REVIEW

Metabolic reprogramming: a hallmark of viral oncogenesis

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More than 1 in 10 cases of cancer in the world are due to chronic viral infections. Viruses induce oncogenesis by targeting the same pathways known to be responsible for neoplasia in tumor cells, such as control of cell cycle progression, cell migration, proliferation and evasion from cell death and the host's immune defense. In addition, metabolic reprogramming has been identified over a century ago as a requirement for growth of transformed cells. Renewed interest in this topic has emerged recently with the discovery that basically all metabolic changes in tumor cells are finely orchestrated by oncogenes and tumor suppressors. Indeed, cancer cells activate biosynthetic pathways in order to provide them with sufficient levels of energy and building blocks to proliferate. Interestingly, viruses introduce into their host cells similar metabolic adaptations, and importantly, it seems that they depend on these changes for their persistence and amplification. The central carbon metabolism, for example, is not only frequently altered in tumor cells but also modulated by human papillomavirus, hepatitis B and C viruses, Epstein–Barr virus and Kaposi's Sarcoma-associated virus. Moreover, adenoviruses (Ad) and human cytomegalovirus, which are not directly oncogenic but present oncomodulatory properties, also divert cellular metabolism in a tumor cell-like manner. Thus, metabolic reprogramming appears to be a hallmark of viral infection and provides an interesting therapeutic target, in particular, for oncogenic viruses. Therapeutic targeting of metabolic pathways may not only allow to eliminate or control the viral infection but also to prevent virus-induced carcinogenesis.

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INTRODUCTION

According to the latest estimations of the International Agency for Research on Cancer, the global burden of human cancers caused by viral infections reaches up to 11% of cancer cases worldwide.¹ Direct oncogenic alterations by insertions of viral DNA into the host cell genome are rare events. Oncogenic viruses rather promote cancer by inducing cellular alterations in the context of long-lasting, chronic infections.² Like any type of oncogenic mechanism, viral-induced oncogenesis is a multistep process that requires the acquisition of all the cellular features responsible for the tumor phenotype, as originally described in the 'hallmarks of cancer', by Weinberg and Hanahan in 2000³ and updated in 2011.⁴ One of these key requirements is a metabolic reprogramming, which is intrinsically linked to deregulated cellular energetics. The interplay between tumorigenesis and metabolism was first described with the pioneer work of Otto Warburg in the 1920s⁵ but has been widely overlooked until the recent discovery that almost all oncogenic pathways are involved in the control of metabolism.⁶ Today, the studies deciphering the close links between metabolic alterations and cancer are flourishing and substantially contribute to our understanding of the forces driving oncogenesis.

As intracellular parasites, viruses depend on the metabolism of infected cells to proliferate. Indeed, viruses acquire both the energy and the building blocks needed to synthesize progeny virions from their host. In order to avoid metabolic exhaustion, viruses manipulate metabolic pathways and associated signaling cascades probably in order to provide sufficient resources to support optimal virion production. Although this applies to many viruses, the degree of metabolic reprogramming varies from one

virus to another. In this review, we describe how viruses induce persistent modifications of the host cell's metabolism and how these modifications contribute to cellular transformation. We recapitulate the main aspects of metabolic reprogramming and associated cell signaling that occur in cancer cells and then review the known metabolic alterations linked to infections with oncoviruses.

PART I. METABOLIC REPROGRAMMING IN CANCER

The Warburg effect

The first investigations on cancer metabolism date back to the pioneer work of Otto Warburg in the 1920s.⁵ This German scientist was the first to observe that tumor tissues metabolize through glycolysis about 10-fold more glucose to lactate than normal tissues, even in the presence of O₂. In 1972, the term 'Warburg effect' was coined to allude to this increase in aerobic glycolysis in cancer cells.⁷ However, contrary to the idea that mitochondria are inactive in tumors, there is now compelling evidence that most cancer cells exhibit increased glucose uptake which is then channeled into intermediate pathways and concomitantly retain mitochondrial tricarboxylic acid (TCA) cycle activity and oxidative phosphorylation (OXPHOS).^{8–12} The advantage for tumor cells is the concomitant generation of sufficient amounts of ATP as well as metabolic precursors to allow increased proliferation. Indeed, both glycolysis and mitochondrial metabolism are central sources of energy and precursors for the biosynthetic pathways required for cancer cell proliferation (Figure 1a). Increased amounts of glycolytic intermediates provide the precursors required for nucleotide, amino acid and lipid synthesis as well as for cellular

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Figure 1. (a) Cancer metabolism. In tumor cells, metabolic fluxes are increased in favor of biosynthetic activities. Colored arrowheads represent the principle enzymes responsible for these metabolic alterations. Refer to text for further details. (b) Oncovirus-induced modulations of cell metabolism. Known alterations of signaling and metabolic pathways by oncoviruses are represented. Refer to panel (a) and text for more details. Abbreviation: AcCoA, acetyl-CoA; ATP, adenosine triphosphate; Cit, citrate; Glc, glucose; Gln, glutamine; GLS, glutaminase; Glu, glutamate; G6P, glucose-6-phosphate; αKG, α-ketoglutarate; Lac, lactate; OAA, oxaloacetate; Pyr, pyruvate; 3PG, 3-phosphoglycerate; RTK, receptor tyrosine kinase.

redox homeostasis. Indeed, reduced nicotinamide adenine dinucleotide phosphate (NADPH), produced from glycolytic intermediates through the oxidative branch of the pentose phosphate pathway (PPP)¹³ (Figure 1a), is the predominant reducing agent against oxidative stress as well as for reduced nucleotide, amino acid and, more importantly, lipid biogenesis. Although lipids of most normal cells are recycled from the circulation, tumor cells preferably synthesize their own lipids. *De novo* fatty acid (FA) synthesis is a hallmark of cancer that was identified in the early 1950s.¹⁴ FAs are predominantly synthesized by tumor cells to be esterified into phospholipids and incorporated into the membranes of the duplicating cell. In many cancers, several key enzymes of lipogenesis have been shown to be upregulated.¹⁵ Importantly, lipid synthesis requires citrate, which is produced in the TCA cycle (Figure 1a). This major process for cancer cell proliferation is hence partly dependent on mitochondrial metabolism. The efflux of TCA cycle intermediates for the biosynthesis of lipids, nucleotides and amino acids is essential for cancer cells and is called cataplerosis. Thus, in order to sustain TCA cycle functions, proliferating cells must find a matching influx of intermediates, a phenomenon called anaplerosis. One possibility is the direct conversion of pyruvate to oxaloacetate by the enzyme pyruvate carboxylase. However, cancer cells depend more on alternative anaplerotic carbons through the activation of glutamine metabolism¹⁶ (Figure 1a). Glutamine contributes to many aspects of cell metabolism and, in particular, metabolic processes that promote proliferation: bioenergetics, generation of macromolecule precursors, and defense against oxidative stress.¹⁷

Oncogenes and tumor suppressors control cancer metabolic pathways

The discovery that most oncogenes and tumor suppressors regulate cell metabolism—in addition to cell cycle and cell

death—has awoken interest among the scientific community and, in particular, in the field of cancer metabolism. Indeed, over the past several years, the idea has emerged that oncogenes and tumor suppressors primarily evolved to regulate metabolism.⁶

Oncogenes

Phosphatidylinositol 3-kinase (PI3K) signaling is one of the most frequently deregulated signaling pathways in cancer. Great strides are being made in our understanding of the diverse roles that PI3K signaling has in cancer initiation, progression and maintenance.¹⁸ The pathway is activated by growth factor receptors and controls most aspects of tumorigenesis, including cell cycle, growth, survival, migration and metabolism.¹⁹ When hyperactivated, AKT—the downstream effector kinase activated by PI3K—is responsible for enhanced glucose uptake and promotion of aerobic glycolysis in cancer.⁶ AKT also directly stimulates *de novo* lipogenesis from citrate through the phosphorylation of the enzyme ATP citrate lyase.²⁰ Importantly, inhibition of tuberous sclerosis complexes (TSC) 1 and 2 by AKT activates the mammalian target of rapamycin (mTOR), which is responsible for many key features of PI3K signaling.²¹ mTOR mainly not only stimulates growth by inhibiting autophagy and promoting ribosome biogenesis and protein synthesis but also induces FA synthesis through the activation of sterol regulatory element-binding proteins (SREBP) 1c and 2^{22,23} and peroxisome proliferator-activated receptor γ.²⁴ Consistent with its major role in the promotion of cell growth, mTOR was also recently shown to stimulate pyrimidine synthesis.²⁵ Moreover, mTOR can activate aerobic glycolysis by increasing hypoxia-inducible factor (HIF) 1α protein level.²³

HIF-1α transcription factor is not a proper oncogene, but it is activated in many cancers. It has a critical role in tumor adaptation to hypoxia and its expression is often associated with a bad

prognosis.²⁶ HIF-1 α is a strong enhancer of glycolysis in cancer, primarily through induction of the expression of almost all glycolytic genes.²⁷ Moreover, HIF-1 α induces the expression of pyruvate dehydrogenase kinase 1, which phosphorylates the pyruvate dehydrogenase complex, hence inhibiting the transport of pyruvate and its conversion to acetyl-CoA in the mitochondria.²⁸ The excess of cytosolic pyruvate is converted to lactate by lactate dehydrogenase A, which is also induced by HIF-1 α .²⁹ Without pyruvate entering the mitochondria, tumor cells cannot synthesize citrate from glucose carbons. To compensate for this loss, HIF-1 α has been shown to activate reductive carboxylation of glutamine, providing a carbon source for *de novo* lipogenesis both *in vitro*^{30,31} and in tumors growing as xenograft in mice.³² Moreover, even if hypoxic cells consume less O₂, they can maintain a functional TCA cycle through glutamine-driven anaplerosis and still produce the majority of their energy via OXPHOS.¹²

Constitutive activation of RAS GTPase proteins following somatic mutations or epidermal growth factor receptor (EGFR) signaling is found in a broad range of human cancers.³³ RAS promotes tumor growth not only by activating proliferation through the mitogen-activated protein kinase (MAPK) pathway but also by strongly increasing anabolic glucose metabolism.³⁴ Activation of either RAS or AKT induces aerobic glycolysis, but unlike AKT, RAS inhibits pyruvate entry in the mitochondria and reduces O₂ consumption, in part through HIF-1 α and 2 α induction.³⁵ However, OXPHOS is still the major source of ATP in RAS-expressing cells, via the activation of glutaminolysis.¹² Interestingly, a new mechanism of glutamine supply, based on macropinocytosis, has been described recently for RAS-transformed cells.³⁶ RAS has also been shown to activate a non-canonical pathway of glutamine use, which ultimately increases NADPH production via the conversion of malate to pyruvate by the malic enzyme.³⁷

MYC (or c-MYC) is the human homolog of an avian retroviral gene responsible for myelocytomatosis (leukemia and sarcoma) and strongly implied in the metabolic adaptations of cancer cells. It was the second oncogene identified in history, in the 1970s, a few years after the discovery of Src.³⁸ MYC expression can be directly or indirectly induced by hormone and growth factor signal transduction pathways such as Wnt/ β -catenin, PI3K/AKT/mTOR and EGFR/RAS/MAPK signaling pathways.³⁹ MYC increases glucose flux by inducing the expression of major glycolytic genes.⁴⁰ Glucose transporter type 1 (GLUT1) as well as several enzymes of glycolysis, including the tumor form of the glycolytic enzyme hexokinase (HK)—HK2—and lactate dehydrogenase A, possess conserved E boxes in their promoters and their expression is activated by MYC.⁴¹ In addition, MYC was described to promote the splicing of the pyruvate kinase M pre-mRNA toward the cancer-specific isoform PKM2.⁴² Furthermore, MYC also participates in the diversion of the glycolytic flux into nucleotide synthesis by upregulating several key enzymes of the serine–glycine–one-carbon metabolism axis.^{43,44} But MYC is also directly involved in mitochondrial biogenesis⁴⁵ and metabolic functions, as shown by its central role in glutamine metabolism. Indeed, MYC overexpression has been shown to induce high rates of glutaminolysis leading to glutamine addiction.^{46–48} Finally, the activation of glutaminolysis by MYC is not only limited to cancer cells but also happens in physiological rapidly proliferating cells, such as activated primary murine T cells.⁴⁹

Tumor suppressors

In addition to the extensively described roles of p53 as an inducer of cell cycle arrest, senescence and apoptosis in response to DNA damage and hyperproliferative signals, many lines of evidence demonstrate that p53 is also a major regulator of metabolic homeostasis.⁵⁰ p53 has been shown to prevent the metabolic

alterations, which would promote cancer cell growth by directly interfering with the levels of glycolytic, lipogenic and mitochondrial enzymes. Furthermore, many of the metabolic effects of p53 are due to its ability to inhibit the PI3K–AKT–mTOR pathway through the activation of TSC1/TSC2 complexes, phosphatase and tensin homolog (PTEN) as well as the AMP-activated protein kinase (AMPK) pathway^{51,52} (Figure 1a).

PTEN lipid kinase activity suppresses PI3K signaling and hence exerts antagonistic effects on all the metabolic features of the PI3K–AKT–mTOR axis.⁵³ A transgenic mouse model with systemic overexpression of PTEN was developed recently. These ‘Super-PTEN’ mice presented several interesting features, including an anti-Warburg effect with reduced aerobic glycolysis and glutaminolysis.⁵⁴

The liver kinase B1–AMPK pathway acts as a central energy and nutrient-sensing metabolic switch that triggers metabolic adaptation and growth arrest in case of low intracellular ATP levels and thus refers stress resistance and augments survival. However, the exact roles and effects of modified AMPK expression or activity in tumorigenesis remain to be determined. AMPK switches on ATP-generating pathways such as glycolysis and amino-acid oxidation and inhibits ATP-consuming anabolic processes, such as gluconeogenesis and lipogenesis. Activated AMPK inhibits the mTOR pathway,⁵⁵ directly inhibits FA and cholesterol synthesis by phosphorylating the enzymes acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase, respectively, and hinders the proteolytic activation of the transcription factor SREBP-1c.^{55,56} In contrast, loss of AMPK promotes a metabolic shift to aerobic glycolysis and overall enhances the uptake and flux of glucose-derived carbon into the TCA cycle for anabolic processes in a HIF-1 α -dependent manner.^{57,58}

Retinoblastoma protein (RB) is absent, owing to genetic loss, or inactivated by oncogenic signaling in a wide range of human cancers.⁵⁹ The best-characterized functions of RB are related to the control of cell cycle progression through the cyclin–CDK–RB–E2F pathway. The first direct link discovered between RB–E2F and metabolism is the transcriptional regulation of key enzymes involved in nucleotide biosynthesis.⁶⁰ In addition, the pRB–E2F axis has been shown to regulate glucose tolerance, central carbon metabolism, glutathione synthesis, mitogenesis and respiration and to mediate the metabolic switch from an oxidative to a glycolytic metabolism that is required for cell proliferation and growth.^{61–63}

Oncogenes and tumor suppressors were first described for their role in the control of cell proliferation and survival. There is now an unequivocal body of evidence that they are also major regulators of signaling events and enzymes that control metabolism (Figure 1a). These findings underline the concept that metabolic reprogramming in cancer cells requires a finely tuned interplay between the control of the progression through the cell cycle and the confection of the future cell components.

PART II. ONCOVIRUSES AND METABOLIC ALTERATIONS

Similar to cells that require metabolic alterations when shifting from a quiescent to a proliferating state, a viral infection also demands metabolic adaptations. Many studies have described a close relationship between viral components of different viruses with the metabolic factory of the cell: the mitochondrion (for reviews, see Claus and Liebert⁶⁴ and El-bacha and Da Poian⁶⁵). Hereinafter, we will present how oncovirus-induced metabolic changes share similarities with tumor-associated metabolic reprogramming. These changes can result from direct interactions of viral components with metabolic enzymes or they are induced indirectly by the virus via modulation of upstream signaling pathways (Figure 1b).

Human papillomavirus (HPV)

HPV is one of the most powerful known oncoviruses, with ca. 600 million people infected worldwide, and is responsible for around 5% of all cancer cases per year.⁶⁶ In particular, all cases of cervical cancer and the majority of anal and vaginal carcinomas as well as cancers of the oral cavity and pharynx are caused by an infection with HPV (Table 1). Although the majority of new infections with HPV regress in 6–18 months, around 10% become persistent, which is a prerequisite for the development of neoplasia. The main risk factors for progression to cancer are immunodeficiency and the HPV type. Types 16 and 18 are the most likely to cause a persistent infection and hence represent the most carcinogenic types of HPV, accounting for roughly 70% of all cervical cancer cases. HPV can only infect differentiating cells.⁶⁷ As the replicative machinery that the circular DNA genome of the virus depends on for its multiplication is lost during the differentiation process, the virus encodes two proteins—E6 and E7—that promote cell cycle progression and prevent apoptosis. In the case of high-risk types of HPV, these changes are more pronounced and E6 and E7 are considered as oncoproteins promoting carcinogenesis. The best-described mechanism by which E6 and E7 promote proliferation is their interaction with p53 and RB, respectively, which initiates proteasomal degradation of these tumor suppressors.^{68,69} In addition, it was shown that E7 protein from type 16 HPV interacts physically with the tumor form of pyruvate kinase, PKM2, inducing the dimeric conformation of this glycolytic enzyme.⁷⁰ PKM2 exists in both dimeric and tetrameric forms. Although the tetrameric form has a high affinity for its substrate phosphoenolpyruvate and catalyzes its conversion into pyruvate, the dimeric form has low affinity for phosphoenolpyruvate and thus induces its accumulation. As a result, glycolytic intermediates are redirected into other biosynthetic pathways, thus favoring the proliferation of tumor cells.⁷¹ Hence, it was hypothesized that E7 also favors

HPV-induced oncogenesis by promoting the low-activity conformation of PKM2.^{70,72} In parallel to the E7-induced modulation of the glycolytic flux, E7 was also shown to activate glutaminolysis, promoting a tumor-like anaplerotic pathway.⁷³ E6- and E7-induced inhibition of p53 and RB activity may release the break that these two tumor suppressors normally apply on cancer metabolism. In addition, both E6 and E7 oncoproteins activate PI3K-AKT-mTOR signaling, even under nutrient-deprivation conditions,^{74,75} as well as HIF-1 α ,^{76,77} which also drives cancer cell metabolism. These changes in metabolism, particularly to the glycolytic flux, appear to be required for the virus. Indeed, treatment with the glycolytic inhibitor 2-deoxyglucose was shown to inhibit HPV-16 and HPV-18 transcription.⁷⁸ Furthermore, PI3K-AKT-mTOR signaling is considered as a promising target in HPV-associated carcinomas.^{79,80}

Adenoviruses

Ad are double-stranded DNA, ubiquitous viruses, which infect different tissues in humans and animals. Among >50 human Ad serotypes that have been identified, only a dozen are associated with clinical syndromes—keratoconjunctivitis, mild respiratory disease and hemorrhagic cystitis and gastroenteritis in infants. Nonetheless, many Ad-associated infections remain subclinical.^{88,89} Ad was the first human virus described as being oncogenic in rodents. However, Ad infections have not been implicated in the development of human neoplasms, probably because contrary to rodents, humans are able to mount an immune response against Ad-transformed cells⁹⁰ (Table 1). *In vitro*, mammalian cells are transformed by the exogenous expression of Ad proteins E1A and E1B in particular through the inhibition of RB and p53 tumor-suppressor pathways, respectively.⁹¹ Interestingly, it was recently discovered that Ad infection induces a tumor-like anabolic glucose metabolism.⁹² The authors described that Ad protein E4ORF1 binds to MYC in the nucleus and enhances the ability of this transcription factor to bind to glycolytic target genes, including HK2. Moreover, E4ORF1-activated MYC is responsible for an induction of the non-oxidative branch of the PPP, leading to increased nucleotide synthesis and optimal Ad replication in lung epithelial cells. These glycolytic changes triggered by E4ORF1 expression appeared to be independent from the induction, by the same protein, of the PI3K-AKT-mTOR signaling pathway.^{93–95} However, it was also reported that Ad infection can activate *de novo* lipogenesis in a PI3K-dependent manner⁹⁶ and through the activation of SREBP-1c.⁹⁷

Hepatitis B and C viruses (HBV and HCV, respectively)

HBV and HCV are completely unrelated in terms of structure and phylogeny. The first one is a partially double-stranded DNA virus belonging to the *Hepadnaviridae* family while the latter is a single, positive-stranded RNA virus of the *Flaviviridae* family. Ca. 300 million people are estimated to be chronic carriers of HBV and 150 million chronic carriers of HCV. Both viruses target the liver, replicate in hepatocytes and represent the main etiologies of hepatocellular carcinoma (HCC) development⁹⁸ (Table 1). HCC is the fifth most prevalent tumor type and the third leading cause of cancer-related deaths worldwide. In total, up to 80% of all HCC cases arise in the context of chronic hepatitis B or C infections. The rate of HCC development among people with >30 years of chronic hepatitis C has been estimated at 1–3% per year while it is <1% in chronic HBV carriers.⁹⁹ A combination of indirect—immune-related—and direct virus-induced mechanisms are believed to participate in the development of HCC linked to chronic hepatitis B and C.¹⁰⁰ Both types of chronic hepatitis lead to oxidative stress and inflammation and trigger rearrangements of the liver tissue architecture. Moreover, both viruses have been shown to activate several pro-oncogenic signaling pathways. In particular, both HBV and HCV can lead to the activation of growth and survival pathways such as the PI3K/AKT/mTOR and the EGFR/RAS/MAPK pathways, as well as the inhibition of p53 and RB

Table 1. Cancers associated with oncoviral infections

Oncovirus	Cancer types
Human papillomavirus	All cervical cancers Majority of anal and vaginal carcinomas Cancers of the oral cavity and pharynx
Adenovirus	Not implicated in the development of human neoplasms Oncogenic in rodents Transforming capacity <i>in vitro</i>
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma Non-Hodgkin lymphoma
Epstein-Barr virus	Burkitt lymphoma Hodgkin lymphoma Lymphomas in immunosuppressed individuals T-cell/NK-cell lymphomas Nasopharyngeal and gastric carcinomas
Kaposi's sarcoma-associated herpesvirus	Kaposi sarcoma Primary effusion lymphoma Plasmablastic variant of multicentric Castelman's disease
Human cytomegalovirus	'Oncomodulator': increases malignancy of infected tumor cells Detected in gliomas, colorectal and prostate cancer
Human T-cell lymphotropic virus type 1	Adult T-cell leukemia and lymphoma

tumor-suppressor activities. HBx, pre-S and S polypeptides for HBV and Core, NS3, NS5A and NS5B proteins for HCV are described as responsible for most of these oncogenic properties.^{100,101} In the case of HBV infection, stimulation of central carbon metabolism, the hexosamine pathway and of nucleotide synthesis have been recently reported.¹⁰² Immune-escape mutants of the pre-S protein have been shown to induce an mTOR-dependent aerobic glycolysis¹⁰³ and FA synthesis.¹⁰⁴ Moreover, HBx has been shown to trigger lipogenesis, especially through a liver X receptor-dependent activation of SREBP-1c.^{105,106} Finally, an intriguing study demonstrated that a large proportion of genes that drove tumorigenesis in a mouse model of HBV-induced HCC were related to aerobic glycolysis and anabolic metabolic processes.¹⁰⁷ Chronic HCV infection—more so than HBV infection—is clearly associated with metabolic alterations. Indeed, patients with chronic hepatitis C often develop secondary metabolic disorders, such as insulin resistance and steatosis.¹⁰⁸ From a molecular point of view, many mechanisms of HCV-induced metabolic alterations have been described, especially with respect to the lipid metabolism. In brief, HCV infection leads to a SREBP-1c-induced lipogenesis,¹⁰⁹ a reduction of FA oxidation¹¹⁰ and the disruption of lipoprotein secretion.¹¹¹ Interestingly, virally induced steatosis is suspected to be a risk factor for HCC in chronic hepatitis C patients.¹¹² Furthermore, HCV infection also increases aerobic glycolysis through the stabilization of HIF-1 α in normoxic conditions.^{113,114} A recent study has shown that the activity of HK2—a target of HIF-1 α —is increased in HCV-infected cells.¹¹⁵ In this paper, the authors confirmed the elevation in glycolytic flux induced by HCV by showing increased glucose consumption as well as lactate production in HCV-infected cells. In addition to its interaction with HK2, HCV has also been shown to interact with the tumor isozyme PKM2 and not with other types of pyruvate kinase.¹¹⁶ In the same study, PKM2 inhibition by shRNA inhibited HCV replication. Finally, a proteomic study in a cell culture model of HCV infection showed that the virus induces the expression of key enzymes implicated in glycolysis, PPP and TCA cycle in favor of biosynthetic activities.¹¹⁷

Epstein–Barr virus (EBV)

EBV is a herpesvirus that preferentially infects B lymphocytes. In immunocompetent hosts, primary infection is usually asymptomatic and occasionally causes infectious mononucleosis. However, EBV was also the first characterized human oncovirus. It is the causative agent of several lymphoproliferative disorders—Burkitt's lymphoma, Hodgkin's lymphoma and lymphomas in immunosuppressed individuals—and epithelial malignancies—mainly nasopharyngeal and gastric carcinomas¹¹⁸ (Table 1). But, despite the very high incidence of EBV infection (around 90%; 5.5 billion carriers worldwide), only a minority of infected individuals will develop EBV-associated cancers, as the transforming ability of the virus is controlled by the host's immune system.¹¹⁹ As a herpesvirus, EBV can establish both latent and lytic infections. *In vitro*, the virus has the ability to transform resting B cells into permanent, latently infected lymphoblastoid cell lines. However, *in vitro* infection of epithelial cells does not activate the full transforming program of the virus. To transform B cells, EBV absolutely requires two latent proteins: EBV nuclear antigen 2 (EBNA2) and latent membrane protein 1 (LMP1).¹¹⁸ EBNA2 is a transcriptional activator that, in particular, induces MYC expression¹²⁰ and the expression of two important EBV proteins: LMP1 and LMP2A. Both of the latter proteins have been described to activate several signaling pathways, including the PI3K–AKT–mTOR and the MAPK pathways.¹²¹ Recently, it was shown that the infection of B cells with EBV triggers the installation of a Warburg effect in the resulting lymphoblastoid cell lines. The authors showed that the interaction of EBNA3 and EBNA5 with polyhydroxylases 1 and 2 led to the stabilization of HIF-1 α ,

followed by an increase of glucose transporter GLUT1 levels and several glycolytic enzymes with the consistent elevation of aerobic glycolysis.¹²² Furthermore, the expression of LMP1 protein in different nasopharyngeal carcinoma cell lines has also been linked with the induction of tumor-like glycolysis.¹²³ In the latter study, LMP1 was shown to mediate a PI3K-dependent induction of MYC, leading to the upregulation of HK2, associated with an increase in aerobic glycolysis and resistance to apoptosis. Interestingly, HK2 was positively correlated with LMP1 levels in biopsies from nasopharyngeal carcinomas. These markers were associated with a poor overall survival of the patients following radiation therapy.

Kaposi's sarcoma-associated herpesvirus (KSHV)

Infection with KSHV is responsible for the development of Kaposi's sarcoma (KS) and two rare lymphoproliferative diseases: primary effusion lymphoma and the plasmablastic variant of multicentric Castleman's disease, both arising from infection of B cells¹²⁴ (Table 1). Unlike EBV, KSHV is not ubiquitous and major variations in prevalence occur geographically, with the highest rates in sub-Saharan Africa (>50%), moderate rates in Mediterranean countries (20–30%) and low rates in Europe, the United States and Asia (<10%).¹²⁵ KS is the most common neoplasm in untreated HIV-infected patients and also occurs in other immunocompromised individuals, including organ transplant recipients. However, the development of highly active antiretroviral therapy against HIV in the late 1990s has been associated with a sharp decline of AIDS-associated KS from 4.8% per year in 1990 to 1.5% per year in 1997.¹²⁶ KSHV can establish either a latent or lytic infection. The virus is present in the majority of KS tumor cells expressing latent viral proteins, but a proportion of cells in KS lesions undergo lytic replication. KSHV latent genes drive cell proliferation and prevent apoptosis, whereas KSHV lytic genes could further contribute to KS tumorigenesis by triggering host signaling cascades that lead to cytokine and growth factor secretion.^{124,127} Similar to HPV, the best-characterized KSHV-induced oncogenic mechanism is the inhibition of p53¹²⁸ and RB¹²⁹ tumor-suppressor pathways by KSHV latency-associated nuclear antigen. In addition, KSHV has been shown to stabilize HIF-1 α transcription factor^{130–133} and deregulate several oncogenic signaling pathways.¹³⁴ In particular, PI3K–AKT–mTOR signaling is activated by the infection and represents an interesting therapeutic target against KS.¹³⁵ In further recent studies, it was demonstrated that KSHV infection of endothelial cells induces a Warburg effect with increased aerobic glycolysis and lactic acid production as well as a glutamine addiction, all required for survival of latently infected cells.^{136,137} These changes were in part mediated by the increased expression of HK2 and the glutamine transporter SLC1A5. Interestingly, inhibition of glycolysis or glytaminolysis with 2-deoxyglucose or the pharmacological glutaminase inhibitor BPTES, respectively, induced apoptosis of infected cells only, showing that the virus-induced metabolic reprogramming induces glucose and glutamine addiction. The authors further confirmed in a metabolic profiling study that commonly altered pathways in cancer cells are also altered by KSHV infection.¹³⁸ These pathways include glycolysis, the PPP, amino-acid production and FA synthesis. In particular, KSHV infection increases *de novo* lipogenesis and the inhibition of this pathway lead to apoptosis of infected cells. In a model of primary effusion lymphoma—a B-cell non-Hodgkin lymphoma caused by KSHV infection—this increase in aerobic glycolysis and FA synthesis was confirmed and was shown to be PI3K dependent.¹³⁹ Some of these metabolic changes may be attributed to the KSHV K5 protein, which has recently been shown to increase aerobic glycolysis and lactate production through modulation of AKT and MAPK signaling pathways.¹⁴⁰

Human cytomegalovirus (HCMV)

HCMV is the largest known herpesvirus with a genome of about 230 kb and >200 open reading frames. It is widespread among the general population with an overall prevalence of 30–70% in developed countries. Homosexual men, individuals of poor socioeconomic groups and residents of developing countries can have seroprevalence rates >90%.¹⁴¹ After primary infection, the virus establishes lifelong latency or persistence, principally in cells of myeloid origin. In immunocompetent adult patients, HCMV infection is generally silent, but long-term immunosuppression can lead to uncontrolled replication and serious diseases, such as pneumonitis and retinitis.¹⁴² Although HCMV is in general not considered as oncogenic, the virus is often described as an 'oncomodulator' which may increase the malignancy of infected tumor cells¹⁴³ (Table 1). HCMV has been detected specifically in several types of human cancers, including colorectal cancer,¹⁴⁴ gliomas^{145–147} and prostate cancer.¹⁴⁸ And it was recently demonstrated that, in the context of a double deletion of tumor suppressors (Nf1 and p53), HCMV contributed to the development of glioblastoma in mice.¹⁴⁹ HCMV proteins can trigger several oncogenic features, such as cell invasion, angiogenesis and inhibition of apoptosis. However, the virus has a negative effect on cell cycle progression, which may explain—at least in part—why HCMV infection is not oncogenic *per se*.¹⁵⁰ Furthermore, HCMV infection leads to a large metabolic reprogramming, which constitutes today the best-described example of virus-induced metabolic alterations in the literature. As early as in 1975, HCMV infection was shown to stimulate total RNA and DNA synthesis and increase the number of cellular ribosomes.¹⁵¹ The virus was also shown >30 years ago to increase glucose uptake in infected fibroblasts.¹⁵² More recently, the evolution of mass spectrometry techniques allowed deciphering in more detail the changes in the metabolic composition of the host cell induced by the infection.^{153,154} HCMV markedly disrupts the metabolic homeostasis of infected human fibroblasts, elevating the levels of glycolytic, TCA cycle and pyrimidine nucleotide biosynthesis intermediates. Metabolic flux experiments using ¹³C-labeled glucose and glutamine confirmed the elevation of glycolysis and glutaminolysis-driven TCA cycle activity and revealed an elevation of *de novo* FA synthesis in infected cells.¹⁵³ These metabolic alterations are correlated with a robust increase of mitochondrial biogenesis by the infection.¹⁵⁵ The importance of glutamine metabolism for HCMV infection was confirmed after observing that human fibroblasts infected with HCMV were more viable than uninfected cells under glucose starvation.¹⁵⁶ In their study, Chambers *et al.*¹⁵⁶ showed that HCMV infection triggers a glutamine-driven anaplerotic program, necessary to feed the TCA cycle, allowing the production of ATP as well as NADPH and citrate for lipid production. *De novo* lipogenesis in HCMV-infected cells is triggered by the mTOR-dependent increase of both acetyl-CoA carboxylase expression and enzymatic activity after SREBP-2 activation.¹⁵⁷ SREBP-1 was also shown to participate in HCMV-induced lipogenesis through a PKR-like endoplasmic reticulum kinase activation.^{158,159} On the other hand, HCMV-induced aerobic glycolysis is dependent on calmodulin-dependent kinase kinase (CaMKK) and the inhibition of CaMKK severely blocks HCMV production.¹⁶⁰ Moreover, HCMV has been shown to activate several metabolic signaling pathways such as the EGFR–RAS–MAPK and PI3K–AKT–mTOR pathways.^{161,162} AMPK signaling is also required during HCMV infection, but AMPK activation probably remains under a certain threshold that allows glycolytic stimulation without blocking FA synthesis.¹⁶³ Finally, the carbohydrate-response element-binding protein—which has a key role in regulating glucose metabolism and lipogenesis in metabolic tissues and cancer cells—is also critical for the metabolic regulations induced during HCMV infection.¹⁶⁴

Human T-cell leukemia virus type-1 (HTLV-1)

HTLV-1 was the first retrovirus characterized as the causative agent of a human cancer, adult T-cell leukemia⁸¹ (Table 1). Worldwide, it is estimated that 5–10 million persons are HTLV-1 carriers.⁸² Among these, the risk of developing adult T-cell leukemia is estimated to be 1–5%.⁸³ Two HTLV-1 proteins, namely, Tax and HBZ, are essential for the oncogenic process. Tax is thought to initiate transformation by activating the PI3K and nuclear factor-κB pathways and by inactivating p53. The role of HBZ is less clear but this protein is believed to maintain the transformed phenotype in adult T-cell leukemia when Tax is no longer expressed.⁸⁴ Recently, HBZ has been shown to activate the mTOR signaling pathway.⁸⁵ However, although GLUT1 is known as a required cellular receptor for HTLV-1,⁸⁶ no clear metabolic alterations following HTLV-1 infection have been described. A preliminary metabolomic analysis of HTLV-1-transformed or Tax-overexpressing cells has reported some metabolic changes but without a clear direction.⁸⁷ The precise knowledge of the consequences of HTLV-1 infection on its host cell metabolism requires further investigation.

The main alterations of cell metabolism linked to viral infections and described above are recapitulated in Figure 1b.

CONCLUSION

The multiplication of all viruses depends on the availability of metabolic constituents in the infected host cells. Indeed, the production of new virions requires the synthesis of viral nucleic acids, proteins and, in many cases, lipid envelopes. However, viruses often infect differentiated quiescent cells where biosynthetic processes—nucleotide, amino acid and lipid synthesis—are attenuated. In order to bypass this limitation, it seems that most viruses had to evolve to reprogram and activate these biosynthetic pathways, even though the requirement of these metabolic adaptations for viral replication still needs to be causally proofed for most viruses. Intriguingly, these metabolic alterations are shared both by cells infected with viruses and transformed cells, suggesting that metabolic reprogramming is an important feature of viral oncogenesis. Although our review focuses on oncogenic viruses, alterations of central carbon metabolism are not only exclusively associated with these types of viruses but have also been linked to other chronic and acute viral infections caused by, for example, vaccinia virus,¹⁶⁵ herpes simplex virus-1,¹⁶⁶ dengue virus,¹⁶⁷ influenza virus,¹⁶⁸ measles virus¹⁶⁹ and HIV virus.¹⁷⁰ These viral infections are good examples that show that metabolic reprogramming is not sufficient by itself for oncogenesis to occur but introduces a cellular environment favorable for oncogenesis. Other cellular changes, such as persistent modulation of cell cycle progression, resistance to cell death and evasion from immune surveillance, must be acquired in order to progress into neoplasia. Furthermore, the augmented production of reactive oxygen species, which can arise following increased metabolic fluxes, is a major driver of genomic instability and cancer.¹⁷¹ Oxidative stress is also closely connected to chronic inflammation, which in the case of HBV,¹⁷² HCV¹⁰¹ and very likely EBV¹⁷³ and KSHV¹²⁴ infections can constitute a determining trigger for neoplasia.¹⁷⁴ Therefore, targeting metabolic alterations in the context of chronic viral infections for therapeutic purposes may have a double advantage: it may reduce or eliminate the virus and prevent the associated cellular alterations leading to malignant transformation in the long term. Interestingly, drugs targeting the major metabolic pathways known to be altered by viruses—such as glycolysis or lipogenesis—have already been described as experimental cancer treatments and their development is mainly at preclinical stages. However, some drugs are already being tested in clinical trials.¹⁷⁵ Importantly, drugs targeting nucleic acid synthesis were among the first chemotherapeutic agents

developed¹⁷⁶ and constitute the large majority of approved antiviral molecules.¹⁷⁷ Finally, exploring the molecular mechanisms underlying metabolic reprogramming induced by viruses may be useful to establish metabolic footprints as potential non-invasive biomarkers for the detection and staging of viral infections and the associated transformation process.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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