



## REVIEW

# A Review of Mitochondrial Involvement in Cell Death Pathways Induced by Oncogenic Viruses

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**ABSTRACT:** Oncogenic viruses include both DNA and RNA viruses which contribute to cancer development by disrupting cellular regulation and interfering in the immune responses. These viruses do not directly cause cancer but instead integrate their genetic material into the host genome thus, affecting cell cycle and tumor suppression. This deregulation also leads to impaired immune function and promotes tumor progression by disrupting the removal of infected cells. Generally, innate immunity consists of two important members, including mitochondria and cell deaths, which impact each other as well. Due to the close correlation between viruses, cell death pathways (apoptosis, necroptosis, and pyroptosis), and mitochondria (mitochondrial antiviral-signaling protein and reactive oxygen species generation), targeting these immune system representatives may offer therapeutic strategies to control the progression of oncogenic viral infections. Some previous studies have covered the association of oncogenic viruses with mitochondria and cell death pathways, respectively, but mitochondria and cell death interact with each other, separately, and this interaction may play a role in the progression of cancer induced by oncogenic viruses. Hence, the purpose of this review is to discuss the relationship between cell death, mitochondria, and viral oncogenesis, focusing on the most surveyed oncogenic viruses' mechanisms of action.

**KEYWORDS:** Oncogenic virus; viral protein; mitochondria; apoptosis; necroptosis; pyroptosis

## 1 Introduction

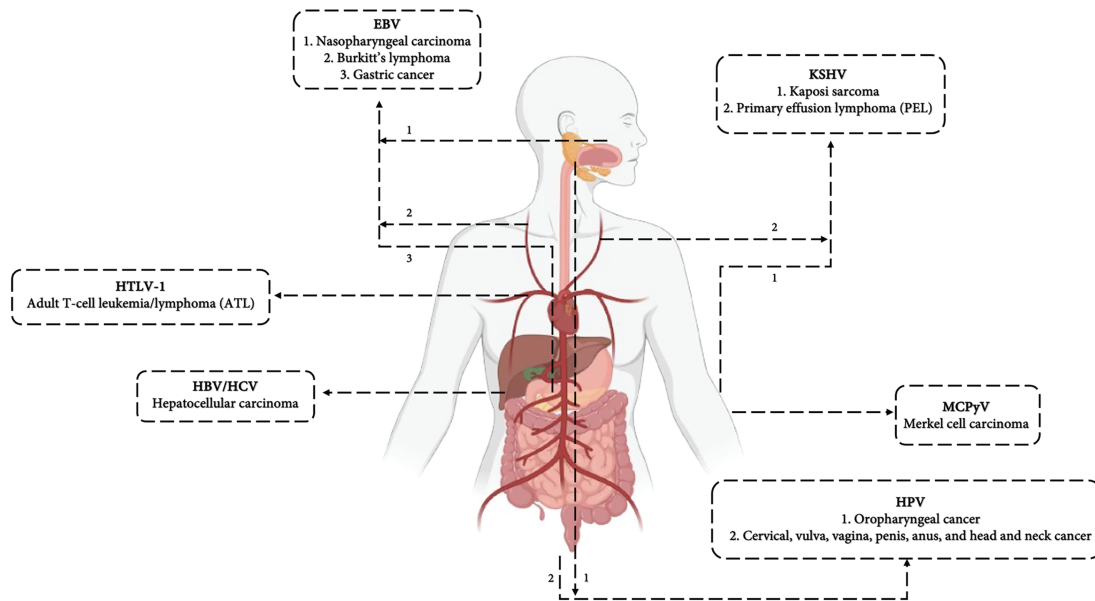
Cancer is a biological term referring to a situation when cells undergo uncontrolled changes in their metabolism and cell cycle. Cells' life cycle is strictly controlled and suppressed to maintain their normal tissue-related function and mortality by molecules such as p53 and retinoblastoma protein (pRb). When a cell cannot be controlled and undergoes severe alteration, the immune system tries to eliminate it to inhibit further damage, but sometimes the cell becomes immortal, which means the cell death pathways are not sufficient to remove it. When faulty cells are accumulated a structure called a tumor is formed, which might be able to perform metastatic behavior [1–3]. Various factors are capable of disrupting cells' standard functions including genetic mutations, physical and chemical damage, and pathogenic invasions, especially by viruses. Detection of viral genome in tumor cells started the hypothesis that viruses can be



the reason behind the inflammations that lead to cancer. These viruses are known as oncogenic viruses. It's estimated that oncogenic viruses are behind about 15%–20% of cancers all over the world [4]. It's noteworthy to know that as a result of cancer development in viral infection, neoplasm can be observed which is not even desirable to the virus itself and they can be as deadly to the virus as they are to the host's cells because the viruses are non-permissive for replication in the tumor cells [5]. Technically, viruses begin to prepare the essential factors and manipulate specific metabolic pathways such as pathways regulating glucose metabolism, fatty acid metabolism, and some oncogene expressions to ensure their persistence, which leads to disruption of the cell cycle machinery and finally alters the cell's proliferation and division, because viruses are not able to replicate independently. Signaling pathways which are manipulated by oncogenic viruses to disrupt the normal function of their host cells and the immune system include Phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR) pathway (PI3K–AKT–mTOR, Mitogen-activated protein kinase (MAPK), Notch, Canonical Wntless-related integration site (Wnt) pathway (WNT/ $\beta$ -catenin), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), DNA damage response pathway (DDR).

If these changes are not controlled and inhibited, they can lead to severe side effects or even death [6]. Hence, oncogenic viruses are not the only reason behind cancer development but their presence can accelerate this process. Generally, viruses have some major mechanisms to contribute to oncogenesis: I) encoding viral oncogenic proteins, called proto-oncogenes, II) beginning a chronic inflammation and suppressing immune system function [7,8], III) creating genomic instability or alterations in the microenvironment of host's cells. Oncogenic viruses can be divided into two groups DNA viruses and RNA viruses based on their genetic materials. Insertional mutagenesis is referred to as viral DNA integration which leads to changes in the host's genomic structure or transcription levels of the genes. DNA viruses are able to directly integrate their genome into the host's genome but RNA viruses have to go through a reverse transcription mechanism [4,7]. Hence, long-term interaction between oncogenic viruses and their host cells is essential to lead to their tumorigenesis ability [1,8,9]. Seven viruses have been recognized to be involved in cancer so far. Among RNA viruses Hepatitis C virus (HCV) and Human T-cell lymphotropic virus type 1 (HTLV-1) and among DNA viruses Kaposi's sarcoma-associated herpesvirus (KSHV), Epstein-Barr virus (EBV), Human papillomavirus (HPV), Hepatitis B virus (HBV), and Merkel cell polyomavirus (MCV or MCPyV) are known to be involved in cancer development and pathogenicity of the oncogenic viruses by some specific proteins encoded by their own genome in order to defeat immune system and ensure viral replication and cells transition including trans-activating transcriptional regulatory protein (Tax), HBZ hemoglobin subunit zeta (HBZ), and P12 encoded by HTLV-1, Epstein-Barr nuclear antigen A2 (EBNA2), Epstein-Barr nuclear antigen leader protein (EBNA-LP), latent membrane protein 1/2A/2B (LMP1, LMP2A, LMP2B), BamHI Epstein-Barr virus replication activator 1 (BZLF1), Epstein-Barr nuclear antigen (EBNA3A, EBNA3B, EBNA3C, EBNA1), BRLF1 encoded by EBV, E6, E7, E2, E5, L1, and L2 encoded by HPV, Hepatitis B virus core protein (HBc) and Hepatitis B virus x protein (HBx) encoded by HBV, non-structural protein 3/4A/5A/5B/s2 (NS3, NS4A, NS5A, NS5B, NS2), E1, E2, and P7 encoded by HCV, Latency-associated nuclear antigen (LANA), viral cyclin (v-Cyclin), VIRF2, Kaposin, Open reading frames 45/52/64 (ORF45, ORF52, ORF64), MIR1, MIR2, K1, and K2 encoded by KSHV, and Large antigen (LT) and small antigen (ST) encoded by MCPyV. The range of host tissue that can be infected by each virus is closely related to its tropism and is exclusive to each of them. For example, HBV is restricted to lead to primary hepatocellular carcinoma, and HTLV-1 causes adult T-cell leukemia/lymphoma. Instead, HPV can develop cervical, head and neck, and anal cancers in addition to squamous epithelial cancer. However, KSHV and EBV can infect a wide range of tissues and cause tumor formation. KSHV is the reason behind endothelial Kaposi's sarcoma, B-cell primary effusion lymphoma as well as a B-cell lymphoproliferative syndrome and EBV causes B-cell lymphomas, nasopharyngeal carcinoma, stomach cancer, T-cell lymphomas, and a rare

form of leiomyosarcoma [6,9]. Fig. 1 mentions these seven oncogenic viruses and the various cancers related to their infection.



**Figure 1:** HPV, HCV, HBV, EBV, KSHV, MCPyV, and HTLV-1 have been recognized as viruses involved in cancer development. Their ability to cause cancer in particular target tissues is related to the virus attachment potential. This figure displays the cancers related to each oncogenic virus, pointing to their tissue targets. For instance, the Hepatitis B virus or Hepatitis C virus (HBV/HCV) are both responsible for hepatocellular carcinoma in liver, Human papilloma virus (HPV) is the reason behind cancer in the genital area in males and females, Human T-cell lymphotropic virus type 1 (HTLV-1) infects blood cells causing T-cell leukemia and lymphoma, Epstein–Barr virus (EBV) infection leads to cancer in lymphatic system and nasopharyngeal carcinoma, and KSHV and MCPyV have been identified to cause specific types of skin cancers such as Kaposi sarcoma (KS) and Merkel cell carcinoma (MCC), respectively

On one hand, the immune system has adopted mechanisms to control and defeat the invasion of pathogenic factors such as viruses, which lead to the normal function and proliferation of the cells to maintain homeostasis. Tumor viruses interact with the immune system members to downregulate the function of immune sensors such as Toll-like receptors (TLRs) which are responsible for detecting viral proteins, negatively influence the DDR which recognizes the viral genetic materials, and disrupt the immune signaling pathway including interferon regulatory factor 3/7 (IRF3/7) and NF- $\kappa$ B, and interrupt the cell death pathways to prevent the efficient immune responses [2,6,8]. The metabolic and immune signaling manipulated by oncoviruses through their oncoproteins are discussed in more detail in Table 1. On the other hand, oncogenic viruses target the cell cycle checkpoints and interact with p53 and pRb molecules by encoding oncoproteins. Oncoproteins induce the S phase of the life cycle to have access to the cellular replication machinery and enhance DNA synthesis in order to accelerate their replication [2,3]. Based on the previous studies, the interaction between oncogenic viruses, mitochondria (Mitochondrial antiviral-signaling protein (MAVS) and mitochondrial reactive oxygen species (mROS) production), and cell death pathways, respectively, has been discovered. Still, the associations of mitochondria and cell death pathways remain inconclusive and need more attention because they might be an appropriate therapeutic target to control cancer development. Here we discuss the interactions between the mentioned oncogenic viruses, mitochondria, and cell death pathways to propose that the cell death pathways and mitochondria cooperation might be a promising target in the process of tumor progression.

Table 1: Summary of different signaling pathways that are affected by various viruses

Signaling pathway	Function	Oncogenic viruses	Mechanism of action for each virus	References
Phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR) pathway (PI3K-AKT-mTOR)	<ul style="list-style-type: none"> <li>Nutrient-sensing mechanism</li> <li>Regulates macromolecule synthesis and metabolism in response to nutrient availability</li> </ul>	<ul style="list-style-type: none"> <li>HPV, EBV, HTLV-1, KSHV, MCPyV</li> </ul>	<ul style="list-style-type: none"> <li>HPV targets the pathway via E5, E6, E7 proteins</li> <li>EBV <i>latent Membrane Protein 2A</i> (LMP2A) activates the pathway, contributing to anti-apoptotic functions</li> <li>HTLV-1 modulates AKT in cluster of differentiation +4 (CD4+) T cells to promote latency</li> <li>KSHV upregulates mTOR signaling via ORF45 and <i>G-protein coupled receptor</i> (vGPCR)</li> <li>MCPyV small T oncoprotein hyperactivates downstream effectors</li> </ul>	[3]
Mitogen-activated protein kinase (MAPK)	<ul style="list-style-type: none"> <li>Signaling cascade in cells that transmits signals from the cell surface to the nucleus in response to various external stimuli, such as growth factors, cytokines, and stress</li> </ul>	<ul style="list-style-type: none"> <li>HCV, HPV, MCPyV, KSHV, EBV, HBV</li> </ul>	<ul style="list-style-type: none"> <li>HCV uses MAPK to promote particle assembly</li> <li>HPV increases virion production through extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) activation</li> <li>KSHV kaposin B activates MAPK pathway, stabilizing cytokine mRNAs</li> <li>HBV HBx activates the ERK pathway, leading to metastasis</li> </ul>	

(Continued)

**Table 1 (continued)**

Signaling pathway	Function	Oncogenic viruses	Mechanism of action for each virus	References
Notch	<ul style="list-style-type: none"> <li>Regulates various aspects of cell development, differentiation, tissue homeostasis, embryonic development, stem cell maintenance, and the regulation of cell fate decisions</li> <li>Responsible for interactions between neighboring cells</li> </ul>	<ul style="list-style-type: none"> <li>EBV, HPV, MCPyV, HBV, KSHV</li> </ul>	<ul style="list-style-type: none"> <li>HPV E6 proteins repress Notch signaling to prevent keratinocyte differentiation</li> <li>EBV nuclear antigen 2 (EBNA2) and Notch compete for <i>Recombination signal binding protein for immunoglobulin kappa J region</i> (RBP-Jκ), affecting B cell transformation</li> <li>HBV x protein (HBx) promotes Hepatocellular carcinoma (HCC) cell proliferation via Notch1</li> <li>KSHV proteins activate Notch signaling, aiding in Kaposi sarcoma pathogenesis</li> </ul>	
Canonical Wnt pathway (WNT/β-catenin)	<ul style="list-style-type: none"> <li>Controls various cellular processes, including cell proliferation, differentiation, migration, gene expression, embryonic development, and tissue homeostasis in adults</li> </ul>	<ul style="list-style-type: none"> <li>EBV, KSHV, HBV, HTLV-1</li> </ul>	<ul style="list-style-type: none"> <li>KSHV latency-associated nuclear antigen (LANA) and <i>Epstein-Barr virus</i> LMP2A stabilize β-catenin</li> <li>HBV proteins like HBx aberrantly activate WNT signaling</li> <li>HTLV-1 HBZ hemoglobin subunit zeta (HBZ) dysregulates WNT to enhance cell migration</li> </ul>	

(Continued)

Table 1 (continued)

Signaling pathway	Function	Oncogenic viruses	Mechanism of action for each virus	References
Nuclear factor kappa-light-chain-activated B cells (NF- $\kappa$ B)	<ul style="list-style-type: none"> <li>Regulating the immune response to infection</li> <li>Involved in processes like inflammation, cell survival, and apoptosis</li> <li>Includes the production of cytokines, chemokines</li> </ul>	EBV, KSHV, HTLV-1	<ul style="list-style-type: none"> <li>EBV LMP1 mimics tumor necrosis factor receptors (TNFR) to activate NF-<math>\kappa</math>B, aiding B cell survival</li> <li>KSHV viral FADD-like apoptosis regulator (FLICE) inhibitory proteins (vFLIP) constitutively activate NF-<math>\kappa</math>B in PEL cells</li> <li>HTLV-1 Tax protein is critical for T cell transformation via NF-<math>\kappa</math>B activation</li> </ul>	
DNA damage response pathway (DDR)	<ul style="list-style-type: none"> <li>Detect and repair DNA damage to maintain the integrity of the genome</li> <li>Protecting cells from mutations</li> </ul>	HPV, MCPyV, EBV, HTLV-1, HCV, HBV	<ul style="list-style-type: none"> <li>HPV E6 and E7 cause DNA damage and mitotic defects</li> <li>MCPyV large T antigen stimulates DDR but may inhibit proliferation</li> <li>HTLV-1 Tax protein induces DNA damage by inhibiting repair pathways</li> <li>HBV HBx degrades structural maintenance of chromosomes protein 5/6 (SMC5/6) to promote viral replication</li> </ul>	

## 2 RNA Viruses

- **Hepatitis C virus (HCV):** Hepatitis C virus is identified as a member of Flaviviridae, and consists of a positive single-stranded RNA genome engulfed within an envelope. This virus establishes a chronic infection leading to liver damage and hepatocellular carcinoma (HCC) [7,8]. The genome of HCV is approximately 9.6 kilobases (kb) and encodes various viral proteins such as core protein, NS3, NS4A, NS4B, NS5A, NS5B, NS2, E1, E2, and P7, which associate in a wide range of cell signaling pathways and the mechanism of tumorigenesis.
- **Human T cell leukemia virus 1 (HTLV-1):** Human T cell leukemia virus 1 is a member of the Retroviridae family. HTLV-1 is recognized as a single-stranded positive-sense RNA virus which is 8.5 kb in length. This virus can form a persistent infection by reverse transcribing its RNA genome and integrating the resulting double-stranded DNA copy of its genome into the host cellular chromatin and forming a provirus. The infection later leads to CD4+ T cell malignancy, called adult T cell leukemia/lymphoma, or HTLV-1-associated myelopathy, which is known as a progressive inflammatory disease of the spinal cord [4,10]. HTLV-1 infection is mostly latent which refers to the ability of the virus to cause asymptomatic infection and production of undetectable proteins [8]. Its genome encodes regulatory factors such as Tax protein, HBZ, p12, p13, p8, p30, and Rex protein which are involved in the pathogenicity and oncogenicity of the virus.

## 3 DNA Viruses

- **Epstein-Barr virus (EBV):** Epstein-Barr virus is a 184 kb double-stranded DNA member of herpesviruses (human herpesvirus 4 or HHV-4) and the first virus that was detected to associate with cancer development [2,7]. EBV's infection pattern is classified into two forms known as latent and lytic infection and the latent phase is divided into three groups recognized as latency I, II, and III based on the expression pattern of the latent phase genes. In latent infection the genome of the virus is partially expressed but, in lytic infection, the EBV genome is completely expressed causing a high expression level of the viral oncogenes [4,7]. Both B lymphocytes and epithelial cells can be infected by the lytic infection of EBV, but in latent infection, the influenced cells are restricted to the B cells. EBV genome encodes six lytic-related antigens (EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, and EBNA-LP) and two latent-related proteins (LMP1 and LMP2) [5,7].
- **Human papillomavirus (HPV):** Human papillomavirus is known as an 8 Kb non-enveloped DNA virus that primarily infects basal keratinocytes of the skin or mucous membranes belonging to the Papillomaviridae family [2]. HPV's genome comprises three regions including I) the early region (E), which encodes E1 to E7 proteins necessary for viral replication and cellular transformation, II) the late region (L), which encodes capsid proteins L1 and L2, III) the long control region, which contains the origin of replication and transcription factor binding sites [5]. HPV is further classified into low- and high-risk groups based on their ability to cause malignant lesions and the high-risk HPVs (types 16 and 18) are the main causes of cervical cancer [4]. HPVs must synchronize their life cycle with that of their host's squamous epithelial cells. Two key signaling pathways govern this process: integrins on basal epithelial cells that promote proliferation and repress differentiation and NOTCH signaling that induces differentiation in detached cells. Persistent and long-term HPV infection can lead to squamous proliferative lesions, such as warts, papillomas, and condylomas by encoding different oncoproteins, most importantly E6 and E7 [11]. The E6 and E7 oncoproteins lead to the immortalization and transformation of host cells by interacting with key cellular proteins such as pRb and p53, promoting their degradation.



- **Hepatitis B virus (HBV):** Hepatitis B virus is a member of the Hepadnaviridae family with a small double-stranded DNA with 3.2 kb in length. HBV genome includes four overlapping reading frames that encode a diverse range of proteins involved in its pathogenesis and oncogenesis (S which encodes the viral surface proteins (HBs), and P which encode the viral polymerase, X that encodes the regulatory X protein (HBx), and pre-C that encodes 'e' and 'c' antigens) [2,5,7]. HBx and HBV core proteins are two of the most important proteins encoded by the virus which play an essential role in the oncogenesis of HBV. HBV forms chronic inflammation that leads to a multi-step process to cause hepatocellular carcinoma (HCC) [12]. Environmental carcinogens including Aflatoxin B, cigarette smoking, and alcohol consumption may promote the tumorigenic properties of HBV [10]. Myeloid differentiation primary response 88 (MyD88), Toll/interleukin-1 receptor (TRIF), and MAVS are recognized to play an important role in controlling HBV replication. Hence, HBV has adopted mechanisms by encoding specific proteins to disrupt immune responses such as Toll-like receptor (TLR) signaling pathways and Retinoic acid-inducible gene 1 (RIG-I) signaling, as well as a stimulator of interferon genes (STING)-mediated interferons (IFN) induction [11].
- **Kaposi's sarcoma herpesvirus (KSHV):** KSHV also known as human herpesvirus 8 (HHV-8) is recognized as the most commonly identified cancer in untreated acquired immunodeficiency syndrome (AIDS) patients [1,4]. KSHV consists of a double-stranded DNA which is 165 kb in length, encoding oncoproteins such as LANA, v-Cyclin, vFLIP, and K12. As a member of gamma herpesviruses, this virus can establish either latent or lytic infections. Initially, KSHV exists in a latent state, making the tumor cells resistant to current antiviral treatments targeting lytic replication. In the latency phase, KSHV expresses some specific proteins such as LANA, v-cyclin, and vFLIP, which contribute to cell survival, proliferation, and immune evasion [13].
- **Merkel cell polyomavirus (MCV):** Merkel cell polyomavirus (MCV), a small non-enveloped virus with a double-stranded DNA genome, belongs to a polyomavirus family. MCC is identified as the reason behind a rare and aggressive skin cancer which can be seen mostly in elderly and immunosuppressed individuals. The genome of this virus, which is 5.4 in length, encodes several proteins involved in its pathogenesis and tumorigenesis, such as large T antigen (LT) and small T antigen (ST), which are involved in the disruption of tumor suppressors such as pRb and p53, facilitating the transformation of normal cells into tumor cells [2,4,5].

Table 2 provides information on the proteins of oncogenic viruses, highlighting their oncoprotein's roles in pathogenicity and oncogenicity.



**Table 2:** A summary of the most important proteins encoded by oncogenic viruses discussed so far, their functions, and impacts on the viral pathogenesis and oncogenesis

Oncogenic virus	Protein	Function and influence on the immune system	References
HCV	Core	• Activates toll like receptor 2 (TLR2)	[2,10,14,15]
		• Promotes liver cell proliferation via the $\beta$ -catenin pathway	
		• Inhibits immune-mediated apoptosis by blocking caspase-8	
		• Disrupts transforming growth factor beta (TGF $\beta$ )-dependent tumor suppression via Jun N-terminal kinase (JNK)/linker-phosphorylated Smad3 (p Smad3L) signaling	
	NS3	• Promotes dedifferentiation, continuous growth, and increased telomerase expression	[10,14]
		• Contributes to angiogenesis	
		• Inhibits interferon regulatory factor 3 (IRF3) phosphorylation	
		• Activates PI3K/Akt/mTOR and epidermal growth factor receptor (EGFR)/RAS/MAPK signaling pathways	
		• Inactivates tumor suppressors (p53 and pRb)	
		• Blocks apoptosis	
NS4A	• A part of the HCV replication complex	[10]	
	• Facilitates nonstructural Protein 5A (NS5A) function		
NS4B	• Disrupts cyclic GMP-AMP synthase (cGAS) stimulator of interferon gene (STING) signaling complexes	[14]	
NS5A	• Binds to p53 and partially sequestering it in the cytoplasm	[2,10,16]	
	• Suppresses p53-mediated transcription and apoptosis		
	• Activates the N-Ras/PI3K/Akt/mTOR pathway		
NS5B	• A part of the replication complex contributes to the replication of the viral genome	[7]	
NS2	• A part of the viral envelope	[2]	
	• Facilitates viral entry into host cells		
E1 and E2	• A part of the viral envelope	[2]	
	• Essential for binding to host cell receptors		
	• Suppresses dsRNA-activated kinase protein kinase R (PKR)		

(Continued)

Table 2 (continued)

Oncogenic virus	Protein	Function and influence on the immune system	References
HTLV-1	P7	<ul style="list-style-type: none"> <li>• Ion channel protein involved in viral assembly and release</li> </ul>	[17]
	Tax	<ul style="list-style-type: none"> <li>• Transactivator of viral replication</li> <li>• Induces anti-apoptotic genes (CASP8 and FADD like apoptosis regulator (CFLAR), tumor necrosis factor receptor superfamily member 9 (TNFRSF9), tumor necrosis factor receptor (TNFR) associated factor 1 (TRAF1), tumor necrosis factor alpha-induced protein-3 (TNFAIP3)</li> <li>• Inactivates p53 and mitotic arrest deficiency 1 (MAD1)</li> <li>• Contributes to genomic instability</li> <li>• Maintains viral latency</li> <li>• Promotes T-cell proliferation by enhancing cluster of differentiation 3 (CD3) signaling</li> </ul>	[16,18]
EBV	HBZ	<ul style="list-style-type: none"> <li>• Represses HTLV-1 transcription by inactivating <i>cAMP response element binding protein-2 (CREB-2)</i></li> <li>• Proliferation of cells</li> <li>• Counters Tax activity</li> </ul>	[4,18]
	P12	<ul style="list-style-type: none"> <li>• Activates T cells by increasing endoplasmic reticulum (ER) calcium influx and/or nuclear factor of activated T-cells (NFAT) activity</li> <li>• Promotes T-cell proliferation via interleukin-2 (IL-2) receptor interaction and signal transducer and activator of transcription (STAT-5) phosphorylation</li> </ul>	[19]
EBV	EBNA2	<ul style="list-style-type: none"> <li>• Activates transcription of viral genes including LMPI, LMP2A, LMP2B, and EBNA1-3, interacts with RBP-J<math>\kappa</math> to activate gene expression; also upregulates cellular genes CD23, myelocytoma (MYC), C-C chemokine receptor type 7 (CCR7)</li> </ul>	[20]
	EBNA-LP	<ul style="list-style-type: none"> <li>• Works in conjunction with EBNA2 to activate transcription of latent and early viral genes</li> </ul>	[20]

(Continued)

**Table 2 (continued)**

Oncogenic virus	Protein	Function and influence on the immune system	References
	LMP1	<ul style="list-style-type: none"> <li>Mimics CD40 signaling; induces transformation of B cells by activating NF-<math>\kappa</math>B signaling, promoting cell survival, and genetic instability</li> <li>Activates NF-<math>\kappa</math>B and mimics CD40 signaling; promotes glycolysis and autophagy modulation</li> </ul>	[20]
	LMP2A	<ul style="list-style-type: none"> <li>Blocks B-cell receptor signaling; maintains latent infection; activates PI3K/Akt signaling pathways; associated with EBV-related malignancies like <i>nasopharyngeal carcinoma</i> (NPC)</li> <li>Activates PI3K/Akt pathway; modulates glycolysis and autophagy; involved in maintenance of latent infection</li> </ul>	[20]
	LMP2B	<ul style="list-style-type: none"> <li>Function not explicitly described, but part of Latency III gene expression program</li> </ul>	[20]
	BZLF1	<ul style="list-style-type: none"> <li>Immediate-early transcription factor regulating the switch between latent and lytic stages; activates transcription of early and late lytic genes</li> <li>Directly interacts with p53 to affect its stability and function; activates lytic replication genes</li> </ul>	[2,21]
	BRLF1	<ul style="list-style-type: none"> <li>Immediate-early transcription factor necessary for lytic replication; activates transcription from lytic gene promoters</li> <li>Activates MAPK pathways essential for lytic replication; small ubiquitin-like modifier (SUMO-1) modification affects transcriptional activity</li> </ul>	[21]
	EBNA3A	<ul style="list-style-type: none"> <li>Part of Latency III; involved in the regulation of cell cycle and immune evasion</li> </ul>	[20]
	EBNA3B	<ul style="list-style-type: none"> <li>Part of Latency III; involved in the regulation of cell cycle and immune evasion</li> </ul>	[20]
	EBNA3C	<ul style="list-style-type: none"> <li>Essential for B-cell transformation; interacts with p53 to inhibit apoptosis and stabilize p53 regulators; targets cell-cycle checkpoints</li> </ul>	[2]
	EBNA1	<ul style="list-style-type: none"> <li>Expressed in Latency I and II; essential for maintaining EBV episomes and preventing apoptosis; involved in genomic instability</li> </ul>	[10]
	EBERs	<ul style="list-style-type: none"> <li>EBV-encoded small RNAs that activate TLRs and contribute to immune responses and viral latency</li> </ul>	[4,14]

(Continued)

Oncogenic virus	Protein	Function and influence on the immune system	References
HPV	E6	• Inhibiting IFN signaling	[4,10,14,16,22,23]
		• Degrades p53 via ubiquitination activity and hindering the p53 pathway and DNA repair	
		• Degrades the proapoptotic Bcl-2 (Bak) inhibiting apoptosis	
		• Increases reactive oxygen species (ROS) production, leading to oxidative stress and promoting cell transformation	
		• Interacts with E6AP, an E3 ubiquitin ligase, forming a complex that targets p53 for degradation	
E7	E7	• Inactivates pRb by binding to it, resulting in uncontrolled cell cycle progression	[4,7,16,22]
		• Activate the PI3K/Akt/mTOR signaling pathway	
		• Promotes calpain-mediated proteasomal degradation of pRb thus, disrupting normal cell cycle control	
		• Induces genomic instability by causing mitotic abnormalities	
		• Localizes to mitochondria, induces oxidative stress, and modulates oxidative phosphorylation	
E2	E2	• Downregulates E6, and E7 expression in normal viral episomal state	[7,10]
		• During viral genome integration into host DNA, E2 is often disrupted, leading to uncontrolled expression of E6 and E7	
		• Downregulates major histocompatibility complex (MHC I) expression	
		• Enhances cell survival by modulating signaling pathways	
		• Involved in the assembly of the viral capsid, enabling viral particle formation and release	
E5	L1 and L2	• Increases susceptibility to TNF- $\alpha$ -induced apoptosis	[10,16,22]
		• Modifies metabolic characteristics of HCC cells	
		• Promotes expression of metabolic enzymes and secretion of metabolites in HCC cells	
		• Activates glycolysis and amino acid metabolism pathways	
		• Involved in the assembly of the viral capsid, enabling viral particle formation and release	
H1Bc	H1Bc	• Increases susceptibility to TNF- $\alpha$ -induced apoptosis	[24]
		• Modifies metabolic characteristics of HCC cells	
		• Promotes expression of metabolic enzymes and secretion of metabolites in HCC cells	
		• Activates glycolysis and amino acid metabolism pathways	
		• Involved in the assembly of the viral capsid, enabling viral particle formation and release	

(Continued)

**Table 2 (continued)**

Oncogenic virus	Protein	Function and influence on the immune system	References	
HBV		<ul style="list-style-type: none"> <li>Regulates HBV transcription and viral replication</li> <li>Inhibits p53 activity leading to the promotion of cell proliferation and genomic instability</li> <li>Blocks mitochondrial antiviral signaling protein (MAVS)</li> <li>Prevents apoptosis and activates NF-<math>\kappa</math>B</li> <li>Upregulates proinflammatory cytokines</li> <li>Promotes glucose metabolism dysregulation, specifically gluconeogenesis</li> <li>Impairs Akt signaling, influencing glucose homeostasis</li> <li>Induces oxidative stress and genomic instability</li> <li>Activates several oncogenic pathways (e.g., Wnt, PI3K/Akt)</li> <li>Regulates cellular and viral transcription, cell growth, angiogenesis, and immune modulation</li> <li>Inhibits IFN-<math>\beta</math> production by competing with IRF3.</li> <li>Inhibits antigen presentation of MHC I and II</li> <li>Associates with cGAS in the cytoplasm to inhibit cyclic GMP-AMP synthase (cGAS) - stimulator of interferon genes (STING) - Interferon regulatory factor 3 (IRF3) pathway and reduce type I</li> <li>IFN production during lytic replication</li> <li>Competes with IRF3 to bind IFN-<math>\beta</math> promoter, reducing IFN transcription</li> <li>Induces cell cycle progression by affecting cell-cycle checkpoint mediators</li> <li>Promotes cellular transformation and survival in latent infection</li> </ul>	[2,7,10,16,25]	
		HBx		
	KSHV	LANA		[4,14,16,26]
		v-Cyclin		[2,10,16]
		VIRF2	Modulates the innate immune response, targeting pattern recognition receptors (PRRs)	[26]
		Kaposin	Induces cytokine expression and cell growth	[16]
		ORF45	Inhibits IRF7 phosphorylation, preventing interferon response	[14,26]
		ORF52	Inhibits cGAS enzymatic activity, preventing cGAS-STING pathway activation	[14,26]

(Continued)

Table 2 (continued)

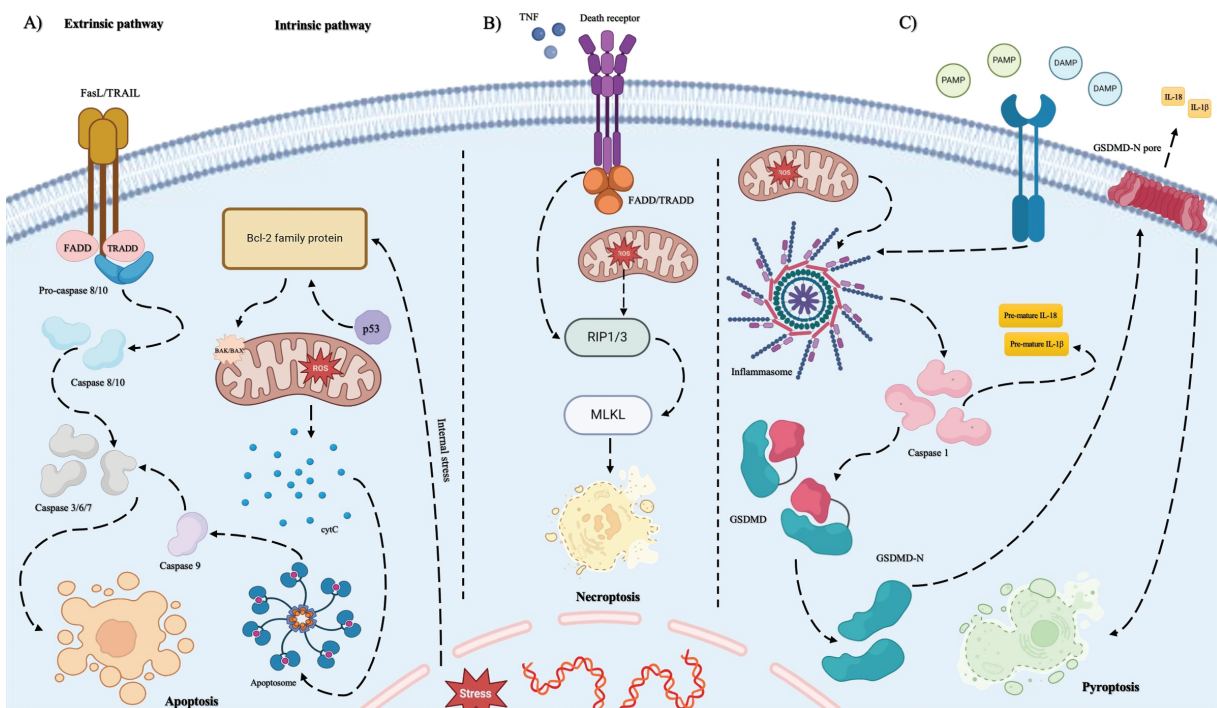
Oncogenic virus	Protein	Function and influence on the immune system	References
MCPyV	ORF64	• Downregulates TLR2 and TLR4, inhibits TLR-mediated innate immune responses	[14,26]
		• Disrupts TLR signaling	
		• Stimulates IRF7 ubiquitination and degradation	
	MIR1	• Downregulates MHC I expression, inhibiting viral antigen presentation	[27]
	MIR2	• Downregulates MHC I expression	[27]
	KI	• Transforms cells, induces angiogenic factors, and inflammatory cytokines	[28]
	K15	• Promotes cell survival via interaction with anti-apoptotic protein	[29]
	LT	• <b>Downregulates TLR9 expression</b>	[4,7,14]
		• <b>Inhibits tumor suppressors Rb and p53 and facilitates viral replication and oncogenesis</b>	
		• <b>Binds to the Rb pathway and disrupts cell cycle control, contributing to carcinogenesis</b>	
	ST	• <b>Disrupts NF-<math>\kappa</math>B signaling</b> , inhibits NF- $\kappa$ B activation by binding to NF- $\kappa$ B essential modulator	[7,14,30]
		• <b>Interacts with protein phosphatase 2A (PP2A)</b> which may contribute to cell transformation and oncogenesis	
		• <b>Stabilizes cMyc pathway</b> and enhances oncogenic signaling	

#### 4 Apoptosis, Necroptosis, and Pyroptosis Act as a Weapon for Innate Immunity

- **Apoptosis:** Apoptosis is known as a caspase-dependent cell death pathway. Caspases are proteolytic enzymes that drive the morphological changes associated with some specific cell deaths [31]. During this type of cell death, cell integrity is preserved, and the release of intracellular components such as cytokines out of the cell cannot be seen thus, apoptosis is immunologically silent [31–33]. To initiate apoptosis a specific signal must be detected by the cells. While the integrity of the plasma membrane is maintained, the phosphatidylserine (PS) moves from the inner leaflet of the plasma membrane to the surface of the cell membrane. Then macrophages detect PS as an “eat me” signal [34]. Phagocytes encapsulate the dying cell and form vesicles known as “apoptotic bodies”. These vesicles act as traps consisting of microbial products which should remain engulfed [35]. Apoptosis is classified into two pathways called extrinsic and intrinsic apoptosis. The intrinsic pathway relies on sensing internal stress such as disruption in mitochondrial membrane integrity and the release of some components such as cytokine C (cytC), DNA damage, and oxidative stress [36]. During apoptosis, the BH3 interacting-domain death agonist (BID) protein translocates to mitochondria and activates the B-cell leukemia/lymphoma 2 protein (Bcl2) family protein and BAK protein. After the loss of mitochondrial outer membrane (MOM) integrity, the release of mitochondrial proapoptotic contents cytC can be observed, which assists the assembly of apoptotic protease activating factor (APAF) and cooperates in the formation of a platform named apoptosome. Apoptosomes induce the activation of initiator caspase 9 which activates the executioner caspases (caspase 3,6,7), especially caspase 3 [37]. The extrinsic pathway is a classical ligand-cell surface receptor interaction dependent on death receptors (DR) and extracellular stresses, which can be sensed by extracellular receptors. When the specific ligands bind to their receptors, apoptosis is induced by the activation of caspases similar to the intrinsic pathway [37,38]. (Fig. 2A)
- **Necroptosis:** Necroptotic cell death is controlled by receptor-interacting protein 1 and 3 (RIP1, RIP3), and mixed lineage kinase domain-like pseudokinase (MLKL). Tumor necrosis factors (TNFs) can activate both apoptosis and necroptosis. When TNF binds to TNF receptor 1, it initiates the trimerization of these receptors leading to the formation of complex 1. Complex 1 undergoes reshuffle and forms complex 2. In complex 2, fas-associated death domain (FADD) protein and RIP3 are recruited leading to MLKL activation [39]. After the formation of complex II, procaspase 8 is recruited by FADD and RIP3. Then RIP3 hires MLKLs and they go through self-oligomerization [40]. MLKLs interact with the N-terminal of phosphatidylinositol phosphate (PIP) in the plasma membrane of the dying cell. This interaction inserts MLKLs into the plasma membrane and forms pores to disrupt plasma membrane integrity [35,36] (Fig. 2B).
- **Pyroptosis:** Pyroptosis is a lytic cell death that includes some common features of both necroptosis and apoptosis [38,41–43]. Pyroptosis leads to inflammatory responses because of the release of cell components [44]. Cysteine-dependent aspartate specific protease (caspase) and gasdermin (GSDM) are two protein families that have the most essential roles in the pyroptosis pathway [38,45,46]. Caspases 1, 4, and 5 are identified to be involved in pyroptotic cell death in humans. GSDM family protein consists of diverse members that each have a particular function in different molecular patterns. The most important member of this family involved in pyroptosis is recognized to be gasdermin D (GSDMD) [33,35,41,42,47]. GSDMD protein contains an N-terminal domain (NTD) responsible for pore-forming activity in the plasma membrane of the dying cell to induce cytolysis [35,44,48]. Activation of pyroptosis is dependent on stimulation of a protein complex known as “Inflammasome”. Inflammasome consists of sensor proteins and adaptor proteins. Sensor proteins are known as pattern recognition receptors (PRRS) such as NOD-like receptors, the DNA receptor Absent in Melanoma 2 (AIM2), and pyrin receptor and adaptor proteins known as apoptosis-associated speck-like protein



(ASC) [35,45,49]. PRRs in inflammasome sense the damage-associated molecular patterns (DAMPs) (such as adenosine triphosphate (ATP) and pathogen-associated molecular pattern molecules (PAMPs) (including viral RNAs) and initiate the cell death process. Once the PRRs are triggered, caspase activity leads to GSDMD cleavage [50]. GSDMDs form structures in the plasma membrane of the dying cell that act as pores to disrupt the integrity of the cell membrane. Mitochondria are also able to trigger NLRP3 inflammasome by its reactive oxygen species (ROS) production and mitochondrial DNA release which act as DAMP for the cell. The release of mitochondrial DNA can be the result of viral infection, especially after sensing the viral RNAs in the host cell [51]. Based on the kind of caspase involved in cell death, pyroptosis can be divided into several groups. The most important pathways are known as “canonical and non-canonical pathways”. Caspase 1 is responsible for the canonical pathway and caspase 4 and 5 in humans initiate the non-canonical pathway [35,44,45,52]. In the non-canonical pathway, caspases 4 and 5 are not able to cleave GSDMD directly, so they initially stimulate the activation of caspase 1. Then, Caspase 1 cleaves GSDMDs which leads to pore-forming activity of GSDMDs [33]. GSDMD-N typically forms large oligomeric ring-shaped structures minutes after the initiation of full-length GSDMD cleavage by caspases [35,53]. The pore formation function of GSDMD causes non-selective ion flux and the release of cytosolic content such as interleukins (IL-1b and IL-18), ATP, high mobility group box 1 (HMGB1) [54], and immunogenic organelles contents such as mitochondrial DNA and cytC into intracellular space. These cytosolic contents act as DAMPs to other cells in order to give them a signal about the infection or unexpected condition [33]. Each oncogenic virus has adopted a specific mechanism by encoding oncoproteins in order to interfere with or disrupt the cell death pathways to control cell signaling (Fig. 2C). Here we have a quick recap on the most studied viruses including HPV, EBV, HCV, HBV, and KSHV, and their impacts on these three mentioned cell death pathways. The information related to cell death pathways differences and the oncoproteins activities are illustrated in Fig. 1 and more discussed in Table 3.



**Figure 2:** The three discussed cell death pathways including apoptosis, necroptosis, and pyroptosis differ at some points in their mechanisms and the molecules involved in their pathways. A) Apoptosis includes two pathways known as the intrinsic pathway and the extrinsic pathway. When the integrity of the mitochondrial outer membrane (MOM) is disrupted by internal stresses such as viral DNA integration into the nuclear DNA of the host cell, the release of proapoptotic factors into cytosol happens. This event is controlled by BID, Bcl-2 family protein. At first, the BID protein translocates to mitochondria. Then, BAK and BAX are activated, and the release of mitochondrial cytochrome c (cytC) can be observed. cytC cooperates in the formation of a platform named apoptosome by its caspase recruitment domain (CARD). Apoptosome induces the activation of initiator caspase 9 then, they activate the executioner caspases, especially caspase 3. This pathway is dependent on extracellular receptors known as death receptors (DR) such as tumor necrosis factor (TNF) superfamily (TNF receptor 1), apoptosis antigen 1, and death receptors 3, 4, and 5. When the specific ligands bind to their receptors, apoptosis is induced by the activation of caspases like the intrinsic pathway. In addition, increased levels of ROS lead to triggering mitochondrial dysfunction and initiating apoptosis by causing an imbalance between pro- and anti-apoptotic factors leads to apoptosis. B) Necroptosis is initiated by cytokines such as TNF when they bind to death receptors such as tumor necrosis factor receptor type 1-associated death domain protein (TRADD). This activation leads to receptor-interacting protein kinase 1/3 (RIP1/3) activation. A high level of RIP3 level prevents apoptotic cell death. Then, MLKL is activated by RIPs which results in necroptosis. Excessive ROS production drives necroptosis in cancer cells. Metformin enhances this process by increasing endogenous ROS and inhibiting antioxidant defenses, amplifying oxidative stress. Phosphorylation of RIPK1, RIPK3, and MLKL further promotes necroptosis, releasing DAMPs that activate the immune system against cancer cells. C) Pyroptotic cell death is primarily activated when DAMPs and PAMPs trigger the cells. Then, inflammasome formation occurs which is a protein complex and leads to caspase 1 activation. As the result of caspase 1 activation, GSDMD molecules are cleaved to have their N-terminal free and the maturation of interleukins is seen, respectively. The free GSDMD-N is responsible for the pore formation activity in the plasma membrane which leads to mature interleukins release and the inflammatory signs of pyroptosis. Moreover, reactive oxygen species (ROS) function as signaling molecules that trigger pyroptosis in endothelial cells. Elevated ROS levels can stimulate multiple intracellular pathways, resulting in inflammation and cell death. One primary mechanism involves the activation of the NLRP3 inflammasome, a crucial regulator of pyroptosis. The oncogenic viruses' impacts on each cell death pathway are mentioned in [Table 3](#)

## 5 Oncogenic Viruses Association with Cell Death Modes

- **HPV:** Oncogenic human papillomaviruses (HPVs) use E6 and E7 proteins in order to disrupt cellular regulation, resulting in cell proliferation. The E6 oncoprotein promotes p53 degradation through the ubiquitin-proteasome pathway, thus blocking apoptosis. E6 has also the ability to degrade the Bak protein independently of p53 [55–59]. Moreover, E7 targets the pRB protein and other apoptosis pathways like tumor necrosis factor (TNF- $\alpha$ ) and tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL) [60]. The E5 protein encoded by HPV downregulates Fas receptors, further inhibiting apoptosis [57,61]. On the contrary, the E2 protein can induce apoptosis via p53-dependent manner, but E6 and E7 counteract this signaling to promote viral persistence [62–66]. High-risk HPV (hrHPV) enables keratinocytes to resist necroptosis by reducing RIPK3 expression, allowing the virus to evade immune responses and facilitating lesion progression [66–68]. Proteins like sirtuin (SIRT1) also inhibit pyroptosis, contributing to persistence of HPV's and cervical cancer progression [69].
- **EBV:** EBV is capable of modulating apoptosis in order to ensure viral persistence and cell transformation. EBNA2 protein promotes cell survival by upregulating pro-survival proteins and downregulating pro-apoptotic members of apoptosis [70]. In addition, EBNA3A and EBNA3C work together to silence tumor suppressors resulting in inhibition of apoptosis [71,72]. LMP1 protein also activates NF- $\kappa$ B, upregulates anti-apoptotic proteins, and modulates caspases to enhance cell survival [73–75]. LMP2A inhibits transforming growth factor (TGF- $\beta$ )-related apoptosis, while viral BCL-2 homologs protect against apoptosis by binding pro-apoptotic proteins [76,77]. When the virus is in its lytic state, proteins such as BZLF1 and BRLF1 balance apoptosis to support viral replication [78]. EBV suppresses necroptosis as well via LMP1, which modulates RIPK3 to prevent necrosome formation [79–81]. It also evades pyroptosis, utilizing BRLF1 which blocks the inflammasome activation [82–84].
- **HBV:** As discussed earlier, the Hepatitis B virus encodes a protein known as HBx which has the most interference in cell death pathways. HBx blocks apoptosis in a p53-dependent and -independent manner, activating survival signals including NF- $\kappa$ B [85–88]. Moreover, elevated levels of RIPK3 protein in HBV-associated infection suggest a role in promoting necroptosis, although it needs to be studied more [89]. HBx also triggers pyroptosis through NLRP3 inflammasome activation, increasing inflammation and contributing to liver disease [90,91].
- **HCV:** Hepatitis C virus core protein is recognized to have dual roles in promoting and inhibiting apoptosis. This protein primarily activates the NF- $\kappa$ B pathway in order to inhibit apoptotic cell death, but also sensitizes hepatocytes to TNF and Fas ligand-induced apoptosis. Some other HCV proteins such as NS4A and NS3 are able to promote apoptosis through mitochondrial pathways, and cytotoxic T-cell responses further drive the death of infected hepatocytes [92]. It is identified that HCV also induces pyroptotic cell death, which is recognized to contribute to inflammation, liver fibrosis, and HCC, driven by NF- $\kappa$ B and ROS production [93,94].
- **KSHV:** Kaposi's Sarcoma-Associated Herpesvirus is capable of preventing apoptosis mainly via its vFlip protein encoded by its genome, which activates anti-apoptotic NF- $\kappa$ B pathways [95,96]. KSHV also suppresses pyroptosis through the SOX protein, which inhibits AIM2 inflammasome activation, and other viral proteins like PAN RNA and ORF63, preventing inflammasome activity [96].

**Table 3:** A summary of oncoprotein encoded by oncogenic viruses and their impacts on cell death pathways

Oncogenic virus	Oncoprotein	Interference with cell death and immune system	References
HPV	E5	• Inhibits apoptosis via Fas receptor downregulation	[55,58,59]
	E6	• Degrades p53 through the ubiquitin-proteasome pathway and prevent apoptosis	
	E7	• Disrupts pRb function and inhibits apoptosis-related pathways	
	EBNA2	• Upregulates pro-survival proteins (Bcl-2)	
EBV	EBNA3A	• Downregulates pro-apoptotic proteins (BAK and BAX)	[75,79,80,82,97 – 99]
	LMP1	• Suppresses necroptosis by inhibiting RIPK3	
	BHRF1	• Sequesters pro-apoptotic proteins	
	BRLF1 and miR-BART15	• Evades pyroptosis via BRLF1 and miR-BART15, inhibiting inflammasome activation	
HCV	Core Protein	• Activates NF-κB and sensitizes cells to TNF and Fas ligand-induced apoptosis	[93,100,101]
	NS4A and NS3	• Promote mitochondrial-mediated apoptosis	
HBV	HBx	• Inhibits apoptosis by activating PI3K-Akt and NF-κB pathways	[85,88]
	vFlip	• Triggers pyroptosis via NLRP3 inflammasome activation	
	LANA	• Activates anti-apoptotic NF-κB pathways	
KSHV	SOX	• Inhibits p53-mediated apoptosis	[98,102,103]
	K7	• Inhibits TNF-α and Fas-induced apoptosis	
		• Inhibits AIM2 inflammasome activation and suppresses pyroptosis	

## 6 Mitochondria, Cells' Power House Which Is Involved in Antiviral Responses

Mitochondria are an organelle in eukaryotic cells with two membranes and their own DNA (mtDNA) which are not dependent on the nucleolus in order to replicate [104,105]. Primarily, this organelle is recognized as the powerhouse of the cell which produces ATP, but also plays important roles in generating reactive oxygen species (ROS), cell signaling, and regulating innate immune responses [106]. However, mitochondria can play a dual role in viral tumorigenesis. They may either aid the viral invasion and tumor development by integrating viral proteins and affecting retrograde pathways, or they might help cease the infection by triggering appropriate immune responses and cell deaths [107]. Mitochondrial dysfunction, caused by factors like oxidative stress or inflammations, can disrupt processes such as cell metabolism, and cell proliferation [108–110]. Recently mitochondria have dragged too much attention and many studies have focused on mitochondria's role in different human diseases. Thus, researches lead to targeting mitochondrial proteins and pathways for drug discovery. Cancer cells rely on mitochondrial adaptation to their changing environment, which affects bioenergetics, susceptibility to cell death, regulation of oxidative stress, and signaling pathways. This correlation has been linked to cancer metabolism since the Warburg effect was discovered in 1956, representing that cancer cells prefer aerobic glycolysis, breaking down glucose into lactic acid, even in the presence of oxygen, rather than relying on full mitochondrial respiration [111].

ROS production is another important function of mitochondria which is associated with viral infections. The production of mitochondrial reactive oxygen species (mROS) primarily results from electron leakage in the electron transport chain (ETC). This process is strictly under control by some pathways such as the ROS scavenging system, comprising both enzymatic and non-enzymatic components. This system efficiently eliminates ROS, including mROS, and is collectively known as the protective enzyme system. Notably, when intracellular ROS levels rise, the mitochondrial antioxidant defense system works to reduce the cytotoxic effects induced by ROS. At low levels, mROS serve as signaling molecules involved in processes like immune response, apoptosis, and adaptation to hypoxia. Thus, controlled ROS levels can help combat pathogens and modulate immune responses and overproduction of mROS can overwhelm the antioxidant defense systems, leading to damage of mitochondrial DNA (mtDNA), proteins, and lipids [112]. For example, high ROS levels can lead to the oxidation of lipids, proteins, and DNA, contributing to genomic instability, which influences the condition of the viruses. So, it's pivotal for tumor cells to maintain ROS at levels that promote proliferation without causing toxicity, highlighting mitochondria's role in cellular adaptability and cancer development. ROS influences tyrosine phosphatases, which regulate carcinogenic signaling pathways involved in cancer cell migration and metastasis [113]. In addition to metabolic pathways and ROS production, mitochondria constantly undergo biogenesis including fission and fusion. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) and PTEN-induced kinase 1 (PINK1) are two of the identified members of the signalling pathways involved in mitochondrial biogenesis, while proteins such as SIRT1 and SIRT3 play critical roles in energy production and oxidative phosphorylation which are some of the targets of viruses [114,115]. Hence, viruses must be able to manipulate mitochondrial dynamics, metabolism, and ROS production in order to control innate immune signaling, affecting early immune responses. Mitochondria is involved in regulating innate immune responses, especially in viral infections with a specific pathway known as MAVS, which was discovered in 2005 [116].

MAVS is located on the outer mitochondrial membrane. Research in 2011 revealed that mitofusin proteins, including Mfn1, and Mfn2 which are involved in mitochondrial fusion and membrane potential interfere in the MAVS function and other innate immune responses such as interferon production [117–119]. Based on the type of viruses (RNA or DNA viruses), different pathways of detection and immune responses are initiated. For instance, the cGAS-STING pathway primarily senses DNA viruses but can also respond to RNA viruses, but the RIG-I-MDA5-MAVS pathway only detects RNA viruses. Finally, both pathways lead



to on NF- $\kappa$ B and IRF3, which regulate the production of type I interferon [120,121]. Then, interferons  $\alpha$  and  $\beta$  trigger the expression of interferon-stimulated genes (ISGs) through the JAK-STAT pathway, inhibiting viral replication in the host cells.

HTLV-1, EBV, HBV, HCV, and HPV are examples of viruses whose interactions with the mitochondria of their host cells have been under investigation. These viruses can manipulate and disrupt mitochondrial functions such as energy supply, calcium homeostasis, ROS production, and cell death to support their survival in the host cell and maintain their oncogenic potentials [120]. Here we discuss the most well-known oncogenic viruses that are involved in the disruption of mitochondrial function which also might interfere in the cell death pathways. Fig. 3 illustrates the involvement of oncogenic viruses in disrupting the normal function of mitochondria.

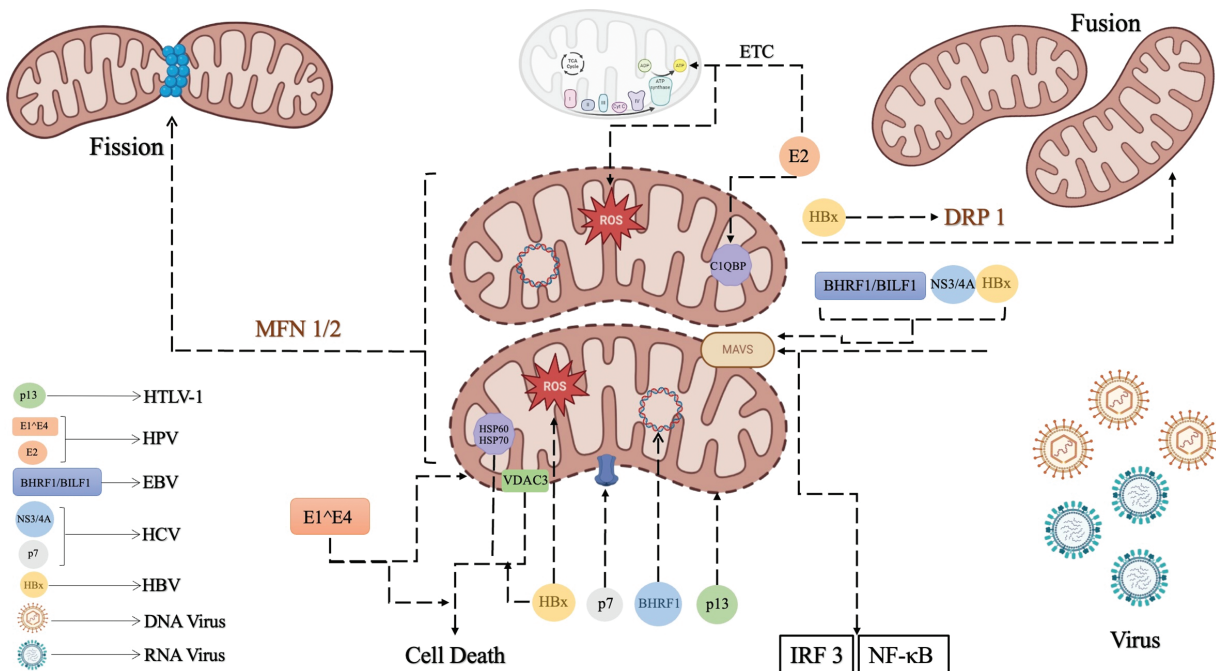
## 7 Oncogenic Viruses Association with Mitochondria

- **HTLV-1:** As discussed earlier, the genome of HTLV-1 encodes several nonstructural proteins, including Tax, Rex, p12, p13, p21Rex, p30/Tof, and HBZ [122]. For instance, Tax is responsible for driving transcription from the viral 5'-LTR (long terminal repeat) promoter critical for the expression of viral genes, Rex promotes the expression of incompletely spliced viral transcripts, including those coding for structural proteins of the virion [123,124]. The protein p13 is a smaller, 87-amino acid protein localized mainly to the inner mitochondrial membrane. Investigation indicates that when this protein is expressed in the HeLa-derived cell line Hltat, it alters mitochondrial morphology, leading to the formation of isolated clusters of rounded, fragmented mitochondria. So p13 might function as a viroporin, a class of small, hydrophobic viral proteins that can alter membrane permeability by forming ion channels or pores in membranes [122].
- **EBV:** EBV encodes several proteins to enhance its viral persistence such as BHRF1, BZLF1, BALF1, and LMP2A. BHRF1 disrupts mitochondrial antiviral signaling protein (MAVS) which inhibits IFN activation and innate immune responses [125]. BHRF1 achieves this by binding to Bcl-2 proteins and preventing the formation of Bax/Bak oligomers on the outer mitochondrial membrane (OMM). This action helps EBV-infected cells survive and supports viral persistence and replication [126–128]. BILF1 is also involved in MAVS and NLRP3 inflammasome activation to block inflammatory responses during reactivation. This allows the virus to suppress immune pathways and promote replication [129,130]. BHRF1 also disrupts mtDNA replication by moving mitochondrial single-stranded DNA-binding protein (mtSSB), which initiates mtDNA replication by a transcription-priming process, from the mitochondria to the nucleus, inhibiting mtDNA replication [131].
- **HCV:** The p7 protein encoded by HCV forms membrane- membrane depolarization, and interacts with interferon-inducible protein 6–16 (IFI6-16). HCV and mitochondria interaction can result in increased mitochondrial ROS production and viral replication [120]. The Hepatitis C virus employs NS3/4A protease and targets the key components of the host's antiviral defense. It specifically cleaves and dislocates MAVS and impairs IFN induction of the antiviral signaling in the host cell. MAVS localization is crucial for its antiviral activity and the disruption in its function by HCV's NS3/4A proves the importance of MAVS in antiviral immune responses [92,132].
- **HBV:** HBx is a multifunctional protein that can localize to various mitochondrial compartments, including the outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), and matrix. It has roles in cellular transcription, cell cycle regulation, calcium signaling, DNA repair, ROS regulation, and apoptosis. Generally, HBV can interact with mitochondria by some of its encoded specific proteins which result in different functions such as HBV polymerase (pol) that has a mitochondrial targeting signal and is localized to mitochondria during HBV replication. It inhibits innate immune responses

and interacts with cellular proteins involved in mitochondrial functions. HBx also interacts with MAVS disrupting MAVS-mediated antiviral signaling and attenuating IFN- $\beta$  induction [133]. Higher levels of mtDNA have also been observed in the peripheral blood of chronic HBV patients and are associated with liver cirrhosis and tumor size in HCC patients. Elevated mitochondrial superoxide and altered mitochondria are also reported. HBx-induced mitochondrial fragmentation and mitophagy are linked to viral persistence and cell survival. These processes also influence ROS generation and carcinogenesis. HBx induces mitochondrial ROS production and alters mtDNA, which can be linked to chronic HBV infection and HCC. Dynamin-related protein 1 (Drp1) is another protein in mitochondria which is essential for mitochondrial fission. HBx interacts with Drp1 and interfere with normal mitochondrial biogenesis [130]. HBx also interacts with various mitochondrial proteins such as Membrane Associated Ring-CH-Type Finger 5 (MARCH 5) which can regulate mitochondrial dynamics and decreases HBx-induced NF- $\kappa$ B and COX-2 activity, AIM2 protein reduction by HBx contributes to HCC metastasis through epithelial-mesenchymal transition (EMT), p53 and Bax, two pro-apoptotic proteins, which HBx interacts with and enhances apoptosis, voltage-dependent anion-selective channel protein 3 (VDAC3) which is an outer membrane mitochondrial protein that HBx binds to it and affects mitochondrial membrane potential and contributes to cell death [133,134], HSP60 and HSP70 (Heat Shock Proteins) that HBx interacts with and enhances apoptosis. Parvulins (Par14 and Par17) also interact with HBx, influencing its nuclear and mitochondrial localization and HBV replication [133]. HBx also induces mitochondrial accumulation of p53 and loss of mitochondrial membrane potential, which contributes to apoptotic cell death [135].

- **HPV:** The E2 protein encoded by HPV enhances mitochondrial biogenesis by up-regulating mitochondrial transcription factor A (TFAM)-interacting protein known as P32/gC1qR. C1QBP is a mitochondrial protein involved in regulating mitochondria and endoplasmic reticulum (ER) morphology and cell metabolism. HPV-18 E2 protein also can directly interact with the respiratory chain, leading to an increase in mitochondrial ROS production. The increase in ROS level is associated with the stabilization of hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) and enhanced glycolysis [136–138]. In addition, in cells lacking cyokeratin, HPV16 E1^E4 protein binds to mitochondria and induces detachment of mitochondria from microtubules, which results in the formation of a large mitochondrial cluster near the nucleus and leads to reduced mitochondrial membrane potential (MMP) and induces apoptotic cell death. E1^E4 also causes the collapse of the cyokeratin network in keratinocytes, which leads to the accumulation of E1^E4 in mitochondria. This clustering is associated with a severe reduction in mitochondrial membrane potential and increased apoptosis [122,139].





**Figure 3:** Mitochondria is known as the producer of the main source of energy in cells but is involved in other cellular signaling too. A) Mitochondria interferes with the antiviral activities by the MAVS pathway. When the viral RNA is sensed its receptors such as RIG-1 like receptors (RLRs), activate MAVS, located in the mitochondrial membrane. Then, MAVS triggers the activation of TANK binding kinase 1 (TBK1) and IRF3/7. This signaling pathway results in the stimulation of NF- $\kappa$ B to activate interferon production to respond to the viral invasion. B) Another important function of mitochondria is its biogenesis which includes fusion and fission. Mitochondrial fusion and fission are strictly controlled by proteins such as DRP1 and MFN 1/2, respectively. Oncogenic viruses have adopted some strategies to disrupt normal mitochondrial functions. Oncogenic viruses' mechanisms by which they interfere with balanced mitochondrial pathways are shown in this Fig. 3. 1) HTLV-1 impacts mitochondria with p13, a protein encoded by its genome. The p13 protein localizes to the inner mitochondrial membrane and functions as a viroporin, which disrupts mitochondrial morphology and membrane permeability by forming ion channels. 2) BHRF1 and BILF1 are oncoproteins encoded by EBV. On one hand, BHRF1 prevents antiviral responses by inhibiting MAVS protein function, helping EBV survival and replication. Moreover, BHRF1 blocks inflammatory responses and enhances viral persistence. On the other hand, BHRF1 interferes with mtDNA replication by relocating mtDNA replication proteins to the nucleus, which disrupts mtDNA processes. 3) HCV interferes with mitochondrial integrity with p7 protein. p7 forms ion channels in the membrane and induces mitochondrial damage, leading to a high level of ROS production, which results in enhanced viral replication. Additionally, its NS3/4A protease targets MAVS, impairing the host's antiviral response and weakening IFN signaling, which is crucial for the immune response. 4) HBx is a protein encoded by HBV which is recognized to disrupt MAVS, blocking antiviral signaling and finally, reducing IFN- $\beta$  production. It also induces mitochondrial fragmentation, promotes ROS production, and alters mitochondrial dynamics. 5) HPV associates with mitochondria with its E2 and E1^E4 proteins. The E2 protein is responsible for stimulating mitochondrial biogenesis by enhancing the expression of the protein P32/gC1qR, which normally regulates its morphology. It also interacts with the mitochondrial respiratory chain, increasing ROS production. Furthermore, the E1^E4 protein encoded by HPV induces mitochondrial clustering near the nucleus, reduces mitochondrial membrane potential, and leads to apoptosis. On the other hand, it is noteworthy to consider that in some cases elevated levels of mtROS can cause cellular oxidative stress, leading to mitochondrial dysfunction and impaired viral replication, especially HBV and HCV.

## 8 Conclusion

Based on the conducted research, the complex interactions between oncogenic viruses, mitochondria, and cell death, highlight the unneglectable role of mitochondria and cell death in viral pathogenesis and tumor development, conversely. Oncogenic viruses, such as HPV, EBV, HBV, and HCV can manipulate mitochondrial functions, including energy metabolism, ROS production, and cell death regulation, to establish persistent infections and evade immune responses. These viruses utilize their encoded oncoproteins to interfere with mitochondrial pathways, often suppressing apoptotic signals while promoting alternative cell death pathways like pyroptosis and necroptosis, depending on their needs and the favorable environment in their host cell. This ability to alter mitochondrial dynamics and functions contributes not only to viral survival but also to its oncogenesis potentials, as these processes lead to immune evasion, chronic inflammation, and genomic instability. Thus, targeting the mitochondria-cell death axis represents a promising therapeutic strategy against virus-induced cancers. Further research is crucial to uncover the detailed mechanisms of how specific viral proteins modulate mitochondrial function, which could lead to new treatments aimed at restoring normal cell death processes and preventing cancer progression. As discussed earlier in this review article, previous research has not directly focused on the possible influences that mitochondria and cell death pathways association might have on the oncogenicity of oncogenic viruses. Here we tried to mention and discuss the discovered associations between mitochondria, cell death pathways, and oncogenic viruses to propose a new hypothesis that these interactions might play a pivotal role in the progression of cancer induced by oncogenic viruses. Hence, this criterion might act as a promising target for personalized medicine and more advanced therapeutic targets to restrict cancer development.

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**Ethics Approval:** Not applicable.

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