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A narrative review: exploring viral-induced malignancies through the lens of dysregulated cellular metabolism and glucose transporters

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Abstract

Introduction In this narrative review, we unravel the complex interplay between oncogenic viruses, cellular metabolism, and glucose transporter (GLUT) dysregulation in viral-induced malignancies.

Methods By explaining the diverse mechanisms through which seven major oncoviruses manipulate metabolic pathways and GLUT expression, particularly GLUT1, we provide novel insights into the critical role of metabolic reprogramming in viral replication and oncogenesis.

Results Our exploration of the molecular pathways targeted by viral oncoproteins reveals a similarity between the metabolic alterations induced by viral infections and those observed in neoplastic transformation. A key finding of our review is the overexpression of GLUTs, particularly GLUT1, as a hallmark of both viral infections and many cancers.

Conclusions By elucidating the complex interplay between viral oncoproteins, oncogene activation, tumor suppressor gene loss, and GLUT overexpression, we highlight the potential of GLUTs as novel targets for diagnosis, prognosis, and therapy of viral-induced malignancies.

Keywords Glucose transporters (GLUTs), Metabolic reprogramming, Viral infections, Cancer metabolism, Warburg effect

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Background

The recent update of the "Hallmarks of Cancer" review has underscored the significance of metabolic transformation in cancer cells, identifying dysregulation of cellular metabolism as an emerging hallmark. This altered metabolism is a critical player in oncogenesis, driven by the activation of oncogenes and the loss of tumor suppressor genes [1].

Glucose, the primary energy source for mammalian cells, undergoes a complete breakdown to produce 36 adenosine triphosphate (ATP) molecules in the presence of oxygen. However, cancer cells favor glycolysis, particularly in hypoxic conditions, a metabolic pathway that yields only two ATP molecules from a single glucose molecule [2]. In fact, in cancerous cells, aerobic glycolysis becomes an increased source of energy. This metabolic phenomenon involves the conversion of pyruvate into lactate using the enzyme lactate dehydrogenase (LDH), even in the presence of oxygen. This effect involves the modulation of crucial regulatory enzymes involved in aerobic glycolysis, including glucose transporters (GLUTs), hexokinase, phosphofructokinase, pyruvate kinase, and LDH [3].

Glucose, as a nonpolar molecule, requires the assistance of GLUTs for active cellular entry, as it cannot passively diffuse into cells. The family of GLUTs plays a critical role in facilitating the initial steps of glucose utilization within cells. Based on their affinity, structure, and functions, 14 GLUT proteins are expressed in humans, and they are categorized into three classes based on sequence similarity [4, 5]. The first class, GLUT1-4, is the most extensively studied. GLUT1 is mainly expressed in erythrocytes, fibroblasts, and various tissues. GLUT2 is primarily found in pancreatic beta cells, the liver, and the kidney. GLUT3 is mainly present in the brain, and GLUT4, an insulin-responsive glucose transporter, is expressed in the heart, skeletal muscle, adipose tissue, and brain [5].

Cancer cells exhibit an increased demand for glucose compared to normal cells, mainly because of their uncontrolled proliferation. This heightened demand is facilitated by the upregulation of GLUTs and the manipulation of various metabolic pathways. Overexpression of these transporters can promote carcinogenesis and enhance tumor invasiveness [6]. Interestingly, their expression could also serve as diagnostic and prognostic markers for cancer.

One notable clinical use of altered glucose metabolism in cancer cells is using glucose analogs, such as fluorodeoxyglucose (FDG), in tumor identification and monitoring. FDG accumulates in cancerous cells due to high expression levels of GLUTs and its inability to undergo glycolysis. FDG has been applied to diagnose various cancers. This method has improved cancer monitoring through positron emission tomography (PET) [7, 8].

Studies have also shown non-specific overexpression of various GLUT isoforms, particularly GLUT1, across diverse human tissues, with pronounced upregulation in hypoxic regions surrounding necrotic zones within tumors. These findings suggest that GLUTs may serve as promising targets for cancer therapeutics [9]. Recent studies have revealed that metabolic reprogramming in cancer is influenced by the activation of oncogenes or the loss of tumor suppressors, contributing to tumor progression [10].

Oncogenic viruses play a significant role in the development of malignancies, accounting for nearly 15% of cancer cases [11, 12]. These viruses exert their influence by manipulating various cellular pathways, particularly those related to glucose metabolism and energy supply. Similar to malignant cells that rely on the Warburg effect for energy supply and proliferation, oncogenic viruses also depend on this metabolic phenomenon for their survival [13, 14]. Previous studies have highlighted the involvement of viral oncogenic proteins in initiating and manipulating various metabolic signaling pathways [15].

Notably, while viral infections commonly result in a dysregulated expression of GLUTs, numerous types of cancer have also reported upregulation of GLUTs due to disruptions in gene expression, protein re-localization, or stabilization. In this paper, we will discuss the molecular mechanisms underlying changes in GLUT expression during viral infections and investigate the specific types of GLUTs that become activated in response to different oncoviruses.

This review will, particularly, investigate the involvement of GLUTs in the development of malignancies caused by several RNA and DNA oncoviruses, including Human Papillomavirus (HPV), Hepatitis C Virus (HCV), Human T-lymphotropic Virus 1 (HTLV-1), Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), and Kaposi's Sarcoma-associated Herpesvirus (KSHV). These viruses are causative agents for various forms of tumors in distinct types of tissues. For example, HPV is responsible for cancer in epithelial cells, whereas HTLV-1 and HBV cause cancer in lymphocytes and hepatocytes, respectively.

What is particularly fascinating is that despite their variations in genetic composition, replication cycle, and the kinds of malignancies they induce, different viruses often impact similar metabolic pathways, especially those involving GLUTs. Oncoviruses successfully manipulate cell processes using glucose transporters, allowing for rapid growth. This shared characteristic emphasizes the significance of GLUTs in the development of cancer caused by viruses and their potential as targets that may be widely used for therapeutic intervention. Hence,

this review will provide valuable insights into the role of GLUTs in the context of both viral infections and cancer.

HPV

HPV is a highly prevalent sexually transmitted infection (STI) with a significant impact on public health. It is caused by a group of more than 200 related viruses, with about 40 types specifically affecting the genital area as well as the mouth and throat [16, 17]. Despite their prevalence, most HPV infections are asymptomatic and do not lead to serious health problems. However, certain types of HPV are associated with the development of genital warts and various cancers [18]. HPV infection, particularly the HPV16 subtype, is implicated in the etiology of lung and cervical cancers. A key aspect of HPV16 oncogenicity is its ability to increase GLUT1 expression in cancer cells, which is driven by the viral oncoproteins E6 and E7 through the manipulation of various pathways to promote malignancy [19] (Fig. 1).

Firstly, the E6 oncoprotein of HPV16 is known to degrade the p53 tumor suppressor protein, thereby inhibiting apoptosis and altering glucose metabolism. This degradation leads to increased glycolysis through Tp53-induced glycolysis and apoptosis regulator (TIGAR) and the upregulation of GLUT1 and GLUT4, which is a hallmark of cancer cell metabolism [9, 20, 21].

Additionally, c-Myc, a well-known oncogene, interacts with E6, resulting in the upregulation of glycolysis-related enzymes, including enolase 1 (ENO-1), hexokinase 1/2 (HK1/2) phosphofructokinase 1/2 (PFK1/2), GLUT1, and lactate dehydrogenase A (LDHA). This interaction underscores the complex network of oncogenic signals that promote cancer cell survival and proliferation [22–24].

In lung cancer cell lines, the overexpression of E6 has been shown to increase the expression of thioredoxin (Trx), a disulfide reductase that plays a role in the intracellular antioxidant system and is necessary for maintaining oxidative stress balance and protecting cells from

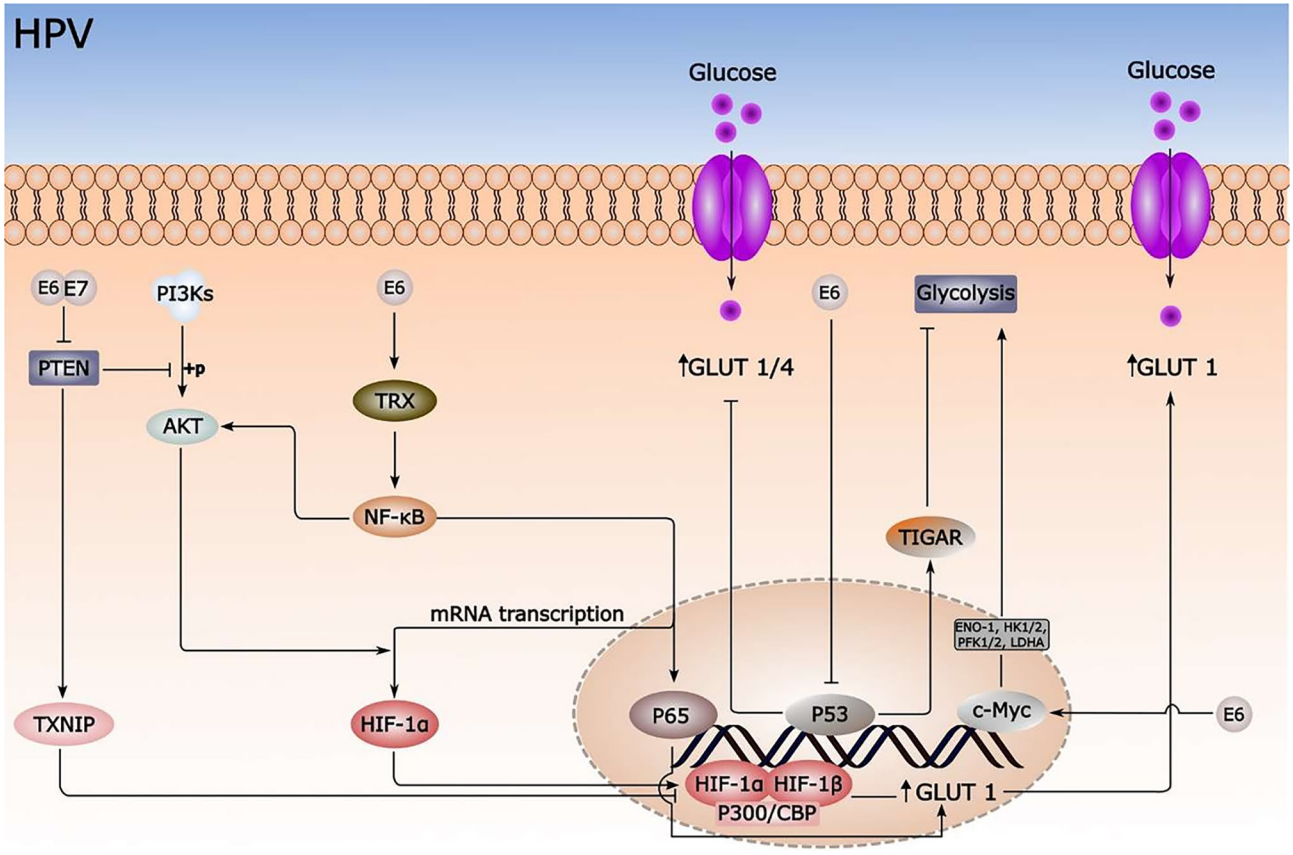

Fig. 1 HPV and GLUTs Dysregulation. The E6/E7 proteins enhance the nuclear accumulation of HIF-1α through the downregulation of PTEN and its downstream TXNIP. Concurrently, E6/E7 proteins activate the PI3K/AKT pathway, which also results in the nuclear accumulation of HIF-1α. The E6 protein increases the expression of TRX, activating the NF-κB pathway and promoting the transcription of HIF-1α. This nuclear accumulation of HIF-1α upregulates GLUT1 expression at both mRNA and protein levels. The E6 protein also degrades the P53 tumor suppressor protein, leading to the upregulation of GLUT1/4 and an increase in glycolysis through TIGAR. Furthermore, the interaction of E6 with c-Myc upregulates ENO-1, HK1/2, PFK1/2, GLUT1, and LDHA, thereby enhancing glycolysis (E6 does not alter Myc expression levels but increases Myc phosphorylation, leading to enhanced stability and transcriptional activity of c-Myc). * '+p' denotes phosphorylation of the associated protein or molecule

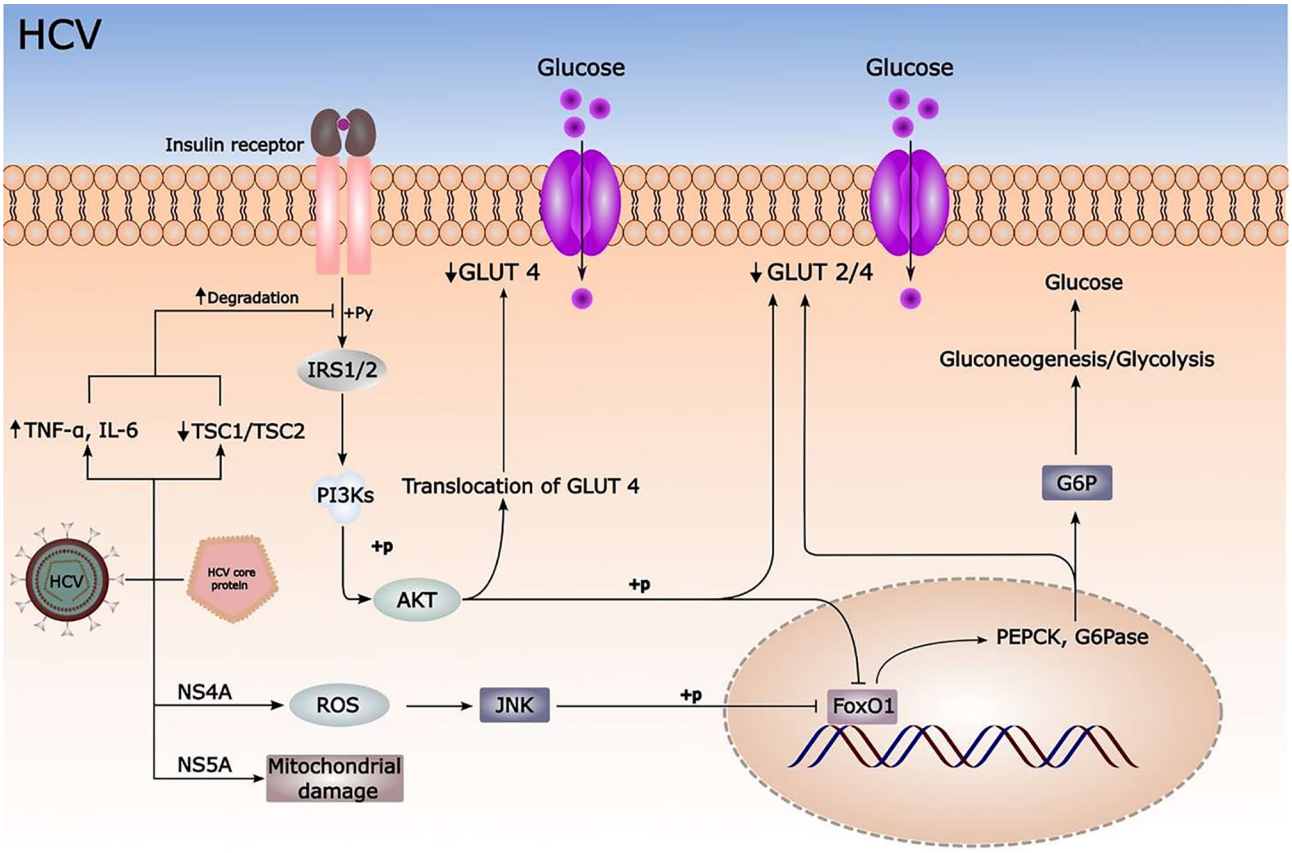

Fig. 2 HCV and GLUTs Dysregulation. The HCV core protein leads to the upregulation of TNF-α and interleukin-6, and the downregulation of the TSC1/TSC2 complex. This combination results in the degradation of IRS1/2, leading to the downregulation of the PI3K/AKT pathway. This downregulation subsequently decreases the translocation of GLUT4 to the cellular membrane and increases the nuclear accumulation of FoxO1. The HCV non-structural proteins NS4A and NS5A induce. mitochondrial damage, leading to the production of reactive oxygen species (ROS) and activation of the JNK pathway. This results in decreased phosphorylation of FoxO1, leading to its nuclear accumulation. FoxO1 is a regulatory protein involved in glucose metabolism. The nuclear accumulation of FoxO1 upregulates gene expression of PEPCK and G6Pase, leading to increased gluconeogenesis and glucose production, and the downregulation of GLUT2/4.* '+p' denotes phosphorylation of the associated protein or molecule

oxidative damage. Trx, in turn, activates the NF-κB pathway, a transcription factor that results in the transcription of hypoxia-inducible factor −1 α (HIF-1α), which upregulates GLUT1 expression. Additionally, the activation of NF-κB results in the nuclear translocation of P65 and, finally, upregulation of GLUT1 mRNA and protein levels [25].

The thioredoxin-interacting protein (TXNIP) regulates the intracellular redox state and glucose metabolism, which are associated with GLUT1 expression and glucose uptake. In lung cancer, HPV16 E6/E7 proteins downregulate PTEN, leading to the inhibition of TXNIP expression. This inhibition results in the accumulation of HIF-1α by inhibiting the translocation of nuclear HIF-1α to the cytoplasm and the upregulation of GLUT1 expression at both mRNA and protein levels [26].

Furthermore, HPV infection, particularly with high-risk types like HPV-16, significantly alters cellular signaling pathways, including the PI3K/Akt/HIF-1α/GLUT axis. The HPV oncoproteins E6 and E7 activate the PI3K/Akt signaling pathway, leading to several downstream effects crucial for cancer progression, including metabolic changes. The activation of the PI3K/Akt pathway can induce the stabilization and activation of HIF-1α, even under normoxic conditions. This HPV-induced pseudo-hypoxic state promotes the expression of genes involved in angiogenesis, metabolism, and epithelial-mesenchymal transition (EMT). HIF-1α activation, in turn, increases the expression of various GLUTs, particularly GLUT1 [27]. When investigating the prognostic value of cervical cancer, high GLUT1 expression and the presence of the HPV16 subtype are independent prognostic factors for overall survival. High GLUT1 expression is associated with older age, squamous cell carcinoma, advanced tumor stage, pelvic lymph node metastases, and a lower rate of hysterectomy. The prognostic impact is particularly significant in the HPV16-positive group, which also exhibits decreased immune cell scores [28]. Furthermore, another study found that cervical tumor cells enhance glucose utilization by upregulating GLUT1. According

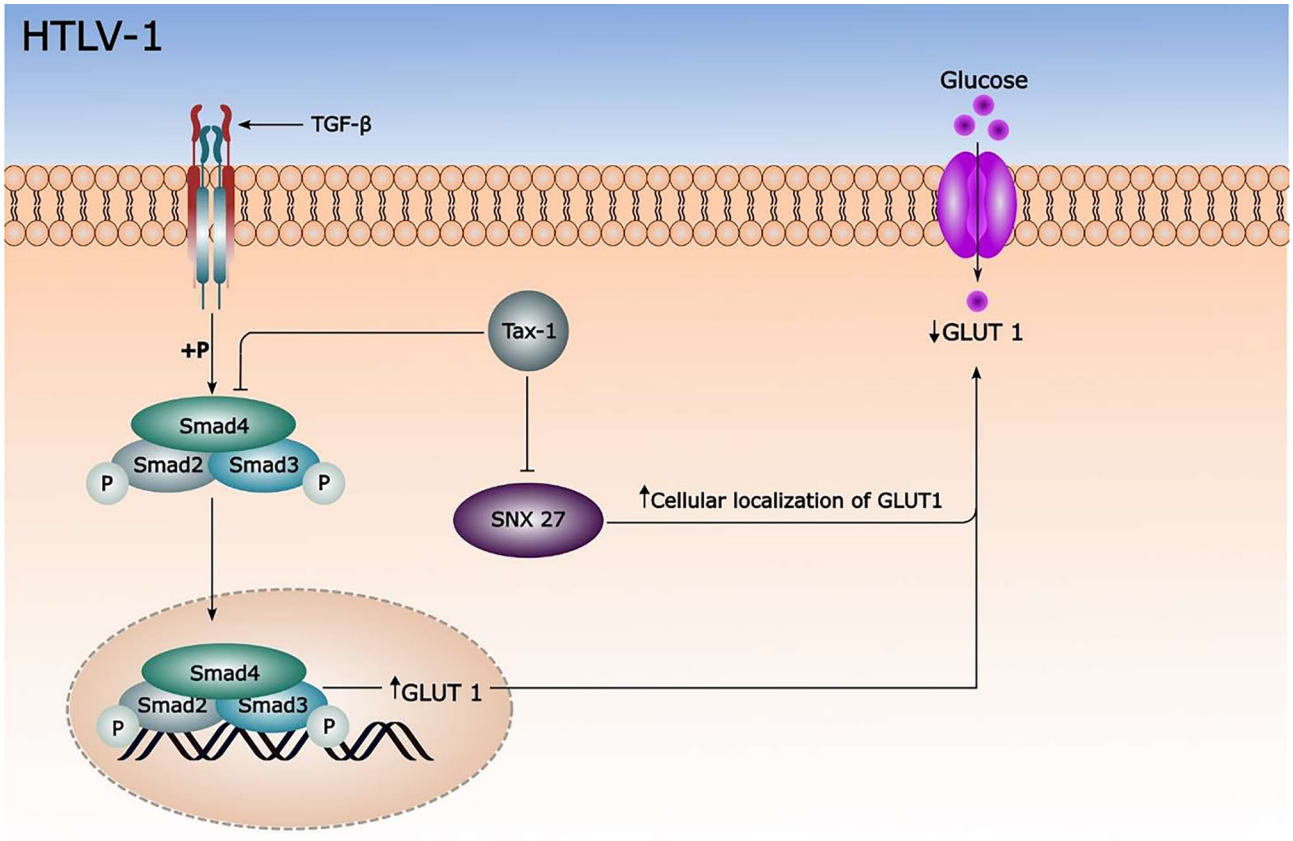

Fig. 3 HTLV1 and GLUTs Dysregulation. TGF-β promotes the phosphorylation of Smad proteins. The phosphorylated Smad 2/3/4 complex translocates to the nucleus, leading to increased expression of GLUT1. The SNX27 protein promotes the recycling of GLUT1 to the plasma membrane. TAX-1 downregulates the Smad and SNX27 pathways, resulting in decreased expression and translocation of GLUT1 *'+p' denotes phosphorylation of the associated protein or molecule. ** 'p' vector indicates phosphorylated proteins

to the strong induction of *GLUT1* mRNA and protein in HPV-positive cervical squamous intraepithelial neoplasia 3 (CIN 3) lesions, it was concluded that GLUT1 overexpression is an early event in cervical neoplasia [29].

In summary, the HPV16 subtype is a critical factor in the development of lung and cervical cancers, primarily through the modulation of glucose metabolism by its E6 and E7 oncoproteins. The upregulation of GLUT1 expression is a key event in this process, with significant implications for cancer prognosis and potential therapeutic strategies.

HCV

HCV is a single-stranded RNA virus that belongs to the Flaviviridae family. Within infected individuals, the RNA replication process of HCV is error-prone, resulting in high genetic diversity and the emergence of genetically related variants called quasispecies. Variations in the hypervariable region can indicate the presence of different quasispecies, which may contribute to the chronicity of HCV infection. The genome of the virus consists of a single open reading frame (ORF), which is made up of 3010 amino acids. This ORF is flanked by non-translated regions (NTRs) at the 5' and 3' ends, which play a crucial role in viral replication and translation. The 5' NTR contains an internal ribosome entry site that is responsible for initiating the translation of the HCV protein. The translation of the HCV protein leads to the formation of a single polyprotein. This polyprotein is then processed by cellular proteases to produce the structural proteins that make up the viral particles, such as the core and envelope glycoproteins E1 and E2. The polyprotein is alternatively processed by viral proteases to produce nonstructural (NS) proteins such as p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. As of 2015, an estimated 71 million people worldwide were affected by chronic HCV infection, with varying prevalence rates across regions. The primary modes of HCV transmission include transfusion of blood products and unsafe healthcare practices [30, 31]. HCV infection is a major cause of advanced hepatic fibrosis and cirrhosis, with a significantly increased risk for the development of hepatocellular carcinoma (HCC) [32] (Fig. 2).

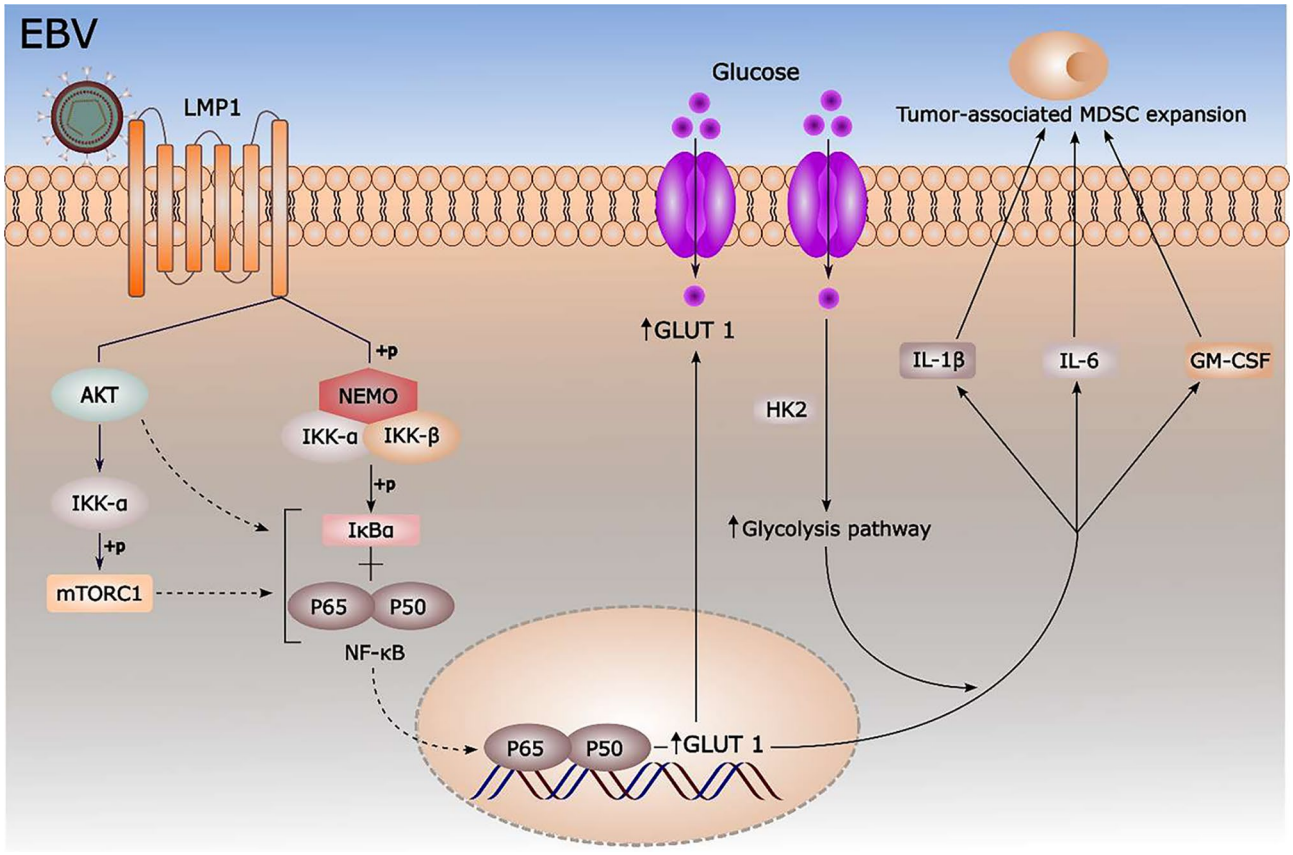

Fig. 4 EBV and GLUTs Dysregulation. LMP1 upregulates the AKT/mTORC1 and NF-κB pathways. Additionally, the activation of AKT/mTORC1 modulates NF-κB. This activation of NF-κB upregulates the expression of GLUT1 through the P50 and P65 heterodimers. The upregulation of GLUT1 and deregulation of HK2 lead to increased production of IL-1β, IL-6, and GM-CSF, resulting in the induction of myeloid-derived suppressor cells (MDSCs). * '+p' denotes phosphorylation of the associated protein or molecule

HCV infection disrupts glucose metabolism through various mechanisms. Notably, the HCV proteins NS4A and NS5A induce mitochondrial damage, leading to the production of reactive oxygen species and activation of the JNK pathway. This ultimately results in decreased phosphorylation and nuclear accumulation of FoxO1, a regulatory protein involved in glucose metabolism of the liver, muscle, adipose tissue, and pancreas, thereby impacting glucose metabolism by upregulating enzymes involved in glucose production pathways, such as glucose-6 phosphatase and phosphoenolpyruvate carboxy kinase 2, which result in increased gluconeogenesis, glycolysis, and down-regulation of GLUT2/4 [33, 34]. The downregulation of GLUT2/4 in HCV infection, while seemingly counterintuitive, aligns with observations in overall hepatocellular carcinoma (HCC). In HCC, GLUT2 expression often decreases in preneoplastic and neoplastic hepatic lesions, while other GLUTs, particularly GLUT1, may be upregulated.

Furthermore, HCV core proteins interfere with insulin signaling pathways by upregulating the Ser312 phosphorylation of insulin receptor substrate 1 (IRS-1) (the key molecule involved in the propagation of insulin signal downstream from the insulin receptor), promoting its degradation and impairing insulin signaling to the PI3K/Akt pathway. Additionally, HCV proteins interact with cellular structures such as the endoplasmic reticulum (ER) and mitochondria, resulting in oxidative stress and the upregulation of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin 8, interleukin 6 (IL-6), transforming growth factor β (TGF-β), suppressor of cytokines (SOC3), and Fas ligand. This infection also down-regulates the TSC1/TSC2 complex and causes subsequent upregulation of mTOR/S6K1, which leads to Ser1101 phosphorylation of IRS-1 and its subsequent degradation. These events, along with the down-regulation of the TSC1/TSC2 complex and the induction of TNF-α/IL-6 production, disrupt insulin-mediated transactivation of the glucose transporter GLUT4, leading to reduced glucose uptake and contribute to insulin resistance and tumorigenesis [35–37].

In HCC, various glucose transporters, including GLUT1, GLUT2, GLUT3, GLUT5, GLUT6, and GLUT9, play complex roles. High expression of GLUT1

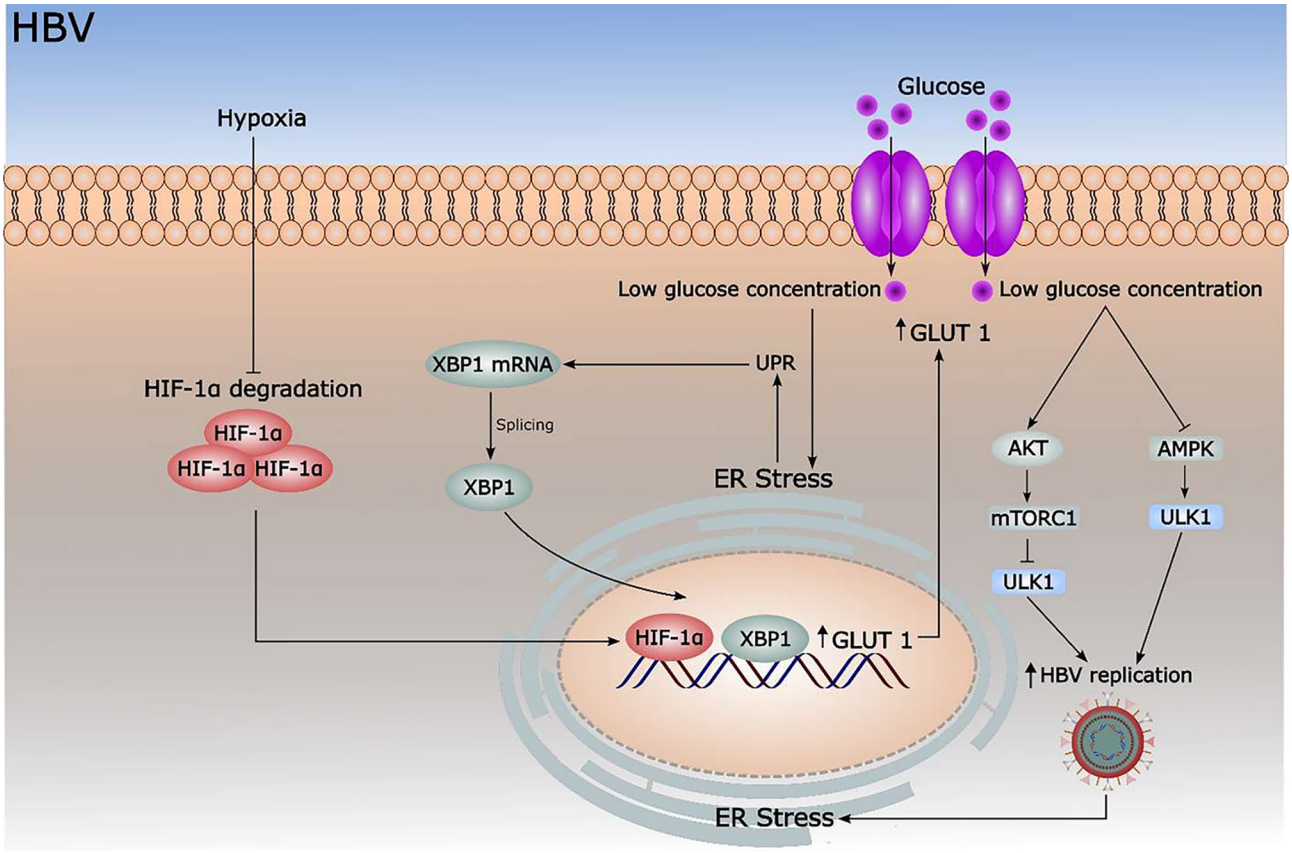

Fig. 5 HBV and GLUTs Dysregulation. HBV replication, in conjunction with low glucose concentration and hypoxia, induces ER stress, which in turn triggers the splicing of XBP1 to its activated form. XBP1 enhances the expression of HIF-1α, which is further stabilized from degradation under hypoxic conditions. XBP1 cooperates with HIF-1α to increase the expression of GLUT1. Additionally, the low glucose concentration in the infected cells augments HBV replication via the AKT/mTORC1/ULK1 and AMPK/ULK1 pathways. Additionally, hypoxia inhibits HIF-1 degradation, leading to HIF-1 nuclear accumulation
*UPR: The Unfolded Protein Response

is associated with larger tumor size, increased vascular invasion, and a poorer prognosis. GLUT2 expression is elevated in HCC but decreased in preneoplastic and neoplastic hepatic lesions. High expression of GLUT3 is linked to elevated α-fetoprotein levels, large tumor size, poor histological differentiation, poor prognosis, and reduced overall survival in HCC [38–40]. Other GLUTs, such as GLUT5, GLUT6, and GLUT9, also exhibit significant involvement in HCC. For example, GLUT5 expression is significantly higher in liver metastases compared to primary lung tumors and is elevated in liver carcinoma [9, 41]. These findings highlight the diverse roles of different GLUTs in HCC and suggest potential implications for future research and therapeutic strategies.

It is important to note that studies specifically discussing GLUT status in HCV-associated HCC are scarce. In this review, we have discussed GLUT regulation in HCV infection and HCC separately, considering the overlapping pathways between HCV infection and HCC development as potentially sharing similar etiologies. While HCV infection influences glucose metabolism through modulation of GLUT1, GLUT2, and GLUT4, the alterations in GLUT expression in HCC are not necessarily specific to HCV-related cases. For instance, the overexpression of various GLUTs, including GLUT1, GLUT2, GLUT3, GLUT5, GLUT6, and GLUT9, has been observed in HCC regardless of etiology. Future research should focus on elucidating the specific mechanisms by which HCV infection may contribute to altered GLUT expression in the context of HCC development.

In summary, HCV infection influences glucose metabolism through the modulation of GLUT1, GLUT2, and GLUT4, contributing to the pathogenesis of the diseases associated with this virus.

HTLV

HTLV-1 is the first human oncogenic retrovirus that has been identified as the causative agent of two severe diseases: adult T cell leukemia/lymphoma and myelopathy/tropical spastic paraparesis [42, 43]. HTLV-1 infects nearly 20 million individuals worldwide, with Japan, Africa, the Caribbean, and South America as the endemic regions [44]. The mechanisms of HTLV-1 infection and its cellular tropism are complex and not fully elucidated.

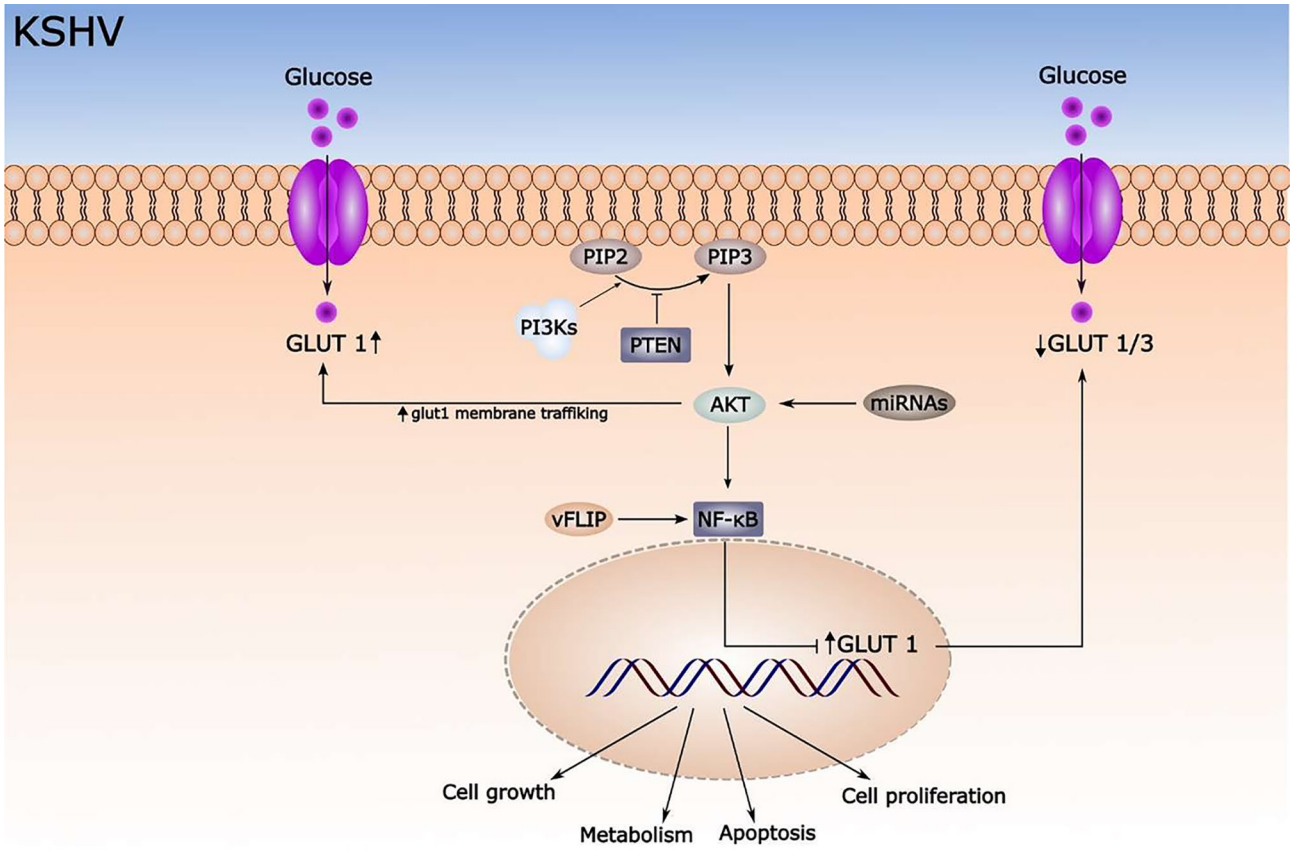

Fig. 6 KSHV and GLUT Dysregulation. The PI3K/AKT/mTORC pathway, which regulates various biological processes including apoptosis, metabolism, cell proliferation, and cell growth, also upregulates membrane localization of GLUT1. KSHV increases membrane trafficking of GLUT1 either by directly targeting PI3K or via PTEN. Conversely, KSHV miRNAs and vFLIP activate AKT and NF-κB, leading to the downregulation of glucose transporters GLUT1 and GLUT3

Several receptors are important in HTLV-1 transmission. For instance, HTLV-1 attaches to heparan sulfate proteoglycan, which is present in the host cell. Additionally, the envelope proteins of the virus, particularly their interactions with the GLUT1 receptor, play a pivotal role in the virus's attachment, entry, and subsequent pathogenicity in host cells [45–48]. The virus's life cycle and pathogenicity are influenced by its regulatory and accessory genes, with the regulatory gene Tax-1 playing a crucial role in virus replication and the transcription of viral gene products. The PDZ binding motif at the carboxyl terminus of Tax-1 is important in cellular transformation. GLUT1 is a key receptor for HTLV-1, and its interaction with the virus's envelope glycoproteins is essential for the virus's entry into host cells. The expression of GLUT1 is not inherent in quiescent primary T cells but is induced upon T cell activation, which is significant as it enhances the infectivity of HTLV-1. Moreover, the expression of GLUT1 on T lymphocytes is increased by mitogens or TGF-β, which in turn increases the infectivity of HTLV-I [49]. Interestingly, while overexpression of GLUT1 in cells that produce HTLV-1 virus-like particles reduces infectivity, overexpression of GLUT3, a closely related protein, does not have the same effect. This specificity suggests that GLUT1's role in HTLV-1 pathogenesis is unique and not easily replicated by other glucose transporters [47] (Fig. 3).

TAX-1 is a multifunctional protein that not only drives the transcription of viral gene products but also interacts with various host cell proteins to modulate the virus's life cycle. One such interaction is with nexin 27 (SNX27), which is involved in the recycling of GLUT1 from endosomal vesicles to the plasma membrane. This interaction is crucial for maintaining GLUT1 expression on the cell surface, and disruption of this interaction leads to reduced surface expression of GLUT1, increased release of HTLV-1 into the supernatant, and decreased cell-to-cell-mediated HTLV-1 infection. The interaction between TAX-1 and SNX27 may alter this regulation, potentially affecting the receptor molecule's availability for HTLV-1. Moreover, plasma membrane-bound receptor molecules have been shown to interfere with virion release and infectivity in other retroviruses, including human immunodeficiency virus (HIV) [50].

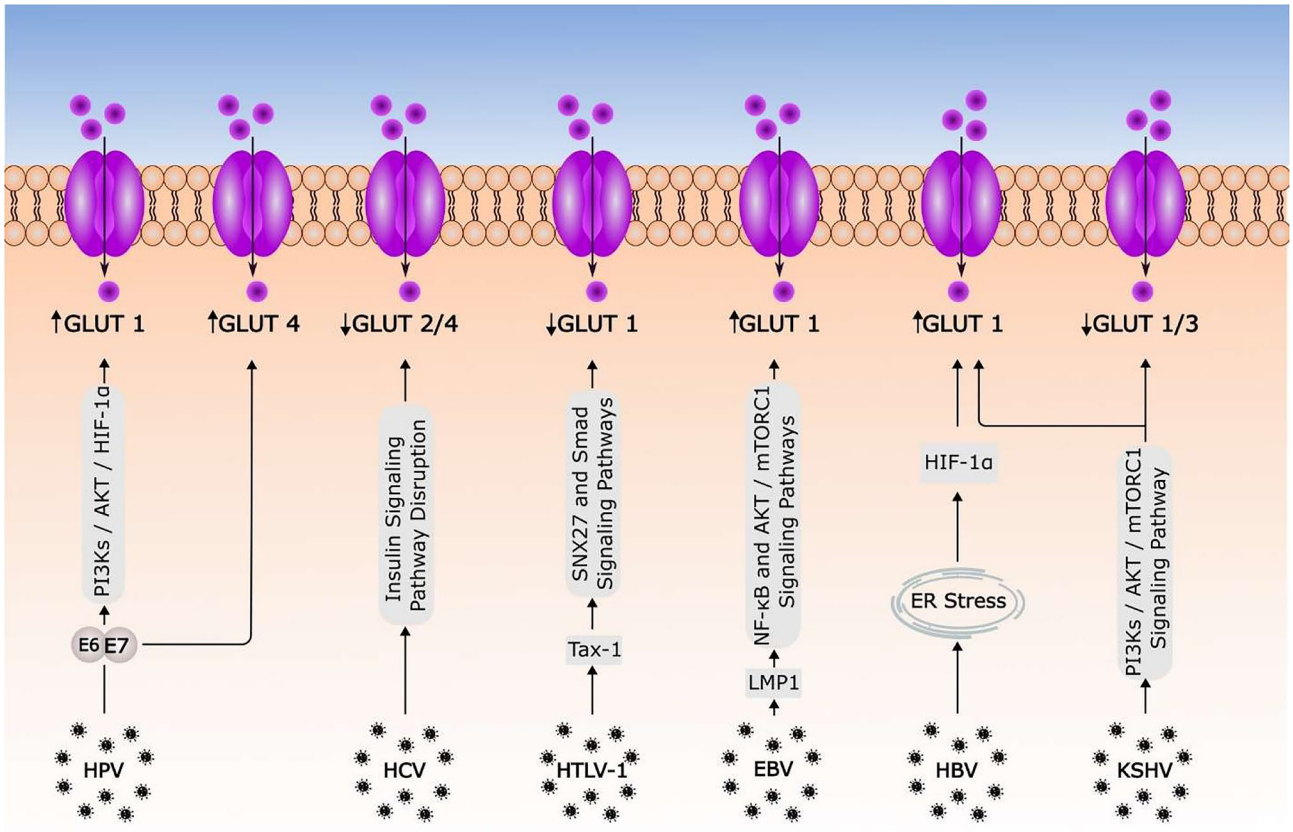

Fig. 7 Oncoviral Manipulation of Glucose Metabolism and GLUT Expression. This figure summarizes the key mechanisms by which oncoviruses (HPV, HCV, HTLV-1, EBV, HBV, and KSHV) alter cellular glucose metabolism and GLUT expression, particularly GLUT1

TGF-β has an important role in preventing the growth of T cells during the mid-G1 phase as well as in promoting tumorigenesis. It achieves this by binding to the Type I (TβRI) and Type II (TβRII) serine/threonine kinase receptor complex, which triggers the phosphorylation of downstream targets, including the Smad proteins. The resulting Smad2/3/4 complex then moves to the nucleus, leading to the increased expression of GLUT1. However, the protein TAX-1 can inhibit this Smad-dependent pathway, which results in a decrease in GLUT1 expression [51].

Overexpression of GLUT1 in HTLV-1-resistant cell lines, such as MDBK, increases the titer of HTLV-1 and HTLV-2 Env-pseudotyped particles [52]. This finding indicates that the level of GLUT1 in target cells correlates with the titer of the HTLV-1/2 Env-pseudotyped virus, suggesting that GLUT1 availability is a limiting factor for HTLV-1 infectivity [53].

In summary, the interactions between HTLV-1, GLUT1, and SNX27 are critical for the virus's life cycle and pathogenesis. The protein interaction between TAX-1 and SNX27 play a significant role in modulating the localization and expression of GLUT1, which in turn affects the infectivity and transmission of HTLV-1. Understanding these molecular mechanisms provides insight into potential therapeutic targets for the treatment of HTLV-1-associated diseases.

EBV

EBV, also known as human herpesvirus 4, is a gamma herpesvirus that infects a large portion of the human population. While generally harmless, EBV can cause infectious mononucleosis, commonly known as mono, in teenagers or young adults. In rare cases, individuals with a healthy immune system can experience chronic active infection [54]. However, EBV has also been linked to various types of cancers, including Burkitt's lymphoma, Hodgkin's lymphoma, natural killer cell lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder, and EBV-positive gastric adenocarcinoma [55]. EBV induces extensive methylation in both the host and viral genomes, which plays a role in facilitating cellular functions that support virus persistence and propagation. Tumors that are positive for EBV exhibit distinct genetic alterations compared to EBV-negative tumors. For example, EBV-positive gastric adenocarcinoma often shows recurring PIK3CA mutations, extensive DNA

hypermethylation, and amplification of the JAK2, CD274, and PDCD1LG2 genes [56].

Nasopharyngeal carcinoma (NPC) is a type of cancer that is strongly associated with EBV. NPC cells tend to have increased expression of GLUT1. This increased expression of GLUT1 is associated with lymph node metastasis and clinical stage [57]. The Epstein-Barr virus latent membrane protein 1 (LMP1) plays a critical role in the transformation of B-cells by mediating NF-κB and AKT/mTORC1 signaling pathways, which in turn influence the expression of GLUT1. As a result, GLUT1, which is typically expressed at low levels, becomes highly expressed during tumorigenesis and is considered a marker of tumor progression. LMP1 upregulates the transcriptional mRNA and protein levels of GLUT1, and knocking down LMP1 expression significantly reduces glucose uptake. Independent data also confirmed these results in different types of EBV-related cancer, such as B-cell lymphomas [58, 59].

Additionally, LMP1 contributes to metabolic reprogramming by disrupting the regulation of glycolysis enzymes such as hexokinase 2 [60]. This reprogramming of EBV-mediated glycolysis in NPC cells leads to increased production of IL-1β, IL-6, and GM-CSF, which results in the induction of myeloid-derived suppressor cells that contribute to T-cell suppression. Similar dysregulation of GLUT1 by LMP1-activated NF-κB has been observed in other types of EBV-related cancers, such as B-cell lymphomas [61].

In summary, EBV, particularly LMP1, influences glucose metabolism in cancer cells, including the upregulation of GLUT1, through the activation of NF-κB and mTORC1 signaling pathways. This alteration in glucose metabolism is a hallmark of various types of cancer, including NPC associated with EBV infection. GLUT1 overexpression in NPC is correlated with tumor progression and metastasis (Fig. 4).

HBV

HBV is a DNA virus that specifically infects hepatocytes (liver cells) and is a leading cause of liver cirrhosis and hepatocellular carcinoma worldwide [62, 63]. The virus enters hepatocytes through the binding of the large HBV surface proteins to the HBV receptor on the cell surface, known as sodium taurocholate co-transporting polypeptide. In chronic HBV carriers, the accumulation of the HBV large surface proteins (LHBs) can trigger an ER overload response, leading to ER stress-mediated cell proliferation, metabolic changes, and genomic instability [64].

One significant consequence of chronic HBV infection is metabolic alterations observed in patients, particularly during the immune-tolerance phase [65]. ER stress signaling, specifically XBP1 (a major, well-conserved component of the unfolded protein response (UPR)), plays a crucial role in regulating glucose metabolism through pathways involving hypoxia-inducible factor 1 (HIF1), GLUT1, and GLUT2. The HIF1 pathway is activated under conditions of low oxygen levels (hypoxia) and plays a vital role in cellular adaptation to hypoxic environments [66, 67]. In the context of HBV infection, HIF1 signaling can induce the transcription of GLUT1 as well as several rate-limiting glycolytic enzymes. This adaptive response may allow hepatocytes to overcome the energy imbalance caused by the hypoxia-induced decline in mitochondrial activity [68, 69] (Fig. 5).

In recent years, many studies have demonstrated that HBV replication depends on the AMPK-ULK1-induced autophagy and Akt/mTOR suppressed ULK1-induced autophagy pathways. Low glucose levels and inhibition of GLUTs activate the AMPK-mTOR-ULK1-autophagy axis in hepatocytes, which is involved in HBV replication [68–71]. Manipulating glucose concentrations and using inhibitors like 2-DG, which inhibit glycolysis and activate the Akt/mTOR pathway, can suppress HBV replication [72].

In summary, HBV infection influences glucose metabolism through the modulation of GLUT1 and GLUT2, contributing to the pathogenesis of the diseases associated with this virus. This understanding of the role of GLUT in HBV infection could provide valuable insights for future research and potential therapeutic strategies.

KSHV

KSHV, also known as human herpesvirus 8, is a virus that can cause several human malignancies, primarily in immunocompromised individuals. These malignancies include Kaposi's sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. KSHV can establish a persistent infection by becoming latent in $CD19^+$ peripheral B-lymphocytes, with the viral genome persisting as a circular episome in the host cell's nucleus. KSHV exhibits a biphasic life cycle consisting of a latent phase and a transient lytic reactivation phase. During the latent phase, the latency-associated nuclear antigen plays a crucial role in maintaining latency and ensuring proper distribution of viral episomes during cell division [73–75]. It is important to note that while KSHV can establish a persistent infection in $CD19^+$ peripheral B-lymphocytes, KS, one of the main malignancies associated with KSHV, is of endothelial cell origin. The prevalence of KSHV varies geographically, with higher rates observed in Sub-Saharan Africa and the Mediterranean region. KSHV infection is most commonly associated with immunodeficiency states, including HIV infection, iatrogenic immunodeficiency, and aging [76] (Fig. 6).

KSHV-infected cells have been found to influence various signal transduction pathways, including the PI3K/

Akt/mTOR signaling pathway. This pathway plays a vital role in regulating multiple biological processes, including apoptosis, metabolism, cell proliferation, and cell growth. By manipulating this pathway, KSHV gains an advantage in promoting the growth and survival of infected cells, particularly those with high proliferation rates that rely on glucose metabolism [76, 77]. PTEN, a dual protein/lipid phosphatase, inhibits the PI3K/Akt pathway primarily by targeting phosphatidylinositol 3,4,5-triphosphate produced by PI3K. In fact, PTEN acts as a tumor suppressor by counteracting the activation of the PI3K/Akt pathway and inhibiting cell growth and proliferation [78].

The PI3K/Akt/mTOR pathway is involved in regulating glucose metabolism, including glucose uptake and glycolysis. Activation of this pathway promotes the expression of GLUT1 and re-localizes it to the cell membrane, thereby increasing glucose uptake [79]. This alteration in GLUT1 expression and membrane exposure is closely linked to cancer progression, as cancer cells require efficient biosynthesis of macromolecules to support their high proliferation rates. The altered GLUT1 membrane trafficking in KSHV-infected cells increases their sensitivity to cell death induced by the glycolysis inhibitor 2-Deoxy-D-glucose (2DG), which inhibits glycolysis [80]. Our review suggests that KSHV-associated malignancies are particularly dependent on glycolysis and glucose uptake through GLUT1. Therefore, therapeutic strategies that target GLUT1 directly or interfere with glycolysis, such as the use of 2DG, may be effective in treating these cancers. By disrupting the altered metabolism that KSHV induces in infected cells, these approaches could potentially inhibit tumor growth and progression. Moreover, the PI3K/Akt pathway has been a target of interest in cancer therapy. Inhibition of this pathway has shown promise in suppressing tumor cell proliferation and inducing apoptosis in vitro and in vivo. Various inhibitors of the PI3K/Akt pathway have been explored in clinical trials as potential anticancer agents [80, 81].

Conversely, it is interesting to note that in another study, it has been suggested that under nutrient stress conditions, KSHV-infected cells downregulate the expression of glucose transporters GLUT1 and GLUT3 through the activation of the AKT and NF-κB pro-survival pathways by KSHV microRNAs and vFLIP, particularly in human KS tumors. This downregulation of GLUT1 and GLUT3 is believed to suppress aerobic glycolysis, which is likely important in these tumors. The study also found that GLUT1 and GLUT3 inhibit the

Table 1 Viral manipulation of glucose metabolism and signaling pathways

Virus	Viral protein	Glycolytic enzymes	Signaling pathways	GLUTs	Associated malignancy	ref
HPV	E6/E7	HK1/2 PFK1/2 ENO-1 LDHA	HIF-1α c-Myc P53 PI3K/Akt NF-κB	GLUT1 GLUT4	Lung Cancer Cervical Cancer	[84] [25, 26] [85]
HCV	NS4A NS5A Core protien	HK2	PI3K/Akt JNK FoxO1	GLUT2 GLUT4	HCC	[86] [87]
HTLV-1	Tax-1	Not known	Smad	GLUT1	ATL HAM/TSP	[88] [89]
EBV	LMP-1	HK2	AKT/mTORC1 NF-κB	GLUT1	NPC DLBCL BL HL NKCL PTLD	[29] [90] [91] [92] [93]
HBV	LHBs	Not known	AKT/mTORC1/ULK1 AMPK/ULK1 HIF-1α XBP1	GLUT1	HCC	[94]
KSHV	miRNA vFLIP	HK2 PKM2 PDK-1	PI3K/Akt, NF-κB, HIF-1α	GLUT1 GLUT3	KS PEL MCD	[95] [73] [82]

HPV: Human Papillomavirus, HCV: Hepatitis C Virus, HTLV-1: Human T lymphotropic virus type-1, EBV: Epstein-Barr Virus, HBV: Hepatitis B Virus, KSHV: Kaposi's Sarcoma-associated Herpesvirus,, E6/E7: HPV-encoded proteins, NS5A: Non-Structural Protein 5 A, NS4A: Non-Structural Protein 4 A, Tax-1: HTLV-1 oncoprotein, LMP-1: Latent Membrane Protein 1, LHBs: hepatitis B virus large surface proteins, miRNA: microRNA, vFLIP: Viral FLICE Inhibitory Protein,, GLUT: Glucose Transporter, HK2: Hexokinase 2, PFK: Phosphofructokinase, ENO: Enolase, PKM2: Pyruvate Kinase M2, PDK-1: Pyruvate Dehydrogenase Kinase 1, HIF-1α: Hypoxia-Inducible Factor 1-α, PI3-K: Phosphoinositide 3-Kinase, mTORC1: Mammalian Target of Rapamycin Complex 1, NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, Akt: Protein Kinase B, AMPK: AMP-activated protein kinase, ULK1: Unc-51 like autophagy activating kinase 1, JNK: c-Jun N-terminal kinases, FoxO1: Forkhead box O1, mTORC: mammalian target of rapamycin complex, HCC: Hepatocellular Carcinoma, ATL: Adult T-cell Leukemia, HAM/TSP: HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis, NPC: Nasopharyngeal Carcinoma, DLBCL: Diffuse Large B-cell Lymphoma,, BL: Burkitt's Lymphoma, HL: Hodgkin's Lymphoma, NKCL: Natural Killer Cell Lymphoma, PTLD: Post-Transplant Lymphoproliferative Disorder, KS: Kaposi's sarcoma, PEL: primary effusion lymphoma, MCD: multicentric Castleman's disease

constitutive activation of the AKT and NF-κB pro-survival pathways [82].

In summary, KSHV infection modulates the PI3K/AKT/mTOR pathway, leading to increased GLUT1 expression and membrane exposure in infected cells. This alteration in glucose metabolism is associated with cancer progression and renders KSHV-infected cells dependent on glycolysis. Targeting GLUT1 and glycolysis inhibitors like 2DG may have potential therapeutic applications in KSHV-associated malignancies.

The Warburg effect, a typical common metabolic shift observed in most tumor cells, is characterized by increased aerobic glycolysis and reduced oxidative phosphorylation for energy production. This adaptation allows cells to thrive in tumor environments and is essential for the survival of tumor cells. During latent infection of endothelial cells, KSHV triggers aerobic glycolysis and lactic acid production while reducing the Warburg effect. Glycolysis inhibitors selectively induce apoptosis in KSHV-infected endothelial cells without affecting uninfected cells [13]. GLUT3 is upregulated in many cancer cell lines under hypoxic conditions, leading to increased glucose uptake. Similarly, GLUT3 expression is synergistically enhanced when KSHV-infected cells are exposed to hypoxia, suggesting that GLUT3 plays a key role in the elevated glucose uptake in KSHV-infected cells [83].

Conclusions

This review provides a detailed explanation of the crucial role played by glucose transporters in the metabolic reprogramming of virally infected cells and cancer cells (summarized in Table 1; Fig. 7). It also explores how oncoviruses exploit these transporters via different metabolic pathways, with a particular focus on the importance of the Warburg effect.

Our analysis emphasized that GLUT1 is significantly elevated in most cancers, whereas GLUT2 and GLUT4 seem exclusive to certain virus types and the infected tissue. Understanding the intricate methods used by oncoviruses to regulate GLUT activity could be helpful in the development of novel cancer treatments. For instance, developing medications specifically targeting certain GLUTs could disrupt the metabolic advantages of viruses to cancer cells, thereby inhibiting their uncontrolled proliferation and expansion.

As a result, it is vital to research to examine the impact of viral load and the latent phase of viral infection on GLUT expression. Furthermore, it is necessary to assess the possibility of therapeutic options that simultaneously target viral components and GLUT-mediated metabolic pathways.

Overall, the interplay of virology with oncology, specifically in GLUT regulation, presents a hopeful avenue for further exploration of potential strategies for cancer therapy by targeting new factors that might enhance patient outcomes.

Abbreviations

ATP	Adenosine Triphosphate
GLUT	Glucose Transporter
LDH	Lactate Dehydrogenase
FDG	Fluorodeoxyglucose
PET	Positron Emission Tomography
HPV	Human Papillomavirus
HCV	Hepatitis C Virus
HTLV-1	Human T Lymphotropic Virus type-1
EBV	Epstein-Barr Virus
HBV	Hepatitis B Virus
KSHV	Kaposi's Sarcoma-Associated Herpesvirus
STI	Sexually Transmitted Infection
ENO-1	Including Enolase 1
HK1/2	Hexokinase ½
PFK1/2	Phosphofructokinase
LDHA	Lactate Dehydrogenase A
Trx	Thioredoxin
HIF-1α	Hypoxia-Inducible Factor 1-α
TXNIP	Thioredoxin-Interacting Protein
EMT	Epithelial-Mesenchymal Transition
CIN 3	Cervical Squamous Intraepithelial Neoplasia 3
TIGAR	Tp53-Induced Glycolysis and Apoptosis Regulator
ORF	Open Reading Frame
NTRs	Non-Translated Regions
NS	Nonstructural Protein
IRS-1	Insulin Receptor Substrate 1
TNF-α	Tumor Necrosis Factor-α
IL-6	Interleukin 6
TGF-β	Transforming Growth Factorβ
ROS	Reactive Oxygen Species
SOC3	Suppressor Of Cytokines
HCC	Hepatocellular Carcinoma
SNX27	Nexin 27
HIV	Human Immunodeficiency Virus
NPC	Nasopharyngeal Carcinoma
ER	Endoplasmic Reticulum
HIF1	Hypoxia-Inducible Factor 1
KS	Kaposi's Sarcoma
2DG	2-Deoxy-D-glucose
LHBs	Large Surface Proteins
LMP1	Latent Membrane Protein 1
UPR	the Unfolded Protein Response

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References

1. Hirschey MD, DeBerardinis RJ, Diehl AME, Drew JE, Frezza C, Green MF, et al. Dysregulated metabolism contributes to oncogenesis. Sem Cancer Biol. 2015;35:S129–50.
2. Pliszka M, Szablewski L. Glucose transporters as a target for Anticancer Therapy. Cancers. 2021;13(16).
3. Girdhar K, Powis A, Raisingani A, Chrudinová M, Huang R, Tran T, et al. Viruses and metabolism: the effects of viral infections and viral insulins on host metabolism. Annual Rev Virol. 2021;8(1):373–91.
4. Ancey P-B, Contat C, Meylan E. Glucose transporters in cancer – from tumor cells to the tumor microenvironment. 2018;285(16):2926–43.
5. Navale AM, Paranjape AN. Glucose transporters: physiological and pathological roles. Biophys Rev. 2016;8(1):5–9.
6. Barron CC, Bilan PJ, Tsakiridis T, Tsiani E. Facilitative glucose transporters: implications for cancer detection, prognosis and treatment. Metab Clin Exp. 2016;65(2):124–39.
7. Contat C, Ancey PB, Zangger N, Sabatino S, Pascual J, Escrig S et al. Combined deletion of Glut1 and Glut3 impairs lung adenocarcinoma growth. Elife. 2020;9.
8. Kim MJ, Lee CH, Lee Y, Youn H, Kang KW, Kwon J, et al. Glucose-6-phosphatase expression-mediated [(18)F]FDG efflux in murine inflammation and Cancer models. Mol Imaging Biol. 2019;21(5):917–25.
9. Szablewski L. Glucose transporters as markers of diagnosis and prognosis in cancer diseases. Oncol Reviews. 2022;16(1):561.
10. Lee SY, Ju MK, Jeon HM, Lee YJ, Kim CH, Park HG, et al. Oncogenic metabolism acts as a Prerequisite step for induction of Cancer Metastasis and Cancer Stem Cell phenotype. Oxidative Med Cell Longev. 2018;2018:1027453.
11. Tempera I, Lieberman PM. Oncogenic Viruses as Entropic Drivers of Cancer Evolution. Frontiers in virology (Lausanne, Switzerland). 2021;1.
12. Nakhaie M, Charostad J, Azaran A, Arabzadeh SAM, Motamedfar A, Iranparast S, et al. Molecular and Serological Prevalence of HCMV in Iranian patients with breast Cancer. Asian Pac J Cancer Prev. 2021;22(7):2011–6.
13. Delgado T, Carroll PA, Punjabi AS, Margineantu D, Hockenbery DM, Lagunoff M. Induction of the Warburg effect by Kaposi's sarcoma herpesvirus is required for the maintenance of latently infected endothelial cells. Proc Natl Acad Sci USA. 2010;107(23):10696–701.
14. Nakhaie M, Charostad J, Kaydani GA, Faghihloo E. The role of viruses in adenocarcinoma development. Infection, Genetics and Evolution. 2020;86:104603.
15. Noch E, Khalili K. Oncogenic viruses and tumor glucose metabolism: like kids in a candy store. Mol Cancer Ther. 2012;11(1):14–23.
16. Okunade KS. Human papillomavirus and cervical cancer. J Obstet Gynaecology: J Inst Obstet Gynecol. 2020;40(5):602–8.
17. Charostad J, Azaran A, Nakhaei M, Astani A, Kaydani GA, Motamedfar A, et al. Upregulation of Interleukin-6 in HPV-Positive breast Cancer patients. Iran J Immunol. 2021;18(4):315–30.
18. Serrano B, Brotons M, Bosch FX, Bruni L. Epidemiology and burden of HPV-related disease. Best Pract Res Clin Obstet Gynecol. 2018;47:14–26.
19. Sitarz K, Czamara K, Szostek S, Kaczor A. The impact of HPV infection on human glycogen and lipid metabolism - a review. Biochim et Biophys acta Reviews cancer. 2022;1877(1):188646.
20. Li S, Hong X, Wei Z, Xie M, Li W, Liu G et al. Ubiquitination of the HPV Oncoprotein E6 is critical for E6/E6AP-Mediated p53 degradation. 2019;10.
21. Suzuki S, Tanaka T, Poyurovsky MV, Nagano H, Mayama T, Ohkubo S, et al. Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. Proc Natl Acad Sci USA. 2010;107(16):7461–6.
22. Dong Y, Tu R, Liu H, Qing G. Regulation of cancer cell metabolism: oncogenic MYC in the driver's seat. Signal Transduct Target Therapy. 2020;5(1):124.
23. Arizmendi-Izazaga A, Navarro-Tito N, Jiménez-Wences H, Mendoza-Catalán MA, Martínez-Carrillo DN, Zacapala-Gómez AE, et al. Metabolic Reprogramming Cancer: Role HPV 16 Variants. 2021;10(3):347.
24. Dang CV, MYC. microRNAs and glutamine addiction in cancers. Cell Cycle (Georgetown Tex). 2009;8(20):3243–5.
25. Gao ZY, Gu NJ, Wu MZ, Wang SY, Xu HT, Li QC, et al. Human papillomavirus16 E6 but not E7 upregulates GLUT1 expression in lung cancer cells by upregulating thioredoxin expression. Technol Cancer Res Treat. 2021;20:15330338211067111.
26. Tang JY, Li DY, He L, Qiu XS, Wang EH, Wu GP. HPV 16 E6/E7 promote the glucose uptake of GLUT1 in Lung Cancer through downregulation of TXNIP due to inhibition of PTEN Phosphorylation. Front Oncol. 2020;10:559543.
27. Zhang E, Feng X, Liu F, Zhang P, Liang J, Tang X. Roles of PI3K/Akt and c-Jun signaling pathways in human papillomavirus type 16 oncoprotein-induced HIF-1α, VEGF, and IL-8 expression and in vitro angiogenesis in non-small cell lung cancer cells. PLoS ONE. 2014;9(7):e103440.
28. Rudlowski C, Becker AJ, Schroder W, Rath W, Büttner R, Moser M. GLUT1 messenger RNA and protein induction relates to the malignant transformation of cervical cancer. Am J Clin Pathol. 2003;120(5):691–8.
29. Zhang J, Jia L, Lin W, Yip YL, Lo KW, Lau VMY et al. Epstein-Barr Virus-Encoded Latent membrane protein 1 Upregulates Glucose Transporter 1 transcription via the mTORC1/NF-κB signaling pathways. J Virol. 2017;91(6).
30. Martinez MA, Franco S. Discovery and Development of Antiviral therapies for Chronic Hepatitis C virus infection. Advances in experimental medicine and biology. 2021;1322:139–57.
31. Manns MP, Buti M, Gane E, Pawlotsky J-M, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nat Reviews Disease Primers. 2017;3(1):17006.
32. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65(4):727–33.
33. Shoji I, Deng L, Hotta H. Molecular Mechanism of Hepatitis C Virus-Induced Glucose Metabolic Disorders. 2012;2.
34. Bose SK, Ray R. Hepatitis C virus infection and insulin resistance. World J Diabetes. 2014;5(1):52–8.
35. García-Monzón C, Lo Iacono O, Mayoral R, González-Rodríguez A, Miquilena-Colina ME, Lozano-Rodríguez T, et al. Hepatic insulin resistance is associated with increased apoptosis and fibrogenesis in nonalcoholic steatohepatitis and chronic hepatitis C. J Hepatol. 2011;54(1):142–52.
36. Parvaiz F, Manzoor S, Iqbal J, Sarkar-Dutta M, Imran M, Waris G. Hepatitis C virus NS5A promotes insulin resistance through IRS-1 serine phosphorylation and increased gluconeogenesis. World J Gastroenterol. 2015;21(43):12361–9.
37. Mihm S, Hepatitis C. Virus, diabetes and steatosis: clinical evidence in favor of a linkage and role of genotypes. Dig Dis (Basel Switzerland). 2010;28(1):280–4.
38. Sun HW, Yu XJ, Wu WC, Chen J, Shi M, Zheng L, et al. GLUT1 and ASCT2 as predictors for prognosis of Hepatocellular Carcinoma. PLoS ONE. 2016;11(12):e0168907.
39. Amann T, Maegdefrau U, Hartmann A, Agaimy A, Marienhagen J, Weiss TS, et al. GLUT1 expression is increased in hepatocellular carcinoma and promotes tumorigenesis. Am J Pathol. 2009;174(4):1544–52.
40. Hamann I, Krys D, Glubrecht D, Bouvet V, Marshall A, Vos L, et al. Expression and function of hexose transporters GLUT1, GLUT2, and GLUT5 in breast cancer-effects of hypoxia. Faseb j. 2018;32(9):5104–18.
41. Gao H, Hao Y, Zhou X, Li H, Liu F, Zhu H, et al. Prognostic value of glucose transporter 3 expression in hepatocellular carcinoma. Oncol Lett. 2020;19(1):691–9.
42. Zarei-Ghobadi M, Sheikhi M, Teymoori-Rad M, Yaslianifard S, Norouzi M, Yaslianifard S, et al. HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) versus adult T-cell leukemia/lymphoma (ATLL). BMC Res Notes. 2021;14(1):109.
43. Cook LB, Melamed A, Niederer H, Valganon M, Laydon D, Foroni L, et al. The role of HTLV-1 clonality, proviral structure, and genomic integration site in adult T-cell leukemia/lymphoma. Blood. 2014;123(25):3925–31.
44. Gonçalves DU, Proietti FA, Ribas JG, Araújo MG, Pinheiro SR, Guedes AC, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 2010;23(3):577–89.
45. Casseb J, de Oliveira AC, Vergara MP, Montanheiro P, Bonasser F, Meilman Ferreira C, et al. Presence of tropical spastic paraparesis/human T-cell lymphotropic virus type 1-associated myelopathy (TSP/HAM)-like among HIV-1-infected patients. J Med Virol. 2008;80(3):392–8.
46. Lim AG, Maini PK. HTLV-I infection: a dynamic struggle between viral persistence and host immunity. J Theor Biol. 2014;352:92–108.

47. Maeda Y, Terasawa H, Tanaka Y, Mitsuura C, Nakashima K, Yusa K, et al. Separate cellular localizations of human T-lymphotropic virus 1 (HTLV-1) env and glucose transporter type 1 (GLUT1) are required for HTLV-1 env-mediated fusion and infection. J Virol. 2015;89(1):502–11.
48. Tanaka A, Jinno-Oue A, Shimizu N, Hoque A, Mori T, Islam S, et al. Entry of human T-cell leukemia virus type 1 is augmented by heparin sulfate proteoglycans bearing short heparin-like structures. J Virol. 2012;86(6):2959–69.
49. Giusti RM, Maloney EM, Hanchard B, Morgan OS, Steinberg SM, Wachter H, et al. Differential patterns of serum biomarkers of immune activation in human T-cell lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis, and adult T-cell leukemia/lymphoma. Cancer Epidemiol Biomarkers Prevention: Publication Am Association Cancer Res Cosponsored Am Soc Prev Oncol. 1996;5(9):699–704.
50. Al-Saleem J, Dirksen WP, Martinez MP, Shkriabai N, Kvaratskhelia M, Ratner L, et al. HTLV-1 Tax-1 interacts with SNX27 to regulate cellular localization of the HTLV-1 receptor molecule, GLUT1. PLoS ONE. 2019;14(3):e0214059.
51. Okajima M, Takahashi M, Higuchi M, Ohsawa T, Yoshida S, Yoshida Y, et al. Human T-cell leukemia virus type 1 tax induces an aberrant clustering of the tumor suppressor scribble through the PDZ domain-binding motif dependent and independent interaction. Virus Genes. 2008;37(2):231–40.
52. Jones KS, Fugo K, Petrow-Sadowski C, Huang Y, Bertolette DC, Lisinski I, et al. Human T-Cell leukemia virus type 1 (HTLV-1) and HTLV-2 use different receptor complexes to enter. T Cells. 2006;80(17):8291–302.
53. Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M, Battini JL. The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. Cell. 2003;115(4):449–59.
54. Houen G, Trier NH. Epstein-Barr Virus and systemic Autoimmune diseases. Front Immunol. 2020;11:587380.
55. Yang X, Zeng X, Huang J, Yang L, Mao S, Chen X, et al. Loop-mediated isothermal amplification linked a nanoparticles-based biosensor for detecting Epstein-Barr virus. Appl Microbiol Biotechnol. 2024;108(1):91.
56. Ko Y-H. EBV and human cancer. Exp Mol Med. 2015;47(1):e130–e.
57. Grabellus F, Nagarajah J, Bockisch A, Schmid KW, Sheu SY. Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma. Clin Nucl Med. 2012;37(2):121–7.
58. Zhu N, Wang Q, Wu Z, Wang Y, Zeng MS, Yuan Y. Epstein-Barr Virus LMP1-Activated mTORC1 and mTORC2 Coordinately promote nasopharyngeal Cancer Stem Cell Properties. J Virol. 2022;96(5):e0194121.
59. Sommermann TG, O'Neill K, Plas DR, Cahir-McFarland E. IKKβ and NF-κB transcription govern lymphoma cell survival through AKT-induced plasma membrane trafficking of GLUT1. Cancer Res. 2011;71(23):7291–300.
60. Xiao L, Hu ZY, Dong X, Tan Z, Li W, Tang M, et al. Targeting Epstein-Barr virus oncoprotein LMP1-mediated glycolysis sensitizes nasopharyngeal carcinoma to radiation therapy. Oncogene. 2014;33(37):4568–78.
61. Cai TT, Ye SB, Liu YN, He J, Chen QY, Mai HQ, et al. LMP1-mediated glycolysis induces myeloid-derived suppressor cell expansion in nasopharyngeal carcinoma. PLoS Pathog. 2017;13(7):e1006503.
62. Liew ZH, Goh GB, Hao Y, Chang PE, Tan CK. Comparison of Hepatocellular Carcinoma in patients with Cryptogenic Versus Hepatitis B etiology: a study of 1079 cases over 3 decades. Dig Dis Sci. 2019;64(2):585–90.
63. Abdoli A, Nakhaie M, Feizi N, Salimi Jeda A, Ramezani A. Harmonized Autophagy Versus full-fledged Hepatitis B Virus: victorious or defeated. Viral Immunol. 2019;32(8):322–34.
64. Schade Hansen C, Pottegård A, Ekelund U, Kildegaard Jensen H, Lundager Forberg J, Brabrand M, et al. Association between QTc prolongation and mortality in patients with suspected poisoning in the emergency department: a transnational propensity score matched cohort study. BMJ open. 2018;8(7):e020036.
65. Schoeman JC, Hou J, Harms AC, Vreeken RJ, Berger R, Hankemeier T, et al. Metabolic characterization of the natural progression of chronic hepatitis B. Genome Med. 2016;8(1):64.
66. Kim DY, Park SH, Yoon Z, Kim J, Kang MK, Kang YH. Eucalyptol ameliorates retinal microvascular defects through modulating ER stress and angiopoietin-Tie Signaling in Diabetic eyes. Int J Mol Sci. 2024;25(14).
67. López-Hernández B, Ceña V, Posadas I. The endoplasmic reticulum stress and the HIF-1 signalling pathways are involved in the neuronal damage caused by chemical hypoxia. Br J Pharmacol. 2015;172(11):2838–51.
68. Khakpoor A, Ni Y, Chen A, Ho ZZ, Oei V, Yang N et al. Spatiotemporal differences in presentation of CD8 T cell epitopes during Hepatitis B Virus infection. J Virol. 2019;93(4).
69. Schurich A, Pallett LJ, Jajbhay D, Wijngaarden J, Otano I, Gill US, et al. Distinct metabolic requirements of exhausted and functional virus-specific CD8 T cells in the same host. Cell Rep. 2016;16(5):1243–52.
70. Liu W, Guo TF, Jing ZT, Tong QY. Repression of death receptor-mediated apoptosis of hepatocytes by Hepatitis B Virus E Antigen. Am J Pathol. 2019;189(11):2181–95.
71. Zhang MH, Yuan YF, Liu LJ, Wei YX, Yin WY, Zheng LZ, et al. Dysregulated microRNAs as a biomarker for diagnosis and prognosis of hepatitis B virus-associated hepatocellular carcinoma. World J Gastroenterol. 2023;29(31):4706–35.
72. Xie N, Yuan K, Zhou L, Wang K, Chen H-N, Lei Y, et al. PRKAA/AMPK restricts HBV replication through promotion of autophagic degradation. Autophagy. 2016;12(9):1507–20.
73. Li T, Zhu Y, Cheng F, Lu C, Jung JU, Gao SJ. Oncogenic Kaposi's Sarcoma-Associated Herpesvirus Upregulates Argininosuccinate Synthase 1, a Rate-Limiting Enzyme of the Citrulline-Nitric Oxide Cycle, To Activate the STAT3 Pathway and Promote Growth Transformation. J Virol. 2019;93(4).
74. Markazi A, Bracci PM, McGrath M, Gao SJ. Pseudomonas aeruginosa Stimulates Inflammation and Enhances Kaposi's Sarcoma Herpesvirus-Induced Cell Proliferation and Cellular Transformation through both Lipopolysaccharide and Flagellin. mBio. 2020;11(6).
75. Rivera-Soto R, Dissinger NJ, Damania B. Kaposi's Sarcoma-Associated Herpesvirus Viral Interleukin-6 Signaling Upregulates Integrin β3 Levels and Is Dependent on STAT3. J Virol. 2020;94(5).
76. Sodhi A, Montaner S, Patel V, Gómez-Román JJ, Li Y, Sausville EA, et al. Akt plays a central role in sarcomagenesis induced by Kaposi's sarcoma herpesvirus-encoded G protein-coupled receptor. Proc Natl Acad Sci USA. 2004;101(14):4821–6.
77. Bhatt AP, Damania B. AKTivation of PI3K/AKT/mTOR signaling pathway by KSHV. Front Immunol. 2012;3:401.
78. Bouali S, Chrétien AS, Ramacci C, Rouyer M, Becuwe P, Merlin JL. PTEN expression controls cellular response to cetuximab by mediating PI3K/AKT and RAS/RAF/MAPK downstream signaling in KRAS wild-type, hormone refractory prostate cancer cells. Oncol Rep. 2009;21(3):731–5.
79. Bao YY, Zhou SH, Lu ZJ, Fan J, Huang YP. Inhibiting GLUT-1 expression and PI3K/Akt signaling using apigenin improves the radiosensitivity of laryngeal carcinoma in vivo. Oncol Rep. 2015;34(4):1805–14.
80. Gonnella R, Santarelli R, Farina A, Granato M, D'Orazi G, Faggioni A, et al. Kaposi sarcoma associated herpesvirus (KSHV) induces AKT hyperphosphorylation, bortezomib-resistance and GLUT-1 plasma membrane exposure in THP-1 monocytic cell line. J Experimental Clin cancer Research: CR. 2013;32(1):79.
81. Han J, Zhang Y, Xu J, Zhang T, Wang H, Wang Z, et al. Her4 promotes cancer metabolic reprogramming via the c-Myc-dependent signaling axis. Cancer Lett. 2021;496:57–71.
82. Zhu Y, Ramos da Silva S, He M, Liang Q, Lu C, Feng P, et al. An oncogenic virus promotes Cell Survival and Cellular Transformation by suppressing Glycolysis. PLoS Pathog. 2016;12:e1005648.
83. Airley RE, Mobasheri A. Hypoxic regulation of glucose transport, anaerobic metabolism and angiogenesis in cancer: novel pathways and targets for anticancer therapeutics. Chemotherapy. 2007;53(4):233–56.
84. Kim BH, Chang JH. Differential effect of GLUT1 overexpression on survival and tumor immune microenvironment of human papilloma virus type 16-positive and -negative cervical cancer. Sci Rep. 2019;9(1):13301.
85. Zhou J, Wei XC, Xu HY, Hu HB, Li FX, Zhou WJ, et al. Blood glucose levels and the risk of HPV multiple infections in high-grade squamous intraepithelial lesions: a retrospective cross-sectional study of Chinese patients. Medicine. 2022;101(37):e30494.
86. Kasai D, Adachi T, Deng L, Nagano-Fujii M, Sada K, Ikeda M, et al. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. J Hepatol. 2009;50(5):883–94.
87. Ezzikouri S, Jadid FZ, Hamdi S, Wakrim L, Tsukiyama-Kohara K, Benjelloun S. Supplementing Conventional Treatment with Pycnogenol® May improve Hepatitis C Virus–Associated type 2 diabetes: a Mini Review. J Clin Translational Hepatol. 2016;4:228–33.
88. Martin JL, Maldonado JO, Mueller JD, Zhang W, Mansky LM. Molecular studies of HTLV-1 replication: an update. Viruses. 2016;8(2).
89. Domínguez MC, Enith González N, Sánchez A, García Vallejo F. Human T-Lymphotropic virus (HTLV) type I in vivo integration in oral keratinocytes. Brazilian J Microbiology: [publication Brazilian Soc Microbiology]. 2011;42(1):310–20.
90. Sommermann TG, Mack HI, Cahir-McFarland E. Autophagy prolongs survival after NFκB inhibition in B-cell lymphomas. Autophagy. 2012;8(2):265–7.

91. Piccaluga PP, Weber A, Ambrosio MR, Ahmed Y, Leoncini L. Epstein-Barr Virus-Induced metabolic rearrangements in Human B-Cell Lymphomas. Front Microbiol. 2018;9:1233.
92. Cao Y, Xie L, Shi F, Tang M, Li Y, Hu J, et al. Targeting the signaling in Epstein–Barr virus-associated diseases: mechanism, regulation, and clinical study. Signal Transduct Target Therapy. 2021;6(1):15.
93. Wang LW, Shen H, Nobre L, Ersing I, Paulo JA, Trudeau S, et al. Epstein-Barr-Virus-Induced one-Carbon Metabolism drives B Cell Transformation. Cell Metabol. 2019;30(3):539–e5511.
94. Mossenta M, Busato D, Dal Bo M, Toffoli G. Glucose metabolism and oxidative stress in Hepatocellular Carcinoma: role and possible implications in Novel therapeutic strategies. Cancers. 2020;12(6).
95. Li T, Gao SJ. Metabolic reprogramming and metabolic sensors in KSHV-induced cancers and KSHV infection. Cell Bioscience. 2021;11(1):176.

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