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Reprogramming of glucose metabolism in virus infected cells

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Abstract
Viral infection is a kind of cellular stress that leads to the changes in cellular metabolism. Many metabolic pathways in a host cell such as glycolysis, amino acid and nucleotide synthesis are altered following virus infection. Both oncogenic and non-oncogenic viruses depend on host cell glycolysis for their survival and pathogenesis. Recent studies have shown that the rate of glycolysis plays an important role in oncolysis as well by oncolytic therapeutic viruses. During infection, viral proteins interact with various cellular glycolytic enzymes, and this interaction enhances the catalytic framework of the enzymes subsequently the glycolytic rate of the cell. Increased activity of glycolytic enzymes following their interaction with viral proteins is vital for replication and to counteract the inhibition of glycolysis caused by immune response. In this review, the importance of host cell glycolysis and the modulation of glycolysis by various viruses such as oncogenic, non-oncogenic and oncolytic viruses are presented.

Keywords Glycolysis · Glucose uptake · Glucose transporters · Virus replication

Introduction

Glycolysis is an energy generating glucose metabolic pathway that occurs in cytosol of the cell. It is a ten-step reaction pathway that converts one molecule of glucose to two molecules of pyruvate involving several intermediate steps. In the presence of oxygen formed, pyruvate enters the TCA cycle and gets completely oxidized to CO_2. In anaerobic condition, formed pyruvate undergoes homolactic fermentation and leads to the formation of lactic acid. Aerobic glycolysis increases as an energy source in case of cancerous cells, i.e., even in the presence of oxygen, pyruvate forms lactate using enzyme lactate dehydrogenase which is known as Warburg effect., Glucose uptake gets increased in case of Warburg effect; cells utilize glucose for the production of macromolecules and give rise to energy to fight against infection. This condition is advantageous to viruses, as they utilize the macromolecules formed during increased glycolysis. Glucose, a large sized hydrophilic molecule which cannot enter through hydrophobic plasma membrane of the cell by simple diffusion, specific carrier proteins, glucose transporters (GLUTs) are required for its transport. It can also enter into the cell via facilitated diffusion or by a secondary active transport. Secondary active transport occurs via sodium-dependent glucose co-transporters. These symporters co-transport glucose with sodium ions. Twelve members of Sodium-glucose co-transporter(SGLT) family are found in humans [1].

GLUTs are a group of facilitative transporters that are present on cellular plasma membrane to transport glucose across it. A total of 14 GLUT (1–14) members are divided into 3 classes on the basis of sequence homology and structural similarity; Class I (GLUT1 to GLUT4), Class II (GLUT5, GLUT7, GLUT9, GLUT11) and Class III (GLUT6, GLUT8, GLUT10, GLUT12). Among them, class I members are the well characterized group of glucose transporters. GLUT1 is a ubiquitously expressed glucose transporter with different degrees of expression in different cell types. It is expressed in erythrocytes [2], fibroblasts [3], and in almost all tissues including brain tissue [4] and is responsible for basal glucose uptake. GLUT2 is present mainly in liver, pancreatic beta cells, intestine and kidney [5]. GLUT3 is mainly expressed in neurons, and in other cell types including sperm, WBCs, and carcinoma cell lines [6]. GLUT4 is insulin mediated glucose transporter found in adipose tissue, skeletal, and cardiac muscles [7]. Increased glucose uptake is not only an intrinsic feature of most of the cancers, but also is an attribute of virus infected cells.

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Cancer cells depend on aerobic glycolysis for its uncontrolled, boundless growth and proliferation; however, under unfavorable conditions, various metabolic pathways are modulated for cell survival. In case of viral infections, many glycolytic enzymes contribute to the virus replication. On the other hand, some viral encoded proteins are likely to be facilitating the glucose uptake by increasing the expression of GLUTs through activated signaling pathways.

Although viruses have common metabolic requirements, still they use different strategies to alter different carbon metabolic pathways for establishing a successful infection in the host. Glucose requirement in the cell can be fulfilled during viral infection via increased glucose uptake from extracellular environment, and during glucose deprivation in the media there will be a shift towards other means/anabolic process like glycogenolysis to fulfill its requirement. The pathways that are regulated are virus and host specific; in some virus infections, it is seen that increased glucose uptake does not lead to enhanced glycolysis, rather it gets diverted to the formation of other nucleotide or amino acid metabolites. Glucose is an important carbon source for the production of amino acids, nucleotides and fatty acids. Metabolic pathways are interconnected and interdependent to maintain cellular homeostasis. Increased lipogenesis and nucleotide synthesis are also reported in association with some viruses [8]. Lipogenesis is mainly observed in cells infected with enveloped viruses to form the viral envelope [9]. Intermediates of glycolysis and the citric acid cycle can be removed at various stages and will be utilized to make other molecules. Metabolic pathways exist in highly regulated manner and they are not closed systems. Many substrates, intermediates, and products of one metabolic pathway are reactants in other metabolic pathways. In actively dividing cell, there is an increased demand for precursors for protein, nucleotide and lipid production in addition to ATP. Consequently, nutrient uptake is increased and metabolic intermediates are diverted from glycolysis and the TCA cycle to biosynthetic pathways. Apart from glycolysis, other pathways of glucose metabolism will also be used by viruses to replicate adequately. The pentose phosphate pathway (PPP) is an important part of glycolysis which branches after first step of glycolysis also reported to be deregulated by viruses. Unlike, glycolysis it does not produce ATP, but produces Ribose 5-phsophate and NADPH for biosynthesis of nucleotides which are used by viruses for the replication of their genome [10, 11]. Likewise, TCA cycle, a metabolic energy pathway after glycolysis has been reported to be modulated by viruses as it is needed for ATP production and biomolecule synthesis [12].

Mammalian cells use two carbon sources for energy production; glucose and glutamine. Some viruses use both the carbon sources for efficient and optimal progeny production in host cells, but certain viruses depend on either of the carbon sources for their replication. Some like vaccinia virus depends on glutamine rather than glucose for its efficient replication thus not modulating glycolysis [13]. Modulation of glucose metabolism by viruses with an emphasis on variations between oncogenic and non-oncogenic viruses has been reviewed in this article.

Modulation of glucose uptake and glycolysis by viruses

Various metabolic pathways of the host can be modulated/exploited by the virus for its efficient replication inside the host; however, which pathway gets regulated depends on the conditions that are optimal for its replication or for its beneficial outcome. Virus not only depends on these metabolic pathways, but also modifies them during infection process. Virus disrupts the metabolic regulation of the host cell, and mounts its own distinct metabolic program. Viral infection usually reprograms metabolic machinery of the host cell to hold or fulfill bioenergetic and biosynthetic requirement for its progeny production. In general, glycolytic metabolism is modulated by viruses by increasing glucose uptake, and increased expression of various glucose transporters via recruiting signal transduction pathways. For example, expression of GLUT1 and GLUT4 proteins is increased in Adenovirus infected human primary skeletal muscle (HSKM) cells which increases glucose uptake via RAS activated PI3 kinase pathway [14]. Increased glycolysis through increased Akt signaling pathway was also reported in murine Norovirus which is independent of type 1 interferon response in infected macrophages [15]. Higher expression of EBV encoded Latent membrane protein (LMP-1) in Nasopharyngeal carcinoma (NPC) cells was reported to be involved in increased glycolysis. In this, activation of mTORC1 by LMP1 modulates NF-κB signaling which upregulates GLUT1 expression resulting in increased aerobic glycolysis in NPC cells [16]. Therefore, one of the therapeutic treatments of EBV-associated NPC is to target the signaling axis of mTORC1/NF-Kβ/Glut-1 [17]. Similarly, another tumor virus, HPV encoded E6 and E7 proteins enhance the GLUT1 expression; however, via activation of HIF-1α in lung tumors. The correlated expression of HIF-1α, and GLUT1 was reported to be significantly high in malignant tumors as compared to benign tumor tissues collected from patients [18]. On the contrary, some viruses quench glycolysis by activating certain signaling pathways under stress conditions. KSHV encoded microRNAs and vFLIP inhibits glycolysis to downregulate GLUT1 and GLUT3 transporters by activating signaling pathway AKT and NF-kβ [19].

Another strategy of viruses to modulate glycolysis was reported to be through upregulation of glycolytic enzymes. Some viruses upregulate only one of the glycolytic enzymes,

while some two or more enzymes. Enzyme Activity is modulated by various components for e.g., Phosphofructokinase (PFK-1) is allosterically modulated by ATP [20], fructose 2,6-bisphosphate [20, 21], citrate [22] or by its phosphorylation status [21, 22]. HSV induces glycolysis by increasing the glucose uptake, efflux of lactate level and ATP. It also increases the expression, and the activity of 6-phosphofructo-1-kinase (PFK-1) [23]. Glucose transport is increased in virus infected cells by different mechanisms such as transcriptional activation of transporter genes [24], stabilization of transporters [25], and the increased translocation of transporters from intracellular vesicles to the plasma membrane [26]. In Mayaro virus infected Vero cells, a two-fold increase in glucose consumption, lactate production, and increased PFK activity was reported which in turn leads to the increased glycolytic flux [27]. Likewise, in rhinovirus infected cells increased glucose uptake is linked with increased expression of PI3K-regulated GLUT1 transporter [8].

Virus is very dynamic in nature, it modulates cellular metabolome and therefore enhances the glycolysis, but it may not be the case with all the viruses. Under stress conditions, glycolysis is suppressed activating other metabolic pathways for optimal replication of some viruses [19]. Interestingly, same virus may use different strategies during the establishment of infection in a host. One study reported induction of aerobic glycolysis in KSHV infected endothelial cells, the phenomena which is called Warburg effect by increasing glucose uptake by GLUT3 transporter, and increased lactate production. Expression of Hexokinase-2, the rate limiting enzyme of glucose metabolism was also reported to be increased in this study [28]. On the contrary, another study on KSHV reported induction of cellular transformation by suppressing aerobic glycolysis, and by downregulating glucose transporters, GLUT1 and GLUT3 through the activation of AKT and NF-κB pro-survival pathways [19]. Some studies had shown that glucose transporters function as cell surface receptors besides their role in glucose uptake. Glucose transporters interact with virus external surface proteins to facilitate virus entry into the host cell. Case in point, White Spot Syndrome Virus encoded envelope protein VP53A interacts with shrimp cell (i.e., host cell) surface receptor, GLUT1 for the entry of virus into the host cell [29, 30].

Why do viruses modulate glycolysis?

Glucose metabolism in a host cell is necessary for some viruses to replicate. Energy is required for its survival and for the synthesis of biomolecules required for virus replication. The energy for all these events comes through the alteration of host cell glycolysis and other metabolic pathways. Thus, inhibition of glycolysis blocks the replication of majority of viruses. The carbon metabolic alterations could either be a cellular response to virus infection or triggered by the virus itself to complete its life cycle. The shift in host cellular metabolism is required to cope up with the imbalance caused by virus infection. One of the reasons for increased glycolysis during virus infection could be apoptosis, as cell death during virus replication induces disruption of mitochondrial membrane resulting in the inhibition of cellular respiration. To compensate this condition, glycolysis and other cellular metabolisms may be increased [31]. There are several types of inhibitors that are used to inhibit glycolysis which in turn inhibit viral life cycle. Glycolytic inhibitors generally result in mitochondrial pathway-induced apoptosis in cancerous cell [32, 33] which is similar to the condition observed in virus infected cells. Glycolytic enzyme inhibitors, glucose transporter inhibitors, ATP by allosteric inhibition, etc., are used to inhibit glycolysis. Reduction of viral RNA synthesis of Norovirus [15], and Dengue virus [34] following inhibition of glycolysis has been demonstrated using glycolysis inhibitors such as 2DG and Oxamate. Thus, glycolysis is an intrinsic host factor that is required for optimal replication of many viruses. Most of the above viruses had shown to be regulating a common strategy; that is increased glycolysis is always linked with increased glucose uptake and the increased expression of glucose transporters. However, some variations between oncogenic and non-oncogenic viruses were reported in the literature. Various viruses that are known to modulate host cell glycolysis and their possible regulatory mechanism are listed in Table 1.

Oncogenic viruses

Oncogenic viruses account for 11.9% of all human cancers, and are known to regulate various host metabolic pathways to maintain the oncogenic phenotype of transformed cells [35]. Cancer cells are mainly dependent on aerobic glycolysis for their high energy demand which is considered as the hallmark of cancer [36, 37] Likewise, virus replication requires loads of energy, and resources from the host cell, therefore Warburg effect is essential in case of oncogenic virus infected cells for their survival [28]. Some cancer cells do utilize glutamine, amino acid or fatty acid metabolism for their proliferation and survival [38, 39]. As both the virus and the cancer cell have the ability to modify the rate of energy metabolism for the endless proliferation, it is likely that the mechanisms regulated by both have originated from a common mechanism [40]. Oncogenic viral proteins stimulate various oncogenic signaling pathways associated with energy metabolism and cell growth to promotes angiogenesis, and metastasis of viral infected/transformed cells [41]. GLUT1 had reported to be the main glucose transporter, transported to the membrane for the survival of cancerous

Table 1 Modulation of glucose metabolism by different viruses

S. No.	Virus	Signalling pathways recruited	Glycolytic enzymes regulated	Viral protein involved	Increased expression of GLUTs	References
1	EBV*	PI3-K, mTORC1/NF-kB FGF2/FGFR1 pathway activity	HK2	LMP-1	GLUT1	[16, 17]
2	HCV#	Akt	HK2	NS5A	Unknown	[44]
3	HPV*	HIF-1α	Not known	E6/E7	GLUT1	[18]
4	KSHV*	PI3K/Akt NF-kB HIF-1α HIF-1	HK2 PKM2 PDK-1 HK2 PKM2	miRNA vFLIP	GLUT1 GLUT3 GLUT1	[28, 45] [19, 74]
5	Polyoma Virus*	PI3K Myc, NF-kB	HK2	Middle Tag Small T Antigen	GLUT1 GLUT1 GLUT3	[43]
6	RSV#	Unknown	Unknown	pp60src	Unknown	[75]
7	Dengue virus#	Unknown	HK2	Unknown	GLUT1	[34]
8	HCMV*	Unknown	HK2, GPI, PFK, TPI, PGK, ENO, PKM, PDH	Unknown	GLUT4	[52, 53]
9	HSV*	Unknown	PFK-1	Unknown	GLUT3	[23]
10	HIV#	PI3K	G6-P	Unknown	GLUT1 GLUT3	[58, 76] [77, 78]
11	Influenza Virus#	HIF-1	HK2, PKM2, PDK3 HK2, GPI, PFK, FBP, ALD, TPI, GAPDH, PK, LDH	Unknown	Unknown	[31, 50]
12	Mayaro virus#	Unknown	PFK	Unknown	Unknown	[27]
13	SARS CoV-2#	HIF-1	Unknown	Unknown	Unknown	[56]
14	SFV#	PI3K/Akt	Unknown	Unknown	Unknown	[79]
15	Vaccina Virus*	HIF-1α	Unknown	Unknown	Unknown	[80]
16	Murine Norovirus#	Akt	Unknown	Unknown	Unknown	[15]
17	WSSV*	Unknown	Unknown	VP53A VP24, VP28, VP31, VP32, VP39B, VP51B, and VP53A	GLUT1 GLUT1	[29, 30]
18	Rhinovirus#	PI3K	Unknown	Unknown	GLUT1	[8]

HK2 Hexokinase-2, *PDK1* Pyruvate dehydrogenase Kinase 1, *G6-P* Glucose -6- phosphate, *GPI* Glucose-6-phosphate isomerase, *PFK* Phosphofructokinase, *PGK* Phosphoglycerate Kinase, *FBP* Fructose-1,6-bisphosphate, *ALD* Aldolase, *TPI* Triose-phosphate isomerise, *GAPDH* Glyceraldehyde-3-phosphate dehydrogenase, *ENO* Enolase, *PK* Pyruvate kinase, *PDH* Pyruvate dehydrogenase, *LDH* Lactate dehydrogenase

*Indicates DNA virus

#Indicates RNA virus

cells [42]. Translocation of GLUT1 to the plasma membrane, and binding of PI3 kinase to middle T-pp60^{c-src} leads to the increased uptake of glucose in polyoma virus transformed cells [43]. In HCV infected cells, the direct correlation between virus encoded NS5A protein, and the increased expression/activation of cellular hexokinase-2 result in intensification of glycolytic rate by increasing glucose uptake and lactate efflux [44]. Whereas in KSHV infected endothelial cells, mainly Akt and HIF signaling pathways appear to be playing a major role in Warburg effect [28]. However, induction of Warburg effect by KSHV is not universal but limited to endothelial cells [28]; while glycolytic inhibitors induce apoptosis in KSHV infected endothelial cells. Another study reported hyperactivation of PI3-K/Akt pathway, and GLUT1 translocation to the plasma membrane increases the oncogenic potential in KHSV infected THP-1 cells [45]. These viral infected cells are more potent to death by glucose inhibitor, 2-DG in combination with bortezomib, an anti-cancer drug [45]. Under nutrient stress conditions, KSHV encoded miRNA and vFLIP genes promote cellular

transformation, and suppresses aerobic glycolysis by activating NF-κβ signaling pathway to downregulate GLUT1 and GLUT3 transporter [19]. However, this paradox in KSHV infections is an important aspect to be investigated in detail.

Oncogenic viral proteins of Human Papilloma Virus, Murine Sarcoma Virus reported to be playing a regulatory role in inducing Warburg Effect, but the underlying mechanism is yet to be understood [18, 46]. In NPC cells, stabilization of transcriptional factor, c-Myc, and the transcriptional activation of Hexokinase-2 by EBV encoded LMP-1 mediated signal pathway causes upregulation of glycolysis and the proliferation of cancerous cells [16]. LMP-1 also upregulates the transcription of GLUT1 which enhances the aerobic glycolysis and the malignancy of the infected cells through mTORC1/NF-κB signaling pathway [17]. Studies on modulated glucose metabolism mentioned above by oncogenic viruses approve that oncogenic virus infected cells develop different mechanisms such as activation of various signaling pathways, increased cellular transporters, and increased nutrient uptake to sustain their high demand for energy. No studies have shown that cells are transformed due to increased glycolysis induced by oncogenic viruses. However, following transformation of cells by oncogenic viruses, viral proteins modulate glycolysis to meet the energy needs of proliferating cells.

Non-oncogenic viruses

It is obvious that oncogenic virus infections lead to metabolic alterations in the host cell because of their high energy demand. Interestingly, in non-transforming virus infected cells as well, glucose metabolism is altered. In case of Mayaro virus infected cells, increased glycolytic flux had been reported in association with increased glucose consumption and lactate production by a significant increase in 6-phosphofructo-1- kinase enzyme activity in infected cell [27].

MDCK cells infected with H1N1 strain of influenza A virus show differential regulation of several enzyme activities of key metabolic pathways to compensate the metabolic imbalance caused by infection [47]. Influenza virus does modulate glycolysis but the exact mechanism is not clear. It our study, rate of glycolysis was observed to be increased in influenza A virus infected cells through increased expression of glucose transporters 1 and 4. Besides, there was an interplay between alpha enolase and pyruvate kinase activity with viral gene expression was also noted (unpublished data). Influenza virus replication is dependent on host cell glucose, and is in dose-dependent manner; treatment of infected cells with glycolytic inhibitors reduces virus replication [48]. While higher level of glucose increases the assembly, and the proton transport activity of Vacuolar type ATPase within the cells increase the viral replication [48]. Enhanced intracellular metabolite concentration of the upper part of glycolysis was reported in influenza virus infected cells following increased glucose uptake and lactate export [31]. One recent study reported upregulation of Hexokinase-2, PKM2 and PDK3 enzymes of glycolytic pathway in A549 cells, and the mouse lung tissue following infection with H1N1 strain of influenza A virus. Earlier we reported, interaction of influenza A virus structural proteins M1 and NP with glycolytic enzymes; alpha enolase and pyruvate kinase [49]; however, the effect of this interaction on glycolysis in infected cells needs to be investigated. HIF-1 pathway, another pathway had shown to be critical for the transcriptional activation of enzymes involved in glycolysis to support virus infection through increased glycolysis. Virus replication gets inhibited upon targeting HIF-1 pathway. This study also showed that the change of H1N1 replication upon glycolysis inhibition or enhancement is independent of interferon signaling [50].

Dengue virus, another non-oncogenic virus alters glycolysis through increased glucose uptake by upregulation of GLUT1 transporter and the first enzyme of glycolysis i.e., hexokinase-2. While the inhibition of glycolytic pathway using glycolytic inhibitors halts the virus progeny production [34]. Adenovirus, although does not induce tumors in its natural host, encodes proteins with an ability to transform normal cells into cancerous in vitro. Adenovirus also reported to be modulating glucose uptake by increased expression of GLUT1, GLUT4 transporters, and the translocation of GLUT4 to the plasma membrane via Ras activated PI3Kinase pathway in an insulin-independent manner [14]. Adenovirus infected primary cultures of cardiac myocytes, and H9c2 cells show upregulation of HIF-1α when subjected to hypoxia in the absence of glucose. On the contrary, addition of extracellular glucose to the medium resulted in decreased HIF-1α levels by almost 50% [51]. In consensus with the above results, adenovirus-induced overexpression of GLUT1 in cardiac myocytes followed by hypoxia reduced the level of HIF-1α [51]. Another study reported the activation of transcriptional factor Myc, followed by Myc-dependent expression of glycolytic enzymes, Hexokinase-2 and PFKM by adenovirus encoded E4Orf1 protein promoting glucose uptake and increased glycolysis in infected cells [40].

Herpes Simplex Virus, also non-oncogenic in nature causes an increased glucose uptake, lactate secretion, and ATP content by elevating the expression and the activity of PFK-1enzyme. Its phosphorylation at serine residue was reported to be viral MOI dependent [23]. A prototype of beta-herpesvirus, HCMV also upregulates the level of metabolic components involved in glycolysis, TCA cycle, and pyrimidine biosynthesis in fibroblasts [52]. HCMV encoded immediate early protein IE72 mediates the inhibition of GLUT1 level in infected cells [53], and the inhibition of GLUT1 results in Akt mediated translocation of GLUT4

onto the cell surface which leads to increased glucose uptake, subsequently increased glycolysis [54].

The ongoing pandemic virus, SARS CoV-2 infected patients had elevated blood glucose levels during the life cycle of the virus which might be providing optimal conditions for the virus to replicate, and evade the host immune system [55]. One recent report showed that the increased glucose level, and the glycolysis promotes Monocytes infecting SARS-CoV-2 replication through HIF-1α-dependent pathway, while the treatment of cells with 2-Deoxy-D-glucose (2-DG), a glycolytic inhibitor blocked viral replication [56]. Thus, the drug 2-DG was used as an anti-viral and anti-inflammatory drug to combat the cytokine storm in COVID-19 patients [57]. All the above reports collectively suggest that most of the viruses irrespective of their genome nature, and oncogenic potential, modulate glucose uptake and glycolysis for successful replication in a host.

Considering different cells types, viruses have been reported to be regulating glucose metabolic pathways in different cell types such as immune cells, glioma cells, fibroblasts as well. The modulation of glycolysis by viruses in these cells are more or less similar to cancer cells; either by increasing proliferative pathways or increased expression and activity of glycolytic enzymes. Elevated level of Glut1 expression in CD4 + T cells contributes to increased glucose transport and increased glycolysis in HIV infected cells [58]. HHV-6 infection was found to promote glucose metabolism in T cells leading to increased glucose uptake, glucose consumption and lactate secretion through increased expression of major glucose transporters and glycolytic enzymes. Activated AKT-mTORC1 signaling was also reported in HHV-6A infected cells, while inhibition of mTORC1 signal pathway blocked HHV-6A mediated glycolytic pathway subsequently viral DNA replication, protein synthesis and progeny production which suggests an interplay between above mentioned signal pathways with glycolysis in HHV-6A infected immune cells [59]. Stimulation of glycolysis in glioma cell lines was reported through upregulation of key glycolytic enzymes hexokinase, GAPDH and alpha enolase by HIV glycoprotein gp120. It led to increased activity of pyruvate kinase and pyruvate synthesis [60]. Overview of glucose uptake and glycolysis regulation in oncogenic and non-oncogenic viruses is shown in Fig. 1.

Oncolytic viruses

Cancer cells are rapidly dividing cells, and depend more on glucose than the normal cells do for ATP generation via

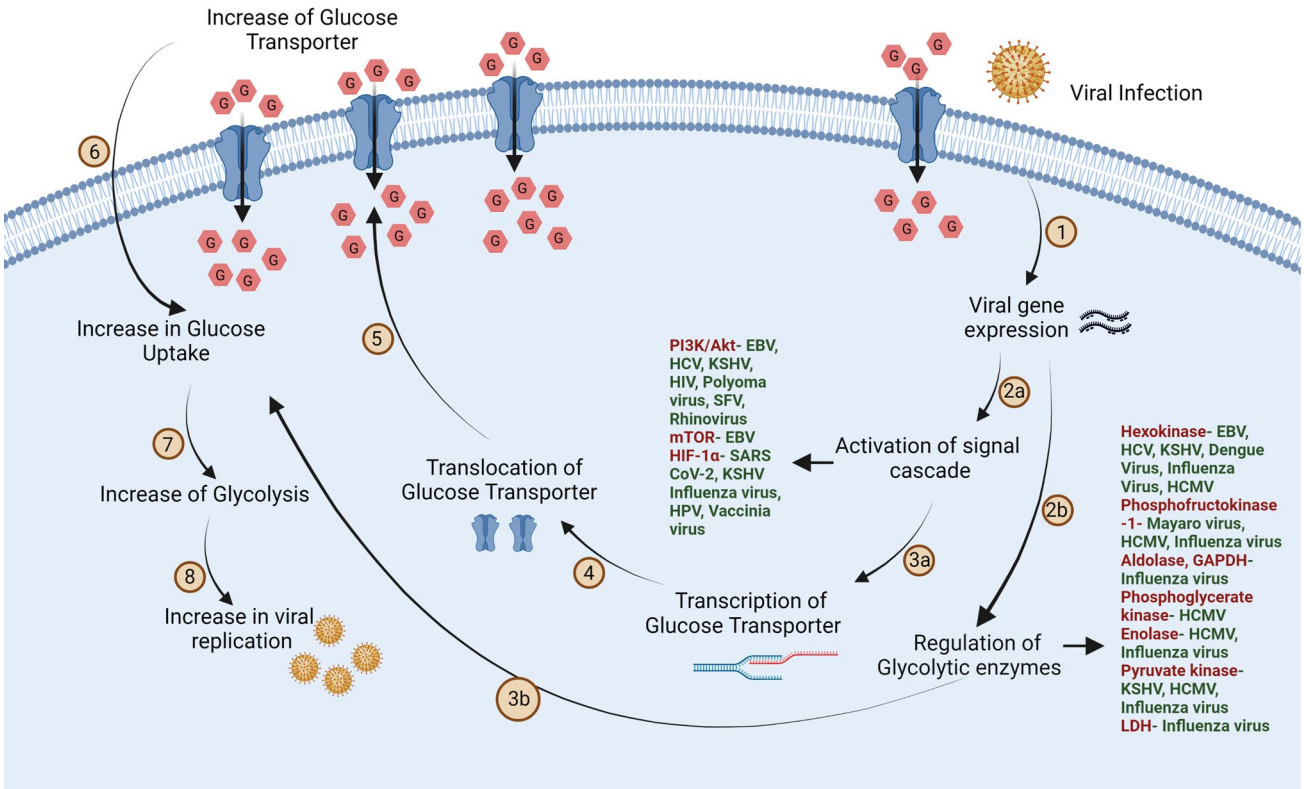

Fig. 1 Overview of glucose uptake and glycolysis in virus infected cells. Figure shows various viruses and their proteins involved in induction of increased glycolysis in infected cells by modulating mechanisms such as deregulation of signal pathways to induce increased expression of glucose transporters and specific glycolytic enzymes. Created with Biorender.com

glycolysis. An aerobic glycolysis is the principal metabolic pathway in cancerous cells, targeting it is the main approach to inhibit cancer cell progression. Viral demand of macromolecule synthesis is similar to cancerous cells. In most viral infected, normal and cancerous cells, glycolysis and uptake of glucose get intensified the use of glycolytic inhibitors results in oncolysis by many viruses [28, 61–63].

As cancer is a complex disease, it demands an effective way of treatment. In the recent past, trials on developing a targeted therapy to lyse cancer cells using virus gaining much interest in the field of cancer therapeutics. Oncolytic virus has an ability to selectively kill cancer cells leaving the normal cells unharmed. Oncolytic viruses work as cancer therapeutics by two major mechanisms; direct lysis or by triggering anti-cancerous immune response. Energy metabolic pathway plays a main role in both the cases to report the outcome of oncolytic virus mediated cell lysis. Oncolytic viruses hijack the host cellular metabolic pathways that are necessary for viral replication which results in oncolysis [64]; it is also reported that by targeting the glycolytic pathway of cancer cell through glycolytic inhibitors may enhance the oncolytic virotherapy activity in cancer cells [65].

New Castle Disease virus (NDV), a natural tumor tropic virus with oncolytic ability downregulates glycolytic enzyme PGK [66]. Glucose analog, 2-DG, an anti-metabolite of cancer cell inhibits the glucose metabolism of cancer cells more effectively in combination with oncolytic NDV to inhibit the tumor growth/ increased cytotoxicity in breast cancer cells through GAPDH downregulation as compared to monotherapy [63]. Another study showed that downregulation of hexokinase via D-Mannoheptulose, a non- metabolize analog of glucose [67, 68], and the use of hexokinase inhibitor combined with NDV infection inhibits glycolysis which in turn induces apoptosis in breast cancer cell line efficiently in comparison to either of the agents administered alone [69]. Dichloroacetate which is a mitochondrial pyruvate dehydrogenase kinase inhibitor reported to increase the NDV-mediated viro-immunotherapy in Hepatocellular carcinoma by enhancing anti-tumor immune response, and viral replication [70]. Lytic potential of M1 virus, a novel oncolytic virus shows its dependence on glycolysis. It had been shown that increased viral replication, and oncolysis is independent of Hexokinase-2 using lonidamine, a hexokinase inhibitor. However, enhanced viral replication, and oncolysis is mediated by downregulation of Myc, an antiviral immune response factor, and by upregulation of ER stress mediated apoptosis. On the contrary, glycolytic inhibitor, 2-DG (glucose analog) in combination with M1 virus not only inhibited the virus replication, but the oncolysis as well [71]. From the above studies, it is evident that virus replication, and cancer cell destruction by therapeutic viruses do require modulation of glycolysis. However, oncolytic virus associated host cell glycolysis needs to be elucidated in detail for developing anti-tumor drugs targeting Warburg effect in combination with oncolytic viro-therapeutics. The first Chinese SFDA approved Oncolytic-based therapy, Oncorine, a recombinant human adenovirus type 5 was approved for clinical use in 2005 against NPC [72]. In 2015, a modified Herpes Simplex Virus, talimogene laherparepvec (T-Vec), the first FDA approved oncolytic virus in United States and Europe were acclaimed for clinical use against metastatic melanoma [73]. Oncolytic virotherapy combined with metabolic interventions that work together may enhance the potential of virus-based cancer therapeutics.

Conclusion

A wide variety of viruses; both DNA and RNA viruses, oncogenic and non-oncogenic viruses evolved various strategies to exploit the host cellular metabolic network especially glycolysis during infection. The importance of glycolysis in promoting replication of various viruses is gaining interest in the recent past. Some viral proteins have been reported to be directly involved in modulating glycolysis either through interacting with rate limiting enzymes of glycolysis or by upregulation/activation of these enzymes in infected cell. Signal pathways that are involved in upregulation of glucose transporters for increased glucose uptake are also reported in cells infected with certain viruses. However, increased glycolysis in association with some viruses was reported with no information on signal pathways recruited, glycolytic enzymes regulated and glucose transporters expression. Furthermore, the studies on modulation of glycolysis by oncolytic viruses are very limited, but had shown to be reprograming the host cell glucose metabolism during oncolysis. Considering the importance of glycolysis in virus infected cells, in addition to targeting viral proteins for the development of anti-viral therapeutics, alternative ways of targeting host factors such as the dependency of viral replication on cellular metabolic pathways may also be explored to develop effective therapeutics. Glycolytic enzyme inhibition can cause ATP depletion, making cancer cells to get insufficient energy for proliferation which in turn leads to apoptosis. Thus, the use of glycolytic enzyme inhibitors against oncogenic viral infections may provide treatment for tumor suppression as well. As the regulation of metabolic pathways control the fate of the cell subsequently virus infection, the transient inhibition of the desired metabolic pathway can be a novel therapeutic approach to reduce/inhibit the active viral replication.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare that they have no competing interest.

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