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The Epstein-Barr Virus (EBV) in T Cell and NK Cell Lymphomas: Time for a Reassessment

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Abstract

While Epstein-Barr virus (EBV) was initially discovered and characterized as an oncogenic virus in B cell neoplasms, it also plays a complex and multifaceted role in T/NK cell lymphomas. In B cell lymphomas, EBV-encoded proteins have been shown to directly promote immortalization and proliferation through stimulation of the NF-κB pathway and increased expression of anti-apoptotic genes. In the context of mature T/NK lymphomas (MTNKL), with the possible exception on extranodal NK/T cell lymphoma (ENKTL), the virus likely plays a more diverse and nuanced role. EBV has been shown to shape the tumor microenvironment by promoting Th2-skewed T cell responses and by increasing the expression of the immune checkpoint ligand PD-L1. The type of cell infected, the amount of plasma EBV DNA, and the degree of viral lytic replication have all been proposed to have prognostic value in T/NK cell lymphomas. Latency patterns of EBV infection have been defined using EBV-infected B cell models and have not been definitively established in T/NK cell lymphomas. Identifying the expression profile of EBV lytic proteins

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could allow for individualized therapy with the use of antiviral medications. More work needs to be done to determine whether EBV-associated MTNKL have distinct biological and clinical features, which can be leveraged for risk stratification, disease monitoring, and therapeutic purposes.

Keywords

T/NK-cell lymphoma; EBV; Lytic; Latent; Prognosis

Introduction

Mature T/NK cell lymphomas (MTNKL) are a very heterogeneous group of neoplasms characterized by poor response to chemotherapy, aggressive clinical course, and short survival [1]. While advances in genomics are beginning to provide a glimpse of the mutational landscape in MTNKL (reviewed in this issue), the factors responsible for their extraordinary clinical diversity, poor prognosis, and the striking differences in incidence across geographic areas, ethnicities, and age groups remain to be determined. The Epstein-Barr virus (EBV) is a known agent of lymphomagenesis worldwide. While its association with lymphoma is not as high in the USA as in East Asia and Latin America, a conservative estimate is that 10–15 % of the 75–80,000 new malignant lymphomas diagnosed annually in the USA are associated with EBV. Depending on how the association is defined, the prevalence may be as high as 40–50 % in MTNKL. It is perplexing, therefore, that the biological and clinical impact of EBV in MTNKL in the USA has not been more assertively investigated, especially since the presence of the virus in lymphoid malignancies may affect prognosis [2–8], serve as a tumor biomarker [3–5, 7, 8], and be effectively leveraged for treatment with EBV-targeting therapies, using immunotherapy [9] or drugs [10–12].

The failure to systematically study the prevalence and role of EBV across the spectrum of MTNKL is due in great part to a convergence of methodological and conceptual challenges. First, while much is known about how EBV infects and transforms normal mature B cells—the virus' normal reservoir—very little is known about the frequency and mechanisms of infection of normal T cells and NK cells; consequently, preclinical models of EBV-induced T/NK cell transformation are lacking. Second, the absence of overt immune deficiency in most patients with MTNKL does not fit the best understood model of EBV-induced lymphomagenesis, according to which immunosuppression leads to EBV reactivation in latently infected memory B cells, followed by the proliferation and expansion of EBV-positive B cell clones, the accrual of genetic and epigenetic aberrations, and eventually the development of clinically overt lymphoma; thus, risk factors and EBV-associated immune signatures in MTNKL, both systemically (blood) and in the tumor microenvironment, have not been well characterized. Third, the link between distinct types of EBV latency and specific lymphoma entities is based on the life cycle of the virus as defined in normal mature B cells. However, the EBV transcriptional programs that are activated in normal and malignant T cells and NK cells have not been well characterized; consequently, attempts to adapt existing models of EBV latency to MTNKL may or may not be justified. Finally, with the exception of extranodal NK/T cell lymphoma (ENKTL) nasal type, the lineage of the

lymphoid cells (B cells vs. T cells vs. NK cells) that are infected by EBV in MTNKL has not been systematically studied; therefore, it has been difficult to understand if EBV is a primary driver of lymphomagenesis, a co-factor, or simply an innocent bystander. The goals of this review are (1) to provide a brief but comprehensive summary of some of the cellular and molecular aspects of EBV-induced lymphomagenesis and (2) to identify some the fundamental issues that have to be addressed when approaching the question of the role of EBV in MTNKL. Two excellent previous reviews provide additional perspective and depth on this topic [13, 14].

Discovery and Characterization of EBV

EBV is a human *gammaherpersvirus* that was first identified in London in 1964 by a research team led by M. Anthony Epstein. Electron microscopy of cell cultures derived from tumor biopsies of Ugandan children affected by what is now known as Burkitt's lymphoma showed that the malignant cells contained viral particles with typical herpesvirus morphology, providing the first evidence of a tumor-associated virus in humans [15]. Samples of the recently discovered virus were sent to the laboratory of Gertrud and Werner Henle in Philadelphia where the newly named "EB" virus was further characterized and the first serological reagents to detect and study it were developed.

In the summer of 1967, a technician in the Henle laboratory developed a febrile illness with pharyngitis, abnormal peripheral blood lymphocytes, and a positive heterophile antibody test (known as Paul and Bunnel's test) [16], consistent with a diagnosis of infectious mononucleosis (IM), a self-limiting B cell lymphoproliferative disease. When she went back to work, she was found to have developed antibodies against the "EB" virus, providing the first clue that EBV might be the causative agent of IM [17]. Serological studies in a large cohort of Yale college students and in healthy populations later confirmed that EBV is in fact the cause of IM and revealed that EBV has ubiquitous distribution worldwide, including areas endemic for Burkitt's lymphoma, where uniquely high titers of antibodies against the virus were detected [18].

While it was observed early on that EBV-infected cells from IM patients grew spontaneously in vitro, in 1973, Pattengale et al. [19] experimentally proved that EBV can efficiently infect and immortalize quiescent human B cells (but not T cells), producing continuous B cell lymphoblastoid cell lines (LCL), which express many EBV-encoded proteins, display several features of "transformed cells," and after prolonged culture develop an aneuploid karyotype and produce transplantable tumors in mice [20]. LCL could also be easily established when peripheral blood mononuclear cells (PBMC) from EBV-seropositive individuals were cultured in vitro [21]. Later work showed that when EBV "seropositive" PBMC are transplanted into immunosuppressed SCID mice (hu-PBL-SCID), they produce aggressive EBV-positive B cell lymphomas that resemble human post-transplant lymphoproliferative disorders (PTLD) [22], with a frequency that is affected by the cytokine microenvironment [23–25] and by the genetic background of the EBV-seropositive donor [26, 27].

Structure and Function of the EBV Genome

The prototypical EBV strain B95-8, used for most of the initial viral genome characterization efforts, including the first sequencing studies [28], was isolated from a secondary primate cell line obtained by infecting cotton top marmoset lymphocytes with EBV from an IM-derived LCL [29]. Studies of the B95-8 strain revealed that EBV virions have a linear, double-stranded DNA genome measuring approximately 172 kb in length and encoding 80–85 genes [30]. We now know that the B95-8 strain of EBV is atypical of the majority of isolates and is missing an 11.8-kb segment of the genome [31]. Sequencing also revealed that EBV can be classified into two major strains, type 1 (EBV-1) and type 2 (EBV-2), based on genetic differences in the Epstein-Barr nuclear antigen (EBNA) genes [32, 33]. Based on this, the B95-8 strain is a type 1 virus. Recent work, including a large-scale sequencing study of EBV isolates from multiple tumor types and healthy carriers [34], suggests that while the distinction between EBV type 1 and type 2 is accurate and reproducible, the genomic diversity of EBV is greater than previously recognized [35]. The impact that this diversity may have on the oncogenic properties of the virus remains unknown.

After entry into B cells, the linear viral DNA is circularized by ligation of the viral terminal repeats (TR), a process that combines the disjointed coding segments of the EBV-encoded LMP-2A gene into a transcriptionally functional unit and at the same time creates a unique short DNA sequence that can be used to assess the “clonality” of the virus in EBV-infected cells and EBV-associated cancers [36]. The viral genome is then arranged onto nucleosomes and packaged into a complex mini-chromosome structure, called *episome*, by recruitment of cellular proteins, such a histones and chromatin remodeling complexes, which can then be post-translationally modified (acetylation, methylation) by the cell’s epigenetic machinery [37, 38]. Epigenetic modifications of the EBV episome, including methylation and demethylation of specific DNA sequences in the viral genome, are essential in regulating the switch from lytic to latent cycle and vice versa [39, 40]. The chromatin-like architecture and DNA methylation of the EBV genome in latently infected cells explain why histone deacetylase (HDAC) inhibitors and demethylating agents are potent inducers of EBV’s lytic cycle activation in vitro [41] and in vivo [42–44], particularly through their effects on repressive epigenetic marks that decorate the promoter region (Zta) of the EBV immediate early gene BZLF1 (also known as ZEBRA) in latently infected cells [45, 46].

These observations have raised concerns about the potential risk of inducing symptomatic EBV reactivation [42] and secondary EBV-associated malignancies [47] in patients exposed to these drugs. Since three HDAC inhibitors (vorinostat, romidepsin, and belinostat) are FDA approved for the treatment of relapsed or refractory MTNKL [1, 48], the issue of prevalence, latency, and possible drug-induced reactivation of EBV in this patient population deserves to be carefully addressed. At the same time, these observations point the way to novel strategies to sensitize EBV-infected tumor cells to the cytotoxic effect of ganciclovir and other antiviral drugs [49–51]. Finally, the “epigenetic dialogue” [52] initiated by latent EBV proteins that hijack the cell’s epigenetic machinery and cooperatively occupy thousands of enhancer sites on the cell’s genome [53, 54] is not only relevant for the regulation of the latency switch but is now increasingly being scrutinized as

a potentially important mechanism of EBV-induced cell transformation [54–56] and as a novel target of therapy [9]. DNA methylation-induced silencing of tumor suppressor genes [56] and features of CpG island methylator phenotype (CIMP) [57, 58] have been observed in several EBV-associated malignancies.

Natural History of EBV Infection in Normal B Cells

The demonstration that EBV most efficiently infects and transforms resting B cells in vitro, using CD21 and HLA class II as coreceptors [59–61], and the observation that patients with IM have large numbers (on average 1 in 10^4) of circulating EBV-infected B cells established the canonical view of EBV's distinct tropism for B cells and led to the development of valuable models of primary infection, replication, latency, and life-long persistence [62–64]. According to these models, which postulate a dynamic interplay between the virus and the B cell compartment in the immune competent host, during primary infection EBV initially replicates in the epithelium or in B cells of the oropharynx and then, under the selective pressure of an effective cell-mediated immune response, turns off most of its genes and enters a state of latency, with resting memory B cells being the primary reservoir. Average adults carry 1 to 50 EBV-infected B cells per 10^6 B cells [63]. The full spectrum of latent EBV genes expressed during the infection of B cells includes six nuclear antigens (EBNA 1, 2, 3A, 3B, 3C, and leader protein [LP]), three latent membrane proteins (LMP1, 2A, and 2B), two small EBV-encoded RNA's (EBER1 and EBER2), and three clusters of micro-RNAs (miRs).

Transcriptional regulation of the latent EBV genes depends on three EBNA promoters, Wp, Cp, and Qp, and two LMP promoters [64]. The roles of the latent genes in the B cell transformation process are diverse and complex [65, 66]. The best defined latent gene products are EBNA2 and LMP-1. EBNA2 is a key EBV transcriptional activator that in collaboration with EBNA-LP uses the cellular Notch1 co-factor RBPJ to induce the expression of a number of key viral (LMP-1, LMP-2A) and cellular (MYC, CD21, CD23) genes that are essential for B cell immortalization and transformation. LMP-1 is a transmembrane protein which acts as a constitutionally activated CD40L receptor, causing nuclear translocation of activated NF-κB and expression of BCL-2, MCL1, and other anti-apoptotic proteins. The mechanistic roles of the other EBNA proteins and of the non-coding RNAs in viral latency and B cell transformation have not been fully characterized, but reverse genetic studies suggest that, in addition to EBNA2 and LMP-1, EBNA3A, 3C, and LP are each required for LCL growth and survival [67].

Based on patterns of expression in normal B cells, three main EBV latency programs have been described, latency 0–I, II, and III, though variations to this schema have been proposed [68]. Latency III involves the unrestricted expression of all EBNAs, EBERs, and LMPs. Many of these proteins are highly immunogenic and prolonged expression is possible only in conditions of impaired T cell immune surveillance. Latency II is limited to EBNA-1, EBERs, LMP-1, and LMP-2A and LMP-2B. Latency 0–I is the most restricted program observed in resting B cell. Depending on the phase of the cell cycle, EBV-infected B cells may express no EBV gene product at all (latency 0) or only EBNA-1 (latency I), in addition to non-coding RNAs. The activation of these distinct transcriptional programs is linked to

promoter usage, with Wp and Cp driving the expression of latency III and II genes and Qp driving the solitary expression of EBNA1 in latency I [69, 70].

Two models have been proposed for the establishment of life-long latency in mature B cells. The *germinal center model* [62, 71] of EBV persistence proposes that the primary infection occurs in naïve B cells. EBV's latency III (growth) program initially drives B cell proliferation and expansion of the infected pool. A proportion of the EBV transformed B cells then enter the germinal center (GC) and switch to the more limited latency II (default) program, where LMP-1 and LMP-2A provide signals for survival and differentiation into memory B cells, by respectively mimicking CD40L-mediated signaling from helper T cells and BCR activation by antigen. As the memory B cells exit from the GC, EBV's gene expression becomes even more restricted (latency I), to escape immune surveillance. According to the *direct infection model* [63, 72], on the other hand, EBV infects memory rather than naïve, B cells or induces a memory phenotype without requirement for participation in the GC reaction. Both models propose distinct roles for latency I, II, and III in the establishment of long-term latency, including the essential role of EBNA1 expression to ensure the duplication and segregation of viral episomes to daughter cells during homeostatic or antigen-induced memory B cell division.

EBV and B Cell Lymphomas

The characterization of the different gene expression programs activated by EBV during normal B cell infection and long-term latency, together with the recognition of the critical role of the host's immune surveillance in maintaining selective pressure against EBV, provided a helpful conceptual framework to understand how a ubiquitous—and therefore presumably harmless—virus could cause cancer and how EBV transcriptional programs could be differentially expressed in various EBV-associated lymphomas. Thus, lymphomas developing in immune suppressed states, such as HIV infection and after solid organ or hematopoietic stem cell transplantation, typically display a latency III program, whereas lymphomas developing in immune competent patients, such as Hodgkin's lymphoma (HL) and Burkitt lymphoma (BL), display a more restricted gene expression program (latency II or I, respectively). A systematic, large-scale analysis of latency gene expression in EBV-associated lymphomas in immune competent patients, however, has not been conducted and significant inter-and intra-tumoral heterogeneity may exist. Furthermore, it is evident that the EBV latency type in lymphoma depends not only on the immunological status of the host but also on the lineage and differentiation of the infected cells. For example, HL and BL in immunocompromised patients, while more often associated with EBV compared to the same entities in immune competent patients, typically retain a latency II and latency I pattern, respectively, rather than acquiring a more permissive latency III [73–75]. Conversely, EBV-associated large B cell and immunoblastic lymphomas more often express latency III regardless of the immune background of the patient [75–81]. These observations are consistent with the fact that activation of the Wp, Cp, and Qp latency-specific EBV promoters depends primarily on the epigenetic and transcriptional machinery of the infected cell [69, 70].

The distinction of EBV-associated lymphomas according to latency types, as currently defined, however is not always informative of the mechanisms used by EBV to induce tumor development and progression. At this time, the role of EBV as an oncogenic driver is most easily grasped and directly understood in latency III B cell lymphomas, where the full "growth program" is expressed, including all EBNA proteins and the bone fide oncogene LMP-1. Moreover, evidence that the adoptive transfer of cytotoxic T cells (CTL) [82] and the restoration of autologous immune surveillance via reduction of immune suppression [83, 84] can produce durable objective responses and tumor clearance in PTLD by targeting latency III and lytic EBV antigens has led to the appreciation of the frequent coexistence of B cells expressing latency III and immediate early (BZLF1/Zebra, BRLF1) and early (BMRF1) lytic proteins in the same lymphoma and has highlighted the important role of these proteins in the establishment and maintenance of EBV-associated lymphomas [85–88]. Whether or not its expression leads to the activation of EBV's full replicative cycle and production of infectious particles, BZLF1 can have a profound effect on both the infected cell and the microenvironment by trans-activating the expression of cytokines, such as interleukin (IL)-8 [89], IL-10 [90], and IL-13 [91].

On the other hand, the exact role of EBV in BL (latency I) remains to be defined, since the only EBV gene expressed is EBNA1, and constitutive c-MYC activation is the dominant oncogenic event in both the endemic (mostly EBV+) and sporadic (mostly EBV−) types [92, 93]. In BL, therefore, EBV is more likely to have a supportive rather than a driving role, possibly by countering the pro-senescence and pro-apoptotic effects of unopposed c-MYC signaling via expression of the late lytic gene BHRF1 and of the BHRF1 and BART miR clusters or through viral-induced epigenetic repression of Bim, a pro-apoptotic protein [94, 95].

Finally, in latency II malignancies, like HL, nasopharyngeal carcinoma (NPC), and ENKTL, the conventional view is that expression of LMP-1, followed by downstream activation of PI3K/AKT and JAK/STAT pathways, is the main oncogenic event. However, LMP-1 expression is often observed only in a subset of EBV-infected cells in NPC and ENKTL [96, 97], and EBV-associated malignancies displaying latency II pattern with variable expression of LMP-1, LMP-2A, and LMP-2B, including variant transcripts, have been described [97, 98]. In these cases, it is possible that subclones of tumor cells in an originally EBV-positive cancer may have evolved alternative, virus-independent, mechanisms to activate and sustain oncogenic signaling pathways (thus potentially losing episomal EBV) [99]. Alternatively, different subsets of the same cancer (i.e., classical HL) may develop and acquire functionally important molecular aberrations, such as upregulation of programmed cell death ligand 1 (PD-L1), through completely different avenues. Green et al. have recently shown in a genetically annotated series of cHL that PD-L1 could be overexpressed via copy number amplification at the 9p24.1 genomic region, in EBV-negative cases, or constitutive LMP1-induced activation of the transcription factor AP1, in EBV-positive cases [100]. Remarkably, these two mechanisms affected mutually exclusive patient subsets, illustrating how the same evolutionary favorable aberrations may arise from two completely different mechanisms (gene amplification in one case and expression of EBV-encoded LMP-1 in the other).

Evidence for EBV Infection of Normal T Cells and NK Cells

The fact that EBV does normally, albeit less frequently, infect T cells and NK cells is often inadequately acknowledged, in part because the mechanism of infection of T/NK cells (typically CD21-negative) has not been established. However, during infectious mononucleosis (IM), low proportions (<10 %) of tonsillar cells can be shown to co-stain for EBER and for T cell or NK cell markers, suggesting that, during primary infection, EBV can infect T cells and NK cells [101–103]. It has been hypothesized that EBV infection occurs while NK cells or T cells are attempting to kill an EBV-infected cell target [104]. The first clear evidence that EBV infection was implicated in the development of MTNKL came from a report describing three patients (two of them adults) with clinical and serologic features of chronic active EBV (CAEBV) who subsequently developed fatal T cell lymphoma [105]. The linkage between CAEBV and the presence of EBV-positive T cells and NK cells, with or without evolution to T cell lymphoma, was further confirmed and characterized mainly in East Asia, where this disease is more common [106–113]. As a whole, these studies clearly proved that pediatric and adult patients with an overlapping spectrum of EBV-associated diseases, including CAEBV, chronic IM, virus-induced hemophagocytic syndrome (VIHS), and fatal IM, have circulating EBV-infected T cells and NK cells. These EBV-positive T/NK cell lymphoproliferations may evolve in vivo into full blown T/NK cell neoplasms and can produce continuous cell lines in vitro. These studies also showed that the EBV-infected cells can express surface markers of CD4, CD8, NK cell, and γ/δ T cells, and some suggested that the initial presentation and clinical course of the patients vary with the lineage of the EBV-infected cell [113]. In contrast, a recent study of US cases of CAEBV reported that—unlike Asian cases—in most patients the EBV-infected cells were B cells, rather than T cells, suggesting that the risk of T cell or NK cell infection by EBV and developing EBV-positive T/NK cell lymphoma varies across populations [114]. Following the report from Jones et al. [105], several other types of MTNKL associated with EBV were described, again with greater prevalence in Asia and Latin America, compared to the USA [115–126]. More recently, Coleman et al. [127] showed that EBV type 2 is able to efficiently infect T cells and induce distinct EBV gene expression programs, although the relevance that this in vitro model may have on the development of EBV-associated T/NK cell lymphoma remains to be defined.

Association of EBV With Extranodal NK Cell Lymphomas

The best direct link between EBV and MTNKL, across all geographic areas, is provided by ENKTL [128, 129]. First, the virus is present in nearly all patients, irrespective of ethnicity [128–131]. Second, all tumor cells within a lesion contain EBV genomes and the virus is demonstrably clonal [128, 129, 132–134]. Third, EBV-encoded transcripts and proteins have been detected [128, 134, 135], usually with a latency program I or II. EBV genome copy numbers within ENKTL biopsies typically number <20 per cell, consistent with latent infection, although higher intracellular viral loads indicative of lytic replication have been observed and may have prognostic relevance [136]. Finally, cell-free plasma EBV DNA levels are elevated in most cases of ENKTL, and the quantity at diagnosis and the pattern of detection during and after treatment have been shown to be predictive of outcome [5, 137]. ENKTL accounts for 15 % of all cases of NHL in the southwest region of China, 6.1 % in

Korea, 7.8 % in Guatemala, 2.6 % in Japan, 2.8 % in Taiwan, 2.4 % in Peru, 2.6 % in Chile, and less than 0.1 % in Europe and North America [128, 129]. A related, even more aggressive but extremely rare neoplasm, aggressive NK cell leukemia (ANKL) is also characterized by the presence of clonal episomal EBV in all tumor cells [138–140]. While some cases of ANKL derive from systemic dissemination of ENKTL, ANKL can also present as a de novo malignancy.

More indolent EBV-associated proliferations of T/NK cells have been described, particularly in pediatric populations in the same areas where ENKTL is frequent. Hydroa vacciniforme (HV) is a disease characterized by an exaggerated sensitivity to insect bites and by vesiculopapular eruptions in sun-exposed areas, mainly on the face and arms, with subsequent ulceration and scarring [141]. HV-like lymphoma (HVLL) is a chronic lymphoproliferative disease that develops in a subset of patients with HV and eventually can progress to a more aggressive systemic neoplasm [142, 143]. It has been clearly shown that EBV infection in this entity occurs in T cells with αβ or γδ phenotype or in NK cells. Interestingly, even in countries where EBV is endemic, HVLL occurs in particular regional areas, such as the south of Peru, suggesting an environmental co-factor [144].

EBV in Nodal Peripheral T Cell Lymphomas (PTCL)

Although a number of early studies revealed that EBV could also be detected in tumor biopsies from a significant subset of patients with nodal PTCL [145–152], the role of EBV in these disorders remains poorly understood, with the exception of angioimmunoblastic T cell lymphoma (AITL). AITL is a malignant expansion of follicular helper T cells (T_{FH}) characterized by frequent systemic symptoms, laboratory markers of B cell activation, and a prominent B cell infiltrate in the tumor microenvironment [153, 154]. EBV is present in approximately 85–95 % of AITL biopsies and in the majority of cases is found in polyclonal B cells [152, 155–157]. While EBV is currently not thought to play a primary role in AITL lymphomagenesis, clones of EBV-infected B cells may emerge due to the survival-promoting effect of the virus [158] and the permissive microenvironment created by the neoplastic T_{FH} cells [159]. Up to one third of cases of AITL have evidence of clonal or oligoclonal populations of B cells by IGH gene rearrangement studies [160]. As AITL progresses, a subset of patients can develop aggressive B cell proliferations with latency patterns II or III, similar to those seen in immunosuppressed individuals [155–157].

In PTCL-not otherwise specified (NOS), EBV has been detected in 25 to 58 % of cases using various techniques [2, 145–152, 160–165] and has been linked to prognosis. One of the first studies to assess the clinical impact of EBV on PTCL was published by d'Amore et al. [144], who reported that the detection of EBV in T cell lymphomas by EBER-ISH in patients without a history of immune deficiency was associated with the worst outcome in a register-based population including various histologic subtypes. Nevertheless, the prognostic significance of EBV inside each PTCL category was not studied independently. In order to more specifically establish the prognostic impact of EBV in PTCL-NOS, Dupuis et al. [2] retrospectively investigated a cohort of PTCL patients with nodal presentation entered on the LNH87 and LNH93 trials of the Groupe d'Etude des Lymphomes de l'Adulte (GELA), using EBER-ISH. The study excluded AITL, ALCL, and other extranodal T cell lymphoma

types. In addition, expression of LMP-1 and EBNA-2 was also assessed by IHC. One hundred ten PTCL-NOS were identified. EBER+ at any level was found in 41 % of the cases. The GELA study showed a 5-year event-free survival (EFS) and overall survival of 21 and 30 % in EBER+ cases. The cutoff for survival impact was between no expression and the presence of one or more EBER+ cells, so any EBER positivity was associated with a lower survival. The infected cell type could only be investigated by double labeling techniques in 12 cases. In most circumstances, the EBER+ cells were B cells, but in a few cases, they were T cells.

The frequent presence of EBV-infected cells in PTCL-NOS was confirmed more recently by the International PTCL Project. Weisenburger et al. [161] reported that 30 % of 222 PTCL-NOS cases were EBER+ (any staining) and that 14 % were strongly EBER+ (3–4+). EBER+ cells were described as being small and large B cells, although lineage assessment was not formally reported. Approximately 70 % of the patients were from the USA and Europe, indicating that the frequency of EBV detection in this cohort was not due to an excess of Asian cases. Presence of strong EBER+ staining was associated with poor survival in younger patients (<60 years), in contrast with the study of Dupuis et al. [2] where the inferior survival linked to EBV was observed in older patients. While the question of which cells are infected by EBV in PTCL-NOS remains unsolved, these two large retrospective studies demonstrated that EBER+ cells are detected in a large subset of European and North American patients with non-AITL PTCL and suggest that presence of EBV may have a prognostic impact in non-Asian patients.

Unlike ENKTL, data on cell-free plasma EBV DNA (pEBVd) detection in PTCL have not been published, although preliminary data presented by our group in abstract form suggest that detection of pEBVd at diagnosis in PTCL is associated with an inferior overall survival [166].

Clues on the Possible Functional Role of EBV in MTNKL

Expressed on the surface of antigen-presenting cells, PD-L1 is the main ligand that engages the PD-1 inhibitory co-receptor on T cells, suppressing T cell activation and receptor signaling [167]. Neoplastic cells can overexpress PD-L1 inducing T cell exhaustion and favoring tumor survival [168]. PD-L1 mRNA expression has been proven to be upregulated in EBV+ B cell PTLD compared to EBV-PTLD [100], and it was recently shown that this effect is induced by EBV-encoded LMP-1 through transcriptional activation [100]. Interestingly, increased expression of PD-L1 has been observed in nasopharyngeal carcinoma [169], ENKTL [170], and classical HL [100]. The role of PD-L1 signaling in other T/NK lymphomas remains unknown, but it is conceivable that expression of EBV-encoded latent genes in PTCL-NOS may similarly affect the tumor microenvironment, regardless of the lineage of the infected cells.

EBV is also known to influence the T-bet/GATA3 axis (Th1/Th2) in T-cells. EBV causes upregulation of GATA3 expression in vitro [171], and the EBV-encoded miR-BART20-5p inhibits T-bet translation in ENKTL, thereby blocking differentiation towards Th1 lineage [172]. Background Th1 or Th2 microenvironments are predictive of prognosis in some

T/NK cell lymphomas. Iqbal et al. recently showed through gene expression analysis that PTCL-NOS cases characterized by high expression of GATA3 were associated with poor overall survival [173].

Conclusions

Our current understanding of the role of EBV in human lymphomagenesis is inextricably grounded in the virus' original characterization as a ubiquitous agent of B cell lymphoproliferation and is conceptually enshrined in the yin yang duality of host's immune surveillance vs. virus latency. This paradigm, however, may not be a good fit for the majority of EBV-associated malignancies worldwide, including MTNKL, where the evolutionary relation between virus and cancer is likely more dynamic and complex.

One could speculate that the life-long presence of EBV in a latent state may be additive or complementary to the risk posed by other carcinogens and that. In addition to age, genetic background, and ethnicity [174, 175], other factors may modify EBV-induced cancer risk, including co-infection with other pathogens [176, 177], EBV strain type [178], development of serious illnesses, and chronic exposure to therapeutic drugs [179]. In this context, the emergence of EBV-associated MTNKL may represent one of many possible neoplastic end results of the prolonged and dynamic interplay between the virus and its aging host. What must be established is whether the subset of MTNKL characterized by the presence of EBV in tumor tissue displays distinct biological and clinical features compared to their EBV-negative counterparts. EBV could then be specifically leveraged for risk stratification, disease monitoring, and therapeutic purposes.

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