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Reprogramming of cellular metabolic pathways by human oncogenic viruses

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Oncogenic viruses, like all viruses, relies on host metabolism to provide the metabolites and energy needed for virus replication. Many DNA tumor viruses and retroviruses will reprogram metabolism during infection. Additionally, some viral oncogenes may alter metabolism independent of virus replication. Virus infection and cancer development share many similarities regarding metabolic reprogramming as both processes demand increased metabolic activity to produce biomass: cell proliferation in the case of cancer and virion production in the case of infection. This review discusses the parallels in metabolic reprogramming between human oncogenic viruses and oncogenesis.

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Introduction

Virus infection and cancer development are both processes that demand increased metabolic activity to produce biomass: cell proliferation in the case of cancer and virion production in the case of infection. As many small DNA tumor viruses and retroviruses demand these metabolic requirements, they reprogram the cell's metabolism during infection. The replication of many viruses depends on the reprogramming of cellular metabolism following infection in ways that are similar to some cancers. For oncogenic viruses, viral reprogramming of metabolism may affect oncogenesis. Since viruses do not encode a metabolic network but require metabolites, metabolism is a barrier to virus replication.

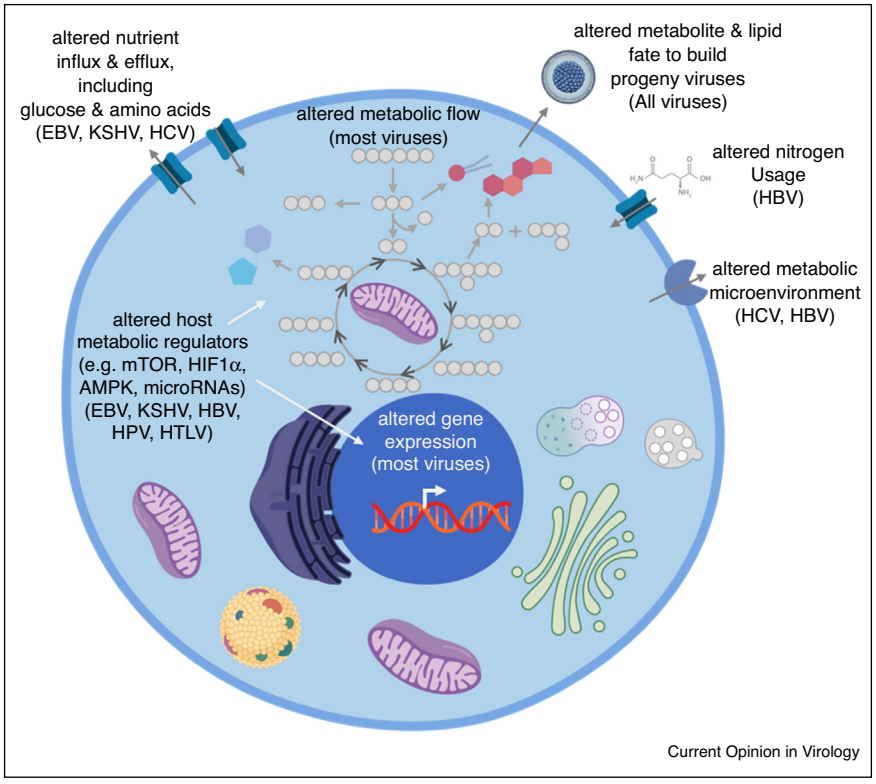
The replication of viruses can place an increasing demand on the number of metabolites, lipids or energy that a cell must produce and the nutrients that they must consume. Virus infection may reprogram host metabolism in various ways, including altering: 1) the influx/efflux of metabolites including glucose and amino acids, 2) the flow of nutrients through metabolic pathways, 3) the use of metabolites for viral biomass including virus genome synthesis, viral protein production, or lipid envelope generation, 4) the usage of nitrogen obtained from amino acids or choline uptake, and 5) host metabolic regulators that may alter host metabolic gene expression (Figure 1).

Like viral infection, the reprogramming of metabolism is a hallmark of cancer [1]. In the almost 100 years since Otto von Warburg described increased consumption of glucose and fermentation to lactate in cancer cells, it is now understood that cancers have altered metabolic activity to generate energy and sustain biomass required for growth. Given its importance to tumorigenesis, Pavlova and Thompson organized cancer-associated metabolic reprogramming into six hallmarks [2]. The proposed six hallmarks are: 1) deregulated uptake of glucose and amino acids, 2) use of alternative ways of obtaining needed nutrients, 3) use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production, 4) increased demand for nitrogen, 5) alterations in metabolite-driven gene regulation, and 6) altered metabolic microenvironment. Individual cancers may exhibit one or several hallmarks, but defining the specific metabolic reprogramming by cancers is important for our understanding of oncogenesis and in directing research for the discovery of new therapeutic targets [2].

Viruses can promote oncogenesis by direct mechanisms, such as encoding oncogenes that affect cell survival and proliferation. In the case of oncogenic herpesviruses, a default program of latent replication occurs where the latency gene products promote cell proliferation as a means to support latent viral DNA replication. This process, when left unchecked by the immune system, can promote malignancy and again links viral infection with increased metabolic activity to increase biomass. While the mechanistic details of the metabolic regulation vary for different oncogenic viruses and cell types, this general framework genetically links oncogenic virus replication to cell proliferation through metabolic reprogramming.

Renewed interest in metabolism by virologists, in part aided by the growing access to metabolomic techniques, has resulted in metabolic studies that have significantly

Figure 1



Reprogramming of host metabolism by oncogenic viruses parallel cancer metabolic reprogramming.
Viral infection alter the: 1. influx/efflux of glucose, amino acids, and other nutrients, 2. flow of metabolites through pathways, including glycolysis & TCA cycle, 3. fate of metabolites and lipids, including to build progeny viruses, 4. usage of nitrogen following the uptake of amino acids and choline, and 5. host metabolic regulators including mTOR, HIF1α, AMPK, and microRNAs. These are similar to the hallmarks of cancer metabolism as discussed in the introduction. Each human oncogenic virus alters host metabolism in several ways generating unique metabolic profiles. All of the viruses alter gene expression of host cells and the fate of metabolites when cells are producing new infectious progeny. Created in part with BioRender.com.

expanded our understanding of the importance of metabolism to oncogenic viruses. Multiple similarities have emerged between metabolic reprogramming by oncogenic viruses and cancers. In this review, we highlight studies investigating the unique relationship between viruses, host metabolism, and oncogenesis. We placed focus on the human oncogenic viruses—gammaherpesviruses (γ-herpesviruses), hepatitis B and C viruses (HBV and HCV), human papillomaviruses (HPV), Merkel Cell Polyomavirus (MCPyV), and human T lymphotropic virus (HTLV). We provide a summary and discussion of recent findings regarding the role of host metabolism in the replication and oncogenesis of these human viruses. Defining how infection alters host metabolism will contribute to better understandings in virology, viral pathogenesis, and cancer development and may contribute to treatment discoveries for these important and common pathogens.

Gammaherpesviruses (γ-herpesviruses)

The γ-herpesviruses, Epstein-Barr virus (EBV) and Kaposi's sarcoma herpesvirus (KSHV), establish life-long latent infection in humans and are the cause of multiple types of cancer. EBV infects B cells and is an etiologic agent of infectious B-cell lymphomas including Burkitt lymphoma, Hodgkin's lymphoma, lymphomas of the immune suppressed (post-transplant and HIV-associated), as well as epithelial cancers including nasopharyngeal carcinoma and gastric carcinoma. KSHV can cause Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman disease. The cellular origin of Kaposi's sarcoma is an infected spindle endothelial cell, while primary effusion lymphoma and multicentric Castleman disease are derived from infected B cells. Infection with EBV and KSHV is associated with alterations in multiple metabolic pathways, which have been reviewed elsewhere [3••,4–7]. Here we focus on recent studies of γ-herpesviruses that demonstrate that metabolism is both a barrier to oncogenesis and virus infection.

EBV infection of primary human B cells initiates a hyperproliferation state. This hyperproliferation state is transient as the rapid proliferation depletes intracellular

pools of nucleotides leading to a metabolic restriction that favors premature senescence or apoptosis rather than B-cell immortalization [8••,9••]. The metabolic profile of B cells is important for the transient nature of the hyperproliferative state [8••]. Importantly, stimulating nucleotide synthesis in infected B cells extends their proliferation [8••]. The metabolic stress-induced senescence in EBV-infected B cells involves altered activity in host regulators of metabolism. For example, growth-restricted cells have reduced mTORC1 activation but an enhancement in AMPK activation [9••], which may limit biomass production by decreasing the metabolic flux in lipid synthesis. These observations suggest that cancers induced by herpesvirus infection must overcome a metabolic barrier, similar to cancers of non-viral etiology [2].

Recent work by the Gewurz lab explicitly implicates the one-carbon metabolism pathway as a key contributor to cell proliferation and survival during EBV-mediated B-cell immortalization [10••]. Using a combination of proteomic and metabolic flux experiments, multiple enzymes involved in *de novo* serine synthesis as well as serine transporters were found to be upregulated by EBV as early as two days post-infection, before the initiation of proliferation. The viral EBNA2 protein through its activation of the cellular MYC oncoprotein led to the induction of methylenetetrahydrofolate dehydrogenase 2 (MTHFD2, this enzyme removes a single carbon from serine to generate glycine and 5,10-methylenetetrahydrofoalte) and serine hydroxymethyl transferase 2 (SHMT2, this enzyme works downstream of SHMT2 to further single carbon metabolism). Inducing MTHFD2 and SHMT2 promotes the catabolism of serine into formate for use in nucleotide synthesis and glycine for glutathione synthesis and redox homeostasis. Importantly, both genetic and pharmacological inhibition of these enzymes as well as depletion of serine significantly inhibited EBV-driven B-cell growth and survival.

In another recent study, EBNA2 and MYC were found to cooperate with sterol responsive element binding protein 2 (SREBP2, a major transcription factor regulating lipid metabolism) to promote the expression of several enzymes important in *de novo* lipid biosynthesis and the mevalonate pathway that controls cholesterol production [11•]. The substantial increase in cholesterol and lipid biosynthesis during the early phase of infection likely facilitates the dramatic expansion in cell size from the resting B-cell state to EBV-infected, continuously proliferating lymphoblasts. Interestingly, mevalonate metabolism supplied geranylgeranyl pyrophosphate (GGPP) that was important for modification of Rab proteins, which supported EBV latent membrane protein 1 (LMP1) and LMP2A trafficking and, ultimately, cell survival later during infection. LMP1 and LMP2A control cell signaling, which can regulate cell proliferation. These findings support a model where the viral EBNA transcription factors cooperate with cell proliferation and metabolic regulators including MYC and SREBP2 to promote the expression and activity of central metabolic programs including one-carbon metabolism, *de novo* lipid biosynthesis, and the mevalonate pathway. This ensures not only robust activation, cell size increase, and long-term proliferation, but also the production of appropriate cellular membrane domains to serve as a signaling platform for the latent membrane proteins, which provide a key survival advantage to EBV-infected B cells.

In contrast to its latent state, lytic replication of EBV has similar metabolic requirements to that of other herpesviruses undergoing lytic replication including nucleotide, protein, and lipid synthesis [9••,12–24]. EBV BGLF4 is a serine/threonine kinase that phosphorylates both viral and host proteins. BGLF4 limits the activity of the host enzyme sterile alpha motif and HD domaining-containing protein 1 (SAMHD1), a dNTPase that restricts some viruses, including herpesviruses [25,26,27•]. It was proposed that phosphorylation of SAMHD1 by BGLF4 and related conserved herpesvirus kinases favor virus replication by decreasing SAMHD1 dNTPase activity [27•]. However, SAMHD1 restriction of the human cytomegalovirus herpesvirus is independent of dNTP concentration, suggesting that its dNTPase activity is unlikely to be required for limiting all herpesvirus [28••]. It is currently unknown if SAMHD1 controls the intracellular concentration of dNTPs during EBV infection or contributes to the restriction of the hyperproliferative state. Further research is needed to understand if SAMHD1 restriction of other herpesviruses is dependent on its control of intracellular dNTP pools. It is also unknown if SAMHD1 affects EBV or KSHV immortalization cells and oncogenesis. Overall, these findings from EBV studies have important health implications, suggesting that increasing the metabolic barrier to oncogenesis would provide a therapeutic benefit. Additionally, the factors and mechanisms—including potential virally encoded mechanisms—that may be involved in lowering the metabolic barrier that enables immortalization remain to be elucidated.

Lipid metabolism is also important for EBV and KSHV infection [23,29,30••,31] and was recently reviewed [3••]. Lange *et al.* have studied the effects of lipid metabolism on infection using the well-studied murine γ-herpesviruses 68 (MHV68) model. They demonstrated that although MHV68 replication requires lipid synthesis, the lipogenic transcription factors liver X receptors (LXRα/β) respond to interferons to limit MHV68 replication in primary macrophages by suppressing the expression of lipogenic genes [32]. The resulting lack of lipid synthesis restricts MHV68 replication and reactivation from latency [32,33]. The levels of LXRα increase following MHV68 infection initially suggesting that lipid metabolism would subsequently

be enhanced; however, the host is likely blocking LXR activity by increasing co-repressors of LXR preventing the virus from creating a metabolic environment that supports replication. This further demonstrates that the host can raise the metabolic barrier needed for virus replication to limit herpesvirus infection.

Hepatitis C virus (HCV)

HCV infection can promote hepatocellular carcinoma and increases the progression of liver cirrhosis. HCV infection creates an environment in the liver that promotes carcinoma development without encoding a viral oncogene. Since the liver is a central organ in regulating and integrating the metabolism of many tissues and organs in the body, infection in the liver or immune responses targeted to the liver may have broad metabolic effects. These effects may include altering the levels of metabolites and lipids in the circulatory system. For this reason, the effects of chronic infection of hepatotropic hepatitis C and B viruses on metabolism can be observed by examining human serum. Eradication of HCV infection is possible by treatment with direct-acting antiviral agents (DAAs) [34]. HCV infection alters the activity of multiple metabolic pathways and increases lipogenesis. Remodeling of metabolism, including lipid metabolism, as a consequence of HCV infection generates lipids required for the building of new virion progeny. Several recent reviews have discussed alterations to host metabolism following acute or persistent HCV infection and the development of hepatocellular carcinoma [35–43]. Here, we have selected to highlight two emerging concepts in understanding HCV biology as it relates to metabolism. First, we focus on the understanding of metabolic changes that occur during DAA treatment. Second, we discuss the role of microRNA control of metabolism during HCV infection.

Recent studies demonstrate that the metabolic profile of HCV patients shifts during DAA treatment [44••,45•]. A study performed in Italy examined serum metabolites from 160 volunteers including 67 HCV-infected patients before and after DAA treatment. Measurement of approximately 30 serum metabolites—mostly amino acids, glycolysis/TCA metabolites, and short-chain fatty acids—allows for the differentiation of HCV-infected, HBV-infected, and healthy controls [44••] demonstrating that HCV and HBV have specific effects on host metabolism. Furthermore, the metabolic profiles of DAA-treated patients at 12-weeks and 24-weeks post-intervention were discernible from the profiles before treatment [44••]. These observations suggest that the measurement of serum levels of water-soluble metabolites may be used to evaluate the effectiveness of DAA intervention. The serum lipid profile of HCV-positive patients is also predictive of liver health [46•], however, lipid profiles were not included in the Italian study. In a study carried out in New Zealand, therapeutic interventions for HCV infection resulted in an increase in total cholesterol and low-density lipoprotein (LDL) serum levels, while no changes in triglyceride or high-density lipoprotein (HDL) levels were observed [45•]. A shift in lipid metabolism during treatment has been proposed to be the result of a decrease in HCV replication [47], however other possibilities including the immune response to infection may also contribute to this observation. Together the Italian and New Zealand studies show that host metabolism associated with HCV infection shifts following DAA treatment. Importantly, these observations further support that liver function improves after DAA treatment [34]. However, it remains to be formally determined if the levels of all metabolites and lipids in HCV-infected patients will return to a virus-naïve state following DAA-mediated sustained clearance of HCV in the blood. Additional studies, including longer longitudinal studies, are needed to address this exciting possibility. Since HCV lacks an oncogene, hepatocellular carcinoma development depends on HCV establishing a chronic infection. Since HCV replication alters metabolism, including enhanced lipid and cholesterol synthesis, chronic infection may create a metabolic state that lowers the metabolic barrier to oncogenesis [48]. It is possible that HCV infection creates a metabolic microenvironment that promotes the initiation or growth of carcinomas.

Host metabolic responses to infection can support or limit HCV replication. In the liver, microRNAs can control lipid metabolism and serum-lipid concentrations [49,50]. *In vitro* studies have demonstrated microRNA control of metabolism is important for HCV replication and host antiviral responses. Control of gene expression of proteins involved in metabolism and cell signaling by miR-146a-5p contributes to HCV viral replication [48]. Conversely, an antiviral microRNA, miR185, inhibits HCV infection by limiting the expression of host lipogenic genes that contribute to HCV replication [51]. Serum microRNA levels are also altered by treatments for HCV infection, including microRNAs that regulate the expression of lipogenic genes [52]. This observation suggests that microRNAs may be involved in altering patients' metabolic profiles following DAA treatment. However, it remains to be determined if microRNAs are necessary for metabolic changes that happen during DAA treatment.

Hepatitis B virus (HBV)

Like HCV, chronic hepatitis B virus (HBV) infection of the liver can promote hepatocellular carcinoma (HCC). HBV is a small enveloped DNA virus that contains four known genes: S (surface protein), P (polymerase), X (regulatory X protein), and C (core protein). HBV DNA integration, gene expression, and infection-induced inflammation are associated with HCC development [53]. HBV infection or the expression of X protein in primary rat hepatocytes using a recombinant adenovirus enhances

the levels of glucose-derived metabolites, including carbon-storage metabolites like fatty acids and carbohydrates [54]. HepG2 cells expressing X protein have a metabolic profile that is consistent with an increase in glucose metabolism [55]. HepG2 cells expressing HBV core protein or containing the HBV genome have an increase in lactate production, suggesting that both HBV proteins may increase glucose utilization and alter the flow of carbons through metabolism [56,57]. The serum levels of lactate are elevated in people with chronic HBV infections relative to healthy controls, further supporting the *in vitro* findings of HBV on glucose and lactate metabolism [44••]. Cells expressing protein X showed a decrease in nucleotide synthesis [55]. However, nucleotide pools were either unaltered or only slightly increased in cells expressing HBV core protein demonstrating that the two viral proteins have divergent effects on metabolism [55,57]. HBV core protein in HepG2 cells increases choline metabolism [56,57]. Choline is an important source of nitrogen for lipid synthesis, demonstrating the HBV infection can alter the flow of nitrogen-containing metabolites and lipids, like phosphatidylcholines. HBV X protein induces the expression of fatty acid-binding protein 1, further suggesting that lipid metabolism is important to HBV infection [58]. However, measurements of serum phosphatidylcholines revealed that while a few of these lipids are elevated by HBV infection, most phosphatidylcholines are lower in the serum of infected people relative to healthy controls [59]. These observations demonstrate that additional work is necessary to connect our understanding from cell culture models of HBV-infection to the effect of infection on carbon and nitrogen metabolism in HBV-infected humans.

Further findings in the adenoviral-mediated infection of rat hepatocyte model suggest that AMPK activation contributes to HBV replication while mTORC1 activity limits HBV genome replication [60]. When ATP level decline and ADP/AMP levels rise AMPK is activated to support energy production over energy storage, that is, enhanced glycolysis and ATP synthesis and suppressed fatty acid synthesis. AMPK may be activated by reduction of ATP levels due to HBV X protein. Consistent with an increase in AMPK activity, phosphorylation of ACC-1 was increased in cells expressing HBV X, suggesting that protein X—when expressed in uninfected cells—suppresses fatty acid synthesis [60]. Alternatively, mTORC1 balances catabolic and anabolic metabolism to favor biomass production including nucleotide and fatty acid synthesis. mTORC1 signaling enhances protein synthesis as well. Further research is needed to determine if mTORC1's role in metabolism and protein synthesis are connected to its role in regulating HBV infection. Based on their recent findings Bagga, et al., propose that AMPK and mTORC1 balance viral replication helping to facilitate a persistent infection, which would suggest that metabolites could regulate chronic HBV infection and hepatocellular carcinoma development.

Human Papillomaviruses (HPV)

High-risk subtypes of human papillomaviruses (HPV), such as HPV16, cause cervical cancers in women. Infection can also lead to other types of cancers in both women and men. HPV E6 and E7 genes are oncogenic, while the other HPV genes promote viral DNA replication and support particle formation, while also potentially influencing cell proliferation [61]. HPV oncogenesis is promoted, rather than viral replication, when HPV16 E6 and E7 are expressed in the absence of proper expression of other viral genes. HPV16 E6 and E7 enhance glucose metabolism in part by increasing glucose transporter 1 [62,63]. HPV infection disrupts the organization of the mitochondrial network [56]. HPV-induced structural changes in mitochondria may alter metabolic functions [56]. Mitochondria are an important site of various metabolic activities including TCA, β-oxidation of fatty acids, and ATP generation via oxidative phosphorylation. Furthermore, overexpression of HPV E2 can alter mitochondria metabolism [64], however, it is currently unknown if this occurs in the context of a natural infection.

In hypoxic cells, HPV enhances the stabilization of hypoxia-inducible factor 1α (HIF1α) [65–67]. HPV E6 is necessary for hypoxic induced glucose consumption and lactate synthesis [65]. HPV E7 can bind pyruvate kinase M2, decreasing its metabolic activity resulting in the accumulation of upstream glycolytic metabolites [63]. It is now recognized that pyruvate kinase has functions beyond its enzymatic role in metabolism. For example, in activated macrophages pyruvate kinase binds HIF1α in the nucleus [68]. Through this interaction, pyruvate kinase may help regulate numerous genes including those in metabolism [69]. It is possible that HPV E7 alters the function of pyruvate kinase in a similar way to regulate host gene expression. Overall, these observations suggest that oncogenic serotypes of HPV alter the uptake and utilization of glucose. However, the importance of these metabolic changes to HPV induced oncogenesis remains to be explored.

Merkel cell polyomavirus (MCPyV)

Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. Most MCC tumors contain DNA from Merkel cell polyomavirus (MCPyV) [70]. MCPyV encodes a large and small tumor antigen. Expression of MCPyV small tumor antigen increased glucose consumption and lactate production in uninfected cells suggesting that virus-induced aerobic glycolysis may enhance MCC growth rate in a Warburg-like state [71••]. RNAseq data suggest that small tumor antigen induces the expression of various nutrient transporters and may alter glutamine usage to support flux through the TCA cycle [71••]. However, this RNAseq observation remains to be confirmed through more

metabolic analyses. Additionally, cells expressing small tumor antigen were enriched in genes related to hypoxia and mTOR [71••], suggesting possibly metabolic regulatory changes following infection. In support of this concept, mTOR activation is observed in MCC [72,73]. Although it is currently unknown if mTOR controls metabolic changes associated with MCC oncogenesis, mTOR inhibitors have been shown to limit the growth of MCC cell lines [73,74].

Further, MCPyV infection correlates with activation of protein kinase Cε (PKCε). Like many members of the PKC family, PKCε is activated by lipid-mediated signaling and is an important regulator of metabolism [75]. This observation suggests that MCPyV infection may alter lipid metabolism. Further studies are needed to test if PKC activity is important to carcinoma development or infection-induced changes in metabolism.

Retroviruses: human T lymphotropic virus (HTLV)

Human T lymphotropic virus type I (HTLV-1) is a retrovirus that causes T cell leukemia and lymphoma malignancies. HTLV-1 encodes an activator of replication and cellular signaling called Tax that is important for reactivation and supporting survival of leukemic cells [76]. Unfortunately, only a few studies have investigated the role of metabolism in HTLV infection suggesting, but not yet clearly linking, HTLV reactivation and oncogenesis to virus-regulated metabolic changes. Glycolysis is required for HTLV-1 gene activation and may be important for the virus to reactivate from a latent state [77•]. HTLV-1 HBZ protein allows for mTOR activation during infection [78], suggesting that mTOR regulated metabolism may be altered by the virus. Further, hypoxia increases HTLV-1 gene expression [77•]. However, the role of HIF1α in mediating the effects of hypoxia on HTLV-1 gene expression or metabolism is uncertain.

HTLV-1 is also the causative agent of a degenerative neurological disease called HTLV-1-associated myelopathy (HAM) / tropical spastic paraparesis (TSP). Imaging of the brains of infected symptomatic patients using 18F-fluorodeoxyglucose suggests that increase glucose uptake and metabolic activity are associated with HTLV-1 neurological disease [79]. Thus, HTLV-1 associated metabolic changes may be important for T cell oncogenesis and neurological pathogenesis induced by the virus.

Conclusions

Metabolism is a barrier to virus replication and oncogenesis since each must promote anabolic processes to support increases in biomass and catabolic processes to generate energy for virion particle production or cell proliferation. Oncogenic viruses overcome this barrier by remodeling host metabolism to support infection and pathogenesis. Each human oncogenic virus reprograms metabolism in a unique and distinct fashion. Blocking infection-induced or oncogenic-driven metabolic reprogramming would limit virus replication and cancer development.

Despite the diverse mechanisms of metabolic regulation, there are multiple similarities shared between oncogenic virus infection-induced and non-virus oncogenic-driven remodeling of metabolism. As discussed in this review, virus infection alters glucose and amino acid metabolism, the use of metabolites for biomass, and the usage of nitrogen obtained from amino acids or choline uptake. Likewise, cancers of non-virus etiology display similar reprogramming of metabolism to support oncogenesis [2]. The reprogramming or deregulation of metabolism in cancers and virus infection involves shared mechanisms. HIF1α, mTOR, or AMPK activity enable many cancer cells to regulate metabolism to support oncogenesis [2,80–83]. Infection with some oncogenic viruses alter the levels of or regulation of HIF1α [66,67,84–91]. In many of these infections, HIF1α controls the expression of host metabolic genes leading to an increase in glycolysis and lactate production. In addition to enhancing host metabolic gene expression, HIF1α contributes to the control of viral gene expression in the case of KSHV [88]. Likewise, mTOR, AMPK, or microRNAs are important to the virus-host metabolism interaction. In EBV-infected cells, growth is arrested by a reduction in mTOR signaling following p53 activation [9••]. These findings demonstrate some of the many parallels between virus and cancer metabolic reprogramming that can contribute to or act as a barrier to infection and oncogenesis.

As highlighted in this review some viruses encode oncogenes (e.g. HPV E6/E7) that can promote cancer development and metabolic reprogramming, genetically linking both processes. However, the connection between metabolism and oncogenesis is not necessarily linked to virus replication. The precursors for virus-induced malignancy for some oncogenic viruses result from abortive replication due to aberrant viral genome integration or gene mutation. For example, oncogenesis is promoted, rather than viral replication, when E6 and E7 are present in a cell, but other viral proteins including E1 and E2 are not produced. In this case, E6 and E7 reprogramming of metabolism may contribute to malignant transformation, not virus production. Alternatively, some viruses promote oncogenesis through indirect mechanisms that do not require a virus-encoded oncogene. In the case of HCV and HBV, an environment of chronic inflammation is associated with cancer development. An interesting possibility that needs more attention is the role of metabolism in altering the environment of infected cells that may contribute to indirect mechanisms of oncogenesis by viruses.

We are in the beginning stages of understanding how metabolism supports or limits virus infection and, in the

case of oncogenic viruses, cancer formation. Many questions remain to be investigated. One emerging concept in cancer biology is the importance of the microenvironment on the cancer cells and the responding anti-cancer immune cells. Infection or cancer development can influence the nutrient and oxygen availability in a tissue microenvironment. Altered influx and efflux of metabolites following infection may influence the microenvironment affecting the ability of the virus to spread to neighboring cells. Oncogenic viruses may encode proteins or microRNAs that alter how the host responds to changes in the microenvironment that favor infection or contribute to oncogenesis. Additionally, the metabolic microenvironment of cancer cells can limit or alter the anti-cancer immune response [92,93]. Viruses may have evolved mechanisms to alter the microenvironment to evade or reprogram the immune response to infection.

In addition to changes in the microenvironment, metabolism can influence cancers beyond providing biomass and energy to support cell proliferation. The oncometabolite 2-hydroxyglutarate inhibits demethylation thereby altering gene expression and broadly affecting metabolism [94–96]. It is currently unknown if any metabolite has a similar effect during viral infection. Further, some metabolic enzymes perform non-enzymatic functions that support cancer development [97]. As discussed above, pyruvate kinase M2 also functions to enhance gene expression by interacting with HIF1α, providing a possibility that HPV E7 interaction with pyruvate kinase M2 may alter gene expression. Studies are needed to determine if these non-canonical functions of metabolic proteins may also contribute to virus replication or infection-induced oncogenesis.

In conclusion, oncogenic virus infection is associated with changes in the host that enable cells to alter nutrient acquisition and utilization to make a metabolic environment that favors or limits infection. Furthermore, infection-associated changes in the host metabolic network can increase or lower the metabolic barrier to oncogenesis. Together, studies of viral and cancer metabolic reprogramming are providing new insights into both virology and cancer biology. Further research is needed to better define the mechanistic processes underlining viral remodeling of host metabolism and the metabolic barriers to virus infection and oncogenesis.

Declaration of interests

Nothing declare.

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