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# Epstein-Barr Virus associated gastric carcinoma

**Review Article**

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**Abbreviations:** Burkitt's lymphoma, (BL); CpG island methylator phenotype, (CIMP); cytotoxic T-lymphocyte, (CTL); EBV-associated gastric carcinoma, (EBVGC); EBV-encoded RNA, (EBER); EBV-encoded small RNA 1, (EBNA1); Epstein-Barr Virus, (EBV); gastric carcinomas, (GCs); Hodgkin's disease, (HD); human leukocyte antigen, (HLA); human leukocyte antigen, (HLA); immediate-early, (IE); Immunohistochemical, (IHC); insulin-like growth factor 1, (IGF1); nasopharyngeal carcinoma, (NPC); natural killer, (NK); origin of replication complexes, (ORCs); small interfering RNA, (RNAi);

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## Summary

**Epstein-Barr Virus (EBV) is a ubiquitous human herpesvirus associated with a variety of human malignancies including lymphoma and so-called lymphoepithelial carcinoma seen in a variety of sites, including the stomach. EBV has been detected in 5-20% of gastric carcinomas worldwide. Evidence is presented which suggests that failure of EBV-specific immunity may play a role in the pathogenesis of EBV-associated malignancy. In this paper, we review the clinicopathologic features, molecular pathology, immunologic aspect, environmental factors in EBV-associated gastric carcinoma and lastly, EBV-targeted therapy.**

## I. Introduction

Epstein-Barr Virus (EBV) is a human oncogenic virus, which was identified as herpesvirus-like particles by electron microscopy in a cell line established from a Burkitt's lymphoma biopsy by Epstein, Achong and Barr in 1964 (Epstein et al, 1964). EBV is implicated in the etiology of many human malignancies, including Burkitt's lymphoma (BL), Hodgkin's disease (HD), nasopharyngeal carcinoma (NPC) and EBV-associated gastric carcinoma (EBVGC) (Shibata and Weiss, 1992; International, 1997).

Several studies have revealed that EBV is associated with 5-20% of gastric carcinomas (GCs) worldwide (Shibata and Weiss, 1992; Rowlands et al, 1993; Fukayama et al, 1994). The clinicopathologic features of EBVGC are distinct and include a male preponderance, frequent accompaniment by atrophic gastritis, predominant involvement of the proximal stomach, moderately differentiated tubular or poorly differentiated solid type of histopathology (Kijima et al, 2003; Lee et al, 2004). Although its specific role in gastric carcinogenesis remains unclear, some studies have shown molecular changes that are characteristic of EBVGCs (see later). The purpose of this review is to provide an updated comprehensive summary of the clinicopathologic features, molecular pathology, immunologic aspects, environmental factors associated with EBVGC. Another important aspect of this review is to highlight EBV-targeted therapy.

## II. Clinicopathologic features

EBVGC has been described in different populations from low incidence gastric cancer areas, such as Western Europe and the United States, to high-risk countries, such as Korea and Japan (International, 1997). Now, it is well known that 5-20% of gastric carcinomas throughout the world reveals monoclonal proliferations of EBV-infected carcinoma cells (Shibata and Weiss, 1992; Rowlands et al, 1993; Fukayama et al, 1994; Osato and Imai, 1996).

The EBVGCs have a lymphoid stroma (Kim et al, 2001; Lee et al, 2004) and these tumor-infiltrating lymphocytes are predominantly human leukocyte antigen (HLA) class I restricted CD8 positive cytotoxic T lymphocytes (Tokunaga et al, 1993). EBVGCs are most often poorly differentiated carcinomas, proximal in location, particularly in the gastric cardia and are more

prevalent in male patients (Chang et al, 2001; Kijima et al, 2003; Lee et al, 2004). The mean age was 53.4 years (range: 53.4 ± 12.7) (Lee et al, 2004). A study showed that gross types were 1 Borrman type I, 2 Borrman type II and 1 early gastric carcinoma type IIc among 4 EBVGCs (Nam et al, 1998). The tumors were composed of syncytial nests of undifferentiated cells having vesicular nuclei with prominent nucleoli, admixed with abundant lymphoplasma cell infiltration in the stroma (Nam et al, 1998). It is also interesting that EBVGC in its intramucosal stage is likely to exhibit a specific histologic pattern with abortive branching-anastomosing tubular structures occupying the middle of the mucosa without destroying the normal mucosal architecture, the so-called lacy pattern (Uemura et al, 1994; Arikawa et al, 1997). Individual carcinoma cells were cuboidal and had oval hyperchromatic nuclei focally with small but distinct nucleoli (Uemura et al, 1994).

The survival rate of the patients with EBVGCs was better than that of the patients with EBV-negative gastric carcinomas, but this was not statistically significant (Kijima et al, 2003; Lee et al, 2004). Even in cases of advanced of EBVGCs, the prognosis was not significantly different from that of patients with EBV-negative carcinomas (Chang et al, 2001).

## III. Molecular pathology

The exact mechanism by which EBV contributes to the carcinogenesis of the gastric mucosa remains unknown. But, recently, promoter hypermethylation that leads to epigenetic silencing of multiple genes has been recognized as an important mechanism in gastrointestinal carcinogenesis (Kang et al, 2002; Feinberg and Tycko, 2004; Issa, 2004; Kim et al, 2005; Chang et al, 2006; Kusano et al, 2006). In this regard, promoter methylation of the so-called CpG islands, which are CpG dinucleotide-rich areas, located within the promoters of approximately 60% of human genes (Feltus et al, 2003), is usually associated with long-term, irreversible epigenetic silencing of X-linked and imprinted genes (Jones and Baylin, 2002).

The $p16^{INK4A}$ gene is a common target of inactivation by epigenetic mechanisms in gastric carcinoma. The product of that gene is an inhibitor of G1/S phase transition, the loss of which promotes uncontrolled cell growth (Toyota et al, 1999; Suzuki et al, 1999). The $p16^{INK4A}$ methylation occurs frequently in EBVGC (Schneider et al, 2000; Kang et al, 2002; Kusano et al, 2006). Thus, it appears that epigenetic silencing of this gene is associated strongly with the development of EBVGC.

E-cadherin is also important protein in the carcinogenesis of the stomach. E-cadherin is a $Ca^{2+}$-dependent cell-cell adhesion molecule that plays an essential role in the formation and maintenance of the normal architecture and function of epithelial tissues (Takeichi, 1991; Takeichi, 1995; Bracke et al, 1996). Abnormalities of the gene and gene expression of E-cadherin have been frequently observed in gastric carcinoma (Oka et al, 1992; Becker et al, 1994; Shino et al, 1995; Tamura et al, 1996; Shun et al, 1998; Machado et al, 1999) and the germline mutation was identified in the hereditary diffuse gastric carcinoma kindred (Guilford et al, 1998). Some studies showed that the abnormality of E-cadherin expression caused by the aberrant methylation of E-cadherin gene promoter was closely associated with the development of EBVGC. The frequency of this aberrant methylation was significantly higher in EBVGC than in EBV-negative GC (Sudo et al, 2004).

Other studies have shown loss of p73 expression through aberrant methylation of the p73 promoter occurred specifically in EBVGC, together with the global methylation of p14 and p16 (Ushiku et al, 2006). The study also suggested that a specific type of gastritis, prone to a higher grade of atrophy and p73 methylation, might facilitate the development of EBVGC (Ushiku et al, 2006). p73 is mapped to the human chromosome 1p36.2-3, a region which is frequently lost in a wide variety of human tumors including neuroblastoma (Kaghad et al, 1997). The sequence-specific DNA-binding domain, the amino-terminal activation domain and the carboxy-terminal oligomerization domains of p73 are similar to those of p53. Accompanying these structural similarities, p73 can act as transcription factors and regulate the expression of similar groups of genes by means of direct binding to what were originally identified as p53-binding sites within promoters. Transcriptional activation of these target genes leads to the induction of cell-cycle arrest and apoptosis (Kaghad et al, 1997; Zhu et al, 1998; Melino et al, 2002). This evidence suggests that p73 may act as a tumor suppressor with an overlapping function with p53. But, interestingly, loss of p73 expression, independent of p53 abnormality, specifically occurred in EBVGC (Ushiku et al, 2006).

Some studies suggested that the accumulation of CpG island methylation simply occurs in the early stage of development CpG island methylator phenotype (CIMP) high gastric carcinoma, without contribution to its further progression (Chang et al, 2006).

There is a negative association between EBV infection and the expression of MUC1, MUC2, MUC5AC, CEA, c-erbB2, smad7 and p53 (Lee et al, 2004).

## IV. Immunologic aspects related to EBV

EBV is a member of lymphocryptovirus genus of gamma herpes family. The EBV genome is a linear, double stranded, 184-kbp DNA (Kieff and Rickinson, 2001). Like all herpesviruses, EBV can establish either a latent or lytic infection in host cells. In infected cells, the EBV genome enters the nucleus, where it forms a circular episome (Kieff and Rickinson, 2001). Episome formation is mediated by 0.5 kb terminal repetitive sequences located at either end of the linear molecule. Fusion of these sequences results in terminal repetitive regions with variable numbers of repeats (Raab and Flynn, 1986). It is believed that individual infection events lead to episomes which differ in their number of repeat of terminal repetitive region; i.e. episomes within a single cell show the same number of repeats. Thus, analysis of the terminal repetitive region by Southern blot hybridization can provide evidence regarding the clonality of the viral genome (Raab and Flynn, 1986).

In the latent forms of infection, the virus is replicated once per cell cycle as an episome using the viral oriP replication origin, the viral EBNA1 protein, the host cell

DNA polymerase (Kieff and Rickinson, 2001). The latent infection of EBV is characterized by the expression of a limited set of viral genes, the so-called latent genes, including two types of non-translated RNA (EBV-encoded nuclear RNAs; EBER1, EBER2), six EBV-encoded nuclear agents (EBNA1, 2, 3A, 3B, 3C, LP), three latent membrane proteins (LMP1, 2A, 2B), among the nearly 100 viral genes that are expressed during replication infection of EBV (Kieff and Rickinson, 2001). The vast majority of EBV infected tumor cells contain one of the three types of latent EBV infection and expression of the latent EBV gene products is sufficient for immortalization of B cells in vitro (Kieff and Rickinson, 2001). LMP1 is considered to be the major EBV oncogene, although several additional latent viral proteins are also required for EBV immortalization of B cells in vitro (Kieff and Rickinson, 2001). Unfortunately, drugs that specifically inhibit the latent form of EBV infection are not currently available. The role of EBV in causing malignancies is thought to vary according to different types of viral latency and associated histologic type. BL that contains EBV represent type I latency, in which viral gene expression is limited to the EBNA1 protein and untranslated viral transcripts (EBERs). Viral gene expression in tumors with type II latency, as seen in nasopharyngeal carcinoma and EBV-associated HD, is restricted to EBNA1, LMP1, LMP2, BARF0. At the other extreme, type III latency, typified by EBV-transformed lymphoblastoid B cell lines (LCLs) in vitro and EBV-positive diffuse immunoblastic lymphomas, in vivo, is associated with expression of all nine latency associated proteins, including EBNA1 as well as a variety of different EBV proteins (in particular, LMP1 and EBNA2) required for EBV transformation of B cells (Kieff and Rickinson, 2001).

In EBVGC, it has been established that the viral gene expression is restricted to latency I genes quite similar to BL, such as EBV-encoded small RNA 1 (EBNA1), EBV-encoded RNA (EBER), BARF0, BARF1, latent membrane protein 2A (LMP2A) (zur et al, 2000). The presence of EBER also has been demonstrated in malignant gastric epithelial cells by in situ hybridization (ISH) (Imai et al, 1994).

EBV preferentially infects B-lymphocytes through the binding of the major viral envelope glycoprotein gp350 to the CD21 receptor on the surface of B cells (Nemerow et al, 1987), through the binding of a second glycoprotein, gp42, to human leukocyte antigen (HLA) class II molecules as a co-receptor (Borza and Hutt-Fletcher, 2002). Infection of other cell types, principally epithelial cells, is much less efficient and occurs through separate, as yet poorly defined, pathways (Borza and Hutt-Fletcher, 2002). The presence of EBV in epithelial cells and B-lymphocytes provokes an intense immune response consisting of antibodies to a large variety of viral antigens. In people with normal immune response, cells expressing EBNAs and LMPs engender EBV-specific, HLA class I restricted, $CD8^+$ cytotoxic T lymphocytes responses (Kieff and Rickinson, 2001). Other defense mechanisms include neutralizing antibodies, cytokines such as interferons, natural killer cells and antibody-dependent-mediated cytotoxicity (Tang et al, 1993; Kieff and Rickinson, 2001). The EBNAs in particular, except for EBNA1, have multiple epitopes that are recognized in the context of common class I determinants. The EBNAs and LMP1 also induce the expression of adhesion molecules, rendering the cell susceptible to T lymphocytes adherence and cytocidal effects. As a consequence of immune responses by normal people to primary EBV infection, the number of proliferating virus-infected B-lymphocytes in the peripheral blood rapidly declines to a level of one infected B lymphocyte in $10^5$ or $10^6$. However, cytotoxic T lymphocytes specific for epitopes from five of the EBNAs and the two LMPs persist forever, indicating that cells expressing the EBNAs and LMPs are at least intermittently present in the normal host (Kieff and Rickinson, 2001).

Many reports have indicated that there are defects in the HLA class I-associated antigen processing and presentation pathway in EBV-associated BL, nasal natural killer (NK) cell/T-cell carcinoma (Frisan et al, 1996; Shen et al, 2001) and EBVGC (Dutta et al, 2006). Furthermore, there is evidence of the interference of certain viral antigens in the locus-specific and functional expression of HLA class I antigens in various malignancies (Fruh et al, 1999; Tortorella et al 2000). The triggering of specific cytotoxic T-lymphocyte (CTL) response (largely CD8-positive) is dependent on the appropriate presentation of viral or tumor-specific antigens in the context of proper HLA class Ia molecules, giving rise to the first step of immune defence (Hicklin et al, 1999). HLA class Ia molecules that are expressed on the surface of nearly all nucleated cells are composed of a polymorphic transmembrane heavy chain and a monomorphic light chain called $\beta_2$ microglobulin ($\beta_2$m). The heavy-chain polypeptides are encoded by 3 closely linked loci, HLA-A, HLA-B, HLA-C. Many alleles are assigned to a particular locus (York and Rock, 1996). Immunohistochemical (IHC) studies in different types of solid tumors have demonstrated defects in HLA class Ia expression (Natali et al, 1989). Moreover, selective down-regulation of the HLA class I A or B locus also has been observed in GC, colon carcinoma, laryngeal carcinoma (Momberg et al, 1989; Lopez et al, 1989). Several other molecules, such as transporter associated with antigen presentation and LMP, have been associated with HLA class Ia antigen presentation (Pamer and Cresswell, 1998). It is noteworthy that malignant cells can escape CTL-mediated immune response by down-regulating HLA class Ia expression; however, then, they may become susceptible to NK cell-mediated lysis (Garrido et al, 1997).

A number of reports have suggested that the expression of insulin-like growth factor 1 (IGF1) and IGF2, which function as autocrine/paracrine growth factors, are potent stimuli for tumor cells of varied origin (Macaulay, 1992). The biologic responses of IGF1 and IGF2 are transmitted through the IGF1 receptor (IGF1R), which is a tyrosine kinase transmembrane receptor with expression that has been observed in several types of tumors (Kaleko et al, 1990). It has been reported that the IGF2 and IGF1R genes are overexpressed in GC (Pavelic et al, 2003). Moreover, increased levels of IGF1 in

primary tissue from EBVGC also have been reported using PCR (Iwakiri et al, 2003). EBV-harboring NK cell/T-cell lymphoma, BL, HD, NPC may suppress local immune response to the infiltrating T cell by up-regulating cytokines and cellular growth factors, such as IGF1 (Herbst et al, 1996; Fujieda et al, 1999; Kitagawa et al, 2000; Shen et al, 2001; Iwakiri et al, 2003; Iwakiri et al, 2005). It is noteworthy that IGF1 has been implicated in the modulation of HLA class Ia expression and in the inhibition of apoptosis in glioma cells (Ly et al, 2000).

One possible explanation for the viral-induced, locus-specific down-regulation of HLA class I genes is the interaction of viral LMP2 and cellular nuclear factor κB (NF-κB). In one study, viral LMP2A expression was observed in some EBVGC samples, although the expression level was considerably low compared with LMP2A expression in the positive control Raji cells (Dutta et al, 2006). The κB motif of enhancer A element of the HLA class I gene is the binding site of NF-κβ/Rel family transcription factors and is highly conserved and present only in HLA-A and HLA-B gene promoters (Le, 1994). However, because of the lack of NF-κβ binding sites on other HLA class I gene promoters, such as HLA-C, HLA-E, HLA-F, they are not regulated by NF-κβ (Gobin et al, 1998). Recently, it was demonstrated that EBV-encoded LMP2A expressed in NPC and GC cell lines down-regulated cellular NF-κβ (Stewart et al, 2004). Analogous to other malignancies, aberrant methylation of HLA class Ia gene promoters may lead to the loss of expression (Nie et al, 2001). Of course, it would be interesting to investigate whether EBV modulates the methylation of HLA genes, as reported for other cellular genes (Kang et al, 2002). Because of the observation that the majority of CTLs recognize peptides presented by HLA-A and HLA-B, whereas cells are protected from NK cell cytotoxicity by HLA-E and HLA-C expression (Littaua et al, 1991; Lee et al, 1998; Yokoyama, 1998), it is necessary to have prior knowledge about locus-specific gene/protein expression to produce a rational immunotherapeutic design.

EBV encodes a unique gene product, BCRF1, that has high amino acid identity with human IL-10 (Moore et al, 1990). Like human IL-10, vIL-10 inhibits the synthesis of IFN-γ by lymphocytes and NK cells and suppresses IFN-γ-mediated cellular events such as the up-regulation of the HLA class I expression and CTL responses. The EBV BARF1 protein functions as a soluble receptor for colony-stimulating factor (CSF)-1. Since CSF-1 normally enhances the expression of IFN-α by monocytes, BARF1 protein may function as a decoy receptor to block the activation of the cytokine (Cohen and Lekstrom, 1999). EBNA1 has been shown to block its own degradation by proteosomes in infected cells (Leviskaya et al, 1997). Since viral proteins are normally broken down by proteosomes to peptides for presentation to CTL, the ability of EBNA1 to inhibit its degradation may allow the protein to avoid triggering the activation of CTL. Also, EBV can modulate the ubiquitin-proteasome system to manipulate the host immune response, promote viral replication and inhibit apoptosis (Masucci, 2004). The release of virokines and the down-regulation of cell adhesion molecules are additional strategies for EBV-infected cells to evade the host immune system.

## V. Environmental factors

Some studies have shown environmental factors may be related to EBVGC. EBVGC is thought to be related to lifestyle, dietary habits and occupational exposure of wood dust, iron filing and tar (Yoshiwara et al, 2005; Koriyama et al, 2005). Although the prevalence of cigarette smoking in EBVGC cases was higher than among non-EBVGC cases, the difference was not statistically significant (Koriyama et al, 2005). Frequent drinking of coffee and high-temperature drinks, as well as frequent intake of salty and spicy foods, were more prevalent among EBVGC cases, but only frequent intake of salty food showed a significant difference between EBVGC and non-EBVGC cases. In addition, patients with EBVGC tended to be exposed to wood dust and/or iron filings and tar (Koriyama et al, 2005). Gastric remnant cancer after a partial gastrectomy for benign gastric disease also shows a statistically higher EBV infection rate than in conventional gastric carcinomas (Yamamoto et al, 1994; Chang et al, 2000). These findings suggest an association between mechanical injuries to the stomach membrane and the high frequency of EBVGC.

## VI. EBV-targeted therapy

Persistent expression of certain EBV-encoded gene products is likely required for the continued growth of many, if not all, EBV-associated lymphomas. Therefore, EBV-based strategies for treating cancer include prevention of viral oncogene expression, inducing loss of the EBV episome, the purposeful induction of the lytic form of EBV infection, enhancing the host immune response to virally encoded antigens (Israel and Kenney, 2003). Although, currently, EBV-targeted therapies are not made a trial in EBVGCs, some studies tried EBV-targeted therapy in EBV-positive gastric carcinoma cell line in vitro (Feng et al, 2002). EBV-based therapies are currently being developed for the treatment of EBV-positive malignancies. Therefore, the knowledge of this therapy will be useful in the treatment of EBVGC.

### A. Loss of the EBV episome

Chronic, low-dose hydroxyurea treatment can induce loss of viral episomes in some BLs and LCLs, although the mechanism of loss is not yet clearly defined (Chodosh et al, 1998). Another technique for episomal targeting is suggested by the observation that the cellular genome contains numerous sites for origin of replication complexes (ORCs) to regulate initiation of DNA synthesis, while EBV episomes are thought to contain only one major ORC. Thus, drugs that inhibit various aspects of ORC formation may eventually prove useful for inducing loss of the EBV episome in tumor cells (Dhar et al, 2001).

### B. Purposeful induction of the lytic EBV infection

The switch from the latent to lytic form of EBV infection is mediated by the two viral immediate-early (IE)

proteins, BZLF1 and BRLF1. The BZLF1 and BRLF1 gene products encode transcription factors that together activate the entire lytic viral cascade of gene expression, ultimately resulting in the production of infectious viral particles (Gutierrez et al, 1996). In vivo, it is thus likely EBV tends to stay in the latent form of infection in quiescent B cells, switches to the lytic form of infection in highly activated B cells. The latent EBV gene product, LMP-2, is thought to play an important role in helping to maintain viral latency in B cells by suppressing the signal transduction cascades which are normally induced by B-cell activation (Miller et al, 1995). Epigenetic factors also play an important role in regulating the state of EBV infection in host cells. In cells containing tightly latent EBV infection, the viral IE promoter DNA is often methylated (Falk and Ernberg, 1999) and the chromatin surrounding the IE promoters is in the unacetylated (inactive) form (Gruffat et al, 2002). Treatment of certain Burkitt's cell lines in vitro with agents that induce histone acetylation (Westphal, et al, 2000), or reverse DNA methylation (Ben and Klein, 1981) is sufficient to induce the lytic form of EBV infection in a subset of cells, although such agents are generally not very effective in inducing lytic EBV infection in EBV-immortalized lymphoblastoid cell lines (Westphal, et al, 2000).

### C. Inhibition of EBV transforming properties

Theoretically, inhibiting one or more of the EBV proteins known to be required for transformation of B cells in vitro (including LMP1, EBNA2, EBNA3a and EBNA3c) might reverse the oncogenic phenotype of at least some EBV-associated tumors. For example, antisense RNA directed against LMP1 decreased the expression not only of LMP1 in EBV-positive LCLs, but also cellular proteins induced by LMP1, such as the antiapoptotic proteins Bcl-2 (Kenney et al, 1998). Furthermore, LMP1-antisense RNA resulted in decreased LCL proliferation, increased apoptosis, increased sensitivity to the cytotoxic drug etoposide (Kenney et al, 1998). Recently, highly effective selective gene inhibition has been achieved with small interfering RNA (RNAi) technology, in which the expression of short (15-20 bp) double-stranded RNA sequences homologous to the gene of interest results in degradation of the target mRNA. This approach has been used successfully to modulate viral expression in vitro of HIV (Coburn and Cullen, 2002), papillomavirus (Jiang and Milner, 2002), poliovirus (Gitlin et al, 2002) model systems.

Downstream effects of LMP1 are mediated in part through activation of NF-kβ (Cahir et al, 2000), inhibition of NF-kβ function using an inducible dominant repressor has been shown to result in spontaneous apoptosis of LCLs (Cahir et al, 2000).

### D. Enhancing the host immune response to viral proteins

EBV proteins expressed in EBV-associated malignancies provide targets for the adoptive immunotherapy with antigen-specific CTL. EBV-specific CTL have been used successfully for the prophylaxis and treatment of EBV-lymphoproliferative disease post hematopoietic stem cell transplantation (Rooney et al, 1995, 1998). EBNA2, EBNA3a, 3b, and 3c and to a lesser extent LMP2, contain the immunodominant epitopes for latent EBV proteins in normal CTL responses (Murray et al, 1992). Post-transplant-type lymphomas, which typically contain type III latency gene expression, express the full complement of latent virus protein immunodominant epitopes for the host CTL response.

The clinical results with EBV-specific CTL therapy for type II latency tumors such as NPC and EBV-associated HD were less effective than for post-transplant lymphomas (Aisenberg, 1999; Chua et al, 2001). Decreased CTL efficacy most likely reflects immune evasion strategies by tumor cells such as down regulation of immunodominant EBV proteins and secretion of inhibitory cytokines (Poppema et al, 1998). To overcome these immune evasion strategies a number of approaches have been developed including targeting CTL to subdominant EBV antigens and genetically modifying CTL to increase their potency (Gahn et al, 2001; Duraiswamy et al, 2003, 2004; Gottschalk et al, 2003; Bollard et al, 2004; Comoli et al, 2004; Lucas et al, 2004; Straathof et al, 2005).

Burkitt's lymphoma cells evade the immune system by down regulating the expression of cell adhesion molecules, MHC class I molecules and EBV latency antigens and thus the prospect for the development of an EBV-specific immunotherapy is problematic. The only EBV antigen expressed in Burkitt's lymphoma, EBNA1, is inefficiently processed for HLA class I presentation due to an internal glycine-alanine repeat region and so far only few endogenously processed HLA class I restricted peptides have been identified that are recognized by CD8 positive T cells (Lee et al, 2004; Voo et al, 2004). Several MHC class II restricted peptides from EBNA1 have been identified, which are recognized by CD4 positive T cells and the potential use of these cells for the adoptive immunotherapy of Burkitt's lymphoma is being actively explored (Paludan et al, 2002; Munz, 2004).

## VII. Conclusion

EBVGC is a unique type of gastric carcinoma that is tagged by clonal EBV. Further studies about EBV pathogenesis, viral gene regulation, immunologic aspect and environmental factors in EBVGC are needed. Finally, additional EBV-targeted therapy of EBVGC and EBVGC prevention program will be developed.

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