG are found in Burkitt Lymphoma. Such responses can be used for diagnostics (243,271,278). Interestingly, whereas antibodies to lytic antigens and EBNA1 are readily detected in patients with nasopharyngeal carcinoma, the humoral immune response to EBV-encoded tumor-associated proteins LMP1, LMP2 and BARF1 is marginal (211,279-282). This may be exploited by development of therapeutic antibodies filling the apparent niche in humoral immunity (282,283).

5.4 EBV immune evasion

To persist life-long in its host, EBV evolved mechanisms to escape from immune recognition. Several immune evasion strategies used by viruses are: 1] reduced protein expression and expression of proteins with low immunogenicity, 2] interference with proteasomal degradation and MHCI antigen presentation, 3] downregulation of MHCII and co-stimulatory molecules, 4] prevention of MHCII and T cell receptor interaction, 5] inhibition of apoptosis of infected cells, 6] modulation of growth factors, cytokines and chemokines and 7] secretion of exosomes. A number of EBV proteins enable one or multiple immune evasion strategies.

During the lytic phase, EBV expresses more than 80 proteins, most of which are highly immunogenic, demonstrated by the strong immune response elicited at the time of primary contact. EBV then switches to a latency profile in which only a few proteins are expressed in low copy numbers. This remarkable plasticity of gene expression results from combined epigenetic modifications of the viral episome, ranging from CpG DNA methylation and histone and chromatin modifications, to higher-order chromosome conformations such as spatial looping to control promotor activation (43,284). Promotor CpG methylation of the EBV genome is well studied and plays an essential role in maintaining viral latency (88,285-287).

EBNA1 is expressed in all latency types and its Gly-Ala repeat domain inhibits efficient translation, thereby limiting the copy number. This Gly-Ala repeat also inhibits proteolytic degradation, in that way protecting EBNA1 from MHCI presentation and CD8+ T cell recognition (129,288-290). EBNA1 may also prevent apoptosis (99,126).
LMP1 has multiple effects that help EBV to stay hidden for the immune system. LMP1 has direct immunosuppressive effects that are ascribed to the LALLFWL domain, affecting T cell proliferation and NK cells cytotoxicity (156). LMP1 inhibits apoptosis by induction of anti-apoptotic genes such as Bcl-2 (40,145,291-293), affects the cytokine and chemokine network by inducing expression of IL-6, IL-8, IL-10, CCL17, and CCL22 (39,142,151,152), and inhibits antiviral signaling by interferons (155). LMP1 secreted via exosomes may also modulate the cellular microenvironment and suppress T cell activation (157,158). By contrast, LMP1 is able to up-regulate expression both of the Transporter associated with Antigen Processing (TAP) proteins and HLA class I, enabling better antigen processing (153,294). While this may seem contradictory, efficient presentation of self peptides that compete with viral peptide presentation might be advantageous. LMP2 prevents B cell activation and thereby induction of highly immunogenic EBV genes (170). The viral microRNAs EBERs and BARTs affect the immune response in the host and neighboring (immune) cells via exosomes (117-119,205). BARF1 may prevent apoptosis (216,221) and secreted BARF1 functions as a decoy receptor for macrophage colony stimulating factor (M-CSF) (86,222-225) consequently interfering with human monocyte-macrophage differentiation (223).
To enable the virus to replicate successfully, a number of early genes affect MHC class I and class II antigen presentation pathways. BNLF2a interferes with both ATP and peptide binding to TAP, and in this manner prevents peptide-loading of MHC class I molecules (295-298). BGLF5 reduces the synthesis of new MHC class I molecules as part of its general host shut-off function (299,300). BILF1 binds to MHC class I, impairing the export of new complexes and target MHC class I molecules for degradation (301,302). BCRF1 encodes for a viral homologue of IL10. Besides the immunosuppressive functions (303,304), vIL-10 causes a reduction in TAP1 mRNA and protein levels, and simultaneously reduces mRNA of the immunoproteasome subunit b1i/LMP2 that shares the same promotor (305,306). BZLF1, encoding the immediate early transactivating protein Z (Zta, ZEBRA) down-regulates MHC class II expression through inhibition of CIITA transcriptional co-activator (307). EBV glycoprotein 42 (gp42) might also modulate the immune response triggered by dendritic cells. Virus particles produced in epithelial cells and high in gp42, entered monocytes and inhibited their development into DCs (308). In addition, Gp42 on the surface of cells during productive infection interferes with MHC class II T cell antigen presentation (309).

6. EBV-related diseases and malignancies

Since its discovery in 1964 in Burkitts lymphoma, EBV has been associated with several benign and malignant proliferative disorders in both immunocompetent and immunosuppressed hosts. Each of these diseases expresses a different set of EBV genes and

can be grouped into the different latency types shown in Table 1. EBV was the first human cancer virus found and is recognized as a class I human carcinogen by the World Health Organization (310).

6.1 Benign EBV-associated diseases

Infectious Mononucleosis (IM)

IM, also known as kissing disease, glandular fever or Pfeiffer's disease is a well known disease affecting mainly adolescents and young adults in developed countries. The connection between EBV and IM was made when a laboratory technician, previously seronegative for the virus, contracted the disease and subsequently developed antibodies to EBV, a process called seroconversion (311). Primary EBV infection mostly occurs asymptomatically during childhood, however, if primary exposure to the virus is delayed until adolescence or adult life, it can cause IM in a proportion of individuals. The disease is clinically characterized by fever, sore throat, tonsillitis, lymphoadenopathy and splenomegaly, with characteristic abundance of atypical lymphocytes and heterophile antibodies, which are representing the strong non-specific immune stimulation during IM (312-314). The limited effect of antiviral drugs indicate that not EBV replication is causative for the clinical symptoms of IM, but rather the strong cytokine storm and abundant T cell reactivity (315). The accurate diagnosis of IM is performed by antibody measurement to specific EBV antigens. Elevated IgM and IgG to EA and VCA can be measured during the acute phase, while ani-EBNA1 IgG antibodies remain negative until few months post acute phase (312,316). Whereas anti-VCA and anti-EBNA1 IgG antibodies persist for life, anti-VCA IgM and anti-EA IgG rapidly decline as the patient recovers (317,318). When serological data is inconclusive, viral load quantitative PCR can assist (319). The immune responses quickly reduce the number of circulating EBV positive B cells within 1-2 months, but occasionally IM may progress into a chronic active infection with life threatening complications (320).

6.2 Immunodeficiency and immunosuppression related disorders

X-linked lymphoproliferative disorder

Patients with primary immunodeficiency X-linked lymphoproliferative disease (XLP, or Duncan syndrome) are highly susceptible to EBV infection. Mutations in SH2D1A gene cause a defect in the Signaling Lymphocyte Activating Molecule (SLAM)- associated protein (SAP) that is important in signaling the lymphocyte immune response. Because the gene is located on the X chromosome, the condition primarily affects males. Due to an inability to control EBV infection, primary EBV infection may lead to Virus-Associated Hemophagocytic Syndrome (VAHS) and fatal lymphoproliferations and lymphoma (1,321).

Oral Hairy Leukoplakia (OHL)

OHL is a benign disorder that is mostly seen in immunocompromised patients, in particular in HIV seropositives and is characteristic for reduced T-cell surveillance during progression to

AIDS. It's a white proliferative, hyperkeratotic, squamous mucosal epithelial cell lesion of the tongue. Latent as well as lytic viral gene expression can be found (322) and EBV particles can be detected in superficial epithelia (47). Lesions regress with acyclovir treatment, but since latent infected cells are not sensitive to this treatment, lesions can reoccur when treatment is stopped.

AIDS-related lymphoma

In healthy individuals the outgrowth of EBV infected B cells is controlled by cell mediated immune responses, which are increasingly defective in patients with acquired immunodeficiency syndrome (AIDS), leading to outgrowth of EBV-infected B lymphocytes with latency type III. The resulting B lymphomas are a heterologous group and include Central Nervous System (CNS) lymphoma, diffuse large B cell lymphoma, Hodgkin's and non-Hodgkin's lymphoma, Burkitt Lymphoma (BL)-like lymphomas and primary effusion lymphomas (323,324). EBV genomes are present in about half of lymphomas that arise in HIV-infected patients (324), and the frequency of EBV infection depends on the subtype of tumor involved (1). It is considered that chronic inflammation and antigen stimulation is a causative factor for lymphoma development.

Post Transplant Lymphoproliferative Disease (PTLD)

After transplantation, patients receive T cell immunosuppressive therapy to avoid rejection. This leads to an increased risk for EBV-driven lymphoproliferative diseases that are almost always of B cell origin and EBV positive. In bone marrow transplants PTLD arise mostly from donor derived EBV infected B cells, while in solid organ transplantation, EBV in lymphoma cells is often of recipient origin (325,326). Therefore it is important to determine EBV serostatus in donor and recipient prior to transplantation. Careful monitoring of EBV DNA load and dynamics in peripheral blood of transplant recipients may be used to screen for early stage PTLD (327,328). Timely intervention may prevent progression to B cell lymphoma. Treatment can involve temporarily lowering of immunosuppression, infusion of EBV reactive T cells, or treatment with Ritiximab (anti-CD20) (329). Late stage PTLD may require more aggressive R-CHOP immunochemotherapy for full regression.

6.3 Lymphomas in immunocompetent individuals

Burkitt's lymphoma (BL)

The endemic form of BL was first described by Dennis Burkitt in 1958 in Africa (330). Epstein-Barr virus was first discovered in lymphoma cells from these tumors (3,4), and almost 100 % of the endemic BL tumors are EBV positive (331,332). Besides endemic BL there is a sporadic form of BL with no specific geographic distribution and an EBV association in 20-30 % of the cases (9). A histological characteristic of BL is the appearance of "starry sky macrophages" within the tumor (333). Another important feature of BL is the translocation between the c-myc oncogene from chromosome 8 (8q24) and either immunoglobulin heavy chain gene on

chromosome 14 (14q32), the kappa light chain loci on chromosome 2 (2p11) or the lambda light chain on chromosome 22 (22q11). The first translocation, t8;14 is the most common and appears in 80 % of the cases (334). This translocation of c-myc results in overexpression, leading to cell survival (335). The mechanism by which EBV contributes to the development of Burkitt's lymphoma is not entirely understood. Malaria infection is considered a co-factor for the development of endemic BL. Malaria infection might compromise EBV immune control, or hyperstimulation of EBV infected B cells by malaria allows for reactivation of EBV. Interestingly, a surface protein on malaria, the plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) was shown to activate B cells (336). BL has a latency type I expression pattern, but expression of other EBV genes is occasionally seen, including those involved in lytic replication (337-339).

Hodgkin's lymphoma

Hodgkins's disease (HD) is a malignant lymphoma characterized by the presence of mononuclear Hodgkin cells and multinucleated Reed-Sternberg (RS) cells in a background of non-neoplastic cell populations including B and T lymphocytes, plasma cells and eosinophiles (340). According to the WHO classification, HL can be histologically divided into four subtypes: lymphocyte predominant (LP), nodular sclerosing (NS), mixed cellularity (MC) and lymphocyte depleted (LD) (341). Not all subtypes harbor EBV to the same degree, with percentage below 25 % in LP and NS, and over 75 % in MC and LD, depending on age, gender, ethnicity and socio-economic background (342,343). In EBV-positive cases, Hodgkin's lymphomas display a latency type II expression pattern with presence of EBNA1, LMP1 and LMP2A (344,345). The role that EBV plays in HD is not fully understood, but EBV association coincides with poor prognosis of the disease (346-348). EBNA1 induced CCL20 expression modulates immune responses in the HD microenvironment (349). LMP1 and LMP2A inhibit apoptosis and allow survival of defective B cells (344,345,350,351). A previous history of infectious mononucleosis is linked with increased risk of developing HD (352).

T cell and NK cell lymphomas

The EBV receptor CD21/CR is only expressed in low levels on T cells, and during acute infection T cells are rarely infected (353). Several types of non-B cell lymphomas are associated with EBV (354-356). Angioimmunoblastic T-cell lymphoma (AITL, or AILD) is a rare, aggressive neoplasm, but is the most common subtype of peripheral T cell lymphomas. While the EBV association with the disease is almost 100 %, EBV is predominantly detected in B cells (357). Gene rearrangements of the T cell receptor and/or Ig heavy chain can be found in the majority of the cases. How EBV is involved in the pathogenesis is unclear and it has also been suggested that high EBV levels are a reflection of the disease process rather than a cause of it.

T/NK cell lymphoma are aggressive, destructive tumors that are prevalent in Southeast Asia. The nasal type is 100 % associated with EBV and show clonal EBV genome (358). The absence of T cell antigens and the expression of the NK cell marker CD56 are evidence that these

tumors are derived from NK cells (359,360). Chronic active EBV infection plays a role in the development of the disease (361,362).

6.4 EBV associated carcinomas

Nasopharyngeal Carcinoma (NPC)

NPC is a cancer of the epithelial lining of the nasopharynx that occurs with extraordinarily high incidence in south-east Asia and with elevated incidence in Inuit populations and in Africans and Arabs of the Mediterranean area (15,363). Histopathologically, NPC is classified into three types, based on the degree of differentiation. Keratinized squamous cell carcinoma (WHO type I) is highly differentiated and characterized by epithelial growth patterns and keratin filaments, non-keratinizing squamous cell carcinoma (WHO type II) retains epithelial cell shape and growth pattern, and undifferentiated carcinoma (WHO type III) does not produce keratin and lacks a distinctive growth pattern. Undifferentiated NPC is 100 % associated with EBV, showing clonal presence of the virus in all tumor cells, and compromises the vast majority of NPCs in endemic areas (14,15). In NPC, EBV shows latency type II, with the expression of EBNA1, EBERs, LMP1, LMP2A and BARF1 (159,160,182,364-367). Early symptoms vary and include nasal obstruction, otitis media, tinnitus and facial pain. Since these symptoms are not specific for NPC, most patients are diagnosed when the tumor reached an advanced stage. Early stage NPC can be cured with only radiotherapy, stressing the need for early diagnosis (368). In more progressed tumors radiotherapy is often combined with chemotherapy. Besides EBV, other aetiological factors such as the consumption of salted dried meats or fish, spicy foods, Chinese herbal drugs, alcohol, smoking and hereditary predisposition have been implicated in the genesis of NPC (369-373). NPC occurs more frequent in male than female and shows a distinct age distribution across different populations (374-376). The first link between EBV and NPC came from seroepidemiological studies that revealed that sera from NPC patients contained elevated antibody titers to EA and VCA antigens (377). Elevated titers of IgG and especially IgA to VCA, EA and EBNA complexes can be indicative for NPC (370,378), but the golden standard for NPC diagnosis is EBER RNA in situ hybridization of an invasive biopsy taken from the nasopharyngeal area (379). In the last decade, less invasive diagnostic methods have been developed such as the measurement of viral DNA load in peripheral blood (380-383), and RT-PCR of specific EBV genes in nasopharyngeal brushings (209,384,385), which can also be used to monitor treatment (386).

Gastric Carcinoma (GC)

Histopathologically, GC is often grouped into three subsets; regular adenocarcinoma not otherwise specified (NOS), lymphoepithelioma-like carcinomas (LELC), and gastric stump carcinomas. Of these subsets, 10 % of NOS, 80 % of LELC, and 40 % of gastric stump carcinomas are associated with EBV, averaging to about 10 % of all gastric cancer cases worldwide (387-391). EBV positive GC represents a distinct disease entity, differing from

Helicobacter-associated GC by localization, age, male predominance, immunological features and prognosis (392,393). Patients suffering from EBV positive GC have a better prognosis than those with an EBV negative tumor, which might be because of anti-tumor immune responses triggered by the presence of the virus (393). EBV GC is hard to group in one latency type because of the distinctive gene expression, but is usually considered latency type I. Besides EBNA1, EBERs, BARTs, gastric carcinomas show expression of the BARF1 gene. Additionally, LMP2A is expressed, but not the major oncogene LMP1 (394-396). The absence of LMP1, which otherwise would reduce immune responses, might explain the presence of the abundant cytotoxic T cell infiltrate in EBV positive tumors, associating with reduced metastasis and better survival (158,393). The precise role of EBV in the pathogenesis of GC remains to be determined, but the lack of the LMP1 oncogene suggests that other EBV genes, likely in combination with cellular defects, function as oncogene in GC. BARF1 might have anti-apoptotic effects (216,221), and recent studies have shown that h-RAS expression synergizes with BARF1 in GC malignant transformation (218). The role of BARF1 as the GC oncogene is further discussed in chapter 2 of this thesis. LMP2A might upregulate DNA methyltransferase I (397), leading to promoter methylation of cancer-related cellular genes in GC (398-400). The absence of EBV infection in pre-malignant gastric lesions supports the suggestion that viral infection is a relatively late event in gastric carcinoma (401). On the other hand is evidence that patients show high antibody titers to EBV antigens years prior to clinical diagnosis of EBV positive GC (402-405). In addition the clonality of EBV DNA in the tumor points towards EBV infection as early event in carcinogenesis (406).

7. Aims and outline of this thesis

As shown in the previous sections, EBV is a very successful virus that infects almost everybody, and exists in a tight balance with the immune system. However, in certain individuals, in combination with other factors such as immune deficiencies or food habits, EBV can cause malignancies of both lymphoid and epithelial origin. In these cancers, only a few viral genes are expressed which are either important for maintenance of the viral episome, modulate the immune system, function as oncogene or a combination of these. This thesis focuses on one of these genes, the BamHI-A Rightward Frame 1 gene (BARF1), which is transcribed in the two epithelial malignancies associated with EBV namely gastric carcinoma (GC) and nasopharyngeal carcinoma (NPC). The aim of the study can roughly be described as ‘to better understand’ this relatively unstudied viral gene. BARF1 is only transcribed in carcinoma and is a secreted protein. Using detection of BARF1 protein directly of detection of human antibodies to BARF1 indirectly as a diagnostic tool would be a vast improvement of NPC diagnosis. In Chapter 3 the question whether there are humoral immune responses to BARF1 that can be utilized in a diagnostic tool is answered, and Chapter 4 investigates the genetic variation of the BARF1 gene in the Indonesian population. Part of the aim of this thesis was to study the functional role of BARF1 as an oncogene in NPC. In Chapter 5 the immune modulating function of BARF1 is thoroughly investigated and

the implications *in vivo* are discussed. EBV keeps a tight control over its genes, reflected in lytic and latent gene expression profiles in various stages of the virus life cycle. In Chapter 6 and 7 the transcriptional regulation of BARF1 in the lytic cycle as well as in latency is analyzed. Chapter 8 focuses on the direct detection of BARF1 protein in the circulation and human tumor tissue which still represents a challenge, despite the use of several new monoclonal antibodies and novel proteomic techniques

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