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REVIEW

# Roles of the PI3K/Akt pathway in Epstein-Barr virus-induced cancers and therapeutic implications

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## Abstract

Viruses have been shown to be responsible for 10%-15% of cancer cases. Epstein-Barr virus (EBV) is the first virus to be associated with human malignancies. EBV can cause many cancers, including Burkett's lymphoma, Hodgkin's lymphoma, post-transplant lymphoproliferative disorders, nasopharyngeal carcinoma and gastric cancer. Evidence shows that phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) plays a key role in EBV-induced malignancies. The main EBV oncoproteins latent membrane proteins (LMP) 1 and LMP2A can activate the PI3K/Akt pathway, which, in turn, affects cell survival, apoptosis, proliferation and genomic instability *via* its downstream target proteins to cause cancer. It has also been demonstrated that the activation of the PI3K/Akt pathway can result in drug resistance to chemotherapy. Thus, the inhibition of this pathway can increase the therapeutic efficacy of EBV-associated cancers. For example, PI3K inhibitor Ly294002 has been shown to increase the effect of 5-fluorouracil in an EBV-associated gastric cancer cell line. At present, dual inhibitors of PI3K and its downstream target mammalian target of rapamycin have been used in clinical trials and may be included in treatment regimens for EBV-associated cancers.



**Key words:** Epstein-Barr virus; Latent membrane proteins 1; Latent membrane proteins 2A; Phosphoinositide 3-kinase/protein kinase B; Carcinogenesis; Drug resistance

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## INTRODUCTION

It is now evident that virus-induced cancers account for 10%-15% of all cancer cases[1,2]. Studies of viruses as causes of cancer have played an important role in the elucidation of the mechanisms of carcinogenesis, as indicated by several Nobel Prizes being awarded to scientists in the field of oncoviruses. The initial work to demonstrate that viruses can induce cancer was done by Peyton Rous[3,4]. He identified Rous sarcoma virus as the cause of chicken sarcoma in 1911, and the discovery earned him the 1966 Nobel Prize. The human analogue of the viral oncogene *v-Src* was found and named *c-Src*, which was the first human oncogene[5,6]. This work led to the awarding of a Nobel Prize to John Michael Bishop and Harold E. Varmus in 1989. More recently, Harald zur Hausen identified human papillomavirus (HPV) as the cause of cervical cancer (Nobel Prize, 2008)[7]. This discovery led to the invention of the vaccines Gardasil and Cervarix which can effectively prevent HPV-associated cervical cancer[8,9]. The Epstein-Barr virus (EBV); [also called human herpesvirus 4 (HHV-4)] is the first virus identified (in 1964) to be associated with human cancers[1]. It belongs to the

B-lymphotropic γ-herpesvirus family with a genome consisting of 172 kb of linear double-stranded DNA[1,10,11]. EBV infects both epithelial and B-cells and, thus, can induce both epithelial cancers and lymphoma[12,13]. After EBV infection, there are two viral phases: lytic and latent[14]. In its lytic phase, the virus replicates in epithelial cells, and, in its latent phase, it transforms B-cells.

Cancer is characterized by the loss of the balance between cell proliferation and apoptosis[15-17]. It has been demonstrated that EBV can increase cell proliferation and decrease apoptosis[18]. EBV has been shown to cause several B-cell lymphomas, including Burkitt's lymphoma, Hodgkin's lymphoma and post-transplant lymphoproliferative disorders (PTLDs). This notion is demonstrated by the detection of EBV virus in these cancers, the replication of the virus and its ability to transform B-cells[18,19]. EBV is also closely associated with epithelial cancers. For example, EBV can cause nasopharyngeal carcinoma (NPC), a highly metastatic cancer[20]. The EBV latent membrane proteins (LMP) 1 and LMP2A are frequently detected in NPC[21]. LMP1 may also lead to metastasis of the cancer, as it has been demonstrated that LMP1 can cause epithelial-mesenchymal transition (EMT) *via* transcription factor Snail[22]. Both LMP1 and Snail are correlated with NPC metastasis[22]. Overall, EBV has been shown to be responsible for about 10% of gastric cancers worldwide[23-25]. However, the mechanisms for EBV-induced gastric cancer are not clear.

Many EBV proteins are expressed in the latent phases and are potentially related to carcinogenesis. These proteins include EBV nuclear antigen (EBNA)-1, -2, -3A, -3B, -3C and leader protein, and LMP-1, -2A and -2B[14]. However, the major identified oncoproteins in EBV are LMP1 and LMP2A[20,26]. These proteins can activate multiple signal pathways, such as the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), the mitogen-activated protein kinase (MAPK) and the signal transducer and activator of transcription 3, all of which are important for carcinogenesis[15,27,28]. LMP1 is considered as an analog of the tumor necrosis factor receptor 1, and it can transform human B-lymphocytes and rodent fibroblasts *via* activation of multiple intracellular signal pathways through its two signaling domains, the carboxyl-terminal activating regions 1 and 2 (CTAR1 and CTAR2)[29]. Activated pathways include the nuclear factor κB (NF-κB), PI3K/Akt, Notch, MAPK and Jun N-terminal protein kinase (JNK) signaling pathways[27,30-32]. It has been demonstrated that point mutations in the C-terminal region of the LMP1 cytoplasmic domain can influence the transforming potential of the EBV by reducing the ability of LMP1 to activate PI3K/Akt, NF-κB and AP1[29]. LMP1 is essential for EBV-mediated B-cell transformation and is sufficient to transform several cell lines, such as rodent fibroblasts[33]. A recent study showed that LMP1 expression is regulated by C/EBP in addition to EBNA2[34]. This article will discuss how EBV-expressed proteins activate the PI3K/Akt pathway to cause carcinogenesis in EBV-associated cancers. Although EBV oncogenes can affect many signal pathways, such as NF-κB, MAPK, and JNK, it seems that the PI3K/Akt pathway is the most important. In an LMP1-mediated transformation of rodent fibroblasts, inhibition of PI3K activity by Ly294002 induced apoptosis and inhibited cell growth, however, the NF-κB inhibitor BAY 11-7085 had no such effect[35]. Another study also showed that the PI3K/Akt pathway, but not the MAPK or NF-κB pathways, can account for the LMP-1-induced transformation[36].

## ROLE OF PI3K/AKT SIGNAL PATHWAY IN CARCINOGENESIS AND METASTASIS

In 1985, Lewis Cantley initially discovered that PI3K plays an important role in cancer[37-41]. PI3K has now been extensively studied with investigation determining its role in carcinogenesis and the potential use of its inhibitors in the treatment of cancers[42-44]. This kinase phosphorylates the 3' OH position of phosphatidylinositol 4,5-biphosphate (PIP2) and converts it to phosphatidylinositol 3,4,5-triphosphate (PIP3), leading to activation of Akt[45,46], which causes a cascade of cellular signal alterations *via* its downstream target proteins[39].

Many factors, such as insulin, insulin-like growth factor-1, vascular endothelial growth factor, and cytokines interleukin (IL)-6, IL-17 can increase the activity of the PI3K/Akt pathway[6,47-52]. Mutations of genes encoding key components in the pathway have been found to cause the pathway activation in many cancers[38,53]. Many cancer-related viruses can also activate the PI3K/Akt pathway and rely on it for their transformations[38,39]. Such viral oncoproteins include polyoma virus middle-T antigen, Rous sarcoma virus oncoprotein v-Src, HPV oncoproteins E6, E7 and the human T-cell leukemia virus type 1 oncoprotein Tax[54-57]. It has also been demonstrated that the PI3K/Akt pathway plays a critical role in the carcinogenesis of EBV viral oncoproteins[27].

Activated Akt, which is phosphorylated by PDK1, can affect many downstream targets[38,42]. The resulting biological effects include increased genomic instability, increased proliferation, decreased apoptosis and changed cytoskeleton. (Figure 1)[58]. Genomic instability is important for the accumulation of genetic mutations necessary for carcinogenesis[59,60]. Recently, it was reported that constitutively active (CA) Met tyrosine kinase (hepatocyte growth factor receptor) can induce chromosomal instability (CIN), as indicated by increased centrosome counts, multinucleated cells and micronuclei formation[61-63]. While CA-Met increased both phosphorylated Akt and phosphorylated Erk, only phosphorylated Akt is critical in CA-Met-induced CIN. The PI3K inhibitor Ly294002, PTEN (an inhibitor of PI3K), and siRNA against Akt all abolished CA-met mediated CIN[62]. It has also been demonstrated that phosphorylation of Akt can block checkpoint kinase 1 (Chk1), which controls cell cycle progression and maintains genomic stability[61,63,64]. The activation of Chk1 will phosphorylate cdc25A and induce the transient arrest of cells in G1 and S phase before

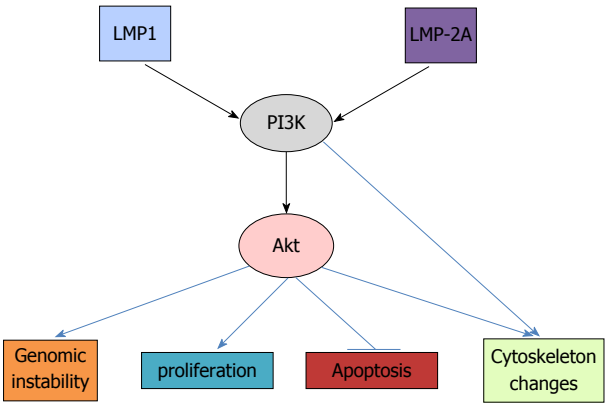


**Figure 1 Epstein-Barr virus activates the phosphoinositide 3-kinase/protein kinase B pathway to transform cells.** The Epstein-Barr virus latent proteins latent membrane protein (LMP)1 and LMP2A activate the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, which promotes carcinogenesis by increasing cell proliferation, genomic instability and cytoskeleton changes and by decreasing apoptosis.

the onset of mitosis[65]. The inhibition of Chk1 has been shown to increase double-strand DNA breaks[66].

The activation of Akt can increase cell proliferation and cell size by accelerating the cell cycle and cell metabolism. Akt can phosphorylate glycogen synthase kinase 3β (GSK3β) and, thus, deactivate it, leading to increased cyclin D1 and Myc[67]. Myc is an oncoprotein that upregulates cyclin-dependent kinase 4 (CDK4)[68]. Additionally, the Akt-mediated inhibition of the forkhead protein results in the downregulation of the cell cycle proteins p27 and p21[69], thus promoting cell cycle progression[70]. Both p27 and p21 are G1-checkpoint CDK inhibitors which can promote G1/S transition and thus, accelerate cell cycle[17,71,72]. Another target activated by the activation of Akt is mTORC1, which plays an important role in the carcinogenesis of many cancers, including Burkitt's lymphoma and NPC[73-75]. Phosphorylated Akt blocks TSC1 and 2 (tuberous sclerosis complex 1 and 2) and, thus, activates Rheb (Ras homolog enriched in brain), thereby activating the mTOC1 complex[38]. The mTORC1 is composed of mammalian target of rapamycin (mTOR), regulatory associated protein of mTOR (Raptor), mammalian LST8/G-protein β-subunit like protein (mLST8/GβL), PRAS40 and Deptor[73]. The activation of mTORC1 can increase protein synthesis, cell growth and cell metabolism *via* its downstream targets[76-78]. The mTORC1 increases protein translation by activating the 70 kDa ribosomal S6 kinase (S6K), and inhibiting the elongation-initiation factor 4E binding protein[79,80]. A recent study using phosphoprome-otic technique and new inhibitor Torin1 revealed many more proteins regulated by mTORC1 including protein Grb 10 which feedback inhibits PI3K[76]. Further study may elucidate the roles of these proteins in mTORC1 mediated carcinogenesis.

The activation of Akt can decrease apoptosis by decreasing Fas ligand transcription *via* blocking the forkhead protein and thus affecting FasL-mediated apoptosis[58]. Akt decreases the pro-apoptotic proteins BAD and BAX and increases anti-apoptotic Bcl-xl, Bcl-2 and Mcl1 to promote cell survival[81]. Akt also inhibits the p53 tumor-suppressor, which can cause apoptosis under stimulation of DNA damage or environmental factors[82,83].

Akt can also regulate cytoskeleton, which is important for cell mobility and the metastasis of cancers[84-86]. The p70 S6K, a downstream target of mTORC1, has been demonstrated to promote actin cytoskeleton change to increase cancer cell migration[87]. In addition, PI3K can cause the change of cytoskeleton independent of Akt. It can activate Rac1, which also causes reorganization of actin cytoskeleton[88-90].

## INCREASED PI3K/AKT PATHWAY IN EBV-INDUCED CANCERS

Examination of activated PI3K in EBV-associated cancers provides evidence for the critical role of the PI3K/Akt pathway in the carcinogenesis of EBV. Adams *et al*[91] (2009) examined eight cases of post-transplant Hodgkin lymphoma and found that all of them expressed PI3K. Analyses of NPC biopsy samples using microarray and affymetrix assays showed PI3K mediated LMP2A-induced expression of the carcinogenic UDP-glucose dehydrogenase (*UGDH*) gene[92,93]. The overexpression of LMP2A in HEK293 cells increased the expression of *UGDH* which was abolished by the inhibition of the PI3K/Akt pathway[92]. Proteomic analyses of the EBV-infected gastric carcinoma cell line NU-GC-3 [EBV (+)] showed that EBV infection upregulated the phosphorylated Akt[94]. The fact that the increased phosphorylated HSP27 was reduced by treatment with the PI3K inhibitors Ly294002 and wortmannin suggests that EBV infection can upregulate the phosphorylation of HSP27 *via* the PI3K/Akt pathway. In PTLDs, protein microarrays of samples from patients showed that PI3K, mTOR and NF-κB were also dysregulated[95].

The activated PI3K/Akt pathway in EBV-associated cancers have been demonstrated to be mediated by LMP1 and LMP2A. A study showed that LMP1 expression in EBV-infected B-cells induced the production of cellular IL-10, an autocrine growth factor for B cell lymphomas, in a PI3K-dependent manner[96]. In these cell lines, PI3K/Akt pathway is activated and the LMP1-mediated IL-10 production is suppressed by mTORC1 inhibitor rapamycin. It has also been demonstrated that expression of dominant negative forms of LMP1 in EBV-immortalized monocytic and lymphocytic cell lines resulted in decreased Akt and NF-κB activities with increased apoptosis[97]. At present, six identified sequence variants of LMP1 including Alaskan, China 1, China 2, Med+, Med-, and NC have been shown to induce the PI3K/Akt signaling pathway to similar extents after being transformed into Rat-1 fibroblasts, HFK cells and BJAB cells[98]. EBV LMP2A has also been shown to activate PI3K in epithelial cells and to affect differentiation[26]. In epithelial cells, the overexpression of LMP2A of Rhesus lymphocryptovirus (LCV), which is highly homologous to EBV LMP2A activated

the PI3K/Akt pathway, indicated by Akt activation and GSK3β inactivation[26]. LMP2A was shown to act as a B-cell receptor (BCR) signal, which results in B cells exiting the bone marrow and decreases B cell apoptosis in the periphery *via* the activation of PI3K[99].

## EBV CAUSES CANCER *VIA* THE ACTIVATION OF THE PI3K/AKT PATHWAY

There are many studies demonstrating that EBV can affect the PI3K/Akt pathway to cause cancers. EBV activation of the PI3K/Akt pathway can increase carcinogenesis *via* multiple downstream targets, including increased genomic instability, cell proliferation, decreased apoptosis and increased cytoskeleton dynamics.

### *EBV increased genomic instability through the activation of the PI3K/Akt pathway*

Genomic stability is important to avoid carcinogenesis and is maintained by the DNA repair system[16,59,60,100-102]. It has been demonstrated that genomic instability plays an important role in EBV-induced cancers[103-107]. In human epithelial cells, LMP1 represses DNA repair *via* the CTAR1-mediated activation of PI3K/Akt pathway[33]. The activated PI3K/Akt pathway resulted in inactivation of FOXO3a, which plays an important role in DNA repair *via* DNA damage-binding protein 1[33]. The critical role of FOXO3a was further demonstrated by the fact that constitutive expression of an active FOXO3a abolished LMP1-mediated repression of DNA repair[33]. Furthermore, a recent study has shown that phosphorylated Akt can block Chk1 to affect genomic instability[62]. This effect may be involved in LMP-1-induced genomic instability and warrants further study.

### *EBV increased cell proliferation through the activation of the PI3K/Akt pathway*

In EBV-immortalized B-cells, also known as lymphoblastoid cell lines, the activation of the PI3K/Akt pathway can promote E2F transcriptional activity to affect the cell cycle and increase proliferation[108]. Inhibition of the PI3K by Ly294002 in these cells reduced both cyclin D2 and cyclin D3, which are two key regulators of cell cycle and increased p27, a cyclin-dependent kinase inhibitor[108]. CTAR1 of LMP1 has been identified to mediate the activation of PI3K signaling and associated induction of cell cycle markers in G1/S transition[30]. This PI3K activating effect was mapped to the TRAF-binding domain within CTAR1. In Rat-1 fibroblast cells, PI3K/Akt has been demonstrated to be a key factor in LMP1 mediated rodent fibroblast transformation[35]. Inhibition of the pathway abolished LMP1-induced cell growth. CTAR1 but not CTAR2 is critical for the activation of the PI3K/Akt pathway and associated cell growth. In human fibroblasts, LMP1 also caused phosphoryaltion of Akt and decreased levels of p27 and thus increased cell proliferation[35]. A study showed that, in an EBV-positive NPC cell line, LMP1 enhanced cell growth and migration through the activation of PI3K/Akt and NF-κB signaling which was reduced by the inhibition of PI3K, Akt, and NF-κB[109]. However, it has been shown that constitutive activation of Akt alone is not sufficient to promote cell growth; NF-κB activation is also required by LMP1 for its effect. Activation of PI3K/Akt and NF-κB has also been demonstrated to increase glucose import which is necessary for increased cell proliferation[110].

### *EBV decreased apoptosis through the activation of the PI3K/Akt pathway*

Several studies have shown that LMP2A can decrease apoptosis *via* the activation of the PI3K/Akt pathway. In LMP2A transgenic mice, peripheral BCR-negative B-cells have CA Ras, an upstream protein of PI3K with correlated increased expression of Bcl-xL, a dowm-stream target protein of PI3K[111]. The specific inhibitors of PI3K and Akt can cause apoptosis of these cells, suggesting the important role of the PI3K/Akt in LMP2A mediated B-cell survival. In an EBV-associated gastric cancer cell line, LMP2A activated PI3K/Akt pathway has been associated with the resistance to apoptosis induced by chemotherapy[112]. In PTLD-derived EBV+ B cell lines, LMP2A increased caspase inhibitor XIAP to block apoptosis *via* the activation of PI3K/Akt pathway[113]. In NPC cell lines, expression of LMP1 activated the PI3K/Akt pathway and its downstream Bcl-2, which in turn suppressed the pro-apoptotic activity of prostate apoptosis response-4[114]. These studies provide sufficient evidence that PI3K/Akt is a key pathway in LMP1 and LMP2A-mediated decreased apoptosis.

### *EBV increased cytoskeleton dynamics through the activation of the PI3K/Akt pathway*

The cytoskeleton plays an important role in carcinogenesis through the control of cell mobility[84-86], and several cancer therapies have been developed targeting the proteins regulating the cytoskeleton[115,116]. The PI3K/Akt pathway has been shown to play a key role in LMP1-induced actin stress-fiber formation[36]. This pathway may be also important in microtubule activity. A study has shown that EBV LMP1 can activate cdc2, which, in turn, phosphorylates Op18/stathmin, a regulator of microtubules[117]. It is possible that this process is mediated by the PI3K/Akt pathway, as Akt has been shown to increase cdc2 activity[118].

## INHIBITION OF PI3K FOR THE TREATMENT OF EBV-ASSOCIATED CANCERS

The PI3K/Akt pathway is not only important in carcinogenesis and maintenance of cancer but is important in metastasis and drug resistance to chemotherapy[119-121]. For example, insulin can increase drug resistance *via* this pathway[47,122-124]. Many studies have been performed to

test PI3K/Akt inhibitors and their utilization in combination with chemotherapeutic agents[125-131]. In EBV-associated cancer, the PI3K/Akt pathway is increased, as described above. Thus, the inhibition of the pathway may be effective for the treatment of these cancers. Indeed, some preliminary studies have shown that inhibiting the pathway increased the effect of chemotherapy on EBV-associated cancers.

In an EBV-positive gastric cancer cell line, SNU-719, Ly294002 was tested in combination with 5-fluorouracil (5-FU), a common chemotherapeutic agent[112,132]. In these cells, the use of 5-FU alone increased phosphorylation levels of Akt and NF-κB. The increased activity of the PI3K/Akt is known to cause drug resistance to chemotherapy[120,121]. By contract, the sequential treatment of 5-FU and Ly294002 decreased their levels, as well as bcl-2 expression, and increased the sensitivity of these cancer cells to 5-FU. The therapeutic efficacy of the mTOR inhibitor rapamycin has been demonstrated; it decreased tumor growth and metastasis in a mouse model of EBV-associated Burkitt's lymphoma established by over-expression of both LMP2A and myc[74]. Ly294002 and Akt inhibitor II also induced the apoptosis of EBV-associated NK/T-cell lymphoma cell lines Hank-1 and NK-YS, which have high levels of activated PI3K[133]. NPC is usually treated by radiotherapy, and studies have shown that inhibition of the PI3K/Akt/mTOR pathway can increase the sensitivity of cancer cells to radiotherapy[131]. Thus, it may be useful to apply PI3K inhibitors in the treatment of EBV-associated NPC.

At present, dual inhibitors of PI3K and mTOR including BEZ235, PI-103, SF1126 and XL756 have been developed and some of them are in clinical trials to treat cancers with activated PI3K[38,134,135]. These inhibitors may be ideal compounds to be added into treatment regimens for EBV-associated cancers. Compounds from traditional medicine have been studied to inhibit signaling pathways; specifically, curcumin and flavonoids can inhibit either the PI3K/Akt pathway or its downstream targets cyclooxygenase-2 and NF-κB[136-142]. These compounds could also be tested for their effects on EBV-associated cancers.

## CONCLUSION

The PI3K/Akt pathway can be activated by the EBV virus proteins LMP1 and LMP-2A and plays an important role in the carcinogenesis of EBV-associated cancers. This pathway is also known to be involved in drug resistance to chemotherapy. Thus, the inhibition of the pathway may have therapeutic implications for EBV-associated cancers. Indeed, some inhibitors of the PI3K/Akt pathway have been tested in EBV-associated cancer cell lines. At present, dual inhibitors of PI3K and mTOR have been developed and may be useful in the treatment of EBV-associated cancers.

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