Cell Insight 3 (2024) 100200

Contents lists available at ScienceDirect

Cell Insight

journal homepage: www.journals.elsevier.com/cell-insight

Hypoxic reactivation of Kaposi's sarcoma associated herpesvirus

Rajnish Kumar Singh, Atharva S. Torne, Erle S. Robertson *

Department of Otorhinolaryngology-Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, 19104, USA

ARTICLE INFO

Keywords:
KSHV
Hypoxia
Reactivation
Replication
Transcription
Epigenetics
LANA

ABSTRACT

Hypoxic reactivation of Kaposi's sarcoma-associated herpesvirus (KSHV) refers to the phenomenon under low oxygen where the virus goes from latent to lytic replication. Typically, healthy cells generally cease cell division and DNA replication under hypoxic conditions due to limited resources, and the presence of physiological inhibitors. This restricted replication under hypoxic conditions is considered an employed strategy of the cell to minimize energy consumption. However, cancerous cells continuously replicate and divide in hypoxic conditions by reprogramming several aspects of their cell physiology, including but not limited to metabolism, cell cycle, DNA replication, transcription, translation, and the epigenome. KSHV infection, similar to cancerous cells, is known to bypass hypoxia-induced restrictions and undergo reactivation to produce progeny viruses. In previous studies we have mapped several aspects of cell physiology that are manipulated by KSHV through its latent antigens during hypoxic conditions, which allows for a permissive environment for its replication. We discuss the major strategies utilized by KSHV to bypass hypoxia-induced repression. We also describe the KSHV-encoded antigens responsible for modulating these cellular processes important for successful viral replication and persistence in hypoxia.

1. Introduction

Typically, most viral families do not exhibit a latent phase of infection, however, a few families are known to enter true latency (Speck & Ganem, 2010). Among them, herpesviruses, which are large double-stranded DNA virus, are the most prevalent and capable of undergoing latent infection across all the subfamilies of these viruses (Speck & Ganem, 2010; Weidner-Glunde et al., 2020). Certain members of this family, which include Kaposi's sarcoma associated herpesvirus (KSHV) are ubiquitous, opportunistic, oncogenic herpesvirus linked to several proliferative diseases, and are reported to infect large world's population (Angeletti et al., 2008). Once infected, the KSHV genome latently persists in the infected individuals for their life time (Damania et al., 2022; Thorley-Lawson, 2015). Other common herpesviruses, which are known to maintain latency includes herpes simplex virus (HSV1 and HSV2), varicella-zoster virus (VZV), and Epstein Barr Virus (EBV) (Cohen, 2020; Sehrawat et al., 2018; Soldan & Lieberman, 2023). During latency, the genome of infecting viruses are highly modified, mostly through epigenetic modifications, to minimize expression of viral-encoded genes (Lieberman, 2016). The expression of a small number of viral-encoded genes is necessary for evading recognition by host immune system (Lieberman, 2016; Sack & Herzog, 2009). During latency exhibited by the majority of herpesviruses, the viral genome persists silently as a chromosome-tethered episome within the infected cells and replicate synchronously with host genome (Kim & Kim, 2022; Sorel & Dewals, 2018). In all cases of herpesvirus latency where chromosome-tethered-episomes are the mechanism of genome persistence, a unique antigen encoded by these viruses plays crucial roles in persistence of the viral genome by tethering it to the host chromosome (Serquina & Ziegelbauer, 2017).

In the case of Epstein-Barr virus, EBNA1 plays a major role in tethering of its genome with the host chromosome (Kang & Kieff, 2015; Serquina & Ziegelbauer, 2017). Here the central Gly-Arg-rich region (amino acids 325–376) of EBNA1 plays a central role in chromosome attachment. However, the N-terminal sequences (8–67) of EBNA1 also play a role in this interaction (Frappier, 2012; Kang & Kieff, 2015; Shire et al., 2006). KSHV-encoded LANA has functional homology with EBV-encoded EBNA1 and plays pivotal roles in KSHV persistence as well as reactivation (Nakajima et al., 2024; Uppal et al., 2014). KSHV episomes are tethered with host chromosome by concomitant interaction of LANA with host chromosomes and KSHV episome. The C-terminal of LANA attaches itself to the host chromosome, while the N-terminal of LANA binds with the terminal repeat region within the KSHV episome (Kumar et al., 2022; Purushothaman et al., 2016). In contrast, alpha herpesviruses establish latency within terminally differentiated,

* Corresponding author.
E-mail address: erle@pennmedicine.upenn.edu (E.S. Robertson).

https://doi.org/10.1016/j.cellin.2024.100200
Received 30 July 2024; Received in revised form 28 August 2024; Accepted 29 August 2024
Available online 7 September 2024

non-dividing neurons, which eliminates the need for the tethering of the viral genome to the host chromosome (Salazar et al., 2023). Consequentially, these viruses are reported to not express any identified protein during latent infection (Salazar et al., 2023). Exceptionally, HHV6 is known to integrate in the telomeric region of the host chromosomes (Kaufer & Flamand, 2014). In addition to herpesviruses, few other viruses are known to undergo latency. The most notable among other viruses are Human immunodeficiency virus1 (HIV1), Human Papillomavirus (HPV) and Hepatitis B virus (HBV) (Lieberman, 2016; Platt et al., 2020). However, unlike most of the herpesviruses, these viruses in general maintain latency by integrating into the host chromosomes (Pantry & Medveczky, 2017). The latent infections of all the above-mentioned viruses, can persist for the life of their hosts. Several internal and external factors have been reported to induce reactivation of the viruses capable of undergoing latency (Traylen et al., 2011). These factors, in general are capable of inducing physiological stress within the host cell. Most prominent physiological stress inducing factors include ionizing radiation, metabolite scarcity, reactive oxygen species, hypoxic conditions or chemical compounds capable of interfering with epigenetic homeostasis can induce viral reactivation (Grinde, 2013; Jones, 2023).

Kaposi's sarcoma-associated herpesvirus (KSHV) represents a typical example of a virus that can undergo reactivation during hypoxia (Aneja & Yuan, 2017; Davis et al., 2001). Nevertheless, other herpesviruses such as HSV, VZV, EBV, and CMV can also undergo reactivation under hypoxic conditions through various mechanisms, including the suppression of the immune response, and activation of specific cellular pathways that promote viral replication (Aneja & Yuan, 2017; Verzosa et al., 2021). Additionally, hypoxia may lead to tissue damage or inflammation, creating an environment conducive to viral reactivation. Hypoxia alters the cellular microenvironment, to stimulate viral replication and production of infectious virions (Castillo-Rodriguez et al., 2022; Thaker et al., 2019).

The non-herpesviruses are also reported to respond within the hypoxic microenvironment in a manner that can promote their reactivation. Hypoxia has been suggested to contribute to HBV reactivation in liver cells by modulating cellular signaling pathways involved in viral replication (Wing et al., 2021). Hypoxic conditions can also impair host immune responses against HBV, leading to increased viral replication. Similarly, hypoxia has been implicated in promoting HCV replication and liver disease progression. Hypoxic conditions in the liver microenvironment can influence HCV replication and the host immune response, contributing to viral persistence and liver damage (Vassilaki et al., 2013). Human Immunodeficiency Virus (HIV) itself does not directly undergo reactivation under hypoxia, but it can enhance its own replication, and disease progression by promoting viral transcription, immune dysregulation, and tissue damage (Zhuang et al., 2020).

Recently, reactivation of Marek's Disease Virus (MRV) in lymphoma-derived latently infected T-lymphocytes was reported in response to hypoxia and HIF1α upregulation (Zhuang et al., 2020). The molecular mechanism of hypoxia-induced reactivation of these viruses have been explained on the basis of up-regulated expression of lytic switch proteins encoded by these viruses, which are required as an activator for replication and transcription of these viruses (Orlando et al., 2020; Yfantis et al., 2023). For example, the promoter region of the KSHV lytic switch protein contains six hypoxia responsive elements (HREs). The most widely accepted core sequence of the putative HRE sequences is accepted as 5′-RCGTG-3′ (R = G/A). Nevertheless, other similar sequences such as TCAGGTG and BACGTSSK (where B = G/C/T, S = G/C, and K = G/T) are also shown to be responsive to HIF1α (Cai, Lan, et al., 2006). In addition to the RTA promoter, promoter regions of several other KSHV-encoded genes have been reported to harbor HREs, suggesting a direct role of HIF1α and hypoxia in regulating the expression of other KSHV-encoded genes, and possibly required for facilitating KSHV reactivation in the hypoxic tumor micro-environment. The most prominent KSHV-encoded genes with tested functional HREs within their promoter region includes LANA and vGPCR (Davis et al., 2023; Singh et al., 2018). Similar to that completed for KSHV, bioinformatics analysis on the complete genome of Marek's Disease Virus showed presence of more than 200 hypoxia responsive elements, which can facilitate expression of a number of MRV-encoded genes in hypoxia (Mallet et al., 2022).

Although, it is evident that hypoxia can regulate activities at the genome and proteome at multiple levels to facilitate reactivation of many viruses, as well as their associated pathogenesis, the understanding of hypoxia-induced viral reactivation remain a major challenge for the field. This is mainly due to adverse and nonpermissive effects of hypoxia on many areas of cellular physiology. Hypoxia, can adversely affect cell cycle progression, DNA replication, transcription and translation (Ortmann et al., 2014). Moreover, hypoxia can mediate epigenetic changes, generation of reactive oxygen species and post-translational modifications (Patterson et al., 2012; Verdikt & Thienpont, 2024). In this current review, we will focus on discussing the different aspects of KSHV reactivation under conditions of hypoxia in the tumor microenvironment.

2. The inhibitory role of hypoxia on cell cycle progression and DNA replication

Hypoxia plays a crucial role in various physiological and pathological processes within the cell that can lead to dysregulation of the cell cycle (Semenza, 2000). Understanding how hypoxia can influence the highly regulated series of events that control the cell cycle is essential for unraveling its role in virus-induced disease states such as cancer (Ortmann et al., 2014; Semenza, 2000). The cell cycle consists of four major phases: G1 (Gap 1), S (Synthesis), G2 (Gap 2), and M (Mitosis). These phases are orchestrated by a complex network of regulatory proteins, cyclins, and cyclin-dependent kinases (CDKs), ensuring precise timing and progression through each stage (Harris, 2002). The transition between phases is tightly regulated to maintain genomic stability and proper replication of the cellular genome to produce daughter cells. Eukaryotic cells, in general respond to hypoxia through various mechanisms orchestrated by the hypoxia-inducible factor (HIF) protein family, primarily HIF-1α and HIF-2α (Hu et al., 2003). Under normoxic conditions, prolyl hydroxylases (PHDs) hydroxylate HIF-α subunits, marking them for degradation via the ubiquitin-proteasome pathway (Strowitzki et al., 2019). In contrast, hypoxia inhibits PHD activity, leading to HIF-1α stabilization and subsequent translocation to the nucleus (Marxsen et al., 2004). There, HIFs dimerize with HIF-1β and bind to hypoxia-response elements (HREs) on the genome, activating the transcription of target genes involved in adaption to low oxygen levels (Marxsen et al., 2004). Hypoxia alters the progression through the G1 phase by influencing the expression of cyclins and CDKs at both transcriptional and post-translational levels (Hubbi & Semenza, 2015). It is known that hypoxia induces cell cycle arrest at G1 by upregulating the cyclin-dependent kinase inhibitors (CKIs) p21 and p27 (Gardner et al., 2001; Hubbi & Semenza, 2015). These CKIs inhibit the activity of cyclin-CDK complexes, thereby halting cell cycle progression and promoting cellular quiescence or senescence (Gardner et al., 2001; Pennycook & Barr, 2020). DNA replication during the S phase is critical for maintaining genomic integrity. In addition, hypoxia-induced HIF activation regulates genes involved in DNA replication and repair (Tang et al., 2021). Under prolonged hypoxic conditions, cells can undergo replication stress due to impaired DNA synthesis and increased DNA damage, leading to genomic instability (Pires et al., 2010). However, the role of hypoxia and its impact on G2/M transition remains an area of further investigation (Druker et al., 2021). Similarly, the regulation of mitotic checkpoints and spindle assembly during hypoxia remains an area of further research (Fischer et al., 2004).

Hypoxia significantly impacts the cell cycle, which is crucial for cellular replication and division. Disruptions in cell cycle due to hypoxia can lead to severe outcomes, including cancer. Therefore, the phases of cell cycle are tightly controlled by proteins which include cyclins and cyclin-dependent kinases (CDKs) to ensure proper cell division, and genomic stability. Under hypoxic conditions, the hypoxia-inducible

factors (HIFs), particularly HIF-1α, are stabilized and so activate genes that help cells adapt to low oxygen microenvironment. Hypoxia often causes cell cycle arrest in the G1 phase by upregulating inhibitors like p21 and p27, halting progression and promoting cellular quiescence or senescence. It also affects DNA replication during the S phase, leading to replication stress and genomic instability.

Notably, hypoxia significantly impacts mitochondrial ATP production due to limited oxygen availability, a limiting substrate for oxidative phosphorylation (Flood et al., 2023). In normoxic conditions, mitochondria utilizes oxygen as the final electron acceptor in the electron transport chain (ETC) to drive synthesis of ATP through oxidative phosphorylation (Taylor & Scholz, 2022). However, under hypoxic conditions, the reduced oxygen levels impair the function of the ETC, leading to a decrease in ATP production (Wheaton & Chandel, 2011). This insufficiency triggers a metabolic shift towards anaerobic glycolysis, where cells increase glucose uptake and lactate production to generate ATP independently of oxygen. Although glycolysis is less efficient than oxidative phosphorylation in terms of ATP yield, it provides a rapid response to energy demands under low oxygen conditions (Weljie & Jirik, 2011; Wheaton & Chandel, 2011). Moreover, prolonged hypoxia can lead to mitochondrial dysfunction and an increase in the production of reactive oxygen species (ROS) (Kung-Chun Chiu et al., 2019), further compromising cellular energy balance and contributing to hypoxia-induced cellular stress and damage. Together, these conditions highly restrict other cellular processes such as transcription and translation. Nevertheless, physiological inhibitors, low ATP conditions and other stresses activate autophagy as well as proteasomal degradation of key proteins required for cell cycle progression and DNA replication (Gomez-Virgilio et al., 2022; Lilienbaum, 2013). The overall inhibitory effect of hypoxia on cell cycle progression and DNA replication is shown in Fig. 1.

In conclusion, hypoxia impairs the ETC, leading to decreased ATP production and a metabolic shift towards anaerobic glycolysis. This shift, though less efficient, provides a rapid ATP source under low oxygen. Prolonged hypoxia can cause mitochondrial dysfunction, increased reactive oxygen species (ROS), and cellular stress. These conditions inhibit key cellular processes, including cell cycle progression and DNA replication, while activating autophagy and proteasomal degradation to manage cellular stress.

3. Metabolic reprogramming of infected cells during hypoxic reactivation of KSHV

KSHV infection can reprogram the metabolic activity of infected cells to favor its persistence and tumorigenesis as well as its reactivation (Delgado et al., 2010; Yogev et al., 2014). Metabolite profiling of KSHV infected cells suggest a wide difference between metabolite pools of KSHV infected cells when compared to control cells, including those which are common to anabolic pathways of most cancer cells (Delgado et al., 2012; Singh et al., 2018). KSHV infection-mediated elevation of metabolites pools are due to enhanced anabolic activity rather than degradation from respective macromolecules (Liu et al., 2021; Singh et al., 2018). This reprogramming, in part is mediated by altering the expression of core metabolic enzymes, and helps in mimicking metabolic

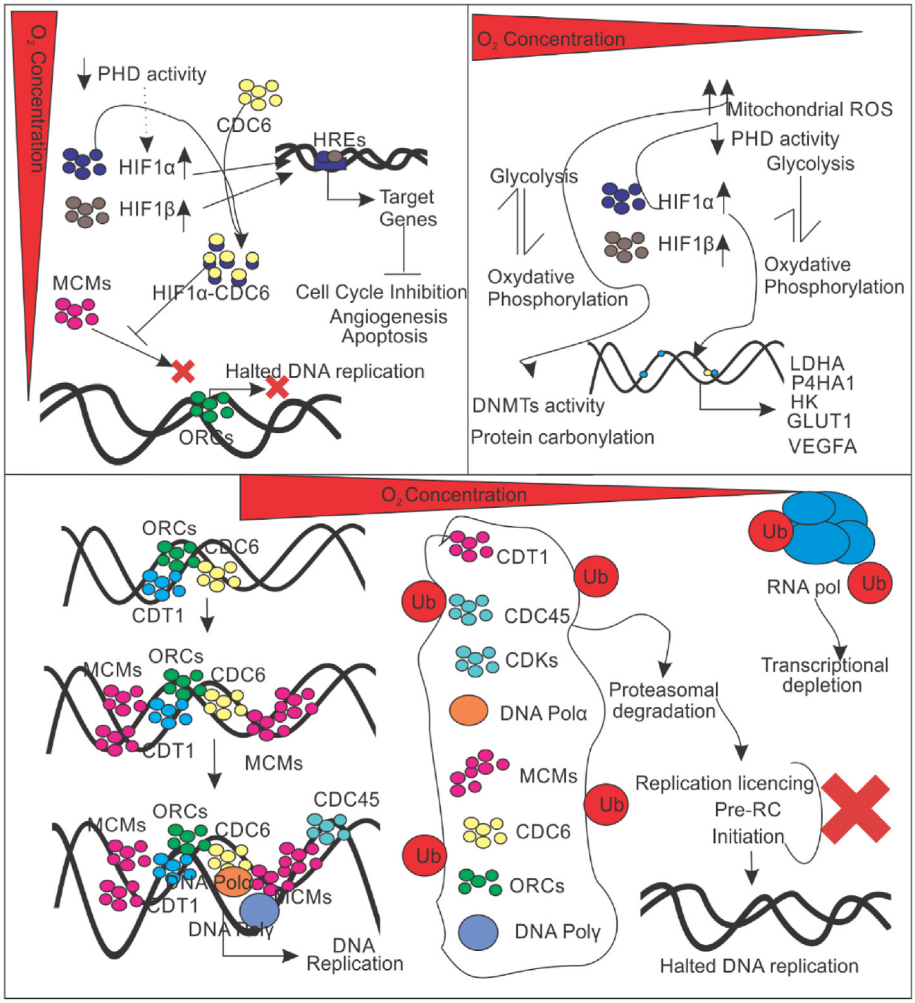

Fig. 1. An inhibitory role for hypoxia on cell cycle progression and DNA replication. Hypoxic conditions lead to inactivation of PHD activities which allows stabilization of HIF1α. In its stabilized condition, HIF1α interacts with CDC6 to facilitate MCMs loading onto replicating DNA but inhibits their activation. In this stabilized condition, HIF1α up-regulates expression of genes required for metabolic reprogramming leading to enhanced glucose uptake and glycolysis. Low oxygen levels also promote reactive oxygen species production, which in turn can mediate protein carbonylation and interfere with DNMTs activity. Hypoxic conditions can mediate degradation of key components of DNA replication and RNA transcription related proteins by promoting their ubiquitination. The tapering end of the red triangle represents a decrease in O_2 concentration.

status as those utilized by cancer cells (Li & Gao, 2021). Here, these cells are highly dependent on glycolytic ATP even in the presence of molecular oxygen, a phenomenon commonly known as Warburg effect (Delgado et al., 2010). This glucose dependency of KSHV positive cells is well evident from high glucose uptake and subsequent high lactate release by KSHV infected cells (Singh et al., 2018). Some of the studies investigating this reprogramming have shown that over-expression of host factors like glucose transporters (GLUTs) and hypoxia-inducible factor (HIF1α) is essential for these changes in KSHV-infected cells (Shrestha et al., 2017). Additionally, a reduction in mitochondrial copy number and down-regulation of EGLN2 and HSPA9 have been observed following over-expression of KSHV-encoded microRNAs, which are thought to contribute to metabolic alterations driven by KSHV (Yogev et al., 2014). Host mitochondria is also targeted during KSHV infection, which not only necessitate up-regulation of glycolysis, but also alters the apoptotic pathways (Holmes et al., 2020). Although, the targeting mechanism of mitochondria by KSHV is not fully understood, mitochondrial localization of KSHV-encoded vCyclin, vFLIP and Kaposin is well established (Holmes et al., 2020).

In addition to reprogramming carbohydrate metabolism, KSHV infection can modulate metabolism of fatty acids and amino acids, where inhibition of key enzymes in these pathways can led to apoptosis of infected cells (Choi et al., 2020; Dai et al., 2017; Delgado et al., 2012; Li et al., 2019). However, it is interesting to observe that, KSHV transformed Rat primary embryonic metanephric mesenchymal precursor cells are more dependent on glutamine than glucose, and glutaminolysis is necessary for their survival and tumorigenesis (Li et al., 2019). In these cells, transcripts related to glutamine metabolism such as Glutaminase (GLS) are reported to be up-regulated, and the up-regulation of Cysteine/Glutamine antiporter (SLC7A11/xCT) by KSHV emphasize the importance of glutamine metabolism in KSHV life cycle (Sanchez et al., 2015).

Similar to the glucose and glutamine metabolism, the alteration in the fatty acid metabolism is also critical for the KSHV latency maintenance and pathogenesis, especially in endothelial cells (Sanchez et al., 2017). Further, well-orchestrated lipid metabolism is crucial for survival of KSHV-infected primary as well as transformed cells (Sanchez et al., 2015, 2017). Metabolic profiling from B-cells as well as KSHV-infected PEL cells demonstrated an increased fatty acid synthesis compared to non-infected primary B cells (Singh et al., 2018). A high abundance of membrane lipids such as phosphatidylcholine and phosphatidylethanolamine has been reported in KSHV-infected cells, which is mainly mediated through high levels of the core fatty acid synthesizing enzyme, fatty acid synthase (FASN) (Bhatt et al., 2012). Furthermore, treatment of KSHV-infected cells with an inhibitor of FASN, such as C75, can effectively affect viability of these cells in a dose-dependent manner (Bhatt et al., 2012).

The stabilization of HIF1α by KSHV infection during normoxia is well established phenomenon, where KSHV-encoded LANA can mediate degradation of vHL, the negative regulator of HIF1α to allow its accumulation under normoxic conditions (Cai, Knight, et al., 2006). HIF1α plays significant role in KSHV latency as well as its reactivation through hypoxia/HIF1α-dependent differential expression of KSHV-encoded genes, which can shift the metabolic equilibrium to favor KSHV reactivation (Shrestha et al., 2017; Singh et al., 2018). Hypoxia and HIF1α are crucial for KSHV-mediated pathogenesis, as they modulate the expression of several KSHV-encoded proteins (Singh et al., 2018). KSHV infection alone can replicate numerous physiological and metabolic changes typical of hypoxia, which is common in cancer cells. Hypoxia also significantly influences the biology of KSHV reactivation, where HIF1α facilitates RTA-mediated reactivation by binding with LANA and upregulating RTA expression (Kumar et al., 2022). Additionally, hypoxia enhances viral reactivation potential of the known inducer of lytic replication, 12-O-tetradecanoylphorbol-13-acetate (TPA) (Davis et al., 2001). The role of hypoxia is also critical in maintaining latency and KSHV-associated pathogenesis, as the promoter of the key latent gene cluster coding for LANA, vFLIP, and vCyclin contains hypoxia-responsive elements and can be activated by HIF1α (Singh et al., 2018). However, the management of the metabolic requirement for KSHV-positive cells during hypoxic reactivation, and which factors are involved in this reprogramming remain a poorly explored domain of KSHV biology.

Whole transcriptomics RNA sequencing studies on KSHV-positive and -negative cells grown under normoxic or hypoxic conditions revealed differential expression of several metabolic pathway genes. Critical host-encoded genes were implicated in redirecting the metabolic flux towards the pentose phosphate pathway, aiding in the production of intermediate metabolites for nucleotide biosynthesis (Singh et al., 2018). The KSHV-encoded vGPCR was identified as a novel target of HIF1α and a major viral component in this metabolic reprogramming, with its HIF1α-dependent expression driven by the functional hypoxia-responsive elements within the vGPCR promoter (Singh et al., 2018, 2021). Expression of vGPCR alone induced changes in the metabolic phenotype similar to those seen in KSHV-infected cells under hypoxic conditions. Silencing HIF1α reversed the hypoxia-associated phenotype in KSHV-positive cells. Analysis of the host transcriptome identified several common targets of hypoxia and KSHV-encoded factors, along with other synergistically activated genes in major cellular pathways, including those involved in carbohydrate, lipid, and amino acid metabolism (Singh et al., 2018, 2021). Additionally, some of the DNA methyl-transferases were synergistically regulated by the combination of KSHV and hypoxia at both the transcript and protein levels (Singh et al., 2018). This synergistic effects of HIF1α and KSHV-encoded proteins on metabolic reprogramming of KSHV-infected cells in the hypoxic tumor micro environment can induce global changes in host gene expression (Singh et al., 2018). The over-expression of vGPCR correlates with increased glucose uptake, and its down-regulated expression in ShHIF1α knock down cells indicates its role as a major player in regulating the metabolic changes of KSHV-infected cells in hypoxia. The similarity in global transcript changes between KSHV-positive and KSHV-negative cells in hypoxia suggests a HIF1α-associated role in KSHV-related pathology and reactivation (Singh et al., 2018, 2021). The schematic for vGPCR-dependent metabolic reprogramming of KSHV infected cells under hypoxic conditions is provided in Fig. 2.

4. Modulation of the replication and transcriptional machinery by KSHV during hypoxic reactivation

DNA replication is a highly orchestrated process ensuring accurate duplication of the genome (Petropoulos et al., 2019). DNA replication starts during the S phase of the cell cycle and involves a series of highly regulated steps (Petropoulos et al., 2019; Sclafani & Holzen, 2007). Specific sequences within the genome serve as origins of replication where licensing of replication commences (Leonard & Mechali, 2013). In eukaryotes, the origins of replication are recognized by the Origin Recognition Complex (ORC) protein, a multi-subunit protein complex that binds to these sites before a cell actually enters in the S-phase (Hu & Stillman, 2023). The binding of subunits of the ORC proteins is the first step in the formation of the pre-replicative complex (pre-RC) (Hu & Stillman, 2023). Following ORC binding at origin of replication, other essential replication proteins such as Cdc6 and Cdt1 are recruited (Chen et al., 2007; Hu & Stillman, 2023). This facilitates the loading of the minichromosome maintenance (MCM) helicases complex onto the DNA (Chen et al., 2007). The MCM complex is composed of six subunits (MCM2-7), and is crucial for unwinding of the DNA helix, a prerequisite for replication (Bochman & Schwacha, 2009). The loading of MCMs completes the assembly of the pre-RC, rendering the origin 'licensed' for replication (Bochman & Schwacha, 2009). However, the helicase activity of MCMs is attained during S phase through its phosphorylation by CDKs (Wei et al., 2013). The activation of Pre-RC complex enables binding of the GINS complex and Cdc45, forming the active CMG (Cdc45-MCM-GINS) helicase to unwind DNA strands (Ilves et al., 2010). The recruitment of DNA polymerases to the replication fork is mediated by the action of primase, a subunit of DNA polymerase α, which synthesizes short RNA primers complementary to the single-stranded DNA.

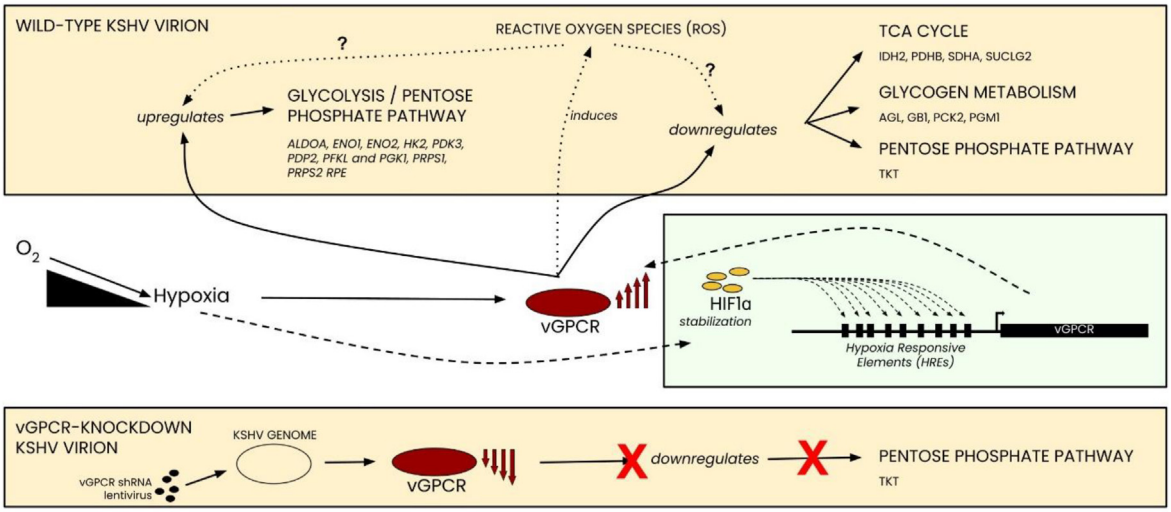

Fig. 2. Metabolic reprogramming during KSHV infection and HIF1α-induced expression of vGPCR. In KSHV infected cells, stabilization of HIF1α following the induction of hypoxia enables sustained expression of KSHV-encoded vGPCR. RNA sequencing data revealed diverse metabolic changes as a direct result of KSHV infection through the action of vGPCR. Expression of glycolytic genes and glucose uptake in particular, is substantially up-regulated in KSHV infected cells, while direct complementary down-regulation of glycogen metabolism and TCA cycle genes has also been shown. vGPCR has been shown to negatively affect transketolase (TKT) in the pentose phosphate pathway, and has been shown to be required for efficient blocking of TKT expression during hypoxia. Frame-shift knock-out of vGPCR or its knock-down, does not result in any significant change in the expression of TKT reported, under similar hypoxic conditions. Further, vGPCR has also been shown to induce the generation of reactive oxygen species (ROS), with a potential role in epigenetic reprogramming viral and host genomes, which mediate changes in the expression of metabolic genes.

These primers provide a starting point for DNA polymerase δ and ε, which extend the primers, synthesizing the leading and lagging strands, respectively (Nasheuer & Meaney, 2024). The initiation of DNA replication is tightly regulated to ensure that each segment of the genome is replicated once and only once per cell cycle, preventing genomic instability (Nasheuer & Meaney, 2024; Sclafani & Holzen, 2007). In addition to these core components, a myriad of other factors, including chromatin remodelers and histone chaperones, facilitate the accessibility of the replication machinery to DNA, ensuring efficient and accurate replication (Chakraborty et al., 2021; Ransom et al., 2010). Hypoxia can significantly impact DNA replication by disrupting several critical aspects of the initiation, elongation and termination (Ransom et al., 2010). Under hypoxic conditions, the cellular environment undergoes a metabolic shift, leading to reduced ATP production and increased generation of reactive oxygen species (ROS) (Ransom et al., 2010; Wheaton & Chandel, 2011). These changes can impair the activity of key enzymes and regulatory proteins involved in DNA replication. The activation of hypoxia-inducible factors (HIFs) under low oxygen conditions can also lead to transcriptional downregulation of essential replication factors, such as components of the minichromosome maintenance (MCM) helicase complex and DNA polymerases, thereby hindering the formation of the pre-replicative complex (pre-RC) and the initiation of DNA synthesis. (Druker et al., 2021; Pires et al., 2010). Additionally, hypoxia-induced oxidative stress can cause DNA damage, activating checkpoint pathways that halt cell cycle progression to allow for repair, further delaying or inhibiting DNA replication (Olcina et al., 2014). The replication stress induced by hypoxia can result in replication fork stalling and collapse, leading to genomic instability and potential cell death if the damage is irreparable (Tsegay et al., 2019; Zhang et al., 2022).

Nevertheless, KSHV and other related viruses are known to undergo reactivation after bypassing these repressive activities (Cai, Lan, et al., 2006; Davis et al., 2001). An analysis for transcript level expression of genes involved in cell cycle progression and DNA replication suggested a similar expression pattern for these genes in both KSHV negative or positive background under hypoxic conditions (Singh et al., 2019). However, proteomic analysis for components of cell cycle progression and DNA replication shows that KSHV infection can rescue hypoxia dependent degradation of these proteins (Singh et al., 2019). Among the KSHV-encoded antigens, Latency associated nuclear antigen (LANA) was reported to interact with specific replication related proteins and protect them from hypoxia-mediated degradation, by inhibiting their ubiquitination under hypoxic conditions (Singh et al., 2019). Similar to the cell cycle and DNA replication components, the major RNA transcribing enzyme RNA-PolII was reported to undergo degradation in hypoxic conditions (Bose et al., 2024). This could explain the compromised transcriptional status of several genes under hypoxic conditions. Interestingly, KSHV-encoded LANA requires supplementation from HIF1α and NEDD4 to prevent its polyubiquitination (Bose et al., 2024). vCyclin, another antigen encoded by KSHV, facilitates KSHV replication during hypoxic condition by regulating levels of HIF1α through interaction and mutual degradation through the lysosomal pathway. Interestingly, HIF1α acts as a transactivator for vCyclin expression and can mediate a vCyclin dominant or depleted phase in infected cells. A more detail description of how vCyclin mediates regulation of HIF1α is provided in the following section. Together, protection of cell cycle, DNA replication and RNA transcription-associated protein by KSHV-encoded LANA can significantly manipulate hypoxia-mediated repression to bypass repression of DNA replication, and hence, promote KSHV reactivation under these conditions (Bose et al., 2024; Singh et al., 2019). A schematic showing KSHV-encoded LANA-mediated modulation of the replication machinery under hypoxic conditions is provided in Fig. 3.

5. Epigenetic reprograming induced by KSHV during hypoxic reactivation

Epigenetic reprogramming plays a pivotal role in establishing latency upon initial infection by KSHV (Campbell et al., 2020). Although, the initial cycles of KSHV replication proceed through lytic means, the KSHV genome undergoes circularization and chromatinization through several layers of epigenetic modification in a concurrent process (Campbell et al., 2020; Uppal et al., 2015). The employed sophisticated array of epigenetic reprogramming by KSHV helps to establish latency by evading host immune responses, which facilitates its pathogenicity (Frohlich & Grundhoff, 2020; Uppal et al., 2015). Upon infection, KSHV rapidly associates with the host cell's epigenetic landscape, manipulating chromatin structure and histone modifications to establish a transcriptionally

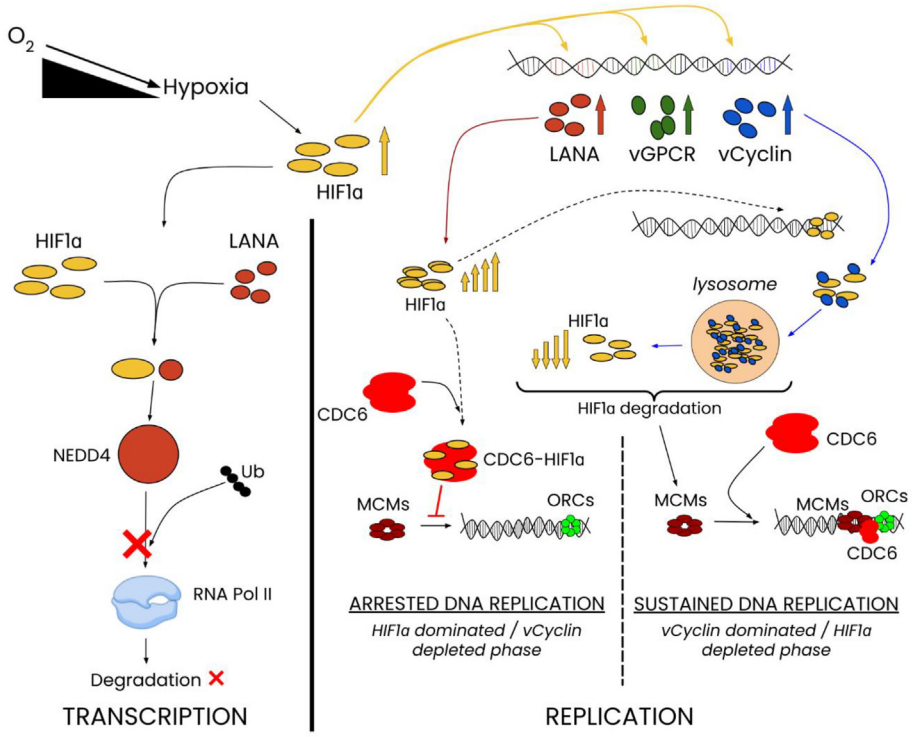

Fig. 3. KSHV-encoded antigens and HIF1α interactions in host cell during DNA replication and transcription. The induction of hypoxia and subsequent stabilization of HIF1α can induce the formation of a HIF1α-LANA complex in KSHV infected cell, which interacts with the NEDD4 ubiquitin ligase which prevents ubiquitination of RNA Pol II to prevent its degradation in hypoxic micro-environment. Similarly, hypoxia and HIF1α stimulates expression of KSHV-encoded LANA, vCyclin, and vGPCR. LANA engages in a feedback cycle wherein HIF1α-induced expression of LANA induces the expression of HIF1α itself, which then allows for the arrest of DNA replication by the formation of HIF1α-CDC6 complex that prevent the binding of MCMs to ORCs. Complementarily, HIF1α-induced expression of vCyclin can abrogate HIF1α activity by generation of HIF1α-vCyclin complexes which are targeted for lysosomal degradation. Following this degradation of HIF1α, CDC6 and MCMs are then able to form the MCMs-ORCs-CDC6 complex necessary for DNA replication, thus allowing for sustained DNA replication under conditions of hypoxic stress.

repressive environment conducive to latency (Lieberman, 2016; Toth et al., 2013). This is primarily mediated through recruitment of host histone deacetylases (HDACs), which remove acetyl groups from histones, leading to chromatin condensation and gene silencing (Hopcraft et al., 2018; Toth et al., 2013). KSHV-encoded LANA plays a pivotal role in genome persistence by tethering the viral episome to host chromatin, ensuring that it is maintained during successive cell divisions (Juillard et al., 2016). LANA also recruits polycomb repressive complexes (PRC1 and PRC2) to the viral genome, facilitating histone H3 lysine 27 trimethylation (H3K27me3), a mark associated with transcriptional repression (Scholl & De, 2022; Toth et al., 2016). Concurrently, KSHV utilizes host DNA methyl-transferases (DNMTs) to methylate CpG islands within its genome, further reinforcing a repressive chromatin state (Campbell et al., 2020; Journo et al., 2021). Despite epigenetic reprogramming of the KSHV genome, a subset of lytic genes remains poised for reactivation, marked by bivalent chromatin domains characterized by the presence of both activating (H3K4me3) and repressive (H3K27me3) histone marks, allowing for rapid transcriptional activation upon reactivation signals (Toth et al., 2010). Additionally, KSHV infection induces changes in the host cell DNA methylation patterns, contributing to oncogenesis (Kuss--Duerkop et al., 2018).

Hypoxia, a common feature in the tumor microenvironment, further influences KSHV epigenetics by stabilizing HIF1α, which in turn activates viral gene expression and can lead to reactivation (Srivastava et al., 2023). The interplay between hypoxia and KSHV epigenetics highlights its ability to exploit cellular stress responses for its advantage. Moreover, KSHV manipulates host chromatin remodeling complexes such as SWI/SNF to facilitate both latency and reactivation (Gwack et al., 2003). During hypoxic reactivation, viral proteins such as RTA (replication and transcription activator) can displace repressive complexes and recruit transcriptional coactivators to activate lytic gene expression (Liang et al., 2002). RTA also interacts with cellular ubiquitin ligases to degrade repressive histone marks, allowing for a swift transition from latency to the lytic phase (Spires et al., 2023). Epigenetic reprogramming by KSHV, especially in hypoxia is not limited to the viral genome; the virus also induces global changes in the host epigenome, contributing to an immune-suppressive and tumor-promoting environment (Singh et al., 2022). Moreover, hypoxia can affect chromatin structure, making DNA less accessible to the replication machinery, thus impeding replication initiation (Batie et al., 2018). We recently observed that KSHV positive cells shows highly up-regulated expression of different histone marks such as H3K4Me3, H3K9Me3 and H3K27Me3, and hypoxia can also synergistically enhance their targeted modification of H3 histones (Singh et al., 2022). The differential enrichment of these markers on the KSHV genome suggests a preferential replication start site during hypoxic reactivation of KSHV (Singh et al., 2022). An investigation to identify the KSHV-encoded factor mediating the up-regulated expression of these markers suggests involvement of multiple KSHV-encoded antigens such as LANA, RTA and vGPCR (Singh et al., 2022). A schematic illustrating the up-regulated expression and the differential enrichment of these markers on the KSHV genome is provided in Fig. 4.

6. HIF1α-mediated repression of DNA replication is bypassed during hypoxic reactivation of KSHV

In addition to the above-mentioned challenges for replication under hypoxic conditions, HIF1α, the master regulator induced in hypoxia, itself, represents a major challenge for replication (Hubbi et al., 2013; Kumar Singh et al., 2021). HIF1α dependent repression of DNA replication is mediated through two major pathways. HIF1α induced senescence represents a critical cellular response to hypoxic stress, characterized by stable cell cycle arrest that prevents proliferation and replication of hypoxic cells (Gao et al., 2023; Welford & Giaccia, 2011). This represents a state of irreversible growth arrest accompanied by changes in cell morphology, gene expression, and the secretion of pro-inflammatory cytokines, collectively known as the senescence-associated secretory phenotype (SASP) (Coppe et al., 2010; van Vliet et al., 2021). This process is mediated through several mechanisms, including the upregulation of cyclin-dependent kinase inhibitors such as p21 and p27, which inhibit the activity of cyclin-CDK complexes, leading to cell cycle arrest (Koshiji et al., 2004). Additionally, HIF-1α can induce production of reactive oxygen species (ROS), and stabilize p53, both of which contribute to the onset of senescence (Zhang et al., 2021). Senescent cells, while no longer proliferating, remain metabolically active and can influence their

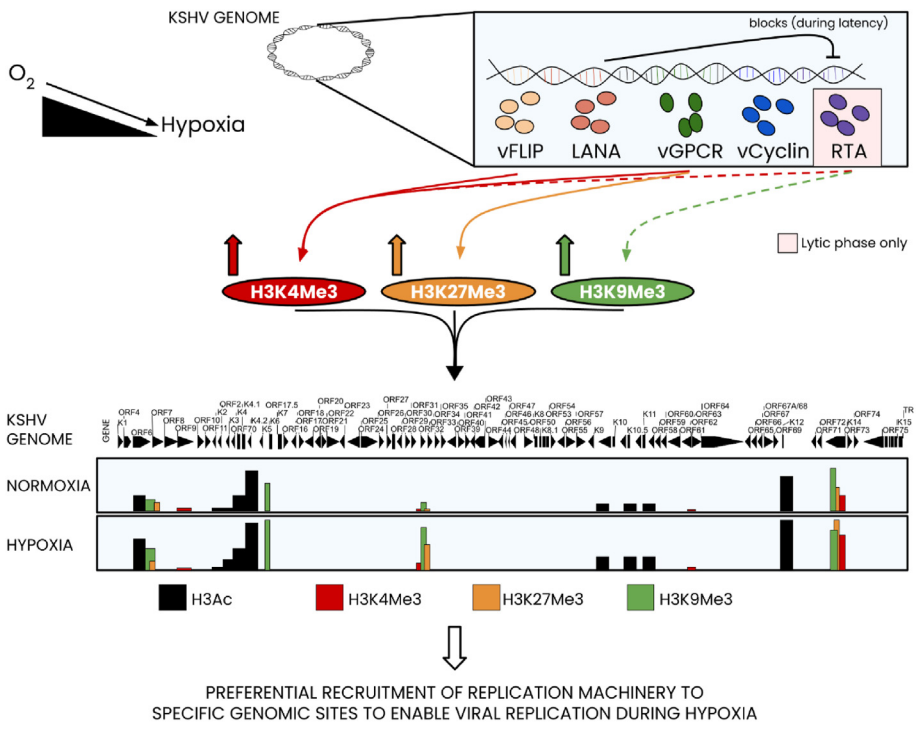

Fig. 4. KSHV-encoded antigens and the differential enrichment of epigenetic markers on the KSHV genome during hypoxia. During induction of hypoxia, major epigenetic histone markers are enriched at critical sites of the KSHV genome. Most notably, H3 acetylation at two major sites and the increase in H3K4 and H3K27 trimethylation across the KSHV genome. This enrichment is facilitated largely by both the latent as well as lytic antigens of KSHV such as LANA, RTA and vGPCR. Although, studies have also shown that the latent-to-lytic switch mediator RTA can also increase the enrichment of specific markers, such as H3K9Me3, in certain conditions. The broad-spectrum effect of these modifications is the marginal stabilization of certain DNMTs in both naturally infected and artificially transfected KSHV-positive cells. The end result of such modification is the preferential recruitment of host replication machinery to specific sites on the KSHV genome. These changes allow the virus to bypass replication checkpoints and replicate during hypoxic conditions. The non-scaled schematic represents various antigens and their downstream effects.

microenvironment through the SASP, impacting tissue function and promoting inflammatory responses (Takasugi et al., 2022). The induction of senescence by HIF1α serves as a protective mechanism against uncontrolled cell division in hypoxic conditions, which can prevent consumption of required energy and metabolite pools (Eales et al., 2016; Takasugi et al., 2022).

Alternatively, HIF1α interaction with CDC6 results in inhibition of MCMs activation, hence preventing licensing of DNA replication (Ortmann et al., 2014). Importantly, KSHV-encoded genes create a feedback loop phenomenon for the expression of HIF1α under hypoxic conditions. Importantly, under hypoxic conditions, KSHV-encoded LANA is known to be stabilized due to HIF1α transactivation, and LANA can recruit the EC5S ubiquitin complex to mediate degradation of the von hippel lindau (VHL) protein, which is a negative regulator of HIF1α (Cai, Knight, et al., 2006). Further, HIF1α is known to up-regulate vGPCR by transactivating functional HREs within its promoter (Singh et al., 2018). vGPCR also facilitates HIF1α expression at the transcript level by activating MAPK and p38 pathway (Sodhi et al., 2000). This situation suggests constitutive upregulated expression of HIF1α in KSHV positive cells. Nevertheless, HIF1α levels and activity must be controlled to bypass replicative repression mediated in hypoxic conditions. Interestingly, vCyclin transcribed from the polycistronic operon also encoding LANA, is now reported to interact physically with HIF1α to mediate its lysosomal degradation (Kumar Singh et al., 2021). The vCyclin-mediated degradation of HIF1α has been shown to release HIF1α mediated repression of replication, and allow KSHV positive cells to proliferate in an anchorage dependent or independent manner (Kumar Singh et al., 2021).

7. Therapeutic targets and strategies against KSHV

While no definitive treatment or cure exists against KSHV infection as of now, several strategies are being investigated for potent relief of KSHV and KSHV-associated diseases. A combination of classical small molecule development and next-generation therapies offer some promise. Currently, therapeutic strategies are largely focused on improving end-stage outcomes for KSHV-associated tumorigenic diseases, with limited focus on eradication of the virus itself.

Interleukin-10 (IL-10) is a cytokine molecule that is speculated or known to modulate several aspects of virus mediated tumorigenesis. Elevated levels of IL-10 also considered a biomarker for Kaposi's Sarcoma Inflammatory Cytokine Syndrome (KICS) patients (Alomari & Totonchy, 2020). Neutralization of IL-10 may offers a prospective mechanism through which KSHV-associated diseases ca be checked. For example, restoration of IFN-y production on HIV-1-specific CD4 T-cells following IL-10 blockade, restores the function of these cells *in vitro* (Porichis et al., 2014; Wilson & Brooks, 2011). There is also evidence that blockade of IL-10 can also mitigate viral infection (Brooks et al., 2006). However, the specific mechanisms that contribute to this remain elusive. Conversely, combination of interleukins and modified compounds, such as the combination of IL-12 and pegylated liposomal doxorubicin, have also been shown to produce therapeutic value in phase II clinical trials, with 83% of enrolled patients reporting complete or partial response to KS tumors (Little et al., 2007). Other trials have focused on the fusion of two IL-12 heterodimers to antibodies to elicit a response to necrotic cells (Sharifi et al., 2001). Similarly, a phase I pilot project in 32 AIDS-KS patients previously showed that administration of IL-12 led to at least partial KS tumour response in 61% of enrolled patients (Little et al., 2006).

Potential of Immunotherapies has been also evaluated against Primary effusion lymphoma (PEL) cell lines and KSHV-associated diseases (Davis et al., 2017). Several immunotherapy candidates are being investigated for their efficacy in primarily treating KSHV-associated diseases, and secondarily treating or limiting KSHV infection. Lenalidomide has been accelerated into a phase II trial with HIV-associated KS patients which reported a response rate of 40% (from a total of 12 participants) (Pourcher et al., 2017). Pomalidomide is reported for its ability to restore MHC-I expression during lytic replication and restoring expression of critical molecules such as ICAM-1 (Davis et al., 2019). Immunotherapies targeting programmed cell death protein 1 (PD1) or programmed death ligand 1 (PD-L1) have been largely successful, in part due to the inhibitory PD-L1 being induced for overexpression in numerous cancers (Wang et al., 2016). Clinical trials with anti-PD-1 antibodies have shown substantial anti-tumour responses in HIV-associated KS patients, and a combinatorial clinical trial combining nivolumab and ipilimumab (an antibody against CTLA-4) in classical KS patients may show enhanced T cell function (Lurain et al., 2022). Rituximab, an anti-CD20 antibody, may indeed have promise in this realm

as it may kill KSHV-infected B-cells at germinal center and thus limit the scope of inflammatory cytokines worsening both infection and associated disease. However, rituximab is currently limited in scope within this context, as a trial involving Multicentric Castleman's Disease (MCD) patients led to flaring of Kaposi's sarcoma and MCD in at least two-thirds of patients (Neuville et al., 2005; Ramaswami et al., 2021). The scope of immunotherapies in KSHV-associated diseases is reviewed extensively in Lurain et al., 2022 (Lurain et al., 2022).

7.1. KSHV vaccines

Notable targets for a KSHV vaccine lie largely in the viral glycoproteome and the latently expressed proteome. Glycoproteins are of fundamental importance to gammaherpesvirus infection, including KSHV and EBV (Spear & Longnecker, 2003). KSHV encodes at least eight glycoproteins within its genome, of which some including gB and gH are partially conserved in herpesviruses, and others are considered critical for various functions including viral entry and attachment (Chandran, 2010; Mortazavi et al., 2020; Zhu et al., 2005). Preliminary studies with some of these putative targets have shown promising data, including the development of neutralizing antibodies in mice administered with these glycoproteins as part of a virus-like particle vaccine candidate (Barasa et al., 2017; Fricke et al., 2022; Mulama et al., 2019). Conversely, targeting latently expressed that are essential for non-structural functions like viral persistence, such as vGPCR, vIL6, and K1, may offer an alternative set of targets for a preventive vaccine against KSHV. However, engineering a vaccine against KSHV is severely limited in scope due to the lack of adequate animal models for KSHV infection and a fundamental short-term inability to test the efficacy of a KSHV vaccine in inhibiting downstream processes like tumorigenesis. As such, most current research is restricted to the study of immunotherapies or the elucidation of novel targets (Casper et al., 2022).

7.2. Novel viral targets

Targeting KSHV DNA polymerases and latent antigens which include LANA and vFLIP, along with targeting broader viral processes like capsid assembly all offer promise in terms of eliminating the malignant effects of KSHV infection. A screen of National Cancer Institute compound libraries has shown that a compound, currently named NSC373989, can inhibit viral reactivation by inhibiting ORF9/ORF59 complex activity *in vitro* (Dorjsuren et al., 2006). Similarly, targeting fundamental compounds necessary for viral processes may indeed limit the scope of viral-mediated cell proliferation. For example, targeting viral DNA binding proteins can inhibit or dysregulate viral DNA replication. Some compounds have shown activity that can dysregulate these proteins. However, much remains to be known about whether these compounds target specific viral DNA binding proteins or larger protein complexes (Yan et al., 2014).

Finally, targeting latent antigens directly may offer a route to viral clearance even after the virus has established latency. Foundational experiments with LANA have shown that targeting the antigen with RNA interference or chemical agents can induce cell death, and treating cells with cell chaperone inhibitors can contribute to the degradation of LANA (Chen et al., 2012; Curreli et al., 2005; Godfrey et al., 2005). Some groups have focused on other viral antigens like vFLIP to report similar results, such as by designing small molecules that can antagonise the vFLIP-IKKγ interaction to promote apoptosis in PEL cell lines (Briggs et al., 2017). However, a fundamental limitation of direct latent antigen targeting is the substantial potential of off-target effects in the host, as well as most strategies leading to cell death. While intrinsically beneficial as cell death can limit viral genome copy number from increasing indefinitely, excessive cell death may trigger alternate host responses that may cause as-of-yet unknown side effects, which largely outweigh the current potential of antigen-targeting as a means to eliminate KSHV from its host. Several comprehensive review of novel targets and classical approaches to the treatment of KSHV infection are now well described (Naimo et al., 2021).

8. Conclusion

Hypoxic reactivation of Kaposi's sarcoma-associated herpesvirus (KSHV) underscores the intricate interplay between viral strategies and host cellular physiology. KSHV leverages hypoxic conditions to reprogram a number of cellular processes, facilitating its reactivation and lytic replication despite the general inhibitory environment. Through detailed mechanisms involving the stabilization of hypoxia-inducible factors (HIFs), reprogramming of metabolic pathways, protection of the replication and transcription machinery, and epigenetic modifications, KSHV can bypass the repressive effects of hypoxia. The ability of the virus to manipulate host cellular mechanisms to its advantage, especially under stress conditions like hypoxia, highlights the complexity of its lifecycle and its potential for persistence associated with its pathogenesis. Understanding the intricate viral-host interactions not only sheds light on the pathobiology of KSHV but also opens avenues for targeted therapeutic interventions aimed at disrupting these processes to control KSHV-associated diseases. Future research focusing on the precise molecular mechanisms and the potential therapeutic targets within these pathways will be crucial for developing effective interventional treatments or strategies to curb KSHV-related malignancies and other hypoxia-induced viral pathologies.

CRediT authorship contribution statement

Rajnish Kumar Singh: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Atharva S. Torne:** Writing – original draft, Conceptualization. **Erle S. Robertson:** Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the National Cancer Institute at the National Institutes of Health through the following awards to E.S.R.: P30-CA016520, R01-CA244074, R01-CA268998-01, and P01-CA281867.

References

Alomari, N., & Totonchy, J. (2020). Cytokine-targeted therapeutics for KSHV-associated disease. *Viruses, 12*(10). https://doi.org/10.3390/v12101097. PubMed PMID: 32998419; PubMed Central PMCID: PMCPMC7600567.

Aneja, K. K., & Yuan, Y. (2017). Reactivation and lytic replication of Kaposi's sarcoma-associated herpesvirus: An update. *Frontiers in Microbiology, 8*, 613. https://doi.org/10.3389/fmicb.2017.00613. PubMed PMID: 28473805; PubMed Central PMCID: PMCPMC5397509.

Angeletti, P. C., Zhang, L., & Wood, C. (2008). The viral etiology of AIDS-associated malignancies. *Advances in Pharmacology, 56*, 509–557. https://doi.org/10.1016/S1054-3589(07)56016-3. PubMed PMID: 18086422; PubMed Central PMCID: PMCPMC2149907.

Barasa, A. K., Ye, P., Phelps, M., Arivudainambi, G. T., Tison, T., & Ogembo, J. G. (2017). BALB/c mice immunized with a combination of virus-like particles incorporating Kaposi sarcoma-associated herpesvirus (KSHV) envelope glycoproteins gpK8.1, gB, and gH/gL induced comparable serum neutralizing antibody activity to UV-inactivated KSHV. *Oncotarget, 8*(21), 34481–34497. https://doi.org/10.18632/oncotarget.15605. PubMed PMID: 28404899; PubMed Central PMCID: PMCPMC5470984.

Batie, M., Del Peso, L., & Rocha, S. (2018). Hypoxia and chromatin: A focus on transcriptional repression mechanisms. *Biomedicines, 6*(2). https://doi.org/10.3390/biomedicines6020047. PubMed PMID: 29690561; PubMed Central PMCID: PMCPMC6027312.

Bhatt, A. P., Jacobs, S. R., Freemerman, A. J., Makowski, L., Rathmell, J. C., Dittmer, D. P., et al. (2012). Dysregulation of fatty acid synthesis and glycolysis in non-Hodgkin lymphoma. *Proc Natl Acad Sci U S A, 109*(29), 11818–11823. https://doi.org/10.1073/pnas.1205995109. PubMed PMID: 22752304; PubMed Central PMCID: PMCPMC3406848.

Bochman, M. L., & Schwacha, A. (2009). The Mcm complex: Unwinding the mechanism of a replicative helicase. *Microbiology and Molecular Biology Reviews, 73*(4), 652–683. https://doi.org/10.1128/MMBR.00019-09. PubMed PMID: 19946136; PubMed Central PMCID: PMCPMC2786579.

Bose, D., Singh, R. K., & Robertson, E. S. (2024). KSHV-encoded LANA bypasses transcriptional block through the stabilization of RNA Pol II in hypoxia. *mBio, 15*(1), Article e0277423. https://doi.org/10.1128/mbio.02774-23. PubMed PMID: 38095447; PubMed Central PMCID: PMCPMC10790784.

Briggs, L. C., Chan, A. W. E., Davis, C. A., Whitelock, N., Hotiana, H. A., Baratchian, M., et al. (2017). IKKgamma-mimetic peptides block the resistance to apoptosis associated with Kaposi's sarcoma-associated herpesvirus infection. *Journal of Virology, 91*(23). https://doi.org/10.1128/JVI.01170-17. PubMed PMID: 28931678; PubMed Central PMCID: PMCPMC5686756.

Brooks, D. G., Trifilo, M. J., Edelmann, K. H., Teyton, L., McGavern, D. B., & Oldstone, M. B. (2006). Interleukin-10 determines viral clearance or persistence in vivo. *Nat Med, 12*(11), 1301–1309. https://doi.org/10.1038/nm1492. PubMed PMID: 17041596; PubMed Central PMCID: PMCPMC2535582.

Cai, Q. L., Knight, J. S., Verma, S. C., Zald, P., & Robertson, E. S. (2006). EC5S ubiquitin complex is recruited by KSHV latent antigen LANA for degradation of the VHL and p53 tumor suppressors. *PLoS Pathogens, 2*(10), Article e116. https://doi.org/10.1371/journal.ppat.0020116. PubMed PMID: 17069461; PubMed Central PMCID: PMCPMC1626105.

Cai, Q., Lan, K., Verma, S. C., Si, H., Lin, D., & Robertson, E. S. (2006). Kaposi's sarcoma-associated herpesvirus latent protein LANA interacts with HIF-1 alpha to upregulate RTA expression during hypoxia: Latency control under low oxygen conditions. *Journal of Virology, 80*(16), 7965–7975. https://doi.org/10.1128/JVI.00689-06. PubMed PMID: 16873253; PubMed Central PMCID: PMCPMC1563785.

Campbell, M., Yang, W. S., Yeh, W. W., Kao, C. H., & Chang, P. C. (2020). Epigenetic regulation of Kaposi's sarcoma-associated herpesvirus latency. *Frontiers in Microbiology, 11*, 850. https://doi.org/10.3389/fmicb.2020.00850. PubMed PMID: 32508765; PubMed Central PMCID: PMCPMC7248258.

Casper, C., Corey, L., Cohen, J. I., Damania, B., Gershon, A. A., Kaslow, D. C., et al. (2022). KSHV (HHV8) vaccine: Promises and potential pitfalls for a new anti-cancer vaccine. *NPJ Vaccines, 7*(1), 108. https://doi.org/10.1038/s41541-022-00535-4. PubMed PMID: 36127367; PubMed Central PMCID: PMCPMC9488886 assigned to the University of Pittsburgh, J.G.O. has a KSHV vaccine patent assigned to the Beckman Research Institute of City of and L.T.K. has a patent for generating reversion-free attenuated and/or replication-incompetent vaccine vectors and has divested herself of potential earnings.

Castillo-Rodriguez, R. A., Trejo-Solis, C., Cabrera-Cano, A., Gomez-Manzo, S., & Davila-Borja, V. M. (2022). Hypoxia as a modulator of inflammation and immune response in cancer. *Cancers, 14*(9). https://doi.org/10.3390/cancers14092291. PubMed PMID: 35565420; PubMed Central PMCID: PMCPMC9099524.

Chakraborty, U., Shen, Z. J., & Tyler, J. (2021). Chaperoning histones at the DNA repair dance. *DNA Repair, 108*, Article 103240. https://doi.org/10.1016/j.dnarep.2021.103240. PubMed PMID: 34687987; PubMed Central PMCID: PMCPMC8827131.

Chandran, B. (2010). Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. *Journal of Virology, 84*(5), 2188–2199. https://doi.org/10.1128/JVI.01334-09. PubMed PMID: 19923183; PubMed Central PMCID: PMCPMC2820927.

Chen, S., de Vries, M. A., & Bell, S. P. (2007). Orc6 is required for dynamic recruitment of Cdt1 during repeated Mcm2-7 loading. *Genes Dev, 21*(22), 2897–2907. https://doi.org/10.1101/gad.1596807. PubMed PMID: 18006685; PubMed Central PMCID: PMCPMC2049192.

Chen, W., Sin, S. H., Wen, K. W., Damania, B., & Dittmer, D. P. (2012). Hsp90 inhibitors are efficacious against Kaposi Sarcoma by enhancing the degradation of the essential viral gene LANA, of the viral co-receptor EphA2 as well as other client proteins. *PLoS Pathogens, 8*(11), Article e1003048. https://doi.org/10.1371/journal.ppat.1003048. PubMed PMID: 23209418; PubMed Central PMCID: PMCPMC3510261.

Choi, U. Y., Lee, J. J., Park, A., Zhu, W., Lee, H. R., Choi, Y. J., et al. (2020). Oncogenic human herpesvirus hijacks proline metabolism for tumorigenesis. *Proc Natl Acad Sci U S A, 117*(14), 8083–8093. https://doi.org/10.1073/pnas.1918607117. PubMed PMID: 32213586; PubMed Central PMCID: PMCPMC7149499.

Cohen, J. I. (2020). Herpesvirus latency. *Journal of Clinical Investigation, 130*(7), 3361–3369. https://doi.org/10.1172/JCI136225. PubMed PMID: 32364538; PubMed Central PMCID: PMCPMC7324166 exists.

Coppe, J. P., Desprez, P. Y., Krtolica, A., & Campisi, J. (2010). The senescence-associated secretory phenotype: The dark side of tumor suppression. *Annual Review of Pathology: Mechanisms of Disease, 5*, 99–118. https://doi.org/10.1146/annurev-pathol-121808-102144. PubMed PMID: 20078217; PubMed Central PMCID: PMCPMC4166495.

Curreli, F., Friedman-Kien, A. E., & Flore, O. (2005). Glycyrrhizic acid alters Kaposi sarcoma-associated herpesvirus latency, triggering p53-mediated apoptosis in transformed B lymphocytes. *Journal of Clinical Investigation, 115*(3), 642–652. https://doi.org/10.1172/JCI23334. PubMed PMID: 15765147; PubMed Central PMCID: PMCPMC1051998.

Dai, L., Lin, Z., Jiang, W., Flemington, E. K., & Qin, Z. (2017). Lipids, lipid metabolism and Kaposi's sarcoma-associated herpesvirus pathogenesis. *Virologica Sinica, 32*(5), 369–375. https://doi.org/10.1007/s12250-017-4027-2. PubMed PMID: 29019168; PubMed Central PMCID: PMCPMC5869022.

Damania, B., Kenney, S. C., & Raab-Traub, N. (2022). Epstein-Barr virus: Biology and clinical disease. *Cell, 185*(20), 3652–3670. https://doi.org/10.1016/j.cell.2022.08.026. PubMed PMID: 36113467; PubMed Central PMCID: PMCPMC9529843.

Davis, D. A., Mishra, S., Anagho, H. A., Aisabor, A. I., Shrestha, P., Wang, V., et al. (2017). Restoration of immune surface molecules in Kaposi sarcoma-associated herpes virus infected cells by lenalidomide and pomalidomide. *Oncotarget, 8*(31), 50342–50358. https://doi.org/10.18632/oncotarget.17960. PubMed PMID: 28881567; PubMed Central PMCID: PMCPMC5584136.

Davis, D. A., Rinderknecht, A. S., Zoeteweij, J. P., Aoki, Y., Read-Connole, E. L., Tosato, G., et al. (2001). Hypoxia induces lytic replication of Kaposi sarcoma-associated herpesvirus. *Blood, 97*(10), 3244–3250. https://doi.org/10.1182/blood.v97.10.3244. PubMed PMID: 11342455.

Davis, D. A., Shrestha, P., Aisabor, A. I., Stream, A., Galli, V., Pise-Masison, C. A., et al. (2019). Pomalidomide increases immune surface marker expression and immune recognition of oncovirus-infected cells. *OncoImmunology, 8*(2), Article e1546544. https://doi.org/10.1080/2162402X.2018.1546544. PubMed PMID: 30713808; PubMed Central PMCID: PMCPMC6343774.

Davis, D. A., Shrestha, P., & Yarchoan, R. (2023). Hypoxia and hypoxia-inducible factors in Kaposi sarcoma-associated herpesvirus infection and disease pathogenesis. *Journal of Medical Virology, 95*(9), Article e29071. https://doi.org/10.1002/jmv.29071. PubMed PMID: 37665216; PubMed Central PMCID: PMCPMC10502919.

Delgado, T., Carroll, P. A., Punjabi, A. S., Margineantu, D., Hockenbery, D. M., & Lagunoff, M. (2010). Induction of the Warburg effect by Kaposi's sarcoma herpesvirus is required for the maintenance of latently infected endothelial cells. *Proc Natl Acad Sci U S A, 107*(23), 10696–10701. https://doi.org/10.1073/pnas.1004882107. PubMed PMID: 20498071; PubMed Central PMCID: PMCPMC2890792.

Delgado, T., Sanchez, E. L., Camarda, R., & Lagunoff, M. (2012). Global metabolic profiling of infection by an oncogenic virus: KSHV induces and requires lipogenesis for survival of latent infection. *PLoS Pathogens, 8*(8), Article e1002866. https://doi.org/10.1371/journal.ppat.1002866. PubMed PMID: 22916018; PubMed Central PMCID: PMCPMC3420960.

Dorjsuren, D., Burnette, A., Gray, G. N., Chen, X., Zhu, W., Roberts, P. E., et al. (2006). Chemical library screen for novel inhibitors of Kaposi's sarcoma-associated herpesvirus processive DNA synthesis. *Antiviral Res, 69*(1), 9–23. https://doi.org/10.1016/j.antiviral.2005.09.005. PubMed PMID: 16337284.

Druker, J., Wilson, J. W., Child, F., Shakir, D., Fasanya, T., & Rocha, S. (2021). Role of hypoxia in the control of the cell cycle. *International Journal of Molecular Sciences, 22*(9). https://doi.org/10.3390/ijms22094874. PubMed PMID: 34062959; PubMed Central PMCID: PMCPMC8124716.

Eales, K. L., Hollinshead, K. E., & Tennant, D. A. (2016). Hypoxia and metabolic adaptation of cancer cells. *Oncogenesis, 5*(1), Article e190. https://doi.org/10.1038/oncsis.2015.50. PubMed PMID: 26807645; PubMed Central PMCID: PMCPMC4728679.

Fischer, M. G., Heeger, S., Hacker, U., & Lehner, C. F. (2004). The mitotic arrest in response to hypoxia and of polar bodies during early embryogenesis requires Drosophila Mps1. *Current Biology, 14*(22), 2019–2024. https://doi.org/10.1016/j.cub.2004.11.008. PubMed PMID: 15556864.

Flood, D., Lee, E. S., & Taylor, C. T. (2023). Intracellular energy production and distribution in hypoxia. *Journal of Biological Chemistry, 299*(9), Article 105103. https://doi.org/10.1016/j.jbc.2023.105103. PubMed PMID: 37507013; PubMed Central PMCID: PMCPMC10480318.

Frappier, L. (2012). The epstein-barr virus EBNA1 protein. *Scientifica (Cairo)., 2012*, Article 438204. https://doi.org/10.6064/2012/438204. PubMed PMID: 24278697; PubMed Central PMCID: PMCPMC3820569.

Fricke, T., Grosskopf, A. K., Ensser, A., Backovic, M., & Hahn, A. S. (2022). Antibodies targeting KSHV gH/gL reveal distinct neutralization mechanisms. *Viruses, 14*(3). https://doi.org/10.3390/v14030541. PubMed PMID: 35336948; PubMed Central PMCID: PMCPMC8953146.

Frohlich, J., & Grundhoff, A. (2020). Epigenetic control in Kaposi sarcoma-associated herpesvirus infection and associated disease. *Seminars in Immunopathology, 42*(2), 143–157. https://doi.org/10.1007/s00281-020-00787-z. PubMed PMID: 32219477; PubMed Central PMCID: PMCPMC7174275.

Gao, H., Nepovimova, E., Heger, Z., Valko, M., Wu, Q., Kuca, K., et al. (2023). Role of hypoxia in cellular senescence. *Pharmacological Research, 194*, Article 106841. https://doi.org/10.1016/j.phrs.2023.106841. PubMed PMID: 37385572.

Gardner, L. B., Li, Q., Park, M. S., Flanagan, W. M., Semenza, G. L., & Dang, C. V. (2001). Hypoxia inhibits G1/S transition through regulation of p27 expression. *Journal of Biological Chemistry, 276*(11), 7919–7926. https://doi.org/10.1074/jbc.M010189200. PubMed PMID: 11112789.

Godfrey, A., Anderson, J., Papanastasiou, A., Takeuchi, Y., & Boshoff, C. (2005). Inhibiting primary effusion lymphoma by lentiviral vectors encoding short hairpin RNA. *Blood, 105*(6), 2510–2518. https://doi.org/10.1182/blood-2004-08-3052. PubMed PMID: 15572586.

Gomez-Virgilio, L., Silva-Lucero, M. D., Flores-Morelos, D. S., Gallardo-Nieto, J., Lopez-Toledo, G., Abarca-Fernandez, A. M., et al. (2022). Autophagy: A key regulator of homeostasis and disease: An overview of molecular mechanisms and modulators. *Cells, 11*(15). https://doi.org/10.3390/cells11152262. PubMed PMID: 35892559; PubMed Central PMCID: PMCPMC9329718.

Grinde, B. (2013). Herpesviruses: Latency and reactivation - viral strategies and host response. *Journal of Oral Microbiology, 5*. https://doi.org/10.3402/jom.v5i0.22766. PubMed PMID: 24167660; PubMed Central PMCID: PMCPMC3809354.

Gwack, Y., Baek, H. J., Nakamura, H., Lee, S. H., Meisterernst, M., Roeder, R. G., et al. (2003). Principal role of TRAP/mediator and SWI/SNF complexes in Kaposi's sarcoma-associated herpesvirus RTA-mediated lytic reactivation. *Molecular and*

Cellular Biology, 23(6), 2055–2067. https://doi.org/10.1128/MCB.23.6.2055-2067.2003. PubMed PMID: 12612078; PubMed Central PMCID: PMCPMC149486.
Harris, A. L. (2002). Hypoxia–a key regulatory factor in tumour growth. *Nature Reviews Cancer, 2*(1), 38–47. https://doi.org/10.1038/nrc704. PubMed PMID: 11902584.
Holmes, D. L., Vogt, D. T., & Lagunoff, M. (2020). A CRISPR-Cas9 screen identifies mitochondrial translation as an essential process in latent KSHV infection of human endothelial cells. *Proc Natl Acad Sci U S A, 117*(45), 28384–28392. https://doi.org/10.1073/pnas.2011645117. PubMed PMID: 33122441; PubMed Central PMCID: PMCPMC7668072.
Hopcraft, S. E., Pattenden, S. G., James, L. I., Frye, S., Dittmer, D. P., & Damania, B. (2018). Chromatin remodeling controls Kaposi's sarcoma-associated herpesvirus reactivation from latency. *PLoS Pathogens, 14*(9), Article e1007267. https://doi.org/10.1371/journal.ppat.1007267. PubMed PMID: 30212584; PubMed Central PMCID: PMCPMC6136816.
Hu, Y., & Stillman, B. (2023). Origins of DNA replication in eukaryotes. *Mol Cell, 83*(3), 352–372. https://doi.org/10.1016/j.molcel.2022.12.024. PubMed PMID: 36640769; PubMed Central PMCID: PMCPMC9898300.
Hu, C. J., Wang, L. Y., Chodosh, L. A., Keith, B., & Simon, M. C. (2003). Differential roles of hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-2alpha in hypoxic gene regulation. *Molecular and Cellular Biology, 23*(24), 9361–9374. https://doi.org/10.1128/MCB.23.24.9361-9374.2003. PubMed PMID: 14645546; PubMed Central PMCID: PMCPMC309606.
Hubbi, M. E., Kshitiz, G. D. M., Rey, S., Wong, C. C., Luo, W., et al. (2013). A nontranscriptional role for HIF-1alpha as a direct inhibitor of DNA replication. *Science Signaling, 6*(262), Article ra10. https://doi.org/10.1126/scisignal.2003417. PubMed PMID: 23405012; PubMed Central PMCID: PMCPMC4124626.
Hubbi, M. E., & Semenza, G. L. (2015). Regulation of cell proliferation by hypoxia-inducible factors. *Am J Physiol Cell Physiol, 309*(12), C775–C782. https://doi.org/10.1152/ajpcell.00279.2015. PubMed PMID: 26491052; PubMed Central PMCID: PMCPMC4683214.
Ilves, I., Petojevic, T., Pesavento, J. J., & Botchan, M. R. (2010). Activation of the MCM2-7 helicase by association with Cdc45 and GINS proteins. *Mol Cell, 37*(2), 247–258. https://doi.org/10.1016/j.molcel.2009.12.030. PubMed PMID: 20122406; PubMed Central PMCID: PMCPMC6396293.
Jones, C. (2023). Intimate relationship between stress and human alpha-herpes virus 1 (HSV-1) reactivation from latency. *Current Clinical Microbiology Reports, 10*(4), 236–245. https://doi.org/10.1007/s40588-023-00202-9. PubMed PMID: 38173564; PubMed Central PMCID: PMCPMC10764003.
Journo, G., Ahuja, A., Dias-Polak, D., Eran, Y., Bergman, R., & Shamay, M. (2021). Global CpG DNA methylation footprint in kaposi's sarcoma. *Frontiers in Cellular and Infection Microbiology, 11*, Article 666143. https://doi.org/10.3389/fcimb.2021.666143. PubMed PMID: 34307191; PubMed Central PMCID: PMCPMC8300563.
Juillard, F., Tan, M., Li, S., & Kaye, K. M. (2016). Kaposi's sarcoma herpesvirus genome persistence. *Frontiers in Microbiology, 7*, 1149. https://doi.org/10.3389/fmicb.2016.01149. PubMed PMID: 27570517; PubMed Central PMCID: PMCPMC4982378.
Kang, M. S., & Kieff, E. (2015). Epstein-Barr virus latent genes. *Exp Mol Med, 47*(1), Article e131. https://doi.org/10.1038/emm.2014.84. PubMed PMID: 25613728; PubMed Central PMCID: PMCPMC4314583.
Kaufer, B. B., & Flamand, L. (2014). Chromosomally integrated HHV-6: Impact on virus, cell and organismal biology. *Curr Opin Virol, 9*, 111–118. https://doi.org/10.1016/j.coviro.2014.09.010. PubMed PMID: 25462442.
Kim, E. T., & Kim, K. D. (2022). Topological implications of DNA tumor viral episomes. *BMB Rep, 55*(12), 587–594. https://doi.org/10.5483/BMBRep.2022.55.12.154. PubMed PMID: 36379513; PubMed Central PMCID: PMCPMC9813422.
Koshiji, M., Kageyama, Y., Pete, E. A., Horikawa, I., Barrett, J. C., & Huang, L. E. (2004). HIF-1alpha induces cell cycle arrest by functionally counteracting Myc. *EMBO J, 23*(9), 1949–1956. https://doi.org/10.1038/sj.emboj.7600196. PubMed PMID: 15071503; PubMed Central PMCID: PMCPMC404317.
Kumar, A., Lyu, Y., Yanagihashi, Y., Chantarasrivong, C., Majerciak, V., Salemi, M., et al. (2022). KSHV episome tethering sites on host chromosomes and regulation of latency-lytic switch by CHD4. *Cell Reports, 39*(6), Article 110788. https://doi.org/10.1016/j.celrep.2022.110788. PubMed PMID: 35545047; PubMed Central PMCID: PMCPMC9153692.
Kumar Singh, R., Pei, Y., Bose, D., Lamplugh, Z. L., Sun, K., Yuan, Y., et al. (2021). KSHV-encoded vCyclin can modulate HIF1alpha levels to promote DNA replication in hypoxia. *Elife, 10*. https://doi.org/10.7554/eLife.57436. PubMed PMID: 34279223; PubMed Central PMCID: PMCPMC8315796.
Kung-Chun Chiu, D., Pui-Wah, T. A., Law, C. T., Ming-Jing Xu, I., Lee, D., Chen, M., et al. (2019). Hypoxia regulates the mitochondrial activity of hepatocellular carcinoma cells through HIF/HEY1/PINK1 pathway. *Cell Death & Disease, 10*(12), 934. https://doi.org/10.1038/s41419-019-2155-3. PubMed PMID: 31819034; PubMed Central PMCID: PMCPMC6901483.
Kuss-Duerkop, S. K., Westrich, J. A., & Pyeon, D. (2018). DNA tumor virus regulation of host DNA methylation and its implications for immune evasion and oncogenesis. *Viruses, 10*(2). https://doi.org/10.3390/v10020082. PubMed PMID: 29438328; PubMed Central PMCID: PMCPMC5850389.
Leonard, A. C., & Mechali, M. (2013). DNA replication origins. *Cold Spring Harb Perspect Biol, 5*(10), Article a010116. https://doi.org/10.1101/cshperspect.a010116. PubMed PMID: 23838439; PubMed Central PMCID: PMCPMC3783049.
Li, T., & Gao, S. J. (2021). Metabolic reprogramming and metabolic sensors in KSHV-induced cancers and KSHV infection. *Cell & Bioscience, 11*(1), 176. https://doi.org/10.1186/s13578-021-00688-0. PubMed PMID: 34579773; PubMed Central PMCID: PMCPMC8475840.
Li, T., Zhu, Y., Cheng, F., Lu, C., Jung, J. U., & Gao, S. J. (2019). Oncogenic Kaposi's sarcoma-associated herpesvirus upregulates argininosuccinate synthase 1, a rate-limiting enzyme of the citrulline-nitric oxide cycle, to activate the STAT3 pathway and promote growth transformation. *Journal of Virology, 93*(4). https://doi.org/10.1128/JVI.01599-18. PubMed PMID: 30463977; PubMed Central PMCID: PMCPMC6364034.
Liang, Y., Chang, J., Lynch, S. J., Lukac, D. M., & Ganem, D. (2002). The lytic switch protein of KSHV activates gene expression via functional interaction with RBP-Jkappa (CSL), the target of the Notch signaling pathway. *Genes Dev, 16*(15), 1977–1989. https://doi.org/10.1101/gad.996502. PubMed PMID: 12154127; PubMed Central PMCID: PMCPMC186409.
Lieberman, P. M. (2016). Epigenetics and genetics of viral latency. *Cell Host Microbe, 19*(5), 619–628. https://doi.org/10.1016/j.chom.2016.04.008. PubMed PMID: 27173930; PubMed Central PMCID: PMCPMC5166714.
Lilienbaum, A. (2013). Relationship between the proteasomal system and autophagy. *Int J Biochem Mol Biol, 4*(1), 1–26. PubMed PMID: 23638318; PubMed Central PMCID: PMCPMC3627065.
Little, R. F., Aleman, K., Kumar, P., Wyvill, K. M., Pluda, J. M., Read-Connole, E., et al. (2007). Phase 2 study of pegylated liposomal doxorubicin in combination with interleukin-12 for AIDS-related Kaposi sarcoma. *Blood, 110*(13), 4165–4171. https://doi.org/10.1182/blood-2007-06-097568. PubMed PMID: 17846226; PubMed Central PMCID: PMCPMC2234790.
Little, R. F., Pluda, J. M., Wyvill, K. M., Rodriguez-Chavez, I. R., Tosato, G., Catanzaro, A. T., et al. (2006). Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood, 107*(12), 4650–4657. https://doi.org/10.1182/blood-2005-11-4455. PubMed PMID: 16507779; PubMed Central PMCID: PMCPMC1475826.
Liu, X., Zhu, C., Wang, Y., Wei, F., & Cai, Q. (2021). KSHV reprogramming of host energy metabolism for pathogenesis. *Frontiers in Cellular and Infection Microbiology, 11*, Article 621156. https://doi.org/10.3389/fcimb.2021.621156. PubMed PMID: 34055662; PubMed Central PMCID: PMCPMC8153180.
Lurain, K., Yarchoan, R., & Ramaswami, R. (2022). Immunotherapy for KSHV-associated diseases. *Curr Opin Virol, 55*, Article 101249. https://doi.org/10.1016/j.coviro.2022.101249. PubMed PMID: 35803203; PubMed Central PMCID: PMCPMC9464688.
Mallet, C., Cochard, J., Leclercq, S., Trapp-Fragnet, L., Chouteau, P., & Denesvre, C. (2022). Hypoxia and HIF-1 trigger marek's disease virus reactivation in lymphoma-derived latently infected T lymphocytes. *Journal of Virology, 96*(5), Article e0142721. https://doi.org/10.1128/JVI.01427-21. PubMed PMID: 34936483; PubMed Central PMCID: PMCPMC8906438.
Marxsen, J. H., Stengel, P., Doege, K., Heikkinen, P., Jokilehto, T., Wagner, T., et al. (2004). Hypoxia-inducible factor-1 (HIF-1) promotes its degradation by induction of HIF-alpha-prolyl-4-hydroxylases. *Biochem J, 381*(Pt 3), 761–767. https://doi.org/10.1042/BJ20040620. PubMed PMID: 15104534; PubMed Central PMCID: PMCPMC1133886.
Mortazavi, Y., Lidenge, S. J., Tran, T., West, J. T., Wood, C., & Tso, F. Y. (2020). The Kaposi's sarcoma-associated herpesvirus (KSHV) gH/gL complex is the predominant neutralizing antigenic determinant in KSHV-infected individuals. *Viruses, 12*(3). https://doi.org/10.3390/v12030256. PubMed PMID: 32111001; PubMed Central PMCID: PMCPMC7150787.
Mulama, D. H., Mutsvunguma, L. Z., Totonchy, J., Ye, P., Foley, J., Escalante, G. M., et al. (2019). A multivalent Kaposi sarcoma-associated herpesvirus-like particle vaccine capable of eliciting high titers of neutralizing antibodies in immunized rabbits. *Vaccine, 37*(30), 4184–4194. https://doi.org/10.1016/j.vaccine.2019.04.071. PubMed PMID: 31201053; PubMed Central PMCID: PMCPMC6876619.
Naimo, E., Zischke, J., & Schulz, T. F. (2021). Recent advances in developing treatments of Kaposi's sarcoma herpesvirus-related diseases. *Viruses, 13*(9). https://doi.org/10.3390/v13091797. PubMed PMID: 34578378; PubMed Central PMCID: PMCPMC8473310.
Nakajima, K., Inagaki, T., Espera, J. M., & Izumiya, Y. (2024). Kaposi's sarcoma-associated herpesvirus (KSHV) LANA prevents KSHV episomes from degradation. *Journal of Virology, 98*(2), Article e0126823. https://doi.org/10.1128/jvi.01268-23. PubMed PMID: 38240588; PubMed Central PMCID: PMCPMC10878079.
Nasheuer, H. P., & Meaney, A. M. (2024). Starting DNA synthesis: Initiation processes during the replication of chromosomal DNA in Humans. *Genes, 15*(3). https://doi.org/10.3390/genes15030360. PubMed PMID: 38540419; PubMed Central PMCID: PMCPMC10969946.
Neuville, S., Agbalika, F., Rabian, C., Briere, J., & Molina, J. M. (2005). Failure of rituximab in human immunodeficiency virus-associated multicentric Castleman disease. *American Journal of Hematology, 79*(4), 337–339. https://doi.org/10.1002/ajh.20418. PubMed PMID: 16044438.
Olcina, M. M., Grand, R. J., & Hammond, E. M. (2014). ATM activation in hypoxia - causes and consequences. *Mol Cell Oncol, 1*(1), Article e29903. https://doi.org/10.4161/mco.29903. PubMed PMID: 27308313; PubMed Central PMCID: PMCPMC4905164.
Orlando, I. M. C., Lafleur, V. N., Storti, F., Spielmann, P., Crowther, L., Santambrogio, S., et al. (2020). Distal and proximal hypoxia response elements cooperate to regulate organ-specific erythropoietin gene expression. *Haematologica, 105*(12), 2774–2784. https://doi.org/10.3324/haematol.2019.236406. PubMed PMID: 33256376; PubMed Central PMCID: PMCPMC7716368.
Ortmann, B., Druker, J., & Rocha, S. (2014). Cell cycle progression in response to oxygen levels. *Cellular and Molecular Life Sciences, 71*(18), 3569–3582. https://doi.org/10.1007/s00018-014-1645-9. PubMed PMID: 24858415; PubMed Central PMCID: PMCPMC4143607.
Pantry, S. N., & Medveczky, P. G. (2017). Latency, integration, and reactivation of human herpesvirus-6. *Viruses, 9*(7). https://doi.org/10.3390/v9070194. PubMed PMID: 28737715; PubMed Central PMCID: PMCPMC5537686.

Patterson, A. J., Xiao, D., Xiong, F., Dixon, B., & Zhang, L. (2012). Hypoxia-derived oxidative stress mediates epigenetic repression of PKCepsilon gene in foetal rat hearts. *Cardiovascular Research, 93*(2), 302–310. https://doi.org/10.1093/cvr/cvr322. PubMed PMID: 22139554; PubMed Central PMCID: PMCPMC3258654.

Pennycook, B. R., & Barr, A. R. (2020). Restriction point regulation at the crossroads between quiescence and cell proliferation. *FEBS Letters*. https://doi.org/10.1002/1873-3468.13867. PubMed PMID: 32564372.

Petropoulos, M., Champeris Tsaniras, S., Taraviras, S., & Lygerou, Z. (2019). Replication licensing aberrations, replication stress, and genomic instability. *Trends Biochem Sci, 44*(9), 752–764. https://doi.org/10.1016/j.tibs.2019.03.011. PubMed PMID: 31054805.

Pires, I. M., Bencokova, Z., Milani, M., Folkes, L. K., Li, J. L., Stratford, M. R., et al. (2010). Effects of acute versus chronic hypoxia on DNA damage responses and genomic instability. *Cancer Research, 70*(3), 925–935. https://doi.org/10.1158/0008-5472.CAN-09-2715. PubMed PMID: 20103649; PubMed Central PMCID: PMCPMC2923514.

Platt, L., French, C. E., McGowan, C. R., Sabin, K., Gower, E., Trickey, A., et al. (2020). Prevalence and burden of HBV co-infection among people living with HIV: A global systematic review and meta-analysis. *Journal of Viral Hepatitis, 27*(3), 294–315. https://doi.org/10.1111/jvh.13217. PubMed PMID: 31603999; PubMed Central PMCID: PMCPMC7383613.

Porichis, F., Hart, M. G., Zupkosky, J., Barblu, L., Kwon, D. S., McMullen, A., et al. (2014). Differential impact of PD-1 and/or interleukin-10 blockade on HIV-1-specific CD4 T cell and antigen-presenting cell functions. *Journal of Virology, 88*(5), 2508–2518. https://doi.org/10.1128/JVI.02034-13. PubMed PMID: 24352453; PubMed Central PMCID: PMCPMC3958087.

Pourcher, V., Desnoyer, A., Assoumou, L., Lebbe, C., Curjol, A., Marcelin, A. G., et al. (2017). Phase II trial of lenalidomide in HIV-infected patients with previously treated Kaposi's sarcoma: Results of the ANRS 154 Lenakap trial. *AIDS Res Hum Retroviruses, 33*(1), 1–10. https://doi.org/10.1089/AID.2016.0069. PubMed PMID: 27405442.

Purushothaman, P., Dabral, P., Gupta, N., Sarkar, R., & Verma, S. C. (2016). KSHV genome replication and maintenance. *Frontiers in Microbiology, 7*, 54. https://doi.org/10.3389/fmicb.2016.00054. PubMed PMID: 26870016; PubMed Central PMCID: PMCPMC4740845.

Ramaswami, R., Lurain, K., Polizzotto, M. N., Ekwede, I., Waldon, K., Steinberg, S. M., et al. (2021). Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases. *Blood Adv, 5*(6), 1660–1670. https://doi.org/10.1182/bloodadvances.2020004058. PubMed PMID: 33720337; PubMed Central PMCID: PMCPMC7993110 research support from Celgene through a cooperative research and development agreement (CRADA) at the NCI. R.R., T.S.U., K.L., and R.Y. report receiving a drug for a clinical trial from Merck through a CRADA with the NCI. R.R., K.L., and R.Y. report receiving a drug for a clinical trial from EMD-Serano through a CRADA at the NCI. R.Y. reports receiving a drug for preclinical studies from Janssen and CTI BioPharma. T.S.U. reports receiving other commercial research support from Roche through a clinical trial agreement with Fred Hutchinson Cancer Research Center. T.S.U., R.Y., and D.W. are co-inventors on US Patent 10 001,483 entitled “Methods for the treatment of Kaposi's sarcoma or KSHV-induced lymphoma using immunomodulatory compounds, and uses of biomarkers." R.Y. is also a coinventor on patents on a peptide vaccine for HIV and the treatment of Kaposi sarcoma with IL-12, and an immediate family member of R.Y. is a co-inventor on patents related to internalization of target receptors, KSHV vIL-6, and the use of calreticulin and calreticulin fragments to inhibit angiogenesis. All rights, title, and interest to these patents have been or should by law be assigned to the US Department of Health and Human Services; the government conveys a portion of the royalties it receives to its employee inventors under the Federal Technology Transfer Act of 1986 (P.L. 99-502). The remaining authors declare no competing financial interests”.

Ransom, M., Dennehey, B. K., & Tyler, J. K. (2010). Chaperoning histones during DNA replication and repair. *Cell, 140*(2), 183–195. https://doi.org/10.1016/j.cell.2010.01.004. PubMed PMID: 20141833; PubMed Central PMCID: PMCPMC3433953.

Sack, B. K., & Herzog, R. W. (2009). Evading the immune response upon in vivo gene therapy with viral vectors. *Curr Opin Mol Ther, 11*(5), 493–503. PubMed PMID: 19806497; PubMed Central PMCID: PMCPMC3584155.

Salazar, S., Luong, K. T. Y., & Koyuncu, O. O. (2023). Cell intrinsic determinants of alpha herpesvirus latency and pathogenesis in the nervous system. *Viruses, 15*(12). https://doi.org/10.3390/v15122284. PubMed PMID: 38140525; PubMed Central PMCID: PMCPMC10747186.

Sanchez, E. L., Carroll, P. A., Thalhofer, A. B., & Lagunoff, M. (2015). Latent KSHV infected endothelial cells are glutamine addicted and require glutaminolysis for survival. *PLoS Pathogens, 11*(7), Article e1005052. https://doi.org/10.1371/journal.ppat.1005052. PubMed PMID: 26197457; PubMed Central PMCID: PMCPMC4510438.

Sanchez, E. L., Pulliam, T. H., Dimaio, T. A., Thalhofer, A. B., Delgado, T., & Lagunoff, M. (2017). Glycolysis, glutaminolysis, and fatty acid synthesis are required for distinct stages of Kaposi's sarcoma-associated herpesvirus lytic replication. *Journal of Virology, 91*(10). https://doi.org/10.1128/JVI.02237-16. PubMed PMID: 28275189; PubMed Central PMCID: PMCPMC5411582.

Scholl, A., & De, S. (2022). Epigenetic regulation by polycomb complexes from Drosophila to human and its relation to communicable disease pathogenesis. *International Journal of Molecular Sciences, 23*(20). https://doi.org/10.3390/ijms232012285. PubMed PMID: 36293135; PubMed Central PMCID: PMCPMC9603650.

Sclafani, R. A., & Holzen, T. M. (2007). Cell cycle regulation of DNA replication. *Annual Review of Genetics, 41*, 237–280. https://doi.org/10.1146/annurev.genet.41.110306.130308. PubMed PMID: 17630848; PubMed Central PMCID: PMCPMC2292467.

Sehrawat, S., Kumar, D., & Rouse, B. T. (2018). Herpesviruses: Harmonious pathogens but relevant cofactors in other diseases? *Frontiers in Cellular and Infection Microbiology, 8*, 177. https://doi.org/10.3389/fcimb.2018.00177. PubMed PMID: 29888215; PubMed Central PMCID: PMCPMC5981231.

Semenza, G. L. (2000). HIF-1 and human disease: One highly involved factor. *Genes Dev, 14*(16), 1983–1991. PubMed PMID: 10950862.

Serquina, A. K., & Ziegelbauer, J. M. (2017). How herpesviruses pass on their genomes. *The Journal of Cell Biology, 216*(9), 2611–2613. https://doi.org/10.1083/jcb.201708077. PubMed PMID: 28819012; PubMed Central PMCID: PMCPMC5584196.

Sharifi, J., Khawli, L. A., Hu, P., King, S., & Epstein, A. L. (2001). Characterization of a phage display-derived human monoclonal antibody (NHS76) counterpart to chimeric TNT-1 directed against necrotic regions of solid tumors. *Hybridoma and Hybridomics, 20*(5–6), 305–312. https://doi.org/10.1089/15368590152740707. PubMed PMID: 11839248.

Shire, K., Kapoor, P., Jiang, K., Hing, M. N., Sivachandran, N., Nguyen, T., et al. (2006). Regulation of the EBNA1 Epstein-Barr virus protein by serine phosphorylation and arginine methylation. *Journal of Virology, 80*(11), 5261–5272. https://doi.org/10.1128/JVI.02682-05. PubMed PMID: 16699006; PubMed Central PMCID: PMCPMC1472174.

Shrestha, P., Davis, D. A., Veeranna, R. P., Carey, R. F., Viollet, C., & Yarchoan, R. (2017). Hypoxia-inducible factor-1 alpha as a therapeutic target for primary effusion lymphoma. *PLoS Pathogens, 13*(9), Article e1006628. https://doi.org/10.1371/journal.ppat.1006628. PubMed PMID: 28922425; PubMed Central PMCID: PMCPMC5619862.

Singh, R. K., Bose, D., & Robertson, E. S. (2021). HIF1alpha-Regulated expression of the fatty acid binding protein family is important for hypoxic reactivation of Kaposi's sarcoma-associated herpesvirus. *Journal of Virology, 95*(12). https://doi.org/10.1128/JVI.02063-20. PubMed PMID: 33789996; PubMed Central PMCID: PMCPMC8316119.

Singh, R. K., Bose, D., & Robertson, E. S. (2022). Epigenetic reprogramming of Kaposi's sarcoma-associated herpesvirus during hypoxic reactivation. *Cancers, 14*(21). https://doi.org/10.3390/cancers14215396. PubMed PMID: 36358814; PubMed Central PMCID: PMCPMC9654037.

Singh, R. K., Lamplugh, Z. L., Lang, F., Yuan, Y., Lieberman, P., You, J., et al. (2019). KSHV-encoded LANA protects the cellular replication machinery from hypoxia induced degradation. *PLoS Pathogens, 15*(9), Article e1008025. https://doi.org/10.1371/journal.ppat.1008025. PubMed PMID: 31479497; PubMed Central PMCID: PMCPMC6743784.

Singh, R. K., Lang, F., Pei, Y., Jha, H. C., & Robertson, E. S. (2018). Metabolic reprogramming of Kaposi's sarcoma associated herpes virus infected B-cells in hypoxia. *PLoS Pathogens, 14*(5), Article e1007062. https://doi.org/10.1371/journal.ppat.1007062. PubMed PMID: 29746587; PubMed Central PMCID: PMCPMC5963815.

Sodhi, A., Montaner, S., Patel, V., Zohar, M., Bais, C., Mesri, E. A., et al. (2000). The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. *Cancer Research, 60*(17), 4873–4880. PubMed PMID: 10987301.

Soldan, S. S., & Lieberman, P. M. (2023). Epstein-Barr virus and multiple sclerosis. *Nature Reviews Microbiology, 21*(1), 51–64. https://doi.org/10.1038/s41579-022-00770-5. PubMed PMID: 35931816; PubMed Central PMCID: PMCPMC9362539 inhibitors of EBNA1. S.S.S. declares no competing interests.

Sorel, O., & Dewals, B. G. (2018). The critical role of genome maintenance proteins in immune Evasion during gammaherpesvirus latency. *Frontiers in Microbiology, 9*, 3315. https://doi.org/10.3389/fmicb.2018.03315. PubMed PMID: 30687291; PubMed Central PMCID: PMCPMC6333680.

Spear, P. G., & Longnecker, R. (2003). Herpesvirus entry: An update. *Journal of Virology, 77*(19), 10179–10185. https://doi.org/10.1128/jvi.77.19.10179-10185.2003. PubMed PMID: 12970403; PubMed Central PMCID: PMCPMC228481.

Speck, S. H., & Ganem, D. (2010). Viral latency and its regulation: Lessons from the gamma-herpesviruses. *Cell Host Microbe, 8*(1), 100–115. https://doi.org/10.1016/j.chom.2010.06.014. PubMed PMID: 20638646; PubMed Central PMCID: PMCPMC2914632.

Spires, L. M., Wind, E., Papp, B., & Toth, Z. (2023). KSHV RTA utilizes the host E3 ubiquitin ligase complex RNF20/40 to drive lytic reactivation. *Journal of Virology, 97*(11), Article e0138923. https://doi.org/10.1128/jvi.01389-23. PubMed PMID: 37888983; PubMed Central PMCID: PMCPMC10688343.

Srivastava, A., Srivastava, A., & Singh, R. K. (2023). Insight into the epigenetics of Kaposi's sarcoma-associated herpesvirus. *International Journal of Molecular Sciences, 24*(19). https://doi.org/10.3390/ijms241914955. PubMed PMID: 37834404; PubMed Central PMCID: PMCPMC10573522.

Strowitzki, M. J., Cummins, E. P., & Taylor, C. T. (2019). Protein hydroxylation by hypoxia-inducible factor (HIF) hydroxylases: Unique or ubiquitous? *Cells, 8*(5). https://doi.org/10.3390/cells8050384. PubMed PMID: 31035491; PubMed Central PMCID: PMCPMC6562979.

Takasugi, M., Yoshida, Y., & Ohtani, N. (2022). Cellular senescence and the tumour microenvironment. *Molecular Oncology, 16*(18), 3333–3351. https://doi.org/10.1002/1878-0261.13268. PubMed PMID: 35674109; PubMed Central PMCID: PMCPMC9490140.

Tang, M., Bolderson, E., O'Byrne, K. J., & Richard, D. J. (2021). Tumor hypoxia drives genomic instability. *Frontiers in Cell and Developmental Biology, 9*, Article 626229. https://doi.org/10.3389/fcell.2021.626229. PubMed PMID: 33796526; PubMed Central PMCID: PMCPMC8007910.

Taylor, C. T., & Scholz, C. C. (2022). The effect of HIF on metabolism and immunity. *Nature Reviews Nephrology, 18*(9), 573–587. https://doi.org/10.1038/s41581-022-

00587-8. PubMed PMID: 35726016; PubMed Central PMCID: PMCPMC9208707 interests.
Thaker, S. K., Ch'ng, J., & Christofk, H. R. (2019). Viral hijacking of cellular metabolism. *BMC Biology, 17*(1), 59. https://doi.org/10.1186/s12915-019-0678-9. PubMed PMID: 31319842; PubMed Central PMCID: PMCPMC6637495.
Thorley-Lawson, D. A. (2015). EBV persistence–introducing the virus. *Current Topics in Microbiology and Immunology, 390*(Pt 1), 151–209. https://doi.org/10.1007/978-3-319-22822-8_8. PubMed PMID: 26424647; PubMed Central PMCID: PMCPMC5125397.
Toth, Z., Brulois, K., & Jung, J. U. (2013). The chromatin landscape of Kaposi's sarcoma-associated herpesvirus. *Viruses, 5*(5), 1346–1373. https://doi.org/10.3390/v5051346. PubMed PMID: 23698402; PubMed Central PMCID: PMCPMC3712311.
Toth, Z., Maglinte, D. T., Lee, S. H., Lee, H. R., Wong, L. Y., Brulois, K. F., et al. (2010). Epigenetic analysis of KSHV latent and lytic genomes. *PLoS Pathogens, 6*(7), Article e1001013. https://doi.org/10.1371/journal.ppat.1001013. PubMed PMID: 20661424; PubMed Central PMCID: PMCPMC2908616.
Toth, Z., Papp, B., Brulois, K., Choi, Y. J., Gao, S. J., & Jung, J. U. (2016). LANA-mediated recruitment of host polycomb repressive complexes onto the KSHV genome during De novo infection. *PLoS Pathogens, 12*(9), Article e1005878. https://doi.org/10.1371/journal.ppat.1005878. PubMed PMID: 27606464; PubMed Central PMCID: PMCPMC5015872.
Traylen, C. M., Patel, H. R., Fondaw, W., Mahatme, S., Williams, J. F., Walker, L. R., et al. (2011). Virus reactivation: A panoramic view in human infections. *Future Virology, 6*(4), 451–463. https://doi.org/10.2217/fvl.11.21. PubMed PMID: 21799704; PubMed Central PMCID: PMCPMC3142679.
Tsegay, P. S., Lai, Y., & Liu, Y. (2019). Replication stress and consequential instability of the genome and epigenome. *Molecules, 24*(21). https://doi.org/10.3390/molecules24213870. PubMed PMID: 31717862; PubMed Central PMCID: PMCPMC6864812.
Uppal, T., Banerjee, S., Sun, Z., Verma, S. C., & Robertson, E. S. (2014). KSHV LANA–the master regulator of KSHV latency. *Viruses, 6*(12), 4961–4998. https://doi.org/10.3390/v6124961. PubMed PMID: 25514370; PubMed Central PMCID: PMCPMC4276939.
Uppal, T., Jha, H. C., Verma, S. C., & Robertson, E. S. (2015). Chromatinization of the KSHV genome during the KSHV life cycle. *Cancers, 7*(1), 112–142. https://doi.org/10.3390/cancers7010112. PubMed PMID: 25594667; PubMed Central PMCID: PMCPMC4381254.
van Vliet, T., Varela-Eirin, M., Wang, B., Borghesan, M., Brandenburg, S. M., Franzin, R., et al. (2021). Physiological hypoxia restrains the senescence-associated secretory phenotype via AMPK-mediated mTOR suppression. *Mol Cell, 81*(9), 2041–20452 e6. https://doi.org/10.1016/j.molcel.2021.03.018. PubMed PMID: 33823141.
Vassilaki, N., Kalliampakou, K. I., Kotta-Loizou, I., Befani, C., Liakos, P., Simos, G., et al. (2013). Low oxygen tension enhances hepatitis C virus replication. *Journal of Virology, 87*(5), 2935–2948. https://doi.org/10.1128/JVI.02534-12. PubMed PMID: 23269812; PubMed Central PMCID: PMCPMC3571389.
Verdikt, R., & Thienpont, B. (2024). Epigenetic remodelling under hypoxia. *Seminars in Cancer Biology, 98*, 1–10. https://doi.org/10.1016/j.semcancer.2023.10.005. PubMed PMID: 38029868.
Verzosa, A. L., McGeever, L. A., Bhark, S. J., Delgado, T., Salazar, N., & Sanchez, E. L. (2021). Herpes simplex virus 1 infection of neuronal and non-neuronal cells elicits specific innate immune responses and immune evasion mechanisms. *Frontiers in Immunology, 12*, Article 644664. https://doi.org/10.3389/fimmu.2021.644664. PubMed PMID: 34135889; PubMed Central PMCID: PMCPMC8201405.
Wang, X., Teng, F., Kong, L., & Yu, J. (2016). PD-L1 expression in human cancers and its association with clinical outcomes. *OncoTargets and Therapy, 9*, 5023–5039. https://doi.org/10.2147/OTT.S105862. PubMed PMID: 27574444; PubMed Central PMCID: PMCPMC4990391.
Wei, Q., Li, J., Liu, T., Tong, X., & Ye, X. (2013). Phosphorylation of minichromosome maintenance protein 7 (MCM7) by cyclin/cyclin-dependent kinase affects its function in cell cycle regulation. *Journal of Biological Chemistry, 288*(27), 19715–19725. https://doi.org/10.1074/jbc.M112.449652. PubMed PMID: 23720738; PubMed Central PMCID: PMCPMC3707676.
Weidner-Glunde, M., Kruminis-Kaszkiel, E., & Savanagouder, M. (2020). Herpesviral latency-common themes. *Pathogens, 9*(2). https://doi.org/10.3390/pathogens9020125. PubMed PMID: 32075270; PubMed Central PMCID: PMCPMC7167855.
Welford, S. M., & Giaccia, A. J. (2011). Hypoxia and senescence: The impact of oxygenation on tumor suppression. *Molecular Cancer Research, 9*(5), 538–544. https://doi.org/10.1158/1541-7786.MCR-11-0065. PubMed PMID: 21385881; PubMed Central PMCID: PMCPMC3096743.
Weljie, A. M., & Jirik, F. R. (2011). Hypoxia-induced metabolic shifts in cancer cells: Moving beyond the Warburg effect. *Int J Biochem Cell Biol, 43*(7), 981–989. https://doi.org/10.1016/j.biocel.2010.08.009. PubMed PMID: 20797448.
Wheaton, W. W., & Chandel, N. S. (2011). Hypoxia. 2. Hypoxia regulates cellular metabolism. *Am J Physiol Cell Physiol, 300*(3), C385–C393. https://doi.org/10.1152/ajpcell.00485.2010. PubMed PMID: 21123733; PubMed Central PMCID: PMCPMC3063979.
Wilson, E. B., & Brooks, D. G. (2011). The role of IL-10 in regulating immunity to persistent viral infections. *Current Topics in Microbiology and Immunology, 350*, 39–65. https://doi.org/10.1007/82_2010_96. PubMed PMID: 20703965; PubMed Central PMCID: PMCPMC3492216.
Wing, P. A. C., Liu, P. J., Harris, J. M., Magri, A., Michler, T., Zhuang, X., et al. (2021). Hypoxia inducible factors regulate hepatitis B virus replication by activating the basal core promoter. *Journal of Hepatology, 75*(1), 64–73. https://doi.org/10.1016/j.jhep.2020.12.034. PubMed PMID: 33516779; PubMed Central PMCID: PMCPMC8214165.
Yan, Z., Bryant, K. F., Gregory, S. M., Angelova, M., Dreyfus, D. H., Zhao, X. Z., et al. (2014). HIV integrase inhibitors block replication of alpha-, beta-, and gammaherpesviruses. *mBio, 5*(4), Article e01318. https://doi.org/10.1128/mBio.01318-14, 14 PubMed PMID: 24987091; PubMed Central PMCID: PMCPMC4161245.
Yfantis, A., Mylonis, I., Chachami, G., Nikolaidis, M., Amoutzias, G. D., Paraskeva, E., et al. (2023). Transcriptional response to hypoxia: The role of HIF-1-Associated Co-regulators. *Cells, 12*(5). https://doi.org/10.3390/cells12050798. PubMed PMID: 36899934; PubMed Central PMCID: PMCPMC10001186.
Yogev, O., Lagos, D., Enver, T., & Boshoff, C. (2014). Kaposi's sarcoma herpesvirus microRNAs induce metabolic transformation of infected cells. *PLoS Pathogens, 10*(9), Article e1004400. https://doi.org/10.1371/journal.ppat.1004400. PubMed PMID: 25255370; PubMed Central PMCID: PMCPMC4177984.
Zhang, C., Liu, J., Wang, J., Zhang, T., Xu, D., Hu, W., et al. (2021). The interplay between tumor suppressor p53 and hypoxia signaling pathways in cancer. *Frontiers in Cell and Developmental Biology, 9*, Article 648808. https://doi.org/10.3389/fcell.2021.648808. PubMed PMID: 33681231; PubMed Central PMCID: PMCPMC7930565.
Zhang, Y., Wu, L., Wang, Z., Wang, J., Roychoudhury, S., Tomasik, B., et al. (2022). Replication stress: A review of novel targets to enhance radiosensitivity-from bench to clinic. *Front Oncol, 12*, Article 838637. https://doi.org/10.3389/fonc.2022.838637. PubMed PMID: 35875060; PubMed Central PMCID: PMCPMC9305609.
Zhu, F. X., Chong, J. M., Wu, L., & Yuan, Y. (2005). Virion proteins of Kaposi's sarcoma-associated herpesvirus. *Journal of Virology, 79*(2), 800–811. https://doi.org/10.1128/JVI.79.2.800-811.2005. PubMed PMID: 15613308; PubMed Central PMCID: PMCPMC538588.
Zhuang, X., Pedroza-Pacheco, I., Nawroth, I., Kliszczak, A. E., Magri, A., Paes, W., et al. (2020). Hypoxic microenvironment shapes HIV-1 replication and latency. *Communications Biology, 3*(1), 376. https://doi.org/10.1038/s42003-020-1103-1. PubMed PMID: 32665623; PubMed Central PMCID: PMCPMC7360605.