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Abstract

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Review

Immune escape by Epstein–Barr virus associated malignancies

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ABSTRACT

Persistent Epstein–Barr virus (EBV) infection remains asymptomatic in the majority of virus carriers, despite the potent growth transforming potential of this virus. The increased frequency of EBV associated B cell lymphomas in immune compromised individuals suggests that tumor-free chronic infection with this virus is in part due to immune control. Here we discuss the evidence that loss of selective components of EBV specific immunity might contribute to EBV associated malignancies, like nasopharyngeal carcinoma, Burkitt’s and Hodgkin’s lymphoma, in otherwise immune competent patients. Furthermore, we discuss how current vaccine approaches against EBV might be able to target these selective deficiencies.

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1. Immune escape mechanisms of latent EBV infection

Epstein–Barr virus (EBV) is a ubiquitous γ1–Herpesvirus that infects more than 90% of the human adult population. The virus establishes persistent infection through its latency in B cells, from which it continuously reactivates lytic replication to produce infectious viral particles for transmission. While it expresses more than 80 lytic antigens, latently infected cells express up to 8 proteins and several non-translated RNAs [1]. The non-translated RNAs are the BamHI A rightward transcripts (BARTs), which are thought to give rise to EBV encoded microRNAs [2], and the EBV-encoded RNAs (EBERs), which have been suggested to protect EBV infected cells from apoptosis [2]. Of the six latent EBV proteins, six are nuclear antigens (EBNA1, 2, 3A, 3B, 3C, LP) and two are membrane proteins (LMP1 and 2). This limited antigen expression is probably one of the essential immune escape mechanisms of latent EBV infection, while EBV expresses more than 80 antigens during lytic replication. In addition to reduced viral protein expression, the virus performs some latency functions with non-translated RNAs which cannot be detected by T cells looking for small peptides presented on MHC class I and II molecules. EBV reduces antigenic protein expression further, dependent on the differentiation stage of the latently infected B cell [4]. While all eight latent EBV antigens can be found in naïve B cells in tonsils, the primary site of EBV infection after...
transmission in saliva, germinal center B cells express only EBNA1, LMP1 and LMP2 (Fig. 1) [5]. Furthermore, infected peripheral blood memory B cells express no EBV antigens or EBNA1 during homeostatic proliferation [6]. Therefore, memory B cells, harboring the EBV genome without any EBV protein expression, are probably the site of long-term EBV persistence [7], and invisible to the immune system.

In addition to the reduced number of viral protein expression during latent infection, the copy number of the expressed EBV antigens and of the antigenic peptides processing for MHC presentation from these is also kept very low. EBNA1 prevents efficient translation by limiting the expressed viral protein number to one peptide per cell [11]. All this evidence suggests that EBV down-regulates detection by limiting the expressed viral protein number as well as the copy number per viral protein as main immune escape mechanisms during latent infection.

Despite the sophistication of the antigen down-regulation during latent EBV infection, every infected individual develops T and B cell responses to the latent EBV antigens, and these are thought to keep persistent EBV infection in check and avoid EBV associated malignancies in most persistently infected individuals. In the following we will however discuss environmental circumstances, like coinfections, and changes in the tumor microenvironment, that favor the development of EBV associated malignancies. A good understanding of these changes is obviously instrumental to develop specific treatments of these EBV associated tumors and to determine possible cancer prevention strategies.

2. Manipulation of EBV specific immune control by coinfections

2.1. HIV associated lymphomas

One environmental trigger for the emergence of EBV associated malignancies is the coinfection with the human immunodeficiency virus (HIV). Since HIV infection causes progressive immune suppression, leading to the acquired immunodeficiency syndrome (AIDS), different EBV associated lymphomas develop at different stages of HIV infection [12]. Primarily HIV coinfection promotes the development of EBV associated non-Hodgkin’s lymphomas of three types. Firstly, immunoblastic or diffuse large cell lymphomas develop after considerable immunosuppression by HIV, and also give rise to the central nervous system (CNS) lymphomas in AIDS patients [13]. These lymphomas carry all latent EBV antigens and are therefore probably comparable to post-transplant lymphoproliferative disease (PTLD), in that quite extensive immunosuppression allows for the escape of EBV from nearly all EBV latent antigen specific immune control mechanisms, and proliferation of B cells via the most aggressive EBV latency program (Fig. 1). Secondly, EBV joins forces with another human γ-herpesvirus, Kaposi’s sarcoma herpesvirus (KSHV) in the development of primary effusion lymphoma (PEL), which is frequently coinfected by both herpesviruses [14]. While PEL is a rare tumor in immunocompetent individuals it arises with increased incidence rates in HIV infected patients. Interestingly, PEL expresses EBNA1 as the only EBV protein, but gains resistance against apoptosis most likely via the expression of this protein as well as non-translated EBV RNAs [15,16]. In addition, KSHV contributes to PEL proliferation probably through upregulation of the cellular oncogene c-myc [17]. Thirdly, EBV associated small noncleaved lymphomas also develop in HIV infected individuals, and within this category 30–40% of AIDS associated Burkitt’s lymphomas are EBV positive [18]. While c-myc is deregulated in PEL by KSHV infection, it is translocated into one of the immunoglobulin loci in Burkitt’s lymphoma and stimulates proliferation of Burkitt’s lymphoma cells in this way [19]. In addition, most EBV associated Burkitt’s lymphomas express the same EBV latency program as PELs (Fig. 1), contributing to apoptosis resistance of these tumors [15]. The later two categories of AIDS associated EBV positive lymphomas, PEL and Burkitt’s lymphoma, develop earlier after HIV infection with Burkitt’s lymphoma being often one of the earliest manifestations of AIDS [18].

Accordingly, two independent studies have found that selective loss of EBV specific CD4+ T cell responses correlates with the development of EBV associated non-Hodgkin’s lymphomas in HIV infected individuals [20,21]. Piriou and colleagues even described that CD4+ and CD8+ T cell responses against EBNA1, the only EBV protein expressed in Burkitt’s lymphoma and PEL, were severely compromised in HIV infected individuals that developed AIDS associated EBV positive lymphomas, while T cell responses against the immediate early lytic EBV antigen BZLF1 were maintained in these patients [20]. This indicated that the selective loss of one particular immune response against EBV predisposes AIDS patients for EBV associated lymphomas. In another study, it was noted that HIV patients who developed EBV associated primary CNS lymphomas had lost EBV specific IFN-γ responses by CD4+ T cells despite maintaining healthy absolute CD4+ T cell counts [21], again arguing that a selective loss of EBV specific CD4+ T cell immune control predisposes for the development of EBV associated lymphomas in AIDS patients. EBV specific CD4+ T cells might be especially important to prevent AIDS associated PEL and Burkitt’s lymphoma since EBNA1, the only EBV protein expressed in these tumors, inhibits its processing onto MHC class I [22], but is recognized by CD4+ T cells...
after intracellular processing via macroautophagy [23,24]. Therefore, EBNA1 specific CD4+ T cells are capable to recognize Burkitt’s lymphoma cells [25,26], even so this tumor down-regulates antigen processing towards MHC class I presentation via c-myc overexpression, and therefore escapes CD8+ T cell immune surveillance [27,28,26,29,30]. These studies suggest that already early during HIV infection, when absolute CD4+ T cell counts are still maintained at normal levels, selective EBV specific CD4+ T cell responses, primarily directed against EBNA1, get depleted, and susceptibility to EBV associated lymphomas, particularly PEL and Burkitt’s lymphoma increases. One could even speculate that antigen persistence due to EBV latency activates these EBV specific CD4+ T cell preferentially, and makes them vulnerable to HIV infection. Irrespective of the mechanism, this preferential depletion of EBV specific immune control might lead to EBV associated lymphomas in AIDS patients.

2.2. Endemic Burkitt’s lymphoma

In addition to HIV infection, EBV associated malignancies are also associated with malaria. Indeed, the tumor, in which EBV was originally visualized is the most common childhood tumor in Sub-Saharan Africa and occurs mainly in holoendemic malaria regions of Africa and Papua New Guinea, where individuals are repeatedly infected with *Plasmodium falciparum*. This B cell lymphoma, endemic in Africa, is nearly 100% EBV associated [31,32]. Similar, to HIV associated Burkitt’s lymphoma, endemic Burkitt’s lymphoma is characterized by c-myc translocation into one of the immunoglobulin loci and expresses EBNA1 as the only EBV protein together with non-translated viral RNAs [33].

Despite its discovery 50 years ago the etiology of Burkitt’s lymphoma is still unclear. Two alternative though not mutually exclusive explanations for a role of malaria in Burkitt’s lymphogenesis are discussed. One is that *P. falciparum* stimulates the B cell compartment, resulting eventually in a c-myc translocation in an EBV infected B cell as a side effect of somatic hypermutation of activated B cells in the germinal center reaction (Fig. 1). The alternate explanation is that malaria infection compromises EBV specific immune control, leading to immune escape of an EBV infected B cell including those in which a c-myc translocation has occurred. Evidence for stimulation of the EBV infected B cell compartment has indeed been found in children from endemic malaria regions. EBV reactivates from this reservoir probably after B cell receptor stimulation and lytic EBV replication is primarily found in plasmablast cells [34]. Accordingly, circulating EBV was detected in malaria infected children [35–37], and elevated antibody titers against lytic EBV antigens are associated with endemic Burkitt’s lymphoma [38].

Two main B cell activation pathways have been suggested that potentially give rise to c-myc translocation in EBV infected B cells. Firstly, *P. falciparum* antigens, like the merozoite surface proteins [39], trigger B cell responses, and it has been shown that activation induced cytidine deaminase (AID) expression in germinal centers, to which activated B cells home, is required for c-myc translocation and lymphoma development [40–42]. In addition to malaria antigen induced B cell activation for AID upregulation, EBV LMP1 mediated B cell activation has also been described to upregulate AID [43]. Secondly, the *P. falciparum* erythrocyte membran protein 1 (PfEMP1) is a polyclonal B cell activator and has been shown to trigger lytic EBV replication in infected B cells [44]. Other pathogen patterns for B cell activation like toll-like receptor (TLR) ligands have been identified in malaria [45], but how this may increase the risk of EBV associated lymphomas has yet to be explored. Therefore, malaria might have the means to directly activate EBV infected B cells to develop into Burkitt’s lymphoma.

In addition, however, these cells might need to escape EBV specific immune control. Indeed, T cell mediated immune control of EBV infected B cells was found to be compromised in malaria infected individuals [46]. Especially in children, in which both malaria and EBV specific immune control need to develop simultaneously, immune suppressive effects of *P. falciparum* might impair the efficient establishment of cell-mediated EBV specific immune control. Accordingly, higher EBV loads, indicative of diminished EBV specific immune control, have been detected in children of holoendemic malaria regions [36]. *P. falciparum* mediated immune suppression could originate from its ability to inhibit early IFN-γ production via PFEMP1 mediated inhibition [47], and the ability of large numbers of *Plasmodium* infected erythrocytes to inhibit immune responses by dendritic cells (DCs) [48]. Whatever the mechanism, impaired EBV specific immune control might contribute to Burkitt’s lymphoma development in children of holoendemic malaria regions. In characterizing specific deficiencies, a lower percentage of 5–9 year old children in holoendemic malaria regions recognized dominant CD8+ T cell epitopes from EBV than children from a neighboring region with sporadic malaria transmission [49]. However, in the responding children the magnitude of EBV specific CD8+ T cell was not significantly different from age matched controls. In contrast to this rather mild deregulation of EBV specific CD8+ T cell control, T cell responses against EBNA1, the only EBV protein expressed in the majority of Burkitt’s lymphomas, were significantly decreased in nearly all children with Burkitt’s lymphoma, while CD4+ T cell responses against malaria antigens and CD8+ T cell responses against other EBV antigens were intact [93]. These results suggest that selective deficiencies in EBV specific immune control assist in the development of Burkitt’s lymphoma, while *P. falciparum* mediated activation of the B cell system generate a higher frequency of Burkitt’s lymphoma precursor cells.

In addition, to these EBV associated malignancies arising in the presence of immune compromising coinfection, some EBV associated tumors seem to condition their microenvironment to induce local or even selective systemic immunosuppression for their growth in otherwise immunocompetent individuals. The two best characterized examples are EBV associated Hodgkin’s lymphoma and nasopharyngeal carcinoma (NPC), which we will discuss next.

3. Tumor microenvironments conditioned by EBV positive tumors

3.1. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is a frequent epithelial cell cancer with a high incidence rate in Southeast China, especially the Guangdong province and neighboring Hong Kong [50]. Since epithelial infection by EBV can be demonstrated in vitro [51], but has not been convincingly documented in vivo, the etiology of this tumor is still quite mysterious. However, it has been clearly documented that EBV is present in 100% of NPCs, and establishes a latency pattern with EBNA1 and LMP1 or LMP2 protein expression [52]. Early after the discovery of EBV association with NPC a deregulation of the EBV specific immune response with elevated IgA titers against the virus was noted [53]. This indicated that the immune response at the site of tumor development was changed, and that the tumor might condition its microenvironment to facilitate growth. Indeed recent studies support the notion that local immune suppression rather that systemic deficiency in EBV specific immune control might contribute to NPC development [54,55]. In these studies, EBV specific CD4+ and CD8+ T cell responses could be reactivated from peripheral blood of NPC patients [54,55]. Even though LMP1 and LMP2
specific CD8+ T cells were enriched in tumor infiltrating lymphocytes, their cytotoxicity and cytokine secretion was impaired [55]. This impairment could be due to the presence of CD4+CD25+FoxP3+ natural regulatory T cells in the tumor tissue, which could suppress EBV specific immune responses against NPC even after correct homing of effector T cells [56,55].

In addition to active T cell suppression at the tumor site, the efficiency with which NPC can present antigens to T cells might also be compromised. While earlier studies based on a limited number of NPC cell lines suggested that antigen processing for MHC class I presentation was intact in NPC cells [57,58], a more recent study on primary tumor tissues suggested that the MHC class I antigen processing machinery is down-regulated in the majority of tumors [59]. Even though no functional deficiency of MHC class I antigen presentation could be tested in this later study, it makes it possible to speculate that in addition to active immune suppression at NPC tumor sites the recognition of tumor cells by CD8+ T cells is also impaired. Together these data suggest that NPC impairs EBV specific immune control locally, while allowing efficient systemic immune responses against this virus.

3.2. Hodgkin’s lymphoma

Hodgkin’s lymphoma is the most common EBV associated lymphoma in the US and Europe. Around 40% of Hodgkin’s lymphomas are EBV associated [14]. Interestingly only a small subset of cells, the so-called Hodgkin–Reed-Sternberg (HRS) cells, are the EBV transformed tumor cells, primarily of B cell origin, in the tumor tissue [60]. HRS cells harbor the restricted EBV antigen expression pattern found in germinal center B cells of healthy EBV carriers (Fig. 1) [61]. The majority of cells in the tumor tissue are infiltrating lymphocytes. This indicates that Hodgkin’s lymphoma has already managed to generate an immunosuppressive environment that allows the tumor cells to grow despite extensive homing of immune cells to the tumor site. A number of immune escape mechanisms have been proposed and those can be subdivided into immunosuppressive functions of the HRS cells themselves and of the infiltrating lymphocytes. HRS cells have been shown to produce immunosuppressive cytokines like IL-10, IL-13 and TGF-β [62–64]. IL-13 has been demonstrated to enhance HRS cell proliferation in an autocrine fashion in addition to its immune suppressive functions, which probably are primarily mediated through the induction of IL-10 producing Th2 polarized cells [63,65]. In addition to immunosuppressive cytokine production by HRS cells, galectin-1 secretion could also contribute to immune escape in Hodgkin’s lymphoma [66]. Elevated galectin-1 levels have been reported in tumor biopsies and recombinant galectin-1 has been shown to inhibit EBV specific T cell proliferation and cytokine secretion. Therefore, HRS cells employ several mechanisms, which are able to immune suppress their microenvironment.

As a result of this, regulatory T (Treg) cell populations seem to be enriched in Hodgkin’s lymphoma tissues. Several regulatory CD4+ T cell populations have been described in Hodgkin’s lymphoma. Among the CD4+ Treg cells are IL-10 producing Tr1 cells and CD4+CD25+ natural Treg cells [67]. These have been shown to suppress peripheral blood cell proliferation and cytokine secretion in an IL-10 and cell contact dependent fashion. In addition, LAG-3 positive CD4+ T cells have been recently described to be selectively enriched in EBV positive Hodgkin’s lymphoma biopsies [68]. They seem to be induced by soluble factors secreted by HRS cells and suppress LMP specific T cell responses. Therefore, regulatory T cell populations may suppress EBV specific immune control locally, and this involves cell-contact as well as the immunosuppressive cytokines IL-10 and TGF-β [64].

In addition, to this local immune suppression, however, selective systemic impairment of EBV specific T cell responses might also contribute to Hodgkin’s lymphoma development. Along these lines, Hodgkin’s lymphoma patients have diminished EBNA1 specific CD4+ T cell responses, while they maintain CD8+ T cell responses against other latent and lytic EBV antigens [94]. These findings suggest that immunotherapeutic approaches should be developed to correct the selective systemic and tumor microenvironment specific deficiencies in EBV specific immune control. Since the tumor cells do not seem to have defects in antigen processing for MHC class I presentation [69,70], interventions to correct the selective systemic loss of EBV specific T cell responses and to overcome the local immune suppression in the tumor tissue should be explored as treatments of this EBV associated malignancy and ideally such modalities could be used for prevention in high risk populations.

4. Vaccine approaches against EBV associated malignancies

Recent evidence suggests that suboptimal initial immune control of EBV, as evidenced by symptomatic seroconversion, predisposes for the development of EBV associated disease. Along these lines, the risk of developing Hodgkin’s lymphoma is fourfold higher with a median incubation time of 4 years after resolution of infectious mononucleosis (IM), which is symptomatic primary EBV infection with high viral titers and therefore massively expanded, primarily EBV specific T cells [71]. Therefore, preventive vaccination to avoid uncontrolled virus replication and successive “scarring” of the immune system [72], could decrease the incidence of EBV associated malignancies. For the prevention of IM, vaccines to induce neutralizing antibodies and T cell responses are under development. For the stimulation of EBV specific humoral immune control, recombinant gp350, the major EBV surface glycoprotein, has been tested. It was able to elicit neutralizing antibodies in a phase I/I trial [73], but the vaccine’s efficacy in preventing IM remains unclear. Alternatively, a single CD8+ T cell epitope vaccine has been tested to elicit protective immunity against IM [74]. While it was successful in eliciting peptide specific T cell responses in a phase I clinical trial, the number of vaccinated individuals was too low to allow conclusions about its efficacy. In addition to these preventive vaccines, therapeutic immunizations against EBV associated malignancies are also being pursued.

The most successful of these is passive immunization by adoptive transfer of EBV specific T cells. This approach was developed from the observation that donor leucocyte infusions could be used to treat PTLD [75]. It was further refined by expanding EBV specific T cells from seropositive donors in co-cultures with irradiated autologous EBV transformed B cells (LCs) and injecting these enriched cultures into PTLD patients [76]. This therapy is to date the most commonly practiced passive immunotherapy involving T cells. Unfortunately, expanding this success story to NPC, Hodgkin’s and Burkitt’s lymphoma has proven difficult, in part due to the fact that LCL stimulation will primarily expand immunodominant T cell responses, specific for the latent EBNA3 antigens, which are not expressed in these tumors. In focusing in vitro T cell expansions to the EBNA1, LMP1 and LMP2 antigens, which are present in these malignancies, recombinant viruses encoding for these EBV products have been utilized to expand specific CD8+ T cells, which could protect against LMP positive tumor growth in mice in vivo [77–79]. However, these T cell lines, targeting a select subset of EBV antigens, are just now starting to be tested in patients. As an alternative to passive immunization by adoptive T cell transfer EBV antigen loaded DCs have been evaluated for inducing protective CD8+ T cell responses against NPC. Although LMP2 specific CD8+ T cells could be expanded after peptide pulsed DC injection in NPC patients, these responses were too weak or transient to achieve
clinical effects [80]. Thus, vaccine approaches that primarily target CD8+ T cells have not yielded sufficient therapeutic success against EBV associated lymphomas.

Learning from these trials and as a result of a better understanding of the crucial role for CD4+ T cells in assisting CD8+ T cell immunity [81], more recent vaccine formulations aim to incorporate both CD4+ and CD8+ T cell antigens. In addition to CD4+ T cell help for CD8+ T cell responses, CD4+ T cells can also target EBV transformed B cells directly [25,82–84], adding to their value as vaccine targets. As above with CD8+ T cell epitope pulsing, many of these immunization strategies target DCs, which have been shown to be more efficient than LCLs in expanding EBV specific T cells [85] and are capable of priming protective CD4+ and CD8+ T cell responses against EBV transformed B cells in vitro [86]. CD4+ and CD8+ T cells, expanded with DCs, which had been infected with a recombinant adenovirus encoding LMP2, were able to kill NPC cells [87]. Furthermore, recombinant modified vaccinia virus Ankara (MVA) has been used to express a fusion protein between the immunogenic C-terminal domain of EBNA1, a reliable CD4+ T cell target [23,88], and LMP2, which is frequently recognized by CD8+ T cells [89]. DCs infected with this recombinant MVA were able to expand EBNA1 specific CD4+ and LMP2 specific CD8+ T cell from seropositive donors. Finally, EBNA1 can also be directly targeted to DCs via fusion to antibodies that are specific for endocytic receptors on DCs [95]. Hybrid antibodies reactive to the DC receptor DEC-205 and carrying EBNA1 were able to elicit EBV specific CD4+ and CD8+ T cell responses in vitro and in vivo. These approaches open promising avenues to enhance or prime selective protective EBV specific immune responses, whose absence might predispose for the development of EBV associated malignancies or which have been suppressed by the tumor cells itself or their microenvironment.

5. Conclusions

There is now mounting evidence that in addition to growth transforming contributions of both EBV and mutations, EBV associated malignancies in otherwise immune competent individuals escape immune control by either immune compromising coinfection or conditioning of their microenvironment. Since these tumors, like NPC, Hodgkin’s and Burkitt’s lymphoma express only a limited group of EBV antigens, only a select group of the protective EBV specific T cell responses need to be compromised to allow their emergence. The challenge of developing immunotherapies against these EBV associated malignancies lies now in formulating vaccines comprised of relevant CD4+ and CD8+ T cell EBV antigens expressed in these tumors with a potent adjuvant that will elicit protective EBV specific Th1 immunity [90,91] with a strong central memory component [92]. The consensus at the moment seems to be that EBNA1 as a promising CD4+ T cell antigen, should be combined with LMP1 and LMP2 for CD8+ T cell stimulation in such a vaccine for both prevention of symptomatic EBV infection as well as immunotherapy against EBV associated malignancies.

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