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Emerging therapeutic strategies for Epstein–Barr virus+ post-transplant lymphoproliferative disorder

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Abstract

De novo malignancies represent an increasing concern in the transplant population, particularly as long-term graft and patient survival improves. EBV-associated B-cell lymphoma in the setting of PTLD is the leading malignancy in children following solid organ transplantation. Therapeutic strategies can be categorized as pharmacologic, biologic, and cell-based but the variable efficacy of these approaches and the complexity of PTLD suggest that new treatment options are warranted. Here, we review current therapeutic strategies for treatment of PTLD. We also describe the life cycle of EBV, addressing the viral mechanisms that contribute to the genesis and persistence of EBV+ B-cell lymphomas. Specifically, we focus on the oncogenic signaling pathways activated by the EBV LMP1 and LMP2a to understand the underlying mechanisms and mediators of lymphomagenesis with the goal of identifying novel, rational therapeutic targets for the treatment of EBV-associated malignancies.

Keywords

Epstein–Barr virus; post-transplant lymphoproliferative disorder; B cell

EBV is a gammaherpes virus that has infected >95% of the world's population (1). In healthy individuals, EBV infection is usually asymptomatic and the virus establishes a latent infection, residing in memory B cells for the lifetime of the host. However, when the immune system is debilitated as in immunosuppressed transplant recipients, opportunistic EBV-associated B-cell lymphomas can arise (2). These lymphomas are the most serious manifestation of PTLD (3). The incidence of EBV-associated PTLD is known to vary widely with the organ transplanted and the serologic status of the recipient (4). Nevertheless, EBV-associated B-cell lymphomas are the most common cancer in children that receive solid organ grafts, representing well over half of the *de novo*, post-transplant malignancies. Children are at particular risk for PTLD, in part, because they are often immunologically naïve at the time of transplant and can acquire a primary infection when receiving a graft

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from a seropositive donor in the setting of immunosuppression (5). Although uncommon, PTLD may also arise from T cells; however, this review will be focused on EBV-induced PTLD, which accounts for 93% of lymphoproliferative disorders in pediatric organ transplant recipients.

The current standard therapeutic approaches for the treatment of EBV-associated PTLD include reduction or elimination of immunosuppression, chemotherapy, radiotherapy, the use of anti-B-cell antibodies such as rituximab, and surgical resection when feasible. Determining the optimal treatment for individual patients, however, remains difficult and requires extensive interaction between transplant specialists and oncologists. The recent emergence of cellular-based immunotherapy holds promise for alternate approaches and underscores the need for new strategies to manage children with EBV-associated B-cell lymphomas.

Current therapeutics for treatment of EBV+ PTLD

The spectrum of EBV infection in transplant recipients is wide, from a primary infection (mononucleosis-like syndrome) to full-blown monomorphic monoclonal lymphoma. Thus, the treatment varies according to the stage of the disease. Furthermore, it is usually individualized and varies greatly according to the treating physician's preference. In a Canadian study that included 33 transplant centers covering the period from 1988 to 1997, reduction of immunosuppression was used in 71%, antiviral agents in 52%, immunoglobulin in 22%, surgical resection in 20%, radiation therapy in 14%, and IFN-α in 12% (6). In this retrospective study the types of organ transplants were: renal (14/33, 42.4%), liver (7/33, 21.2%), heart (6/33, 18.2%), lung (3/33, 9%), pancreas (2/33, 6%), and intestinal (1/33, 3%). The survival after PTLD at two yr was 51.0% (6). In a similar study from Spanish centers, the treatment strategies were somewhat different: reduction of immunosuppression in 91%, chemotherapy in 59%, rituximab in 33%, and antiviral agents in 13% of the patients (7).

For EBV-induced PTLD, reduction of immunosuppression appears to be effective in 23–50% of cases (8). The difference in response seems to be related to degree of reduction (or withdrawal) of immunosuppression. For example, in pediatric heart transplantation, reduction of immunosuppression may result in acute rejection leading to arrythmias, cardiogenic shock, and death. Thus, physicians are less willing to significantly reduce the intensity of the immunosuppression. In contrast, reduction or withdrawal of immunosuppression in liver transplant recipients is readily carried out as acute rejection of the liver is seldom a life-threatening complication. In kidney transplantation, the immunosuppression should be reduced; however, it should be discontinued in those patients with aggressive PTLD refractory to treatment. The patient's life should not be put at risk by trying to save the kidney (9, 10). The response also depends on the time of the onset of disease. Patients with early onset of the disease experience a better outcome with the reduction of the immunosuppression than those who present with late onset PTLD, particularly in patients with risk factors such as high LDH, organ dysfunction, and multiorgan involvement (11). In a series of 42 adult recipients of solid organ transplants, 89% without any of these risk factors had a good response with the reduction of immunosuppression, compared to none of seven patients with two or three risk factors (11).

The length of time of reduction of immunosuppression remains unknown. In our own institution, we maintain our PTLD liver transplant recipients with low or no immunosuppression until the patients experience an episode of rejection. An interesting observation is that many of these patients did not experience rejection and thus immunosuppression was not restarted (12). How the reduction of immunosuppression is carried out also varies according to the type of organ transplant as well as the transplant team's preference. Some will discontinue or reduce the dose of calcineurin inhibitors and keep the patients on low-dose steroids. The risk of this treatment is potential graft loss from rejection, but such complication seems to be infrequent. Others may substitute the calcineurin inhibitors for sirolimus (mTOR inhibitor) with the hope that this treatment will abrogate the proliferation of B cells as sirolimus is known to have antiproliferative properties *in vitro* (13). However, caution must be undertaken with this approach as PTLD has been observed (and the incidence may be increased) in clinical trials of patients treated with sirolimus in combination with other immunosuppressive agents (14).

The utilization of *antiviral therapy* for the treatment of PTLD is common practice, but whether or not antiviral therapy is effective on latent or transformed forms of EBV remains unresolved (8). It does decrease viral shedding in early onset of EBV infections such as plasmacytic hyperplasia and mononucleosis-like syndromes. The efficacy of acyclovir or gancyclovir for the treatment of PTLD comes mostly from anecdotal reports. There is no consensus if one is more effective than the other. Foscarnet has also been shown to be effective in individual case reports (15), but because of its potential toxicity, most protocols include acyclovir or gancyclovir. In summary, there is no evidence that antiviral therapy is effective in the latent phase of PTLD, although they may be effective in the lytic phase of EBV infection (8).

Intravenous immunoglobulin is often included in treatment protocols for PTLD in transplant recipients. Its efficacy is unknown as it is often used in combination with reduction of immunosuppression and/or antiviral therapies (16). As mentioned previously, the initial treatment for patients with monoclonal malignant lymphoma is to reduce or discontinue the immunosuppression. If there is no response, anti-B-cell antibodies, chemotherapy, and/or radiation and occasional surgical resection may be necessary for control of the disease.

Treatment with *chemotherapy* will include protocols often used for the treatment of lymphoma such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). There are modifications of this protocol by using lower doses or different chemotherapy agents (17-19). The complexity of managing transplant patients on chemotherapy (because of its potential toxicity) requires the participation in tandem of highly specialized oncologic and transplant teams as many of these patients have some degree of end organ failure (renal dysfunction, for example) from the prolonged treatment with nephrotoxic drugs such as cyclosporine or tacrolimus. PTLD involvement of the CNS system also poses a significant challenge as many of the chemotherapy drugs do not cross the brain barrier. Reported treatments for PTLD involving the CNS include the use of antivirals, immunotherapy, radiation, and chemotherapy, but the prognosis is poor (20). High-dose-MTX has been found to be effective in patients with PTLD involvement of the CNS. At our institution, we used a combination of high-dose MTX along with intrathecal MTX successfully in a child

who had underwent a combined liver and intestinal transplantation complicated by PTLD involvement of the brain (21).

Immunotherapy, particularly the anti-CD20 antibody, rituximab, seems to be receiving wide acceptance as first line of treatment for those patients who do not respond to reduction or discontinuation of immunosuppression. In a prospective study of 43 patients with previously untreated B-cell PTLD, the overall response rate to rituximab was 40% and the survival rate at one yr was 67% (22). In a different retrospective study of 19 patients, the administration of rituximab was associated with a 68% response rate of the patients (23). Recently, rituximab has been used in combination with low-dose chemotherapy in those patients who did not respond to reduction of immunosuppression and the results were encouraging (24). Bortezomib, a protease inhibitor, was successfully used in an adult patient who developed PTLD-multiple myeloma after kidney transplantation (25). PTLD-multiple myeloma accounts for 4% of PTLD observed in transplant recipients. To our knowledge, bortezomib has not been used for the treatment of PTLD in pediatric transplant recipients. Likewise, anti-CD21 and anti-CD24 murine antibodies were investigated in a series of 58 patients (31 of them recipients of solid organ transplants) with PTLD and the response and relapse rate was 61% and 8%, respectively (26). The overall response rate of chemotherapy for the treatment of malignant PTLD is about 70% (27).

The experience with the utilization of IFN-α for the treatment of PTLD is rather limited and amounts to individual institutional reports. One of the studies included a series of 16 patients with disseminated PTLD. Of the patients who received at least three wk of IFN-α therapy, eight of 14 experienced remission. No relapse was noted among the eight who responded, but two developed a new neoplastic clone (28). The potential risk of IFN-α in transplant recipients is the potential risk of the drug promoting steroid resistant rejection. This has been observed in kidney transplant recipients with co-existent hepatitis C infection who were treated with IFN-α as an attempt at eradicating the hepatitis C virus.

There are other modalities of treatment that were studied in the past or are currently undergoing investigation: adoptive immunotherapy using lymphokine-activated killer cells, infusions of donor leukocytes or EBV–specific cytotoxic T cell lines, administration of photosensitizing agents such as methoxalen, induction of the latent viral thymidine kinase gene in the tumor cells followed by treatment with gancyclovir and the mTOR inhibitor, rapamycin (29-32). Although promising, such therapies continue to remain in the realm of experimentation. In summary, a range of therapeutic approaches has been utilized for patients diagnosed with EBV+ PTLD, but their efficacy remains to be established.

EBV: Insights from the normal life cycle

One approach to identifying new treatment strategies is to understand how EBV infects and persists in normal human B cells and how this, in turn, can result in the development of EBV-associated malignancies. Along these lines, the life cycle of EBV highlights the ability of the virus to co-opt normal B-cell function to enter into the memory B-cell reservoir, where infected cells can escape immunosurveillance by EBV-specific CTLs. The life cycle

of EBV very closely mimics the stages of B-cell differentiation, from antigen activation via the BCR through the GC into the memory B-cell reservoir (33).

Models have emerged to explain how expression of particular viral genes promotes viral persistence through the B-cell differentiation process (34) (Fig. 1). In particular, the EBV LMP1 and LMP2a play critical roles in driving infected cells into the memory B-cell compartment. During B-cell differentiation, B cells require signals both from the antigen engagement of the BCR and from engagement of CD40 with CD154 on activated T helper (T_H) cells or FDCs to proceed to the memory compartment; without receiving either signal during this phase, activated B cells undergo apoptosis. LMP1 and LMP2a may provide signals independent of the antigen-driven interactions with T_H cells or FDCs that are required for B-cell differentiation. The EBV protein LMP2a, a functional mimic of the BCR, simultaneously blocks signals through the BCR while providing the tonic signals required for B-cell survival (35-37). EBV also expresses a functional CD40 mimic, LMP1, which delivers these potent survival signals in the absence of T cell help (38). Unlike their B-cell counterparts, both viral proteins provide constitutive signals, independent of antigen, through self-aggregation. Signals from these two viral proteins – LMP1 and LMP2a – likely act as the mediators for the survival of infected B cells into the long-lived, peripheral memory B-cell pool. Additionally, recirculating tonsillar memory B cells can express LMP1 and LMP2a, potentially assisting in ensuring the long-term survival of this latently infected memory B-cell pool (39).

Signal mimicry: LMP1 and LMP2a

LMP1 is the primary oncogene of EBV, as its expression is sufficient to transform rodent fibroblasts and it is essential for EBV-induced B-cell transformation *in vitro* (40, 41). LMP1 functionally resembles the tumor necrosis factor receptor (TNFR) superfamily member CD40 (42, 43). Studies of LMP1 signaling *in vivo* have revealed that the constitutive signaling of LMP1 abrogates the requirement for EBV-infected B cells to form a GC before entering the memory compartment (44).

LMP1 signaling induces expression of cell-surface adhesion molecules and activation antigens (41). LMP1 also upregulates anti-apoptotic proteins, including Bcl-2, A20, and cFLIP, that protect infected cells against apoptosis (45-47). Additionally, LMP1 induces secretion of the autocrine growth factor IL-10 (48). Much of the oncogenicity of LMP1 can be ascribed to its constitutive activation of multiple cellular signaling pathways that promote cellular growth and activation. Interactions of cellular TRAF and TNFR-associated death domains (TRADD) adaptor proteins with the LMP1 C-terminal tail signaling domains, carboxy-terminal activating region 1 and 2 (CTAR1 or CTAR2), initiate signal transduction through a variety of pathways including the p38, Erk, and JNK MAPK and NF-jB pathways (42, 49-52). Recent studies have also implicated LMP1 in the activation of the PI3K/Akt signaling pathway; activation of PI3K/Akt has been shown to depend primarily upon the CTAR1 domain of LMP1 (48, 53, 54).

Like LMP1, LMP2a is a functional, constitutively active mimic of a B-cell activation signal, in this case the BCR. In transgenic mice, B-cell restricted expression of LMP2a in lieu of the

immunoglobulin heavy chain abrogates normal B-cell development, driving Ig-negative cell colonization in peripheral lymphoid organs (55). While not required for B-cell transformation *in vitro*, LMP2a expression can transform epithelial cells and enhance their adhesion and motility (56). LMP2a expression can, however, rescue survival of GC B cells with crippling mutations in the BCR (57). This suggests that LMP2a can contribute to the transformation of primary B cells (58, 59). LMP2a expression in B cells sequesters the key tyrosine kinases, Lyn and Syk, away from the BCR, blocking normal BCR signaling (35, 59). Self-aggregation of LMP2a (60) delivers a constitutive, BCR-like signal to latently infected cells through Syk, Lyn, Btk, BLNK, PI3K/Akt, and other signaling mediators. These signals, coordinated by Syk activation, function to maintain viral latency, sustain survival, and induce expression of a range of genes involved in cell-cycle induction, inhibition of apoptosis, and suppression of cell-mediated immunity (35-37, 57, 61-64).

Therapeutics in development that target pathways activated by LMP1 and LMP2a

Emerging therapeutics for the treatment of PTLD fall into two general categories: cellular immunotherapies and strategies targeting EBV-specific mechanisms of lymphomagenesis. Cellular immunotherapies include the infusion of autologous or allogeneic EBV-specific CTLs (65); while well tolerated, their efficacy in the presence of immunosuppressive drugs has been mixed. Recent studies by our laboratory and others have elucidated cellular signaling pathways initiated by LMP1 and LMP2a in infected B cells, and thereby has revealed new opportunities for treatment of PTLD. For the purposes of this review, we focus specifically on the small molecule inhibitors in clinical development for other malignancies or diseases that target molecules relevant to the survival signals driven by the EBV proteins LMP1 and LMP2a (Fig. 2).

Syk

Ligand-independent, or tonic, signals from the BCR are required for the survival of all benign (66-69) and most malignant (70, 71) B cells. These tonic signals are executed primarily through the activation of Syk tyrosine kinase, which coordinates the activation of a myriad of downstream pathways. The EBV viral homolog of the BCR, LMP2a, is expressed in PTLD and activates Syk. LMP2a expression can rescue B-cell development and survival in mice unable to generate a functional BCR (36) only when LMP2a is able to bind and activate Syk (64), highlighting the importance of Syk activation by LMP2a for B-cell survival.

Pharmacological or genetic targeting of Syk has been pursued as a therapeutic strategy for the treatment of B-cell lymphomas. Currently, the only Syk inhibitor in clinical trails, according to clinicaltrials.gov, is fostamatinib (Rigel/Astra-Zeneca). We have shown that the Syk inhibitor fostamatinib reduces proliferation and induces apoptosis of EBV+ B-cell lymphomas lines derived from patients with PTLD *in vitro* (72). Fostamatinib also reduces the proliferation and induces the apoptosis of lymphoma cells, including those from DLBCL and B-cell CLL, *in vitro* (73-76). In murine models of NHL and CLL inhibition of Syk

induces tumor regression or remission (77, 78). Finally, in phase I/II clinical trials, fostamatinib was efficacious in patients with DLBCL, FL, SLL, CLL, and MCL (79).

In contrast, however, current data also suggest that Syk can act in a tumor suppressive fashion in breast cancer and other epithelial cancers. For example, in breast cancer, a direct examination of the role of Syk revealed loss of Syk expression results in more aggressive, metastatic tumors and correlates with poorer clinical prognosis (80, 81). However, unbiased gene expression profiles do not include Syk in gene signatures associated with predictors or poor prognostic outcomes of breast cancer (82-84). Intriguingly, fostamatinib has been linked to lymphoma peripheralization. In the phase I/II clinical trial for fostamatinib, a transient increase in circulating lymphocytes observed in SLL and CLL patients (79). Thus, it is plausible that Syk is involved in multiple cellular functions such that additional studies are warranted to fully understand the consequences of inhibiting Syk for treatment of EBV+ PTLD.

SFK

Upstream of Syk activation are the SFK, a large family of kinases including Lyn, Fyn, Lck, Hck, Fgr, Blk, Yrk, Yes, and c-Src. Similar to the BCR, LMP2a activates the Src family kinase Lyn upstream of Syk (85). Additionally, we have observed that LMP1 can also activate Fyn, another member of the Src family of kinases (O. Hatton, S.L. Lambert, S.M. Krams, O.M. Martinez, unpublished data). Displaying robust anti-proliferative and antitumor activity in both solid and hematologic tumors, the orally available c-Src inhibitor dasatinib (Bristol Myers-Squibb) variably inhibits the other SFKs (86, 87). Saracatinib (AstraZeneca) is a pan-SFK inhibitor, which has been shown to have an antitumor effect in pancreatic cancer and prostate cancer xenografts (88, 89). Bosutinib (Wyeth), another c-Src inhibitor with activity against other SFKs, has shown modest activity in colon and pancreatic cancer xenografts (90, 91). All three inhibitors have entered phase I or II clinical trials, both as monotherapies and in combination with other agents, with preliminary data suggesting that these agents are well tolerated at clinically relevant doses (92). Based on our observations with Syk, however, SFK may be involved in the activation of numerous pathways that would preclude achieving a specific effect on survival without undesirable side effects. Additionally, the Src kinases inhibitors that are currently in clinical development display a wide range of off-target effects, including inhibiting ABL and c-kit (92). However, more studies will be needed to address the possibility of Src family kinase inhibitors in the treatment of PTLD.

PI3K/Akt

Downstream of Syk activation, the PI3K/Akt, and Erk MAPK signaling pathways have been implicated as executors of the Syk survival signal in B-cell lymphomas. PI3K/Akt signaling is of particular interest, as PI3K/Akt dysregulation is one of the most frequent occurrences in human cancers, including B-cell lymphomas (93, 94). PI3K/Akt signaling plays a central role in cell growth, proliferation, and metabolism (95). Both LMP1 and LMP2a activate the PI3K/Akt pathway, and inhibition of this pathway *in vitro* by the dual PI3K/mTOR inhibitor LY294002 induces apoptosis of B cells from LMP2a-transgenic mice (63), as well as EBV+ PTLD-derived B-cell lines (72). Finally, both PI3K and Akt lie upstream of mTOR and we

have previously shown that rapamycin, an mTOR inhibitor, markedly suppresses the growth of EBV+ PTLD-derived B-cell lines *in vitro* and in a xenogeneic model of PTLD (13).

Given its involvement in a diverse number of malignant pathologies, it is not surprising that there are a considerable number of inhibitors for the PI3K/Akt/mTOR pathway in clinical development (96, 97). These inhibitors come in one of three flavors: PI3K inhibitors, Akt inhibitors, and dual PI3K/mTor inhibitors. The PI3K inhibitors in clinical development include PX-866 (Oncothyreon), XL147 (Exelixis), NVP-BKM120 (Novartis), GDC-0941 (Genentech), and CAL-101 (Calistoga/Gilead). PX-866 was successful in treatment of tumor xenografts with PI3K-activating mutations (98), and resulted in stable disease in 25% of patients in the phase I clinical trial (99). XL147 monotherapy produced durable disease control in 6 of 39 treated patients, according to preliminary reports (100). In addition to reported preclinical anti-tumor activity (101, 102), partial responses in two breast cancer patients have been reported in preliminary reports from the preclinical studies with NVP-BKM120 (103). One partial response in a breast cancer patient has been reported from the phase I trials of GDC-0941 (104). CAL-101 is the first small molecule inhibitor specific for the PI3K p110d isoform, which is predominantly expressed in leukocytes. *In vitro*, CAL-101 has been efficacious in inducing apoptosis of B-cell malignancies, including CLL and B-cell acute lymphoblastic leukemia (105, 106). In preliminary results from the phase I study, partial responses have been seen in 33% of patients with CLL, 57% of patients with indolent NHL, and 67% of patients with MCL (107). CAL-101 is currently entering phase II studies as a monotherapy for indolent NHL and in combination with rituximab for CLL in elderly patients.

In preclinical studies with lung and ovarian cancer lines, the Akt inhibitor MK-2206 (Merck) has been efficacious both in combination with cytotoxic agents and the targeted therapies erlotinib and lapatinib (108). According to preliminarily results, MK-2206 established stable disease in six of 19 patients in its phase I clinical trials, with tumor shrinkage observed in up to 23% of patients, in advanced solid tumors (109). Phase II trials in advanced endometrial cancer, colorectal cancer, and relapsed Hodgkin's lymphoma and NHL are underway (clinicaltrials.gov). Additionally, MK-2206 is also being evaluated in combination with the MEK/Erk inhibitor AZD6244 (AstraZeneca); however, MEK/Erk inhibition has not been efficacious in inducing apoptosis of B cells from LMP2a-transgenic mice (63), as well as from our EBV+ PTLD-derived B-cell lines (72). Other Akt inhibitors in the early stages of clinical development include GSK690693 and GSK2141795 (GlaxoSmithKline), GDC-0068 (Genentech), and LY2780301 (Eli Lilly).

Owing to the structural similarity of the mTOR and the p110 subunit of PI3K, dual PI3K/mTOR inhibitors have also been developed. SF-1126 (Semafore) has been efficacious in preclinical solid tumor xenograft models of prostate cancer and glioblastoma (110). Preliminary results from the clinical trial have shown the establishment of stable disease in 19 of 38 patients with solid tumors, as well as partial responses in combination with rituximab in patients with B-cell lymphomas (CLL or DLBCL) (111). NVP-BEZ235 (Novartis) was efficacious in achieving tumor stasis or regression in preclinical solid tumor xenografts of breast cancer, prostate cancer, and glioblastoma (112, 113). Preliminary reports from the clinical trials show partial responses in two patients, with 14 of 51 patients

achieving stable disease for four months or greater (114). Finally, preclinical models utilizing XL765 (Exelisis) have shown shrinkage of GBM xenografts, both as a monotherapy and in combination with TMZ (115). In the phase I monotherapy study, preliminary results in patients with solid tumors include the achievement of stable disease in 12 of 83 enrolled patients (116). Both Genentech (GCD-0980) and Pfizer (PF-04691502 and PF-05212384) also have dual PI3K/mTOR inhibitors entering clinical trials; however, these are in earlier stages of development than those discussed above.

In conclusion, EBV+ PTLD remains an important problem in solid organ transplantation. An improved understanding of viral mechanisms of transformation and persistence, coupled with the development and testing of inhibitors of the Akt/PI3K/mTOR pathway for other human malignancies, may reveal new opportunities for treatment of PTLD.

Abbreviations

BCR	B-cell receptor
CLL	chronic lymphocytic leukemia
CTL	cytotoxic T lymphocyte
DLBCL	diffuse large-B-cell lymphoma
EBNA	EBV nuclear antigen
EBV	Epstein–Barr virus
FDC	follicular dendritic cell
FL	follicular lymphoma
GC	germinal center
MTX	methotrexate
IFN-α	interferon-α
LMP1	latent membrane protein 1
LMP2a	latent membrane protein 2a
MCL	mantle cell lymphoma
NHL	non-Hodgkin’s lymphoma
PTLD	post-transplant lymphoproliferative disorder
SFK	Src family kinases
SLL	small lymphocytic leukemia
TNFR	tumor necrosis factor receptor
TRADD	TNFR-associated death domains
TRAF	TNF receptor-associated factor

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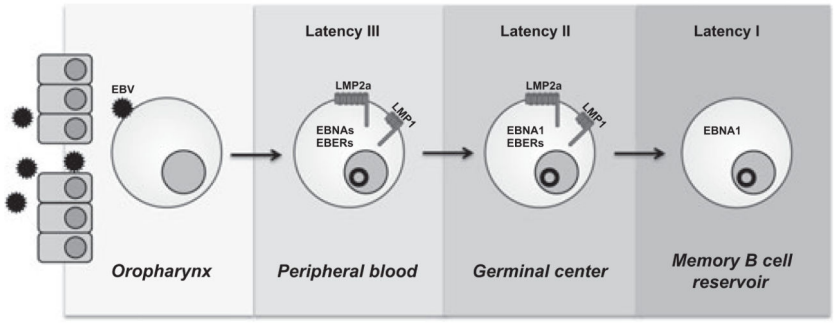

Fig. 1.

Viral gene expression during the life cycle of EBV. EBV preferentially establishes an infection in naïve, tonsillar B cells. While a minority of infected cells remains permissive for the production of infectious viral particles, a latent infection is established in the majority of infected cells. Infected cells displaying this form of latency (latency III) express the EBV nuclear antigens (EBNAs) 1, 2, 3A, 3B, 3C, LP, LMP1 and LMP2a, and EBV small RNAs (EBERs 1, 2). Expression of a type III latency has been proposed to promote activation of the naïve B cell to become a proliferating lymphoblast, similar to B-cell activation by antigen. Infected cells then transition through a latency II, which is characterized by the loss of EBNA 2, 3A, 3B, 3C, and LP expression. During latency II, LMP1 (the CD40 homolog of EBV) and LMP2a (the BCR homolog of EBV) have been proposed to provide signals independent of the antigen-driven interactions with T_H cells or FDCs that are required for B-cell differentiation through the GC and into the memory B-cell compartment. Finally, EBV persists for the lifetime of the host in the peripheral memory B-cell reservoir by switching to a type I latency. In this program, latently infected cells escape immunosurveillance by EBV-specific cytotoxic T lymphocytes by not expressing any latent genes. To ensure passage of the viral episome during cell division, the poorly immunogenic EBNA1 is periodically expressed in latently infected memory B cells.

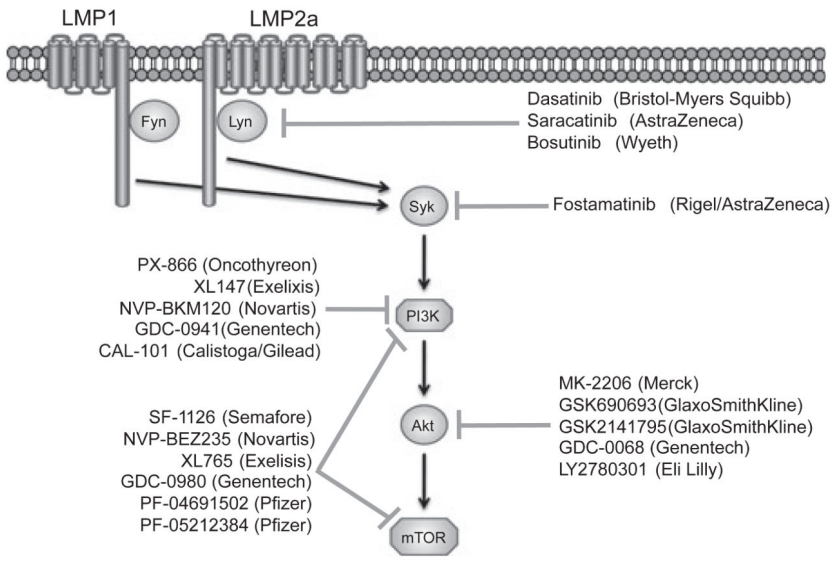

Fig. 2.

Therapeutics in development that target survival pathways activated by LMP1 and LMP2a. Both LMP1 and LMP2a activate members of the SFK (Fyn and Lyn, respectively) upstream of Syk activation. Syk then activates the PI3K/Akt/mTor signaling pathway. Small molecule inhibitors of these signaling molecules that are currently in preclinical or clinical development in other malignancies are listed next to their described target.