Immune Responses to EBV in the Immunocompromised Host

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Immune Responses to EBV Infection in Immunocompetent Individuals

Innate Immunity

Most data on innate responses to EBV are derived from studies performed on blood samples from young adults with infectious mononucleosis (IM), a self-limiting EBV-triggered symptomatic disease, or from EBV seropositive healthy subjects during EBV established infection entailing virus latency and episodic viral reactivations. Innate immune cells, including monocytes/macrophages, plasmacytoid dendritic cells (pDC), and conventional (c)DC and NK cells, provide the first, non-specific line of defense against EBV infection [1, 2]. A memory-like function for innate effectors (e.g., NK cells and monocytes/macrophages), known as trained immunity, was described to occur upon secondary encounters with pathogens [3, 4]. This confers enhanced immunity to secondary infections and may be relevant to EBV infection as well. Innate cells through their germline-encoded pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), sense pathogen-associated molecular patterns (PAMPs), and in response they trigger the induction of MyD88-dependent phosphorylation of MAPKs and activation of NF-kB and IRFs [5]. As a result, inflammatory cytokines, chemokines, and cytotoxic molecules are directly released and contribute to pathogen neutralization and lysis of pathogen-infected cells. Subsequently these inflammatory mediators promote and shape the generation of potent pathogen-specific $CD8^+$ and $CD4^+$ T cell adaptive immunity. EBV can be sensed mainly by TLR9 and TLR3 expressed by innate cells, although other TLRs were recently identified to play a role in EBV recognition.

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TLR9 expressed by monocytes and plasmacytoid DC (pDC) senses EBV-derived unmethylated CpG dsDNA motifs and promote production of type-1 interferon (IFN)-α/β and transforming growth factor-β (TGF-β) as well as release of the danger signal molecule HMGB1 [6]. All these mediators contribute to the immediate host defensive inflammatory responses leading to inhibition of EBV reactivation and subsequent lytic replication, as well as priming and activating adaptive immunity. In addition, B cells, who are infected by EBV and thus may function as innate immune cells, can sense EBV and respond to TLR9 stimulation [7]. Conversely, the virus can down-modulate TLR9-triggered signaling in B cells and thus protects itself from innate control [8]. More recent data demonstrated that EBV can directly infect primary human monocytes and subsequently may specifically induce activation of the inflammasome and caspase-dependent IL-1β production [9].

TLR3 expressed by macrophages and conventional (c)DCs may recognize non-coding EBV small interfering RNA (siRNA) and EBERs. These RNA species may be released by EBV-infected cells as exosomes [10] and may be detected free in the sera of patients with active EBV diseases or in the EBV^+ tumor tissue [11]. These may trigger TLR3 expressed by macrophages and cDCs to upregulate their Ag cross-presentation capability and release type-1 interferons and inflammatory cytokines such as IL-12p70 and IL-6, leading to further activation of innate and adaptive immune cells [12]. In addition, myeloid antigen-presenting cells via EBV-TLR2 triggering may result in MCP-1 release that may further upregulate TLR2 expression on myeloid cells [13].

NK cell contribution to the innate immune control against EBV is quite significant during primary infection, whether symptomatic IM or asymptomatic infection [14, 15]. NK cells become activated directly following NK cell-TLR3 ligation by (i) small EBV RNA molecules; (ii) pro-inflammatory cytokines IL-12p70 and IL-18 secreted by myeloid innate cells; and (iii) IFN-γ secreted either by $CD4^+$ and $CD8^+$ T cells or by NK cell themselves. As a consequence, the $CD56^{bright}$ NK cell subset produces elevated levels of cytokines (IFN-γ/TNF-α) that interfere with EBV infectivity, while $CD56^{dim}$ subset upregulates activating cytotoxic molecules (NKp30, NKp46, NKG2D) and releases perforin and granzyme B that leads to increased lysis of EBV-infected cells. Moreover, tissue-resident (tonsillar) NK cells were shown to be more effective at controlling B cell transformation than blood NK cells, a process depending on IFN-γ release in response to IL-12p70 stimulation [16].

Altogether, the magnitude of the innate responses and the combination of effector mediators released at one time may directly correlate with the immunopathologic and clinical manifestations caused by active EBV infection [17, 18].

Adaptive Immunity

EBV-specific T cell responses in healthy individuals reflect EBV life cycle that entails expression of both latent and lytic viral proteins. Both provide good Ag sources for priming effectors of adaptive immunity that control primary EBV infection and for memory generation and maintenance to survey EBV latent state and its

lytic replication during established infection. There are six EBV nuclear Ag (EBNA1, 2, 3A, 3B, 3C, LP) and three EBV membrane proteins (LMP1, 2A, 2B) expressed by infected B lymphocytes within lymphoid tissues (tonsils and lymph nodes). In addition, there are numerous EBV lytic Ag. The immediate early (IE) genes ($n = 2$) are critical for inducing the switch from latency to EBV production, whereas the early (E) ($n > 30$) and late (L) ($n > 30$) genes contribute to viral replication and may be expressed in both B cells and epithelial cells of the nasopharynx [19, 20]. The different locations and sources of EBV Ags impact the EBV Ag-specific $CD4^+$ and $CD8^+$ T cell responses in terms of their phenotypic profiles, function, and trafficking capabilities. More importantly, monitoring of EBV-specific $CD4^+$ and $CD8^+$ T cells in the peripheral circulation by flow cytometry using fluorochrome-tagged EBV Ag-loaded HLA tetramers in conjunction with fluorochrome-tagged mAbs allows for an accurate assessment of Ag-specific T cell phenotype, differentiation state, and function at any given time.

T Cell Responses During Primary EBV Infection

During infectious mononucleosis (IM), literature describes a significant expansion of EBV lytic-specific type-1 $CD8^+$ T cells (IFN-γ/GzB/Perf), whose frequencies may represent up to 50% of the expanded $CD8^+$ T cell repertoire in the peripheral circulation of patients [21, 22]. The immunodominance hierarchy of these Ag-specific $CD8^+$ T cells consists of IE>E>L and most likely reflected EBV antigen availability and differential accessibility to the HLA class I processing pathway for $CD8^+$ T cell priming [23]. EBV-latent-specific $CD8^+$ T cell responses were also detected, but at significant lower levels, with individual epitope specificities directed mostly against immunodominant EBNA3A, 3B, and 3C epitopes and the subdominant LMP2A epitope and with frequencies representing approximately 5% of the peripheral $CD8^+$ T cell population [23, 24]. EBNA1 $CD8^+$ T cell responses may not be detected, since the glycine/alanine repeat domain within EBNA1 protects it from the MHC class I processing pathway [25]. In addition, circulating EBV-specific $CD8^+$ T cells during IM are phenotypically activated ($CD38^+$, $CD69^+$, HLA-DR^+), proliferating ($Ki67^+$), in an effector memory ($CD45RO^+CD62L^-$) (EM) phase. They also express $CXCR3^+$ and were highly functionally (IFN-γ^+) active [21, 26, 27]. Moreover, the $CD8^+$ T cell responses to some of the immunodominant epitopes involve highly conserved T cell receptor (TCR) usage, with possible consequences for cross-reactive recognition of other target antigen structures.

Upon IM resolution, EBV-specific $CD8^+$ T cell frequencies decline, and their phenotype and function display resting profiles [28]. Interestingly, EBV-latent- but not EBV-lytic-specific $CD8^+$ T cells gain $CD45RO^+CD62L^+$ expression, indicative of central memory (CM) phenotypes. These may be recruited to the B cell follicles of the tonsils, to control local EBV latent B cell transformation. EBV-lytic-specific $CD8^+$ T cells remain in the EM phase or re-express CD45RA and are poorly represented in the tonsils, consistent with the continued high-level shedding of virus in saliva [28].

EBV-specific $CD4^+$ T cell responses during IM are minimal compared to $CD8^+$ T cell responses, are dominated by latent-specific responses over lytic-specific

responses, and present also activated phenotypes [29]. During IM resolution, the % of EBV-specific CD4+ T cell responses diminish as well. Interestingly, EBNA1-specific CD4+ T cell responses could be detected in peripheral circulation at later times. EBNA1-specific CD4+ T cells are fully functional and can recognize and lyse EBNA1+ lymphoma cells in vitro [30]. This is important since EBNA1-specific CD8+ T cell responses are minimal due to poor accessibility of EBNA1 to be processed and presented via MHC class I pathway.

There are few studies that monitored healthy children or young adults undergoing asymptomatic primary EBV infection. These individuals presented with elevated activated EBV-specific CD8+ and CD4+ T cells, similar to those from IM cases, but at much lower level of expansion and activation as those from IM patients [31].

Memory T Cell Responses During Established Infection

EBV-specific CD8+ T cell memory responses could be easily detected in peripheral circulation of EBV-positive individuals and are directed against same lytic Ag and latent Ag specificities as seen in IM patients, but here EBV-lytic-specific CD8+ T cells do not exceed on average more than 2% of the total CD8+ T cells. The levels of latent Ag-specific CD8+ T cells are even smaller, up to 1% of the total CD8+ T cells [32]. EBV-latent-specific responses are directed primarily to EBNA3A/C and LMP2a, and the epitope choices for each Ag are HLA allele specific. In most healthy individuals, over time, EBV appears to establish a stable balance with the host's immune response, although occasional fluctuations in the size and function of the EBV-specific CD8+ T cell compartment are seen, possibly due to subclinical occasional EBV lytic and latent reactivation [33].

EBV Ag-specific memory CD4+ T cell phenotype and size differ significantly from those of EBV Ag-specific memory CD8+ T cell in the circulation of healthy EBV-positive individuals [34]. While the memory CD8+ T cell repertoire against EBV lytic and EBV latent Ags is broad and encompasses immunodominant and subdominant responses [23], the memory CD4+ T cell repertoire is more focused and dominated by EBNA1-specific responses [35], due to its accessibility to the MHC-II pathway within the infected cell itself via autophagy [36]. EBV-specific CD4+ T cell responses directed against other lytic and latent Ag specificities have been also reported and are minimally represented in circulation. Of note, in addition to their principal helper role (e.g., co-stimulatory molecules and cytokine production), EBV-specific memory CD4+ T cells still can recognize and kill infected B cells or established EBV+ tumors [30].

EBV Evasion from Innate and Adaptive Immunity

EBV exploits innate immune control through multiple mechanisms [37]. Several EBV gene products (e.g., BCRF1 or vIL-10, BNLF2, BGLF5, LMP1) may interfere with MHC class I peptide loading and presentation or may trigger down-modulation of TLR expression, resulting in downstream intracellular signaling inhibition of

NFkB and IRFs, with subsequent decreased transcription and expression of pro-inflammatory cytokines and chemokines and diminished cell proliferation [8, 38, 39]. The untranslated EBERs and siRNAs released from EBV-infected cells may also contribute to EBV immune evasion through multiple mechanisms by concomitantly conveying subtle inhibitory signals that are sensed by regulatory networks, allowing EBV to protect itself from host immunity [39, 40]. In addition, EBV may confer EBV-infected cell resistance to cell death signals by allowing the upregulation of several anti-apoptotic genes (including bcl-2, bfl-1, mcl-1, A20, and cIAP2) or by activation of the Ras/PI3K/Akt signaling axis in B cells [41, 42].

EBV evasion from adaptive immunity was also described and may interfere at several levels. It may reduce immunogenicity of antigen-presenting cells (APC) by hindering MHC class I and II loading with EBV peptides or by down-modulating MHC expression. It can also diminish the ability of APC to secrete anti-viral type-1 pro-inflammatory cytokines such as IL-12p70 while enhancing production of anti-inflammatory cytokines IL-10 and TGFβ and therefore rendering the microenvironment tolerogenic.

All these events allow EBV to establish latency or to undergo lytic reactivations and thus to survive, co-exist, and persist with the host rather than be eliminated by host immunity. In addition, these events may contribute to EBV-associated malignancies due to the failure of the immune system to eliminate EBV-transformed cells.

Immune Responses to EBV Infection in Immunocompromised Solid Organ Transplantation Recipients

While EBV infection in healthy individuals is dominated by its latent phase with protracted viral antigen exposure, and interrupted by occasional EBV reactivation, both well controlled by a functional type-1 innate and adaptive immunity, EBV infection after organ transplantation may become at times uncontrolled due to the iatrogenic immunosuppression burden on host immunity. In addition, EBV evasion mechanisms may become prevalent in individuals with impaired cellular immunity and can easily tip the balance toward favoring EBV-triggered B cell oncogenesis and development of post-transplant lymphoproliferative disorders (PTLD) [43].

The vast majority of patients undergoing transplantation are EBV positive, display memory responses to EBV, and are at low risk of PTLD. For those patients who EBV seroconvert post-transplant in the presence of high levels of immunosuppressive drugs, or for those with less mature immunity (e.g., mixed type 1/type 2), EBV can easily switch its latency phenotypes from the expected, benign latency 0/I (no Ag or EBNA1 expression) to the dangerous latency III (EBNA1–6, LMP1, LMP2a and LMP2b) or latency II (EBNA1, LMP1, and LMP2a) [44]. These latency phenotypes are indicative of the stages where B cell lymphoproliferation occurred, where EBV latent Ag-specific immune control failed, and whether the immunodominance hierarchy of these responses is perturbed or not [45]. Impaired immunity against EBV lytic Ags can also develop to allow EBV to undergo frequent productive reactivations, translated in part by increased immune evasion and accumulation of high

EBV loads in peripheral circulation. Together, these concur to the development of progressive immune functional exhaustion of innate and adaptive immune responses and to an increased risk for EBV$^+$ PTLD.

Specifically, EBV-negative pediatric patients receiving an EBV-positive transplant are at highest risk of developing chronic high EBV load (HVL) carrier status and PTLD [46, 47]. Indeed, clinically asymptomatic chronic HVL status in pediatric transplant carriers, specifically heart recipients, was proven not to be a benign state, but a strong predictor for PTLD [48]. Understanding the defects in innate and adaptive immune control against EBV after transplantation and identifying the concomitant occurrence of immune regulatory and exhausted networks paralleled by EBV immune evasion mechanisms are important elements in predicting the risk of EBV-associated PTLD and in determining how to harness immunity for therapy of this complication [49].

Perturbations of Innate Immunity

A longitudinal study conducted on peripheral blood mononuclear cell (PBMC) samples from 45 adult kidney recipients during the first 24 months post-transplant showed impaired inflammatory cytokine secretion by CD14$^+$CD16$^+$ monocytes in response to EBV peptide stimulation and retrospectively identified patients at increased risk of infectious complications [50]. In another longitudinal study, significant elevated levels of IL-10 and IL-6 were detected in plasma of 38 adult transplant recipients undergoing treatment for PTLD. Interestingly, IL-6 levels, but not IL-10, correlated with disease progression, highlighting the role of IL-6 as a B cell growth factor to enhance B cell proliferation, a phenomenon seen with PTLD [51, 52]. In a model of lymphoproliferative disease using humanized NOD-SCID mice, Lim et al. showed that EBV-stimulated pDCs produced IFN-α that promoted activation of NK cells and of IFN-γ producing CD3$^+$T cells, a phenomenon dependent on cell-to-cell contact, in part mediated by TLR-9 signaling. When pDC function was preserved, mice EBV-related mortality was delayed, whereas when pDC were impaired, EBV-driven mortality was significantly increased, highlighting the importance of pro-inflammatory IFN-α for PTLD control [53]. All these suggest that perturbations in the pro-inflammatory/anti-inflammatory milieu may be permissive for impaired EBV antigen presentation and T cell immune control, leading to increased risk for complications.

The importance of NK cells in EBV control after organ transplantation was emphasized by several groups. A cohort of pediatric liver transplant recipients displayed a significant decrease in the percentage of circulating NK cells immediately post-transplant, while the expression of NK natural cytotoxicity triggering receptor NKp30 was significantly increased. NKp46 and NKG2D levels remained stable through follow-up [54]. In a cohort of six pediatric heart transplant recipients with PTLD, our group has identified decreased circulating CD56^{bright} and CD56^{dim}CD16$^+$ NK cell subset levels that downregulated NKp46 and NKG2D and significantly upregulated inhibitory molecule PD-1. These phenotypic changes were paralleled

by NK functional impairment, resembling cellular exhaustion. Interfering with PD-1/PD-L1 pathway resulted in increased NK cytotoxic function [55]. A decrease in NK cell number accompanied by a reversed CD4:CD8 ratio with increased $CD8^+$ T cells was shown to predispose to recalcitrant EBV-PTLD in 14 pediatric PTLD cases [56].

Defects in T Cell Immune Responses

To assess the functional polarization and potency of EBV-specific memory T cells after transplantation, our group has investigated a cohort of adult kidney transplant recipients. We reported that patients exhibited similar circulating EBV-specific $CD8^+$ T cell frequencies and EBV-epitope specificities as compared to those of healthy controls. In contrast, they displayed significantly elevated EM phenotypes, decreased IFN-γ production, and elevated IL-10 in response to EBV peptide stimulation in vitro. These cells suppressed noncognate $CD4^+$ T cell proliferation via cell-cell contact, suggesting their induced Tr1 polarization. These changes were induced at least in part by chronic immunosuppression that altered cDC phenotype and function, in a NFkB-dependent manner [57–59]. Moreover, our results suggested that even in EBV-positive, stable immunosuppressed transplant patients, regulatory pathways in the myeloid compartment are elevated and trigger alternative activation (re-programing) of EBV-specific CD8+ T cells with potential clinical consequences for certain patients that carry genetic or epigenetic alterations.

T Cell Responses During Primary EBV Infection After Transplantation

Given that EBV-negative patients receiving an EBV-positive organ are at higher risk of EBV complications post-transplantation, the issue of EBV seroconversion after solid organ transplantation was investigated by several groups. Longitudinal monitoring of EBV-specific T cell response in an adult EBV seronegative recipient following cardiac transplantation determined that effective EBV-specific immune response can be initiated quickly after primary EBV infection post-transplantation [60]. EBV-specific $CD8^+$ T cell frequency and IFN-γ production increased upon each subsequent viral reactivation. Falco et al. have investigated circulating EBV-lytic- and EBV-latent-specific $CD8^+$ T cells in a cohort of EBV-negative pediatric liver transplant recipients after EBV seroconversion [61]. These immune cells were easily detected in a few weeks post-EBV seroconversion and displayed activated/EM phenotype. These studies support that an EBV-specific T cell response capable of adequate control of a primary EBV infection and of subsequent viral reactivations can develop in EBV-seronegative adult and pediatric transplant recipients in the presence of severe immunosuppression. However, IL-10 production by $CD8^+$ T cells was not measured in these studies.

Memory T Cell Responses and EBV Load After Transplantation

EBV pediatric patients that develop chronic high EBV load in peripheral circulation have a 45% risk for PTLD [48]. To address this clinical observation, our group

has focused on analyzing EBV $CD8^+$ T cell immunity in a cohort of EBV asymptomatic pediatric heart transplant recipients. As compared to the EBV asymptomatic adult kidney recipients, pediatric recipients displayed a subverted EBV-specific $CD8^+$ T cell immunity from the Tr1 (IFN-γ/IL-10) seen in adult kidney recipients to a mixed "Type-0" (IFN-γ/IL-5/IL-10) polarization in pediatric heart transplant recipients [62]. Pediatric patients that carried an EBV load (either low viral load, LVL, or high viral load, HVL) displayed significant increased levels of EBV-lytic-specific $CD8^+$ T cells over EBV-latent-specific $CD8^+$ T cells, with activated phenotypes ($CD38^+$ and EM). Moreover, EBV-specific $CD8^+$ T cells from HVL patients concomitantly displayed exhausted phenotypes ($PD\text{-}1^+CD127^-$) and function (low IFN-γ), unlike LVL patients whose EBV-specific $CD8^+$ T cells were functional (high IFN-γ) and lacked phenotypic features of exhaustion [62]. Moreover, approximately 1/3 of LVL patients displayed EBV-specific $CD8^+$ T cells that co-expressed CXCR5, a chemokine receptor that may localize them in CXCL13-rich areas, and IL-7Rα that may confer a potential for self-renewal. These findings provide a potential mechanistic explanation for differences in outcomes between LVL and HVL carriers in this cohort [63] . Anti-viral $CXCR5^+CD8^+$ T cells, termed follicular cytotoxic T (T_{FC}) cells, were previously described during persistent viral infections [64]. They seem to co-localize with B cells in the B cell follicles and have a significant role in viral control; and therefore may represent valuable therapeutic targets to explore, specifically since B lymphocytes in the follicles are the reservoire of EBV. We have also evaluated global and EBV-specific $CD4^+$ T cell immunity in this cohort and identified a selective $CD4^+$ T cell immunosuppression in HVL patients [65]. While these heterogeneous states of EBV-specific T cells have been identified in different categories of EBV load transplant carriers, the complex molecular and cellular mechanisms contributing to such diverse outcomes after transplantation still need further elucidation.

Memory T Cell Responses During PTLD

T cell immune monitoring of patients undergoing PTLD is of great interest as it may provide mechanistic understanding of the immunopathogenesis of this heterogeneous entity. Hinrichs et al. studied lymphocyte subsets of 38 adult transplant recipients with PTLD. They identified $HLA\text{-}DR^+CD8^+$ T cells significantly elevated in PTLD cases that correlated with impaired cytotoxic T lymphocytes in PTLD [51]. Smets et al. reported that while the numbers of EBV-specific $CD8^+$ T cells were maintained, $CD4^+$ T cell levels were lower in a cohort of pediatric transplant recipients with PTLD. The overall capacity of T cells to secrete IFN-γ in response to EBV peptides was progressively lost and coincided with the significant increase in circulating EBV load. Therefore, the ratio between IFN-γ and EBV load may be used as a marker for PTLD risk [66]. In contrast, in a cohort of 16 patients with PTLD, there were no changes in the numbers of EBV-specific $CD4^+$ and $CD8^+$ T cells or levels of IFN-γ when compared to control groups. EBV-specific T cells tended to be lower in early PTLD compared with late PTLD cases, and $CD4^+$ and $CD8^+$ EBV-specific

T cells increased in most patients treated with rituximab [67]. Interestingly, in a separate study, peripheral blood lymphocytes from two PTLD patients stimulated with an EBV peptide mix resulted in decreased polyfunctional EBV-specific T cells, expressing TNF-α and CD107 release but no IFN-γ production [68]. While these results obtained on peripheral blood from patients with PTLD generated by different groups are somewhat contradictory, this is expectable, due to the (i) heterogeneity of PTLD (early vs late; monomorphic vs polymorphic, etc.), (ii) timing of the samples (at diagnosis; before or after treatment), and (iii) differences in technical approaches.

Due to the possible contribution of PD-1/PD-L1 pathway to the failed EBV-specific T cell and NK cell immune control during PTLD [55, 62], this pathway may be considered a tempting target for PTLD treatment. However, this therapeutic approach for transplant patients with PTLD may represent a double-edged sword. On the one hand, exhausted EBV-specific T cells may be unleashed functional against the EBV$^+$ PTLD; on the other hand, allo-reactive T cells may become revigorated as well and may inflict graft injury and graft loss. Therefore, personalized immune monitoring to assess the presence of EBV-specific vs allo-specific CD8$^+$ T cells with phenotypes of Tbet^{hi}PD-1^{int} exhausted progeny (rescuable by checkpoint inhibitor blockade) and Eomes^{hi}PD-1^{hi} terminally exhausted progenitors (non-responsive to checkpoint inhibitor blockade) may identify significantly variability between patients and may indicate those patients likely to benefit from this treatment [69]. In addition, the same PD-1/PD-L1 checkpoint inhibitor blockade may also target EBV-specific CXCR5$^+$CD8$^+$ T_{FC} cells when present. These may respond with a proliferative burst of functional cells and replenish the exhausted EBV-specific CXCR5$^-$CD8$^+$ T cells. Alternatively, EBV-specific CXCR5$^-$CD8$^+$ T cells may be turned into EBV-specific CXCR5$^+$CD8$^+$ T_{FC} cells-like by (i) culturing them in a T_{FC}-inducing cytokine milieu; (ii) using vectors to generate CXCR5$^+$ CAR T cells; or (iii) expressing T_{FC}-promoting transcription factors [64]. In addition, monitoring for the recently described soluble PD-L1 decoy that hinders the success of PD-1/PD-L1 checkpoint inhibitor blockade therapeutic approach in some patients may also prove of value [70].

In conclusion, the dominant expression of regulatory cytokines (IL-10, IL-6) and of inhibitory molecules (PD-1) triggered by chronic immunosuppression and the multiple EBV evasion mechanisms encountered after transplantation and during PTLD [43, 71, 72] together contribute to the attenuation of anti-viral innate and adaptive immune control and allow for autocrine growth of EBV in its target cells. Unfortunately, till date there is no consensus on what marker or combination of markers may be of value to monitor in order to predict EBV complications/PTLD after transplantation. However, accumulation of improved technologies, of personalized monitoring and diagnosis, coupled with the prospect of novel immunotherapies that may target the complex and heterogeneous mechanistic interplay between EBV biology and human immune responses to EBV after organ transplantation, may soon allow for significant improved PTLD outcomes.

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