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The Role of PI3K/Akt in Human Herpesvirus Infection: from the Bench to the Bedside

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Abstract

The phosphatidylinositol-3-kinase (PI3K)-Akt signaling pathway regulates several key cellular functions including protein synthesis, cell growth, glucose metabolism, and inflammation. Many viruses have evolved mechanisms to manipulate this signaling pathway to ensure successful virus replication. The human herpesviruses undergo both latent and lytic infection, but differ in cell tropism, growth kinetics, and disease manifestations. Herpesviruses express multiple proteins that target the PI3K/Akt cell signaling pathway during the course of their life cycle to facilitate viral infection, replication, latency, and reactivation. Rare human genetic disorders with mutations in either the catalytic or regulatory subunit of PI3K that result in constitutive activation of the protein predispose to severe herpesvirus infections as well as to virus-associated malignancies. Inhibiting the PI3K/Akt pathway or its downstream proteins using drugs already approved for other diseases can block herpesvirus lytic infection and may reduce malignancies associated with latent herpesvirus infections.

Keywords

PI3K; Akt; herpesvirus; herpes simplex; varicella-zoster; cytomegalovirus; Epstein-Barr virus; Kaposi's sarcoma associated herpesvirus

Introduction

The phosphatidylinositol-3-kinase (PI3K)-Akt signaling pathway regulates multiple key cellular functions including protein synthesis, cell growth, glucose metabolism, and inflammation. Viruses are obligatory intracellular pathogens and they usurp host functions for viral gene transcription and translation, genome replication, and progeny virion production. Viruses also suppress host cell stress responses induced by accumulation of viral proteins, free DNA ends associated with virus replication, nutrient and energy depletion, or

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hypoxia. To manipulate the intracellular environment for optimal viral replication, viruses including the human herpesviruses, have evolved multiple ways to hijack cellular signaling pathways that are critical for maintaining normal cellular functions such as mitogen-activated protein kinase (MAPK), NF-κB, JAK/STAT, and PI3K/Akt pathways. There are eight human herpesviruses-herpes simplex virus (HSV)-1 and -2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus (HHV)-6 and HHV-7, and Kaposi sarcoma-associated herpesvirus (KSHV, HHV-8). Each of these viruses replicate in the nucleus and have dual life cycles- lytic replication and latent infection. They encode from about 70 (in the case of VZV) to over 200 (in the case of CMV) proteins, and differ in cell tropism, replication kinetics, and disease manifestations. Like other viruses, human herpesviruses exploit the PI3K/Akt pathway to optimize virus entry, replication, latency, reactivation, and modulation of host innate immune responses (reviewed in (Alwine, 2008; Bhatt and Damania, 2012; Buchkovich et al., 2008; Cooray, 2004; Diehl and Schaal, 2013; Dunn and Connor, 2012; Tsalikis et al., 2013; Walsh and Mohr, 2011)). Here we highlight recent findings on the ability of human herpesviruses to modulate the PI3K/Akt signaling pathway, the effects of mutations in PI3K on herpesvirus infections in humans, and potential strategies to inhibit PI3K to treat herpesvirus infections and virus-associated malignancies.

The PI3K/Akt pathway

PI3K is activated when extracellular stimuli such as cytokines, growth factors, or viruses bind to cell surface receptors such as G protein coupled receptors (GPCRs), B cell receptors (BCR), or integrins that have tyrosine kinase activity (**Fig. 1**). This results in translocation of the PI3K complex, which usually consists of a p85 regulatory domain and a p110 catalytic domain, from the cytoplasm to the plasma membrane. Binding of the phosphorylated tyrosine residues on receptors or adapter proteins to the p85 regulatory subunit of PI3K relieves its inhibitory activity on the p110 catalytic domain of PI3K (Cuevas et al., 2001) and allows p110 to phosphorylate membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). This results in recruitment of pleckstrin homology domain containing proteins, including phosphoinositide-dependent protein kinase 1 (PDK1) and the proto-oncoprotein serine/threonine kinase Akt to PIP3 to the plasma membrane. PDK1 phosphorylates Akt at threonine 308, and the mammalian target of rapamycin (mTOR) complex 2 (mTORC2) phosphorylates Akt at serine 473 site to fully activate Akt. PIP3 also binds to its receptor on the endoplasmic reticulum (ER), leading to calcium release from the ER, and activation of calcium signaling which is important for cytoskeletal organization, filopodia formation, and cell-cell fusion.

Activated Akt induces phosphorylation of multiple downstream targets. Phosphorylation of cell cycle inhibitors $p21^{Cip1}$ and $p27^{Kip1}$ inactivates these proteins and enhances progression of cells from the G1 to S phase of the cell cycle. Phosphorylation and inactivation of glycogen synthase kinase (GSK)-3β by Akt promotes cell growth. Akt phosphorylation of pro-apoptotic proteins BAD, Bim, caspase 9, and phosphorylation of the transcription factor FOXO1results in inactivation of these proteins and inhibits apoptosis. Similarly, increased expression of the anti-apoptotic proteins X-linked inhibitor of apoptosis protein (XIAP), Bcl-xL, Bcl-2, and myeloid cell leukemia 1 (Mcl-1) by Akt enhances cell survival.

Phosphorylation and inactivation of the tuberous sclerosis protein 2 (TSC2) results in mTOR1 activation which in turn phosphorylates and inhibits the translational inhibitor eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) and activates S6K1 to stimulate protein synthesis (Hassan et al., 2013; Hemmings and Restuccia, 2012; Vanhaesebroeck et al., 2012).

PI3Ks are divided into three subclasses on the basis of structure, regulation, and lipid substrate specificity. Class I PI3Ks are often involved in the pathogenesis of human cancers and are extensively targeted by viruses (Engelman, 2009; Walsh and Mohr, 2011). Class I PI3Ks are heterodimers consisting of a p110 catalytic subunit (p110α, β, δ, or γ) and a regulatory subunit (p50, p55, p85, or p101). PI3K p110α and p110β are ubiquitously expressed, whereas p110δ and p110γ are primarily found in white blood cells (Okkenhaug, 2013).

PI3K/Akt activity is tightly controlled at multiple steps. PI3K signaling is negatively regulated by several phosphoinositide phosphatases, including the tumor suppressor phosphatase and tensin homolog (PTEN) which dephosphorylates the 3-phosphate from the inositol ring of PIP3 (Stambolic et al., 1998), inositol polyphosphate-4-phosphatase, type II (INPP4B) which dephosphorylates the 4-position phosphate from the inositol ring of PIP2, the PH domain and leucine rich repeat protein phosphatase 2 (PHLPP2) which dephosphorylates Akt at Ser 473 (Brognard et al., 2007), and the protein phosphatase 2 (PP2A) which dephosphorylates Akt at Thr 308 (Andjelkovic et al., 1996; Kuo et al., 2008).

Enhanced PI3K/Akt signaling has been identified in many human cancers including mutation or amplification of the genes encoding catalytic subunits of PI3K p110α and p110δ the gene product of *PIK3CA* and *PI3KCD*, respectively) (Angulo et al., 2013; Lucas et al., 2014; Perez-Tenorio et al., 2007; Samuels et al., 2004), loss of function of PTEN (Perez-Tenorio et al., 2007), and/or INPP4B (Balakrishnan and Chaillet, 2013; Bertucci and Mitchell, 2013; Gewinner et al., 2009), or mutation and/or amplification of the proto-oncogenes *AKT1* and *AKT2* (Ruggeri et al., 1998; Staal, 1987). Therefore, the PI3K/Akt pathway is an important target for drug development for treatment of human malignancies as well as for virus infections.

Herpesviruses modulate the PI3K/Akt pathway

Herpesviruses enhance their replication by modulating the intracellular environment through altering cell signaling pathways to control transcription and translation, regulate cell cycle progression, inhibit apoptosis, evade host defense systems, and alter cellular metabolism. Herpesvirus activation of the PI3K/Akt pathway manipulates many of these activities to favor virus replication or latency. Activation of PI3K/Akt signaling can occur at multiple steps during the virus life cycle including (a) entry and virus glycoprotein binding, (b) release of tegument proteins after virus delivery into the cell, (c) virus replication, and (d) virus latency and reactivation.

Entry of herpesviruses in cells induces activation of PI3K/Akt

Human herpesviruses infect different cell types including epithelial and endothelial cells, macrophages, and lymphocytes. These viruses can enter cells by viral glycoprotein binding to receptors and fusion of viral and cellular membranes either at the cell surface or after endocytosis. The envelope of human herpesviruses contains several glycoproteins, including gB and gH/gL which are shared by all herpesviruses and are essential for mediating membrane fusion. Additional glycoproteins are important for entry of specific viruses such as gD for HSV, gp350 and gp42 for EBV, and UL128, UL130, and UL131A for CMV.

Binding of HSV virions to cellular receptors on the plasma membrane induces changes in cellular gene expression resulting in activation of PI3K/Akt, NF-κB and JAK/STAT signaling (MacLeod and Minson, 2010). Activation of the PI3K/Akt signaling pathway is required for HSV entry into cells. Chemical inhibition of PI3K activity with LY294002 blocked HSV entry and fusion mediated by viral glycoproteins (Tiwari and Shukla, 2010). Inhibition of PI3K with wortmannin blocked trafficking of HSV virions to the periphery of the nucleus (Nicola and Straus, 2004). PI3K inhibition with LY294002 reduced expression of HSV-1 ICP0 and increased the cleavage of caspase-3, caspase-7, and poly ADP-ribose polymerase (PARP), implying that PI3K may reduce apoptosis in HSV-infected cells (Hsu, Wu et al. 2010). HSV infection triggers Akt phosphorylation within minutes after infection (Cheshenko et al., 2013; Hsu et al., 2010; MacLeod and Minson, 2010). Inhibiting Akt expression with siRNA or with miltefosine, which blocks Akt phosphorylation, inhibited virus-induced release of calcium, HSV entry, and plaque formation (Cheshenko et al., 2013). Deletion of HSV glycoprotein D (gD) or gB prevents virus-induced Akt phosphorylation, and Akt interacts directly with gB, but not with gD (Cheshenko et al., 2013) (**Table 1**).

Integrins serve as HSV entry mediators and HSV gH binds to $\alpha_v\beta_3$ integrin (Parry et al., 2005). The binding of gH to $\alpha_v\beta_3$ integrin activates Akt and triggers intracellular calcium release (Cheshenko et al., 2007; Cheshenko et al., 2014). Inhibition of integrin αvβ3 expression with siRNA reduced virus entry, calcium release, and plaque formation. HSV deleted for gH binds to cells and activates Akt, but is impaired for calcium signaling and virus entry. Activation of Akt by HSV is followed by integrin signaling, release of intracellular calcium, and phosphorylation of focal adhesion kinase (FAK) which provides a favorable environment for entry of the virus into the cell (Cheshenko et al., 2014). Binding of HSV-1 to cells also activates the epidermal growth factor receptor (EGFR)- PI3K signaling pathway, resulting in phosphorylation of cofilin and polymerization of actin which facilitates virus entry (Zheng et al., 2014).

CMV attachment and receptor binding, like HSV, induces PI3K/Akt signaling. CMV infection triggers PI3K activation in serum-starved human embryonic lung fibroblasts within the first 30 minutes of infection with UV-inactivated CMV. PI3K activation subsides 2 hours after infection and resumes 4 hour after infection (Johnson et al., 2001; McFarlane et al., 2011). While CMV protein synthesis is dispensable for the first phase of PI3K activation, it is necessary for the second phase of activation. Inhibition of PI3K with LY294002 delays CMV entry, and reduces immediate-early and early gene expression, and viral DNA replication. Infection of cells with CMV results in phosphorylation of platelet-

derived growth factor receptor (PDGFR)-α which interacts with the p85 subunit of PI3K and activates Akt (Soroceanu et al., 2008). Akt activation may be mediated by CMV gB binding to cells, since overexpression of gB induces phosphorylation of Akt and PDGFR-α (Cobbs et al., 2014). Treatment of cells with CMV neutralizing antibody reduced Akt activation (Andreoni et al., 2002). HCMV activates PI3K/Akt and inhibits apoptosis in monocytes by upregulating Mcl-1 (Chan et al., 2010).

Entry of EBV and KSHV into cells also induces PI3K/Akt signaling. EBV gp350 binding to CD21, the virus receptor on B cells, triggers Akt and GSK-3β activation (Barel et al., 2003). The interaction of KSHV glycoproteins with integrins induces phosphorylation of FAK and subsequently Src, PI3K, and c-Cbl (Chakraborty et al., 2011; Krishnan et al., 2006; Naranatt et al., 2003; Sharma-Walia et al., 2004; Valiya Veettil et al., 2010; Veettil et al., 2006). KSHV gB induces phosphorylation of Akt (Sharma-Walia et al., 2004; Zhang et al., 2005). PI3K is important for induction of Cdc42 Rho and RhoA GTPases and cytoskeletal changes in KSHV-infected cells (Sharma-Walia, Naranatt et al. 2004). PI3K inhibition reduces infectivity and cytoskeletal changes associated with KSHV gB, but does not affect virus binding to cells (Valiya Veettil, Sadagopan et al. 2010 Tiwari and Shukla 2010). KSHV induces phosphorylation of the p85 subunit of PI3K within one minute of infection which return to normal levels 30 minutes after infection (Kerur et al., 2010).

Herpesvirus tegument proteins activate PI3K/Akt

Herpesvirus tegument proteins are located between the viral envelope and capsid and are released into the cell immediately after virus entry. HSV encodes two tegument proteins, VP11/12 and US3 protein kinase, that modulate the PI3K/Akt pathway (Benetti and Roizman, 2006; Eaton et al., 2014; Wagner and Smiley, 2011). VP11/12, the most abundant HSV tegument protein, is phosphorylated by Lck and interacts with the p85 subunit of PI3K. VP11/12 is essential for activation of PI3K/Akt by HSV (Wagner and Smiley 2011). The carboxyl terminal region of VP11/12 contains a PI3K p85 subunit binding domain (YTHM) and two Src family kinase (SFK) motifs (YETV and YEEI) which together are important for activation of Lck and binding to PI3K p85 (Strunk et al., 2013).

HSV US3, one of two HSV encoded protein kinases, does not share sequence homology with Akt or activate Akt directly, but serves as an functional homolog of Akt and phosphorylates several Akt substrates including GSK-3β, FOXO1, TSC2 (Chuluunbaatar et al., 2010). Phosphorylation of TSC2 by US3 at the same sites as those phosphorylated by Akt results in activation of mTORC1, which enhances protein translation and HSV replication. Phosphorylation of GSK3β by US3 inactivates GSK3β and promotes stable microtubule formation and virus spread (Naghavi et al., 2013). Infection of cells with an HSV US3 null mutant results in constitutive Akt activation. Deletion of US3 results in increased phosphorylation of VP11/12 by SFKs and by the HSV UL13 protein kinase (Eaton et al., 2014). Thus, US3 inhibits phosphorylation of VP11/12 by SFKs and UL13 resulting in inhibition of VP11/12 signaling and Akt activation. While Akt is activated throughout the entire replicative cycle during infection of cells with an HSV US3 null mutant, Akt is only activated at early time points after infection with wild-type HSV (Benetti and Roizman, 2006).

VZV infection activates Akt and inhibition of PI3K or Akt reduces VZV replication (Rahaus et al., 2007; Sen et al., 2014). Infection with VZV results in phosphorylation of downstream targets of Akt including mTOR, FOXO1, 4EBP1, and S6K1. Expression of VZV protein kinases ORF47 and ORF66 increases Akt activation; conversely VZV deleted for ORF47 and ORF66 results in reduced phosphorylation of Akt and GSK-3β. The VZV ORF12 tegument protein associates with the p85 subunit of PI3K and activates Akt at both threonine 308 and serine 473 (Liu and Cohen, 2013). Activation of Akt by ORF12 protein is important for cell cycle progression in VZV-infected cells, since inhibition of Akt activity reduces the differences observed in cell cycle progression with wild-type and ORF12 deleted VZV. The role of CMV, EBV, and KSHV tegument proteins in activating the PI3K/Akt pathway has not been reported.

Activation of the PI3K/Akt pathway by herpesvirus proteins expressed during virus replication

While entry of herpesviruses into cells and subsequent release of tegument proteins can transiently activate the PI3K/Akt pathway, viral protein synthesis is required to sustain activation of PI3K/Akt. HSV 2 UL39 encodes the large subunit of HSV ribonucleotide reductase (ICP10) which contains an amino terminal serine–threonine protein kinase domain (ICP10PK). ICP10PK functions as a constitutively activated growth-factor receptor that activates PI3K/Akt and Ras/ERK pathways (Laing et al., 2008; Laing et al., 2010; Smith, 2005). While ICP10PK mediated PI3K activation was initially believed to responsible for preventing apoptosis in HSV-2 infected cells (Laing et al., 2008; Laing et al., 2010; Perkins et al., 2002a; Perkins et al., 2002b), more recent studies indicate that ICP10PK protects cells from apoptosis by binding to caspase-8 and disrupting its interaction with FADD, which is independent of activation of PI3K (Dufour et al., 2011). These observations are supported by the fact that the HSV-2 homolog of UL39 in HSV-1 (ICP6) does not have similar serine-threonine kinase activity and does not activate Akt, but also binds caspase-8 and blocks apoptosis (Chung et al., 1989; Dufour et al., 2011).

While activation of Akt by CMV can be detected 96 hours after infection, long term activation requires the expression of CMV proteins during viral replication. Expression of CMV major immediate-early protein 1 (IEP72) or 2 (IEP86) activates PI3K and Akt and inhibits apoptosis (Cobbs et al., 2008; Yu and Alwine, 2002). PI3K activity is required for upregulation of the anti-apoptotic protein c-FLIP by CMV IEP86 (Chiou et al., 2006).

EBV encodes two immediate-early proteins BRLF1 and BZLF1 which are essential for lytic replication and reactivation from latency. Overexpression of BRLF1, but not BZLF1, in normal human fibroblasts activates PI3K/Akt signaling (Darr et al., 2001). Activation of PI3K/Akt signaling is required for BRLF1 activation of the BZLF1 and BMRF1 early promoters, but not the SM early promoter, in epithelial cells.

KSHV G-protein-coupled receptor (vGPCR), transmembrane protein K1, and viral IL-6 (vIL-6) all activate PI3K/Akt. KSHV vGPCR activates multiple signaling pathways including ERK, p38, NF-AT, and PI3K (Bais et al., 1998; Cannon and Cesarman, 2004; Montaner et al., 2001; Pati et al., 2003; Smit et al., 2002). Expression of KSHV vGPCR results in translocation of Akt to the plasma membrane and increased levels of bcl-2 mRNA

and protein which inhibits apoptosis (Abboud et al., 2013). Activation of PI3K/Akt by vGPCR results in inactivation of GSK-3β and activation of NF-AT which is a transcription factor that mediates expression of inflammatory cytokines (Bais et al., 1998; Cannon and Cesarman, 2004; Montaner et al., 2001; Pati et al., 2003; Smit et al., 2002). PI3K/Akt activation by GPCR also results in phosphorylation of TSC-2, mTOR, 4EPB1, and S6K1 to enhance translation and cell proliferation (Sodhi, Chaisuparat et al. 2006). Constitutive activation of Akt by vGPCR has an essential role in KSHV sarcomagenesis (Sodhi et al., 2004). KSHV K1, which is a functional mimic for BCR signaling, has a carboxyl terminal ITAM motif and recruits Lyn, Syk, and the p85 subunit of PI3K to constitutively activate PI3K/Akt (Prakash et al., 2005; Tomlinson and Damania, 2004; Xue et al., 2014). KSHV K1 activation of Akt is associated with phosphorylation and inhibition of FOX01, GSK3β, and BAD which are important for inhibition of apoptosis, and phosphorylation of mTOR which may increase translation and endothelial cell transformation (Wang et al., 2006). K1 also inhibits expression of PTEN, which inhibits the activity of PI3K. KSHV vIL-6 binds to its receptor gp130 to activate PI3K/Akt and the JAK2/STAT3 pathway which contributes to reprogramming of endothelial cells to lymphatic cells (Morris et al., 2008; Morris et al., 2012). Expression of the KSHV immediate-early protein Rta, which is required for reactivation from latency, also activates Akt (Li et al., 2012).

Activation of PI3K during herpesviruses latency and reactivation

Herpesviruses establish latency in different cell types with limited or no expression of viral proteins. The PI3K/Akt pathway is activated in cells latently infected with human herpesviruses, and is important for both latency and reactivation. Additional signaling pathways are also important for EBV and KSHV that infect B cells to allow latent infection in these proliferating cells as well as to inhibit apoptosis.

HSV latently infected neurons express no viral proteins, but do express the latency-associated transcript (LAT) which is important for virus reactivation. Mouse neuroblastoma cells stably expressing LAT have higher levels of phosphorylated and total Akt and are more resistant to apoptosis after serum starvation compared with cells not expressing LAT (Li et al., 2010). Maintenance of HSV-1 latency requires persistent PI3K activation which is established by binding of nerve growth factor to the TrkA receptor tyrosine kinase (RTK) (Camarena et al., 2010). The p110α subunit of PI3K is essential to activate PDK1 and maintain HSV-1 latency; treatment of latently infected neurons with inhibitors of PI3K results in HSV-1 reactivation.

Primary B cells latently infected and transformed with EBV express EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs) and have activated PI3K/Akt (Wlodarski et al., 2005). LMP1 is a functional homolog of constitutive CD40 signaling, and LMP2A is a mimic for constitutive BCR signaling; these viral proteins activate multiple cell signaling pathways required to initiate and maintain B cell transformation and virus latency. LMP1 is a transmembrane protein with intracellular carboxyl terminal activating regions CTAR1 and CTAR2. The CTAR domains associate with TNF receptor–associated factors (TRAFs) to activate multiple signaling pathways including PI3K/Akt, NF-κB, MAPK, JNK, AP1, and JAK/STAT that regulate cell growth and transformation (Brinkmann and Schulz, 2006;

Eliopoulos and Young, 2001; Lam and Sugden, 2003; Mainou et al., 2007; Soni et al., 2007). The CTAR1 domain of LMP1 associates with the p85 subunit of PI3K to activate PI3K (Dawson et al., 2003) and contributes to transformation of rodent fibroblasts and growth of EBV-positive nasopharyngeal carcinoma cells in soft agar (Mainou et al., 2005; Shair et al., 2008). Similarly, survival and growth of LMP-1 transgenic B lymphocytes and lymphoma cells requires activation of Akt signaling (Shair et al., 2007). LMP1 activation of PI3K/Akt results in inactivation of FOXO3α, reduction of expression of DNA damage-binding protein 1 (DDB1), and repression of the DNA repair response which may increase genomic instability and the risk of transformation (Chen et al., 2008). Activation of PI3K/Akt by LMP1 is required for interleukin (IL)-10 production and phosphorylation of GSK-3β and S6K1 (Lambert and Martinez 2007).

LMP1 activation of Akt has an important role in preventing apoptosis. Activation of PI3K/Akt by LMP1 inhibits apoptosis mediated by TRAIL and increases expression of the anti-apoptotic c-FLIP protein (Li et al., 2011). Akt inhibits translocation of the pro-apoptotic protein Bax from the cytoplasm to the mitochondria; Bax localization in the mitochondria results in cytochrome release and apoptosis (Tsuruta et al., 2002). LMP1 activation of Akt/PI3K and FOXO3 induces expression of miR-21 (Yang et al., 2013) and upregulates Mcl-1 both of which reduce apoptosis (Kim et al., 2012).

EBV LMP2A is a transmembrane protein expressed during latency. LMP2A mimics BCR signaling and is important for EBV latency and virus-induced oncogenesis (Fotheringham et al., 2012; Scholle et al., 2000; Swart et al., 2000). LMP2A associates with Syk and Lyn tyrosine kinases and with scaffold protein Shb to activate Ras, PI3K and Akt (Fukuda and Longnecker, 2007; Matskova et al., 2007; Swart et al., 2000). The ITAM motif of LMP2A is required for activation of Akt (Morrison and Raab-Traub, 2005). Activation of Akt increases the level of XIAP (Hatton et al., 2011) and BclxL (Portis and Longnecker, 2004) which increase survival of EBV-infected B cells. LMP2A activation of Akt in nasopharyngeal carcinoma cells results in activation of mTOR and phosphorylation of 4EBP1 which enhances translation of cellular proteins (Moody et al., 2005). LMP2A activation of Akt also increases survival of epithelial cells (Scholle, Bendt et al. 2000) and inhibits apoptosis mediated by TGF-β in epithelial and Burkitt lymphoma cells (Fukuda, 2004). Activation of PI3K/Akt by LMP2A is important for phosphorylation of FOXO1 and GSK-3β, and for translocation of β-catenin to the nucleus of epithelial cells which may inhibit their differentiation (Morrison et al., 2003). EBV latent EBNA-2 may also contribute to P13K/Akt activation by induction of the p55α regulatory subunit of PI3K (Spender et al., 2006).

Other mechanisms can lead to activation of Akt in EBV-infected cells. EBV encodes microRNA miR-BART7-3p that targets PTEN, enhances activation of Akt, and increases cell migration of nasopharyngeal carcinoma cells (Cai et al., 2014). Hypermethylation of the promoter of INPP4B, a phosphatase that inhibits PI3K/Akt signaling, enhances the PI3K/Akt pathway in EBV-positive nasopharyngeal carcinoma cells (Yuen et al., 2014).

PI3K/Akt has an important role in EBV reactivation from latency. Inhibition of PI3K reduces EBV reactivation induced by BCR signaling in EBV-positive Burkitt lymphoma cell

lines (Iwakiri and Takada 2004, Goswami, Gershburg et al. 2012). Similarly, blocking PI3K impairs TGF-β-induced reactivation of EBV in Burkitt lymphoma cells (Oussaief et al., 2009) and methotrexate-induced EBV reactivation in lymphoblastoid cell lines (Feng et al., 2004).

Activation of Akt/PI3K by KSHV is important for survival of latently infected primary effusion lymphoma cells (Uddin et al., 2005) and monocytes (Gonnella et al., 2013), and for tubule formation in endothelial cells (Wang and Damania, 2008). Akt activation contributes to increased expression of XIAP, phosphorylation of FOXO1 and GSK-3β, prevention of cytochrome c release from mitochondria, and inhibition of cleavage of caspase-3, caspase-9, and PARP in KSHV-positive primary effusion lymphoma cells (Uddin et al., 2005).

The KSHV latency associated proteins include LANA (ORF73), v-cyclin (ORF72), v-FLIP (ORF71), Kaposins, LANA2, vIRF3, and K10.5. Inhibition of PI3K activity results in increased cytoplasmic localization of LANA2 which may reduce the ability of LANA2 to block apoptosis (Munoz-Fontela et al., 2005). KSHV v-FLIP induces secretion of cytokines which activate Akt (Sharma-Walia et al., 2012). Inhibition of Akt activity inhibits KSHV reactivation from latently infected primary effusion lymphoma cells induced by treatment with a p53 activator or a Cdk1 inhibitor, but enhances KSHV reactivation induced by treatment with phorbol ester (TPA) (Li et al., 2012; Peng et al., 2010). Inhibition of PI3K reduces KSHV reactivation induced by BCR signaling in KSHV-positive Burkitt lymphoma cell lines, and this effect is associated with reduced expression of KSHV Rta (Kati et al., 2013).

Thus the PI3K/Akt pathway is critical for maintaining HSV, EBV, and KSHV latent infection; inhibition of PI3K/Akt reduces EBV and KSHV reactivation induced by BCR signaling, but enhances reactivation of HSV and of KSHV induced by treatment with other stimuli.

PI3K and immunodeficiencies

Recently two immunodeficiencies have been reported in association with mutations in the p110 catalytic or p85 regulatory subunits of PI3K. Two groups have reported patients with severe herpesvirus infections who have heterozygous gain-of-function mutations in *PIK3CD*, which encodes PI3Kδ (Angulo et al., 2013; Lucas et al., 2014a). These patients presented with fatal varicella-zoster virus pneumonia, persistent CMV viremia, CMV lymphadenitis, persistent EBV viremia, EBV-positive B cell lymphomas, or other infections including severe otitis, sinusitis, pneumonia, and bacterial meningitis. They also had prominent lymphadenopathy, nodular lymphoid hyperplasia, increased levels of IgM, and impaired responses to vaccination. In each patient a dominant gain-of-function mutation in one allele of *PIK3CD* resulted in constitutive activation and phosphorylation of Akt and increased activation of mTOR. The patients had reduced CD4 T cells, reduced naïve T cells, reduced memory B cells, increased effector memory T cells, increased senescent CD8 effector T cells, and enhanced activation-induced T cell death. Treatment of one patient with sirolimus reduced lymphoid hyperplasia, and increased naïve T cells (Lucas et al., 2014a), while hematopoietic stem cell transplant was curative in another patient (Angulo et al., 2013). The disease is referred to as APDS (activated PI3K-delta syndrome (Angulo et al.,

2013)) or PASLI (p110delta-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (Lucas et al., 2014). Additional patients have been described with EBV-negative lymphomas and with infections due to pathogens other than herpesviruses (Crank et al., 2014; Hartman et al., 2014; Kracker et al., 2014).

Patients with heterozygous gain-of-function mutations in *PIK3R1*, which encodes the p85 regulatory subunit of PI3K, were reported with an immunodeficiency syndrome with recurrent bacterial upper and lower respiratory tract infections (Deau et al., 2014; Lucas et al 2014b). One patient had persistent asymptomatic CMV and EBV viremia as well as gastroenteritis due to enterovirus. Like patients with mutations in *PIK3CD*, patients with mutations in *PIK3R1* also have increased phosphorylation of Akt, increased mTOR signaling, increased IgM, reduced naïve T cells, reduced memory B cell function, increased senescent CD8 T cells, and enhanced activation-induced T cell death. The disease is referred to as APDS2 (activated PI3Kdelta syndrome 2).

PI3K/Akt pathway in herpesvirus associated malignancies

EBV and KSHV are oncogenic viruses associated with B cell and epithelial cell malignancies. PI3K/Akt is activated in EBV-positive post-transplant lymphoproliferative disease, Hodgkin lymphoma, nasopharyngeal carcinoma, and gastric carcinoma (Alsayed et al., 2008; Chen, 2012). Similarly, the PI3K/Akt pathway is activated in Kaposi's sarcoma and primary effusion lymphoma (Bhatt et al., 2010; Sodhi et al., 2004; Uddin et al., 2005). Therefore, inhibition of the PI3K/Akt pathway is a potential target for the treatment of EBV and KSHV associated malignancies.

Targeting the PI3K/Akt pathway to inhibit virus replication and virus-associated malignancies

While a number of small molecule inhibitors are available to block PI3K/Akt activity in vitro and many of these have been shown to inhibit herpesvirus replication, most of these drugs are not licensed for use in humans. Recently miltefosine, which blocks Akt phosphorylation, has been approved for use in leishmaniasis. Pre-treatment of cultured cells with miltefosine, followed by HSV-2 infection, inhibited virus plaque formation (Cheshenko, Trepanier et al. 2013). Further studies showed the miltefosine blocked virus entry into epithelial cells, calcium release, and reactivation of virus from explanted ganglia to epithelial cells. Miltefosine inhibited replication of acyclovir-sensitive and acyclovir resistant HSV-2 strains. Several PI3K inhibitors are currently in trials for treatment of malignancies (Bauer et al., 2014; Blachly and Baiocchi, 2014; Tasian et al., 2014). Recently, a small molecule inhibitor of PI3Kδ (idelalisib) was approved for treatment of patients with relapsed chronic lymphocytic leukemia and follicular B cell lymphoma (Furman et al., 2014; Gopal et al., 2014). Thus, Akt or PI3K inhibitors might be used for treatment of anti-viral resistant herpesvirus infections in the future.

The PI3K/Akt pathway results in activation of mTOR. While several mTOR inhibitors are in clinical trials for cancer therapy (Bauer et al., 2014; Blachly and Baiocchi, 2014; Tasian et al., 2014), at present only sirolimus (also known as rapamycin), everolimus, and temserolimus are approved for use in humans. These drugs are immunosuppressive and used

in transplant recipients and for treating selected malignancies. Sirolimus inhibits the growth of KSHV primary effusion lymphoma cells in vitro (Sin et al., 2007). Replacement of cyclosporine with sirolimus therapy in 15 kidney transplant recipients with Kaposi's sarcoma resulted in the resolution of Kaposi's sarcoma skin lesions (Stallone et al., 2005). Substitution of calcineurin inhibitors with sirolimus in 14 patients with post-transplant Kaposi's sarcoma resulted in complete remissions in two patients and partial responses in 8 patients (Lebbe et al., 2006). Similarly, a pooled analysis from several transplant centers showed that substitution of immunosuppressive regimens in 12 renal transplant recipients with regimens containing either sirolimus or everolimus resulted in resolution of Kaposi's sarcoma lesions in 11 patients (Campistol and Schena, 2007).

Sirolimus also inhibits EBV-positive B cell lymphomas in a xenogenic mouse model and in EBV LMP2/Myc transgenic mice (Cen and Longnecker, 2011; Nepomuceno et al., 2003). In three patients with EBV-associated post-transplant lymphoma, replacement of calcineurin inhibitors and mycophenolate mofetil or azathioprine with sirolimus resulted in complete resolution of B cell lymphomas in two patients and a temporary remission of a T cell lymphoma in one patient (Boratynska and Smolska, 2008). A pooled analysis of 19 renal transplant recipients with post-transplant lymphoproliferative disease from multiple European transplant centers showed that substitution of calcineurin inhibitors with sirolimus or everolimus, along with rituximab therapy in six patients and chemotherapy in six patients, resulted in complete remission of disease in 15 patients (Pascual, 2007). While sirolimus has a partially inhibitory effect on EBV-positive B cell lymphoma lines and resistance to sirolimus is associated with high levels of phosphorylated Akt, the addition of a PI3Kδ inhibitor to sirolimus enhanced the ability of the latter to kill the cells (Furukawa et al., 2013). Similarly, an experimental drug that inhibits both PI3K and mTOR was more effective than either PI3K or mTOR inhibitors to inhibit the growth of KSHV-positive primary effusion lymphoma cells in vitro and in a xenograft tumor model (Bhatt, Bhende et al. 2010

Conclusions

Human herpesviruses express multiple proteins during the immediate-early, early, and late phases of the virus replication cycle and during latency that activate the PI3K/Akt pathway. Activation of PI3K/Akt by viral glycoproteins such as gB in HSV, CMV, and KSHV, HSV gD, and EBV gp350, as well as tegument proteins of HSV and VZV present during herpesvirus entry is important for preparing the cell for virus infection to optimize virus replication. Similarly, activation of PI3K/Akt by immediate-early proteins such as CMV IE1 and IE2, and Rta in EBV and KSHV are important for the initial stages of virus infection. Herpesvirus proteins expressed in the early phase of virus replication, such as KSHV vIL-6 and vGPCR, also contribute to PI3/Akt activation. PI3K/Akt is also critical for maintaining latent herpesvirus infection and this pathway is activated by HSV LAT and the EBV latency proteins LMP1, LMP2, and EBNA-2. PI3K-Akt signaling is required for optimizing protein synthesis, cell growth, transformation, and inhibiting apoptosis. Constitutive activation of PI3K due to mutations in the cellular genes *PIK3CD* or *PIK3R1* result in severe herpesvirus infections due to impaired cellular immunity.PI3K/Akt is activated in several EBV and KSHV associated B cell and epithelial cell malignancies. Recently, several drugs that block

Akt or PI3K have been licensed for treatment of malignancies or for a parasitic infection. These include miltefosine, which blocks Akt phosphorylation and inhibits HSV in vitro and idelalisib, which blocks PI3Kδ. These drugs, and others currently under development, might be used to treat human herpesvirus infections or virus-associated malignancies. Inhibitors of mTOR, such as sirolimus, everolimus, and temserolimus, which block signaling downstream of PI3K/Akt might also have a role in treating herpesvirus infections. Thus, further studies and development of inhibitors of the PI3K/Akt pathway may lead to novel therapies for both acute herpesvirus infections and for virus-associated malignancies.

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Highlights

- Human herpesvirus replication and latency proteins activate the PI3K/Akt pathway.
- PI3K/Akt is important for protein synthesis, transformation, and blocking apoptosis.
- Constitutive activation of PI3K is associated with severe herpesvirus infections.
- PI3K/Akt is activated in several EBV and KSHV associated malignancies.
- Drugs that block PI3K/Akt might be used to treat herpesvirus infections or cancers.

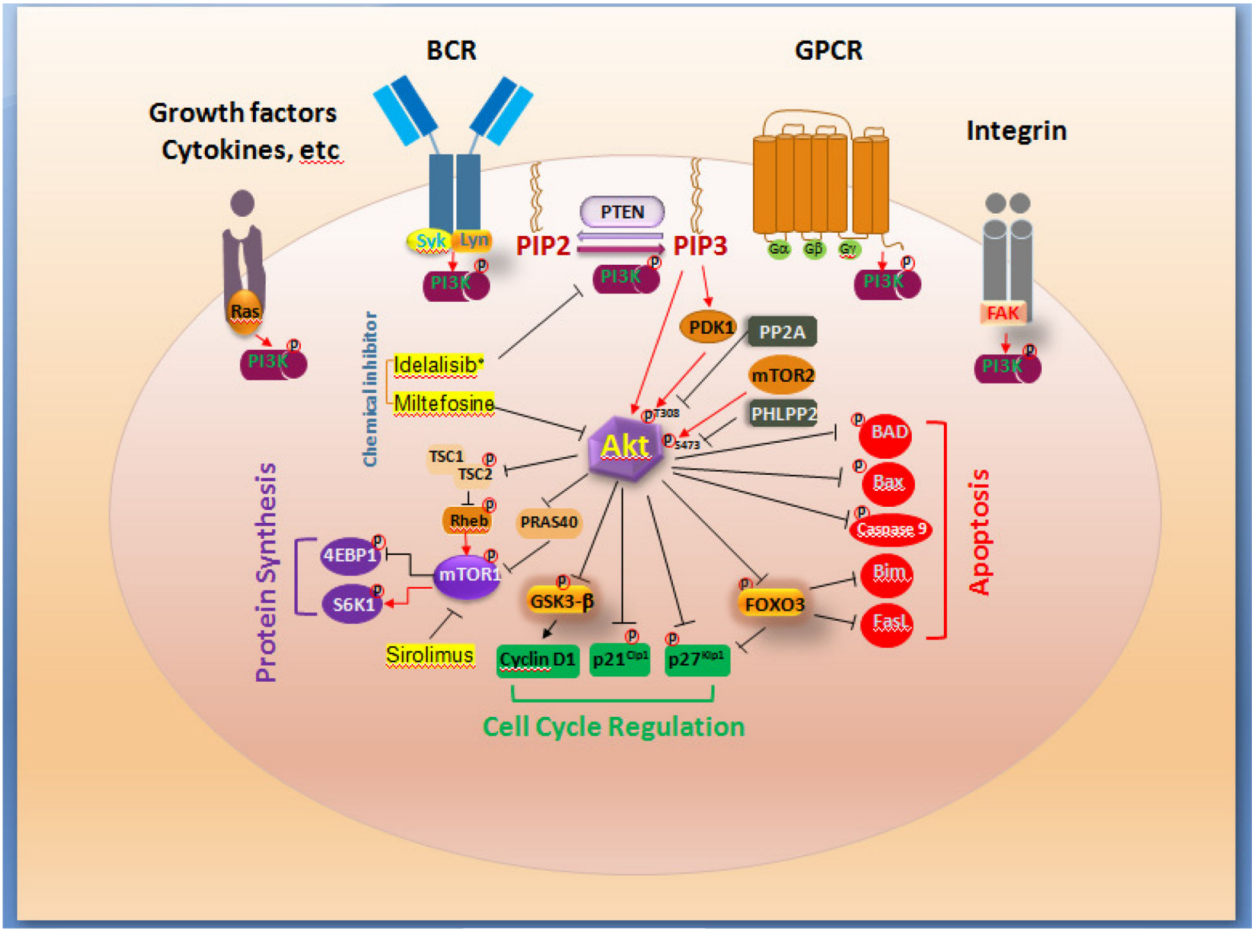

Fig. 1.

Receptor-mediated activation of PI3K-Akt pathway and signaling. Binding of ligands to cell surface receptors induces activation of PI3K. Activated PI3K converts membrane-bound PIP2 to PIP3. PTEN dephosphorylates PIP3 to form PIP2. PIP3 recruits PDK1 and Akt to the plasma membrane, resulting in Akt phosphorylation by PDK1. Akt can be dephosphorylated by PP2A and PHLPP2. Activated Akt (a) stimulates protein synthesis by phosphorylation of mTOR inhibitor TSC2, leading to mTOR1 activation, and phosphorylation of 4EBP1 (an inhibitor of translation) and S6K1, (b) stimulates cell cycle progression by phosphorylation of cell cycle inhibitors $p21^{Cip1}$ and $p27^{Kip1}$ for their degradation, and phosphorylation and inactivation of transcriptional factors GSK-3β and FOXO3, leading to increased cyclin D1 and reduced $p27^{Kip1}$ expression, and (c) inhibits apoptosis by phosphorylation and inactivation of proapoptotic proteins BAD, Bax, caspase 9, and transcriptional factor FOXO3 to reduce Bim and FasL expression. * indicates that idelalisib blocks PI3Kδ only.

Table 1

Herpesvirus proteins that modulate the PI3K/Akt pathway

	Virus Protein	Location in virus, expression kinetics	Cellular target for viral protein	Effect of modulating PI3K/Akt signaling
HSV1	gB	Envelope, γ	Akt, PILRα	Virus entry
		Envelope, γ	Nectin-1, HVEM, 3-OS HS	Virus entry
	gH	Envelope, γ	integrins	Virus entry
	VP11/12	Tegument, γ	Lck, p85 subunit of PI3K	
	US3	Tegument, γ	GSK-3, FOX1, TSC2	Protein translation
	LAT	Latency		Latency
HSV2	ICP10	Lytic, β	caspase-8	Anti-apoptosis
VZV	ORF12	Tegument, γ*	p85 subunit of PI3K	Cell cycle progression
	ORF47	Tegument, γ*		
	ORF66	Tegument, γ*		
HCMV	gB	Envelope, γ	integrins	Virus entry
	IE1	Lytic, α		Anti-apoptosis
	IE2	Lytic, α		Anti-apoptosis
EBV	gp350	Envelope, γ	CD21	Virus entry
	BRLF1 (Rta)	Lytic, α		Reactivation from latency
	LMP1	Latency	CD40 mimic, TRAFs, p85 subunit of PI3K	Anti-apoptosis, protein translation, transformation
	LMP2A	Latency	BCR mimic, Syk, Lyn, Shb	Anti-apoptosis, protein translation
	EBNA-2	Latency	p55α subunit of PI3K	B cell proliferation
KSHV	gB	Lytic, γ*	Integrins	Virus entry
	K1	Lytic, β, low level expression in latency	BCR mimic, p85 subunit of PI3K, Syk, Lyn	Anti-apoptosis, protein translation
	vGPCR	Lytic, β	GPCR mimic	Anti-apoptosis, protein translation
	vIL-6	Lytic, β, low level expression in latency	IL-6 mimic (binds to gp130)	Anti-apoptosis; Reprogramming of endothelial cells to lymphatic cells
	Rta	Lytic, α		Reactivation from latency

PILRα, paired immunoglobulin-like type 2 receptor-α; HVEM, herpesvirus entry mediator; 3-OS HS, 3-O-sulfated heparan sulfate

*Putative kinetic assignment, inferred from its homolog in HSV