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Review Paper
Ras/MAPK Pathway in Viral Associated Cancers

Fariba Rafiei[1], Hossein Goudarzi[2], Shaian Tavakolian[3], Mohammad Javad Roustaye Gourabi[2], Ebrahim Faghihloo[1, 2*]

1. Clinical Research Development Center, Shahid Modarres Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Department of Microbiology and Immunology, the Peter Doherty Institute for Infection Immunity, University of Melbourne, Melbourne, Australia.

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ABSTRACT

Viruses account for around 12 to 20 percent of cancers affecting humans globally, with seven viruses—hepatitis C virus (HCV), hepatitis B virus (HBV), human papillomavirus (HPV), Epstein-Barr virus (EBV), human T-cell leukemia virus type 1 (HTLV-1), Merkel cell polyomavirus (MCPyV), and Kaposi's sarcoma-associated herpesvirus (KSHV)—being directly implicated in tumorigenesis. These oncoviruses target the Ras/MAPK signaling pathway, which is a pivotal regulator of key cell processes such as growth, differentiation, and programmed cell death. Dysregulated activation of the Ras/MAPK pathway is a major driver of cancer development, progression, and sustenance. By hijacking this pathway, oncoviruses drive tumorigenesis through mechanisms such as upregulating growth factor receptors, inducing angiogenesis, and promoting invasion and metastasis. They also induce the MAPK/ERK pathway by downregulating tumor suppressors, creating a pro-oncogenic environment. For example, HPV infects cells by binding to heparan sulfate proteoglycans and entering via endocytosis. The integration of viral DNA into the host genome leads to the overexpression of E6 and E7 oncoproteins. These proteins degrade the tumor suppressors p53 and pRb, respectively, disrupting cellular safeguards and promoting tumorigenesis. Blocking the E6-p53 and E7-pRb complexes could be a promising strategy to suppress viral infections and halt cancer progression. Similarly, in HTLV-1-associated adult T-cell leukemia, the Tax1 oncoprotein increases Ras-GTP levels and ERK phosphorylation, promoting an anti-apoptotic state that facilitates viral replication. Targeting this pathway with agents like Ras farnesylcysteine mimetics has demonstrated potential in restoring apoptosis sensitivity. Therefore, understanding these mechanisms provides critical insights into therapeutic targets for virus-associated cancers. Further research into these interactions is essential for developing effective therapies to combat these malignancies.

*** Corresponding Author:**
Ebrahim Faghihloo, Associate Professor.
Address: *Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
Tel: *+98 (21) 23872556*
E-mail: *faghihloo@sbmu.ac.ir*

1. Context

Approximately 12 to 20 percent of global cancer cases are linked to viral infections, underscoring the significant role of oncoviruses in human malignancies [1]. Prominent among these are hepatitis C virus (HCV), hepatitis B virus (HBV), human papillomavirus (HPV), Epstein–Barr virus (EBV), human T-lymphotropic virus 1 (HTLV-1), Merkel cell polyomavirus (MCPyV), and Kaposi's sarcoma-associated herpes virus (KSHV) [2].

In humans, innate immune receptors, including membrane-bound receptors like Toll-like receptors (TLRs) and cytosolic sensors such as RIG-I-like receptors and DNA sensors, are essential for detecting viral genetic material throughout infection processes [3]. Viruses, however, have evolved various mechanisms. Typically, viruses with larger genomes possess a greater variety of immune evasion mechanisms that prolong viral replication and facilitate their spread [4]. Oncogenic viruses often employ mechanisms such as promoting genomic instability, enhancing cell proliferation, resisting apoptosis, interfering with DNA repair, and altering cell polarity. These processes are frequently accompanied by tactics that allow viruses to bypass the host's antiviral immune responses [5]. Furthermore, viruses may indirectly contribute to carcinogenesis through immunosuppression, induction of chronic inflammation, or prolonged stimulation of the immune system by viral antigens [5]. Proteins encoded by DNA viruses can also modulate host cell signaling pathways, influencing key cellular functions such as cell division, programmed cell death, and genomic stability [6]. As an illustration, EBV expresses the LMP1 protein, which mimics the activity of the CD40 receptor, activating critical signaling pathways in the host cell, including NF-κB, MAPK/ERK, and JAK/STAT pathways. This activation results in enhanced cell growth, suppressed programmed cell death, and disruption of the normal cell cycle. The consequence of these disruptions creates a favorable environment for oncogenesis and diseases such as Hodgkin lymphoma and nasopharyngeal carcinoma [7]. Clarifying the molecular signaling pathways of viral agents in human cells can have therapeutic implications [2].

These viruses have developed advanced mechanisms to hijack cellular signaling pathways, particularly the Ras/mitogen-activated protein kinase (MAPK) pathway, which is implicated in a significant proportion of human cancers [8]. The Ras/MAPK signaling pathway is essential for controlling critical cellular processes such as proliferation, apoptosis, and survival, and is activated by signals from cytokines, growth factors, and viral oncoproteins. Oncoviruses often exploit this pathway to disrupt normal cell cycle control, suppress programmed cell death, and enhance their replication and persistence within the host. These disruptions contribute significantly to the development of cancer [9].

For instance, EBV utilizes its oncoprotein LMP1 to upregulate the Ras/MAPK pathway, resulting in elevated expression of vascular endothelial growth factor (VEGF), fibronectin, and Gas6—a ligand for receptor tyrosine kinases [10]. This activity not only stimulates angiogenesis but also reinforces the activation of signaling pathways, thereby accelerating tumor progression. In a similar manner, Kaposi's sarcoma-associated herpesvirus (KSHV) virions interact with integrin receptors, leading to the stimulation of extracellular signal-regulated kinase (ERK) and the upregulation of activator protein 1 (AP-1), both of which contribute to increased cell proliferation [11]. On the other hand, the HBV oncoprotein HBx triggers the Ras/MAPK signaling cascade, upregulating transcription factors such as AP-1 [12], NF-κB [13], as well as matrix metalloproteinase-9 (MMP-9) [14], which are critical for metastasis (Table 1).

Oncoviruses further manipulate the Ras/MAPK pathway by targeting its endogenous inhibitors. For instance, the HBV X protein (HBx) suppresses the expression of dual specificity phosphatase 1 (DUSP1), a key negative regulator of ERK signaling. This downregulation results in prolonged activation of the pathway, thereby promoting oncogenic transformation and tumor progression [15]. Similarly, KSHV encodes miR-K12-11, which silences DUSP1, creating a pro-tumorigenic environment [16]. Meanwhile, HPV E6 disrupts cellular safeguards by suppressing pRb, further amplifying oncogenic signaling cascades [17]. Targeting the Ras/MAPK pathway has emerged as a potentially effective therapeutic approach for the treatment of virus-induced cancers. For instance, the MEK1/2 inhibitor trametinib has been demonstrated to reduce the expression of viral oncogenes such as E6 and E7 mRNA levels, diminish viral DNA levels, and reduce the expression of the L1 capsid protein, collectively contributing to marked tumor regression [18]. Similarly, microRNA-101 regulates cell proliferation and apoptosis by directly targeting MEK1 within the Ras/RAF/MAPK pathway [19]. Inhibition of this pathway disrupts key survival mechanisms in virus-infected cells. For instance, blocking the VEGF receptor (KDR) leads to degradation of the viral oncoprotein Tax in HTLV-1-infected cells, impairs NF-κB activation, and reduces viral transmission [20]. Additionally, combining ribavirin with interferon reduces ERK phosphorylation, effectively suppressing viral RNA and protein levels [21].

Table 1. Mechanisms of oncogenic viral interactions with the Ras/MAPK signaling pathway

Oncovirus	Oncoprotein (s)	Interaction with Ras/MAPK Pathway	Clinical Outcome	Ref.
HPV	E6, E7	E6 upregulates Nurr1, activating MEK/ERK to suppress p21/p27 and upregulate MMP9 and KLF4.	Cell proliferation, metastasis, self-renewal	[22]
		E6 activates MEK/ERK to enhance translation of VEGF, cyclin D1, and ODC1 mediated by EIF4E.	Cell proliferation, angiogenesis	[23]
		E7 binds to pRb, inactivating it and elevating RRM2 transcription, leading to ROS production and ERK1/2/HIF-1α/VEGF activation.	Angiogenesis	[17]
		E7 activates CK2, leading to ERK activation and inhibition of Rho-GTP, promoting actin stress fiber formation.	Cell proliferation	[24]
		E6 and E7 activate ERK1/2/HIF-1α/VEGF pathway.	Angiogenesis	[25]
		E6 and E7 increase COX-2 expression via EGFR/Ras/MAPK/AP1.	Angiogenesis	[26]
		E6 and E7 upregulate SNHG12, influencing ERK/Slug pathway to reduce E-cadherin.	EMT	[27]
		E6 and E7 upregulate EGFR, activating EGFR/ERK pathway and NF-κB to repress E-cadherin.	EMT	[28]
EBV	LMP1, LMP2A	LMP1 activates Ras/MAPK, upregulating VEGF, fibronectin, and Gas6.	Angiogenesis, to stimulate RTK/ERK pathway	[10]
		LMP1 activates STAT3 via MEK1/ERK1/2, inducing VEGF transcription.	Angiogenesis	[29]
		LMP1 stimulates AP-1, NF-κB, and SRF via ERK1/2, resulting in expression of VEGF, MMP9, and COX-2, as well as Bcl-2 and A20	Angiogenesis, metastasis, anti-apoptosis	[30]
		LMP1 upregulates ERK phosphorylation during G1/S phase, enhancing microtubule polymerization.	Cell proliferation, metastasis	[31]
		LMP1 inhibits LKB1/AMPK via MEK/ERK.	Cell proliferation	[32]
		LMP2A phosphorylates c-Jun via ERK, increasing MMP9 expression.	Metastasis	[33]
		LMP2A phosphorylates Bim via ERK leading to proteasome-dependent degradation of Bim.	Anti-apoptosis	[34]
		LMP2A enhances Sp1 phosphorylation via ERK, increasing UGDH expression.	Metastasis	[35]
		LMP2A suppresses AHR via ERK phosphorylation	Cell proliferation	[36]
		LMP2A induces ERK phosphorylation, activating DNMT3a, resulting in AQP3 suppression.	Metastasis	[37]
KSHV	VGPCR, vIL6, gB, gpK8.1A, vPK	VGPCR activates MAPK via Ras phosphorylation, inducing HIF-1α and VEGF.	Angiogenesis	[38]
		GPCR and vIL6 upregulate Ang2 via Ras/Raf-1/MEK/ERK.	Angiogenesis	[39]
		KSHV suppresses DUSP1 via miR-K12-11, increasing VEGF, IL-6, and IL-8.	Angiogenesis, inflammation	[16]
		gB and gpK8.1A activate PI-3K/PKCζ/MEK/ERK, increasing transcription of VEGF, ICAM1, and transcription factors (c-Jun, STAT1α, etc.).	Angiogenesis, inflammation, anti-apoptosis, cell proliferation	[40]
		vPK phosphorylates ERK1/2, regulating ATF2, ATF3, c-Jun, c-Myc, IL-8, and Bcl-2.	Inflammation, anti-apoptosis	[41]
HBV	HBx	HBx represses miR-148a, activating AKT/ERK pathways and upregulating cyclin D1 and c-myc.	Cell proliferation	[42]
		HBx phosphorylates GSK-3β via ERK, stabilizing β-catenin and upregulating c-myc and cyclin D1.	Cell proliferation	[43]
		HBx activates Ras/Raf/MAPK, phosphorylating Elk-1 and CREB, resulting in cyclin A expression.	Cell proliferation	[44]
		HBx activates ERK1/2, upregulating FOXM1 and promoting MMP-7, RhoC, and ROCK1 expression.	Metastasis	[45]
		HBx downregulates HNF4α via ERK.	Cell proliferation	[46]
		HBx activates Notch1, suppressing DUSP1 and enhancing ERK activity.	Anti-apoptosis, cell proliferation	[15]
		HBx stimulates SATB1 via ERK and MAPK p38	Metastasis	[47]

Oncovirus	Oncoprotein (s)	Interaction with Ras/MAPK Pathway	Clinical Outcome	Ref.
HCV	Core, NS5A, NS3, E2	HCV activates ERK, upregulating c-Fos, c-Jun, and cyclin D1.	Cell proliferation	[48]
		NS5A suppresses AP-1 via MAPK/ERK downregulation.	Anti-apoptosis	[49]
		Core protein activates Raf-1, triggering HB-EGF expression and anti-apoptotic pathways Akt and IKK.	Anti-apoptosis	[50]
		NS3 upregulates NF-κB, COX-2, and MMP-9 via ERK1/2.	Angiogenesis, metastasis	[51]
		E2 activates MAPK/ERK via CD81 and LDLR, enhancing ATF-2.	Cell proliferation	[52]
		HCV reduces BRD7 expression, facilitating Ras/Raf/MEK/ERK signaling.	Anti-apoptosis, cell proliferation	[53]
		HCV binds to EGFR and induces expression of AREG, IL8, CCL20, IGFBP1, VNN3	Angiogenesis, inflammation	[54]
HTLV	Tax, p12I	Tax increases GTP-Ras, activating Ras/Raf-1/MEK/ERK/CREB.	Anti-apoptosis	[55]
		Tax interacts with Erbin, activating Ras/Raf/MEK/ERK.	Anti-apoptosis, cell proliferation	[56]
		p12I increases Ras/MAPK and AP-1 phosphorylation.	Cell proliferation	[57]
MCPyV	LT, sT, MT	LT and sT stimulate expression of IL-33 and its receptors, activating MAPK/ERK1/2 and transcription factors (AP-1, ATF/CREB, c-MYC).	Anti-apoptosis, cell proliferation	[58]
		MT activates ERK via Ras/Raf, upregulating BRAF.	Cell proliferation	[59]

These findings highlight the critical role of the Ras/MAPK pathway in virus-induced oncogenesis and underscore the therapeutic potential of its inhibition. By targeting this pathway, researchers can develop innovative strategies to disrupt viral persistence and prevent tumor progression.

1.2. Evidence acquisition

In this review, we highlight the complex interactions between oncoviruses and the Ras/MAPK signal transduction pathway. A primary mechanism by which oncoviruses modulate this pathway is the upregulation of the epidermal growth factor receptor (EGFR) or its associated ligands [60]. This initial activation initiates a signaling pathway leading to the phosphorylation and subsequent activation of crucial transcription factors, including NF-κB, AP-1, CREB (cAMP response element-binding protein), and HIF-1α (hypoxia-inducible factor 1-alpha) [60]. Activation of these factors has multiple biological consequences, including increased cell proliferation, elevated inflammatory responses, induction of angiogenesis, facilitation of metastasis, and suppression of adhesion-related proteins like cadherins [60].

In addition to activating the Ras/MAPK pathway, oncoviruses can also inhibit the activity of tumor suppressors that normally regulate this pathway [15]. By silencing these tumor suppressors, oncoviruses can stabilize the Ras pathway, thereby promoting cancer development and progression [15]. Certain oncoviruses can interact with other key cellular pathways that intersect with the Ras/Raf/MEK/ERK pathway. For example, HBV is capable of initiating the Notch signaling pathway, resulting in the downregulation of ERK1/2 repressor DUSP1 expression and maintaining the integrity of Ras/MAPK signaling [15].

In conclusion, oncoviruses have developed sophisticated strategies to manipulate the Ras/MAPK pathway, thereby promoting cancer development. Clarifying the underlying molecular processes of oncovirus-host interactions is essential for designing effective anticancer treatments. Due to the importance of this issue, the present review summarized the relationship between some viral agents (HPV, EBV, KSHV, HBV, HCV, HTLV, and MCPyV) and the Ras/MAPK signaling pathway in different kinds of malignancies.

2. Ras/MAPK Pathway

Cell signaling is a sophisticated communication system that enables cells to interact with their neighboring cells and extracellular environment [61]. Cells detect environmental changes through glycoprotein or glycolipid receptors on their plasma membranes. When a ligand binds to its receptor, it triggers signal transduction, a series of intracellular processes resulting in specific cellular responses. This process regulates cell proliferation, differentiation, regeneration, homeostasis, and immune function [61].

A key player in cell signaling is the Ras/MAPK pathway, which translates extracellular stimuli into diverse intracellular responses. The Ras/Raf/MAPK pathway, activated by stimuli like cytokines, hormones, growth factors, pathogens, and stress, regulates critical processes such as transcriptional regulation, cellular viability, programmed cell death, and differentiation [61]. Signal transmission in this pathway relies on intermolecular signaling, transmitting cues from the membrane to the nucleus [61]. Activation of the Ras/MAPK pathway begins with stimulation of receptors on the plasma membrane, initiating a phosphorylation sequence that includes Ras, Raf, MEK1/2, and ERK proteins [62]. Ras functions as the central regulator of this signaling cascade, becoming activated upon binding to and receiving signals from membrane receptors such as tyrosine kinase receptors, cytokine receptors, or G protein-coupled receptors [63]. Upon engagement of membrane-bound receptors, the RAS protein undergoes a structural alteration via GTP substitution for GDP and becomes active. Raf activation requires direct interaction with GTP-bound RAS, which facilitates dephosphorylation and dimerization of Raf proteins, leading to the conformational changes necessary for Raf activation [63, 64]. In addition, the function of Raf proteins is tightly regulated by 14-3-3 proteins. Phosphorylation of residues S259 and S621 of Raf provides binding sites for the 14-3-3 dimer, which can maintain Raf in an inactive state through intramolecular interactions [63]. The 14-3-3 dimer can also stabilize Raf dimerization and sustain its functional activity [63]. Raf phosphorylates MEK1/2, initiating MEK1/2 activity, subsequently leading to ERK1/2 activation. The activated ERK1/2 (p-ERK1/2) performs functions within cytosolic and nuclear compartments, where it regulates transcription factors that control gene expression involved in various cellular processes [62]. Certain oncoviruses can modulate the Ras/MAPK signaling pathway by influencing these MAPKs. By altering the activity of MAPKs, these oncoviruses can impact the duration and intensity of Ras/MAPK signaling [64]. Beyond direct engagement, the Ras-MAPK signaling pathway can also be activated through interactions with other intracellular signaling pathways and act as an intermediary in the transduction of mitogenic signals [64]. In this regard, some oncoviruses are able to regulate and modulate this signaling pathway by interfering with key cellular pathways that intersect with the Ras/Raf/MEK/ERK axis [15]. These interactions may lead to targeted initiation or inhibition of molecular communication routes, ultimately influencing cell proliferation, survival, and other tumorigenic processes.

3. Result

3.1. HPV

HPV is among the most prevalent viruses infecting humans, with over 200 genotypes classified. These genotypes are categorized into two groups based on their cancer-causing potential: low-risk (LR) and high-risk (HR). LR types primarily lead to benign conditions such as genital warts, whereas high-risk types—most notably HPV-16 and HPV-18— are firmly associated with the onset of multiple malignancies, particularly cervical, genital, and head and neck cancers. Globally, HR HPVs are estimated to cause about 5% of all cancers, including over 90% of cervical cancer cases, underscoring their significant public health impact [65, 66]. Its oncogenicity primarily arises from the functional roles of E6 and E7, its principal oncoproteins. These proteins disrupt the cell cycle and ultimately lead to uncontrolled cell growth by degrading tumor suppressors such as p53 and pRb [65, 67]. The HPV infection process begins with initial attachment to host cell membrane proteoglycans enriched in heparan sulfate and then entry into the cell via clathrin- or caveolae-mediated endocytosis. A critical step in HPV-associated carcinogenesis is the incorporation of viral genetic material into the cellular chromosomal framework, which leads to the stabilization and increased expression of the E6 and E7 oncogenes [68]. These oncoproteins could significantly influence tumor onset and progression through modulation of the Ras-MAPK cascade.

E6 oncoprotein plays a pivotal role in cancer progression, particularly through its induction of MEK-ERK pathway signaling. This pathway, once activated, stimulates the translation initiation factor eIF4E, which enhances the synthesis of proteins critical for tumorigenesis. These proteins include VEGFA, which promotes angiogenesis; cyclin D1, which drives cell cycle progression; and ornithine decarboxylase (ODC1), which supports cellular growth and metabolism [23]. In NSCLC cells, E6 further facilitates tumor growth by inducing the accumulation of HIF-1α [69]. This induction leads to the upregulation of angiogenesis-stimulating agents, including VEGF and IL-8 via the ERK1/2 pathway [69]. The resulting angiogenesis provides essential nutrients for tumor expansion, while the associated chronic inflammation creates a microenvironment conducive to cancer progression [69]. Targeting HIF-1α, VEGF, and the VEGF receptor is a promising strategy for HPV-associated cancers, as it restricts tumor nutrient supply [70]. Notably, VEGF itself can upregulate growth factor receptors, which are

key activators of the RAS/MAPK pathway, potentially amplifying its oncogenic effects [71]. This highlights the importance of its inhibition in HPV infections.

E6 oncoprotein upregulates Nurr1, which activates the MEK/ERK signaling pathway, driving key oncogenic processes [22]. This pathway suppresses cell cycle inhibitors p21 and p27, promoting proliferation, and upregulates MMP9 to enhance metastasis through extracellular matrix degradation. Additionally, ERK activation induces Kruppel-like factor 4 (KLF4), boosting cellular self-renewal [22]. Collectively, these mechanisms facilitate anchorage-independent growth, migration, invasion, and tumor progression [22, 72]. Pharmacological blocking of MEK and ERK signaling offers a plausible intervention to curb unregulated cell division, downregulate oncogenic drivers, and manage HPV-related malignancies. A recent study using a mouse model demonstrated that MEK inhibitors, in particular, can be highly effective [18]. The MEK inhibitor reduced HPV transmission by suppressing viral replication and downregulating primary viral gene transcription [18]. This highlights the pivotal role of the role of MEK-ERK signaling in directing the transcription of HPV oncogenes and replication of viral DNA [18].

E7 is another key player in cancer progression, contributing through multiple mechanisms. One of its actions involves binding to and inactivating the retinoblastoma protein (pRb), a crucial regulator that restricts tumorigenic progression [17]. This inactivation leads to the upregulation of ribonucleotide reductase regulatory subunit M2 (RRM2), which increases the production of reactive oxygen species (ROS) [17]. These ROS subsequently activate multiple signaling pathways, including ERK1/2, HIF-1α, and VEGF, thereby facilitating tumor growth, angiogenesis, and cell survival [17]. Blocking the E7-pRb complex could be a promising strategy to suppress viral infections and halt cancer progression [66, 73]. Although LR HPV6-like particles activate the Ras/MAPK pathway through β4 integrin binding, LR HPV E7, despite its high-affinity binding to pRb similar to HR HPV E7, cannot transform primary cells or degrade pRb, highlighting the limited oncogenic potential of LR HPV compared to HR HPV [66, 73]. This functional difference underscores the limited oncogenic potential of LR HPV compared to HR HPV.

E7 further drives cancer progression by activating casein kinase 2 (CK2), a potent suppressor of apoptosis [24]. CK2 amplifies ERK signaling, causing disassembly of actin filament structures —cytoskeletal structures crucial for maintaining cell shape and adhesion [24]. By preventing the accumulation of Rho-GTP—a critical regulator of actin cytoskeleton organization—the E7 oncoprotein facilitates unchecked cell proliferation and is critically involved in reprogramming infected cellular states [24]. Inhibition of CK2 has been identified as a viable approach for antiviral intervention, with the potential to disrupt key signaling pathways essential for viral persistence and oncogenic progression [74].

Both E6 and E7 play pivotal roles in driving cancer progression through shared and complementary mechanisms. In cervical cancer cells, they collaboratively activate the ERK1/2–HIF-1α–VEGF signaling axis, promoting increased neovascularization and cellular expansion [25]. Moreover, both oncoproteins promote the production of EGFR ligands, which in turn activate the Ras/MAPK/AP-1 intracellular communication relay and induce the expression of cyclooxygenase-2 (COX-2) [26]. This process increases prostaglandin levels, further promoting angiogenesis [26]. Moreover, E6 and E7 work together to downregulate E-cadherin, thereby enhancing cell migration and invasion. They achieve this through elevating *EGFR* gene expression and triggering the ERK–Slug pathway [27]. Specifically, HPV16 E6 and E7 are capable of inducing SNHG12, a regulatory lncRNA that is highly expressed in tumors and detectable at all stages of tumor development [27]. SNHG12 enhances the expression of Slug, a transcriptional regulator containing zinc-binding motifs that downregulates E-cadherin, thereby promoting cell migration, invasion, and epithelial-mesenchymal transition (EMT) [27]. Additionally, via stimulation of the EGFR–ERK signal transduction axis, these oncoproteins increase the expression of pirin, which subsequently activates NF-κB. Such pathway activation triggers the upregulation of regulatory transcription proteins that suppress E-cadherin expression (Figure 1) [28]. Notably, EGFR displays elevated expression levels in almost 90% of cases of head and neck squamous cell carcinoma (HNSCC), identifying it as a critical therapeutic target. Cetuximab, an anti-EGFR monoclonal therapeutic agent presently utilized in managing relapsed and disseminated HNSCC, and preclinical data indicate that EGFR inhibition enhances tumor sensitivity to radiotherapy [66]. Furthermore, targeting the transcription factor AP-1, a key driver of angiogenesis and tumorigenesis, presents an additional strategy for suppressing tumor growth [75].

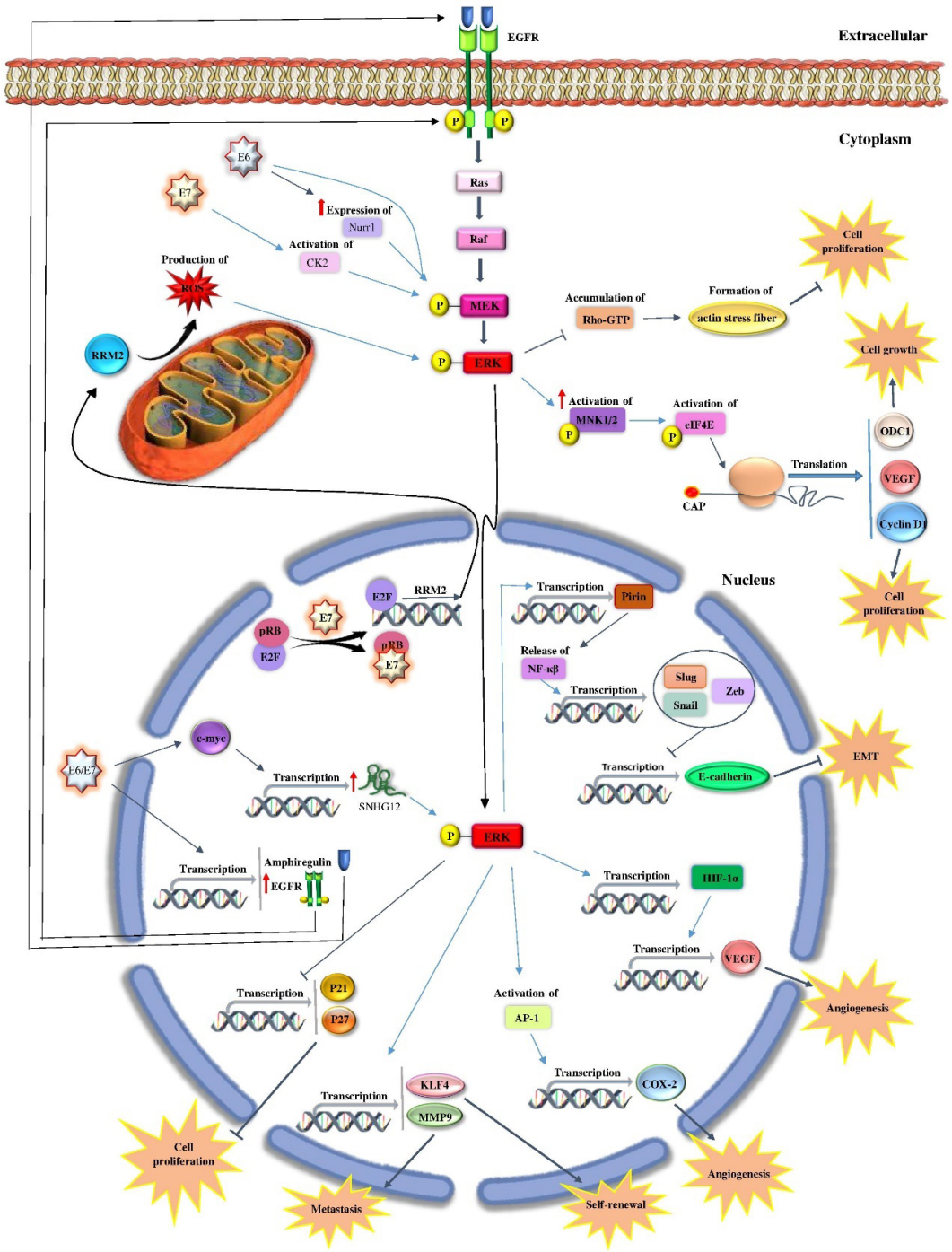

Figure 1. Schematic model of the HPV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: HPV oncoproteins E6 and E7 drive cancer progression by hijacking cellular signaling pathways. E6- and E7 -mediated amphiregulin production activates the EGFR→Ras→MAPK→AP-1→COX-2 pathway, enhancing proliferation and inflammation. E6 and E7 activate the transcription factor c-Myc and modulate SNHG12 and Slug expression in malignancies, downregulating E-cadherin. E6 and E7 also upregulate the expression of EGFR and induce EGFR→MEK→ERK→PIR →NF-κB→Snail, ZEB, and Slug pathway, which ultimately leads to EMT. By binding to pRb, the E7 oncoprotein induces ROS production, activating ERK→HIF-1α→VEGF pathway, promoting angiogenesis. E7 induces Rho-GTP accumulation and cell proliferation by activating the CK2→MEK→ERK pathway. E6 triggers Nurr1→MEK→ERK cascade by up-regulating Nurr1 expression. This cascade suppresses p21 and p27 and upregulates MMP9 (metastasis) and KLF4 (stemness). E6 also stimulates the MEK→ERK→MNK1/MNK2→eIF4E pathway, which increases the translation of oncoproteins (Cyclin D1→proliferation; ODC1→growth; VEGFA→angiogenesis).

Overall, within HPV-related malignancies, E6 and E7 viral oncoproteins can stimulate the RAS/MAPK pathway, inducing HIF-1α and VEGF expression, which play key roles in angiogenesis and nutrient supply for tumor growth. Additionally, the upregulation of EGFR by these oncoproteins further promotes angiogenesis and metastasis. Studies have identified various proteins involved in this signaling cascade, such as HIF-1α, VEGF, VEGF receptor, MEK/ERK, CK2, and EGFR, as potential therapeutic targets, with ERK inhibition being particularly effective.

3.2. EBV

As a member of the herpesvirus family, EBV contains a linear double-stranded DNA genome that becomes circular after infecting the host cell [75]. There are two different EBV types (EBV1 and EBV2) according to differences in genetic sequences, and studies have reported that EBV1 is more common among patients suffering from various malignancies including Burkitt lymphoma, Hodgkin lymphoma, B-cell lymphoproliferative disorders, and many other kinds of cancers [76]. This virus possesses oncoproteins such as LMP1 and LMP2, which are implicated in accelerating cancer progression. It is estimated that EBV infections contribute to approximately 200,000 new cases of cancer annually [75].

Studies have demonstrated that latent membrane protein 1 (LMP1) encoded by EBV, can activate the Ras/MAPK signaling pathway in nasopharyngeal epithelial cells. This activation results in the upregulation of VEGF, fibronectin, and growth arrest-specific 6 (Gas6), which serves as a signaling ligand for tyrosine kinase receptors —all of which are involved in key processes such as angiogenesis, cell adhesion, and cell survival [10]. Increased levels of VEGF stimulate angiogenesis, allowing for efficient oxygen and nutrient supply to proliferating tissue and neoplastic growths [10]. In addition, the LMP1 protein induces *VEGF* gene transcription and thus enhances angiogenesis through complementary signaling pathways, including activation of STAT3 via the MEK1/ERK1/2 pathway [29]. Studies have shown that nasopharyngeal carcinoma (NPC) tumors lacking LMP1 protein expression have lower lymphoid cell infiltration than LMP1-positive tumors [77]. In a study published in 2023, a novel drug called an Affibody molecule was introduced that suppresses the MEK1/2–p90RSK branch of the Ras–MAPK pathway in malignant nasopharyngeal cells through selective interaction with the C-terminal domain of the LMP1 protein. This inhibition leads to a decrease in the expression of angiogenic factors such as VEGF and Gas6, ultimately suppressing neoplastic cell expansion and replication. This therapeutic approach, by specifically targeting EBV proteins, has significant potential for the targeted treatment of EBV-associated nasopharyngeal cancer [78]. In phenotypic skin transgenic tissue, LMP1 stimulates AP-1, NFκB, and serum response factor (SRF) through ERK1/2. These transcriptional regulators contribute to the modulation of blood vessel formation, tissue infiltration, and metastatic progression [30]. In a study conducted by Charalambous et al., mouse models expressing the Cao strain of EBV LMP1 protein in the host epithelium were utilized. The findings revealed that activation of the Ras/MAPK signaling pathway significantly influenced the upregulation of molecules promoting angiogenesis—including VEGF, MMP-9, and COX-2—as well as genes that inhibit programmed cell death, including Bcl-2 and A20. These results underscore the critical role of the Ras/MAPK pathway in modulating angiogenesis and promoting the survival of EBV-infected cells [30]. A study by Fukuda et al. further emphasized the involvement of LMP1 in promoting angiogenesis. Their research demonstrated that LMP1-mediated activation of the NF-κB signaling pathway in the GT38 gastric epithelial cell line led to increased expression of transforming growth factor-β1 (TGF-β1), thereby enhancing the proliferation of EBV-infected cells [79]. This growth promotion is directly linked to the Ras/MAPK signaling [79]. LMP1 can activate ERK1/2 phosphorylation through various mechanisms in numerous malignancies. For instance, in nasopharyngeal cancer cells, LMP1 induces overexpression of ERK1/2, leading to the phosphorylation of histone H3 and increased cell proliferation [80]. Additionally, LMP1 influences the protein OP18/stathmin, which is involved in cell cycle processes [31]. By upregulating ERK phosphorylation during the G1/S phase, LMP1 enhances the interaction between ERK and OP18/stathmin, promoting microtubule polymerization and subsequent cell proliferation [31]. LMP1 also contributes to enhanced cell proliferation by modulating cellular energy metabolism. Specifically, stimulation of the MEK/ERK pathway via the C-terminal activation region 1 (CTAR1) domain of LMP1 has been shown to inhibit the liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) pathway [32]. This inhibition leads to the inactivation of LKB1 and a resulting reduction in AMPK phosphorylation levels and its downstream substrates. Since AMPK is a central regulator of cellular bioenergetic balance, proliferation, and epithelial cell transformation, its suppression by LMP1 supports oncogenic processes in EBV-infected cells [32].

Beyond LMP1, the LMP2A protein is capable of modulating the Ras–MAPK signaling cascade, resulting in the phosphorylation of c-Jun which can cause transformation and carcinogenesis, and it is promoted through ERK signaling [33]. To counteract these effects, MEK/ERK inhibitors such as PD98059 and U0126 could be useful. These drugs inhibit the phosphorylation of ERK by inhibiting MEK1/2 kinases, thereby attenuating the functional activity of c-Jun. By reducing c-Jun activity, oncogenic processes are inhibited and cancer cell growth is reduced. Therefore, inhibition of this pathway could be effective as a targeted therapy for cancers associated with the EBV LMP2A protein [81].

Similar to the effects of LMP1, LMP2A increases the transcriptional upregulation of MMP9, but via stimulation of the ERK1/2 and Fra-1-associated molecular pathway [82]. LMP2A also possesses anti-apoptotic activity since it phosphorylates Bim (an anoikis inducer) via ERK, leading to proteasome-dependent degradation of Bim and preventing apoptosis [34]. Furthermore, LMP2 is critically involved in promoting cellular replication by enhancing the phosphorylation of the Sp1 transcription factor via the ERK pathway [35]. This phosphorylation event leads to increased expression of the UGDH enzyme [35]. Consequently, elevated levels of UDP-glucuronate are produced, providing more glucuronoconjugates and glycosaminoglycan synthesis, which are crucial for cell proliferation and metastasis [35].

The role of the aryl hydrocarbon receptor (AHR) in cancer remains controversial. While elevated AHR expression has been linked to tumor progression in certain cancer types, other studies have proposed potential tumor-suppressive functions for this signaling pathway [36]. In a study by Jiang Wei and colleagues focusing on gastric carcinoma linked to EBV infection, it was demonstrated that the viral protein LMP2A suppresses AHR pathway activation by downregulating AHR expression and inducing ERK phosphorylation [36]. This evidence implies a potential involvement of LMP2A in carcinogenesis through modulation of host cellular signaling pathways [37]. Further supporting this, another study investigating the impact of LMP2A on the ERK pathway in gastric carcinoma found that LMP2A-induced ERK phosphorylation enhances transcription of DNA methyltransferase 3A (DNMT3A). This upregulation leads to increased methylation of CpG-rich domains within the promoter region of the aquaporin 3 (AQP3) gen—a transmembrane channel protein associated with tumor progression and metastatic dissemination—resulting in its transcriptional silencing in EBV-associated gastric carcinoma (Figure 2) [37].

Overall, EBV contains oncoproteins LMP1 and LMP2, which are involved in the progression of cancers. This virus is particularly prevalent in patients with lymphomas and various cancers. LMP1 activates the Ras/MAPK pathway, increasing vascular-promoting elements including VEGF and facilitating neoplastic expansion. LMP2A, like LMP1, increases MMP9 and prevents apoptosis. These proteins play a critical role in cellular propagation and oncogenic progression. In addition, LMP2A can suppress the AHR pathway. In EBV-related therapies, MEK/ERK inhibitors such as PD98059 and U0126 inhibit LMP2A-induced cancer cell growth by reducing ERK activity. Also, an Affibody molecule, introduced in 2023, inhibits the Ras/MAPK pathway by binding to the LMP1 protein and reduces the production of pro-vascularization mediators like VEGF, contributing to therapeutic efficacy against EBV-related neoplasms.

3.3. KSHV

Human herpesvirus 8 (HHV-8), commonly known as Kaposi's sarcoma-associated herpesvirus (KSHV), belongs to the Gammaherpesviridae subfamily and is recognized as the cause of multiple human malignancies, such as Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman disease, and B-cell neoplasms associated with KSHV [83]. Like other cancer-causing viruses, KSHV contributes to tumor development by producing viral oncoproteins that stimulate pro-angiogenic and pro-inflammatory signaling molecules [83]. The virus's disease-causing mechanism involves proteins produced throughout both lytic replication and latent infection phases. Furthermore, genes active during latency—such as vIL-6 and various viral microRNAs— are pivotal in initiating and promoting tumorigenesis [83].

One such regulatory molecule is the KSHV-encoded viral G protein-coupled receptor (vGPCR), which stimulates the MAPK cascade by inducing Ras phosphorylation [38].

Activated MAPK stimulates HIF-1α and VEGF expression, providing enough nutrients for cancer cells [38]. In another similar study, GPCR and vIL6 were found to induce a paracrine up-regulation of angiopoietin-2 (Ang2) through the activation of the Ras/Raf-1/MEK/ERK1/2 pathway [39]. One of the effective drugs in inhibiting this process is celecoxib, which prevents angiogenesis and tumor growth by inhibiting the COX-2 enzyme, which is increased by the vGPCR-mediated stimulation of the ERK signaling cascade. As a result, the expression of VEGF and HIF-1α is reduced and tumor growth is inhibited. Celecoxib can be used as a

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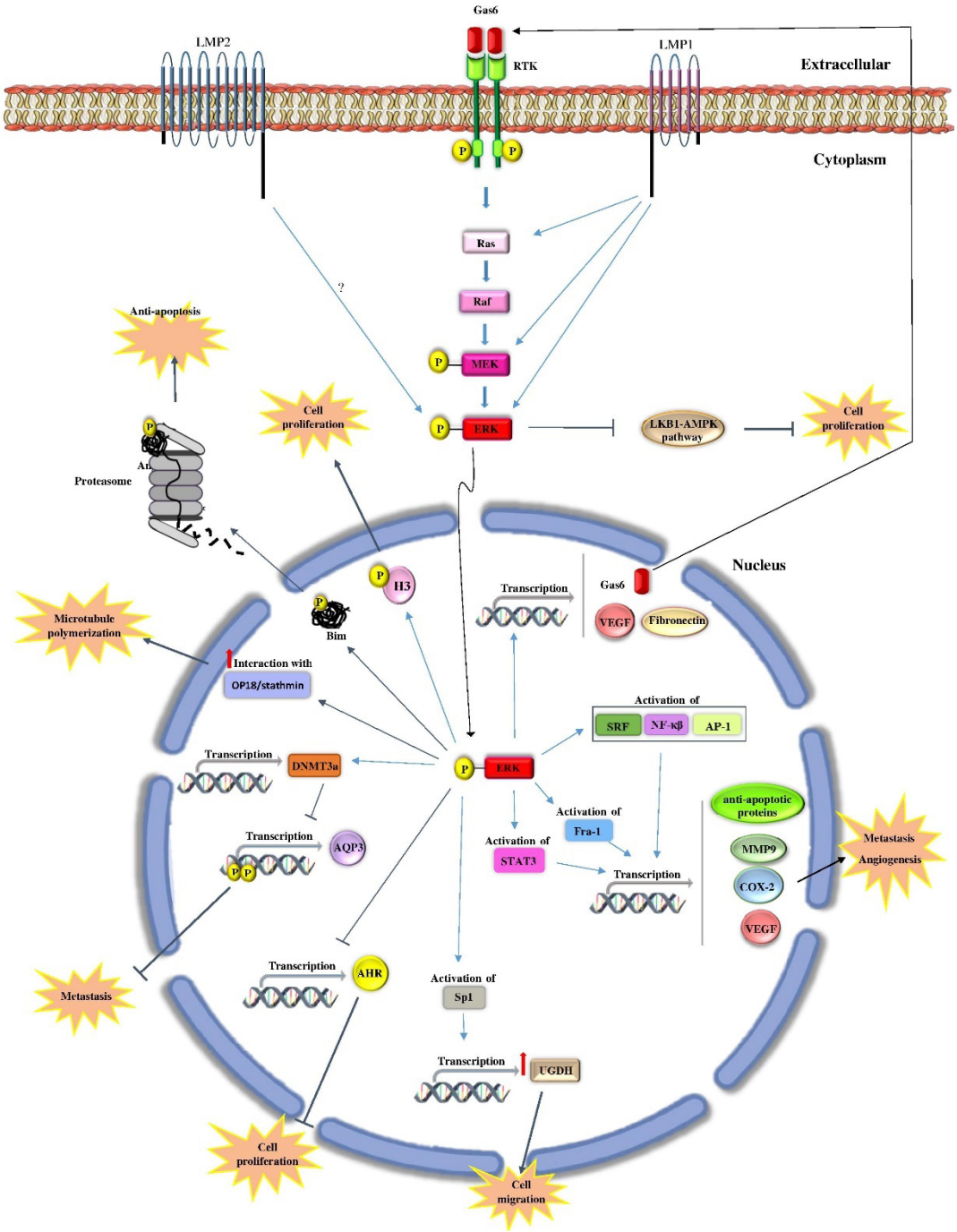

Figure 2. Schematic model of the EBV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: The EBV oncoproteins LMP1 and LMP2A drive cancer progression through multiple signaling pathways. LMP1 activates the Ras→Raf→MEK→ERK cascade, inducing VEGF, fibronectin and Gas6 expression to promote angiogenesis and reinforce the RTK/ERK pathway. It also stimulates VEGF via MEK→ERK→STAT3 signaling and upregulates anti-apoptotic genes (*Bcl-2*), VEGF, MMP9 and, COX-2 through ERK→AP-1, NF-κB, and SRF activation, enhancing metastasis and angiogenesis. LMP1-mediated ERK activation phosphorylates histone H3, inhibits the LKB1-AMPK tumor suppressor pathway, and interacts with OP18/stathmin to disrupt microtubule dynamics. LMP2A triggers ERK→Fra-1→MMP9 cascade independently of Ras and activates the ERK→Sp1→UGDH pathway to drive metastasis and cell proliferation. Activation of ERK by LMP2A increases Bim phosphorylation and its proteasome-dependent degradation, preventing apoptosis. Furthermore, LMP2A induces ERK-mediated DNMT3A upregulation, leading to AQP3 promoter methylation and subsequent loss of this metastasis-associated protein. Similarly, LMP2A activates the MAPK/ERK pathway, which is responsible for the inhibition of AHR expression. The effects of LMP2A pathways are seen in metastasis, anti-apoptosis, and cell proliferation.

targeted therapy option against vGPCR-related cancers [84]. It is also worth noting that KSHV contributes to tumorigenesis by suppressing the expression of DUSP1, an ERK deactivator, thereby facilitating tumorigenesis [16]. Specifically, the viral microRNA miR-K12-11 encoded by KSHV increases the expression of the 14-3-3β protein, which indirectly suppresses the expression of the phosphatase DUSP1 and ultimately increases production of pro-angiogenic and pro-inflammatory mediators, including VEGF, IL-6, and IL-8 [16]. KSHV envelope glycoproteins gB and gpK8.1A can activate the phosphatidylinositol-3 kinase (PI3K)/protein kinase C zeta (PKCζ)/MEK/ERK pathway via the focal adhesion kinase (FAK) [40]. As a result, phosphorylated ERK1/2 (p-ERK1/2) facilitates the transcriptional upregulation of critical host genes, including DUSP5, heparin-binding EGF-like growth factor (HB-EGF), VEGF, and intercellular adhesion molecule 1 (ICAM-1) [40]. To block this signaling pathway, the compound LY294002 has been identified as a specific inhibitor of PI3K. Research indicates that pre-treating target cells with LY294002 significantly decreases KSHV entry and replication. By targeting PI3K, this inhibitor impairs the signaling progression through key downstream effectors such as PKCζ, MEK, and ERK, ultimately resulting in diminished transcription of genes involved in oncogenic progression [85].

stimulates the expression of multiple transcriptional regulators containing c-Jun, STAT1α, myocyte enhancer factor-2 (MEF2), c-Myc, activating transcription factor (ATF2), and c-Fos [40]. These events play significant roles in angiogenesis, enhanced cell proliferation, and inflammation [40]. Supporting this, there is evidence that KSHV virions binds to their receptors, activating Ras and integrin-mediated FAK, ERK, and AP-1, further emphasizing the role of these signaling cascades in KSHV-induced cellular processes [11]. Another significant protein produced by KSHV is the viral serine/threonine protein kinase (vPK), which has been demonstrated to activate ERK1/2 through phosphorylation [41]. This phosphorylation event subsequently modulates the transcription of various regulatory factors such as ATF2, ATF3, c-Jun, and c-Myc [41]. Additionally, vPK-mediated ERK1/2 phosphorylation influences the expression of important cellular proteins such as IL-8 and Bcl-2, which are implicated in inflammatory responses and apoptosis regulation (Figure 3) [41].

Overall, KSHV promotes cancer progression by producing oncoproteins during its latent and lytic cycles, which activate molecular cascades such as the MAPK and PI3K/ERK pathways. These pathways increase the expression of angiogenic factors like VEGF and HIF-1α, as well as inflammatory cytokines. Drugs such as celecoxib (a COX-2 inhibitor) and LY294002 (a PI3K inhibitor) can suppress tumor growth by blocking these pathways. Additionally, KSHV proteins like vGPCR and vPK directly contribute to oncogenesis by activating these signaling cascades.

3.4. HBV

HBV continues to pose a major global health burden, with 316 million people (4.1% of the population) chronically infected worldwide. Despite four decades of effective vaccination, 8-20% of carriers develop cirrhosis, and 2-5% of these progress to liver cancer [86]. Although vaccination and antiviral treatments have reduced mortality, the virus still causes approximately 555,000 deaths annually [86]. HBV produces a regulatory transacting protein known as the HBV X (HBx) protein that constitutively activates several pro-inflammatory and pro-carcinogenic pathways [86].

It has been established that miR-148a expression in hepatocytes lowers the levels of hematopoietic B-cell leukemia transcription factor (HPIP) [42]. HBx suppresses miR-148a, enabling the modulation of the signaling axis governed by the mammalian target of rapamycin (mTOR) by activating the AKT and ERK signaling cascades [42]. Consequently, this activation results in the phosphorylation of downstream effectors, including p70 S6 kinase 1 (S6K1) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), potentially leading to increased expression of cyclin D1 and the c-myc oncoprotein [42]. Supporting this, research has shown that HBx upregulates c-myc and cyclin D1, promoting cell proliferation [43]. To target this pathway, the drug rapamycin (Rapa), also known as sirolimus, a specific mTOR inhibitor, has been proposed. Sirolimus inhibits mTOR activity and consequently blocks the phosphorylation of downstream effectors S6K1 and 4E-BP1. This leads to reduced expression of genes that drive cell proliferation. Research has shown that mTOR inhibitors can significantly curb the growth of liver cancer cells, offering a promising therapeutic option for HBV-related hepatocellular carcinoma (HCC) [87, 88].

HBx is capable of inducing phosphorylation of glycogen synthase kinase-3β (GSK-3β), leading to its functional inhibition through activation of the ERK signaling pathway, which leads to a sudden increase in β-catenin levels. β-catenin subsequently functions as a co-activator of T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription regulators and stimulates the induction of gene expression for targets including c-Myc and cyclin D1 [43].

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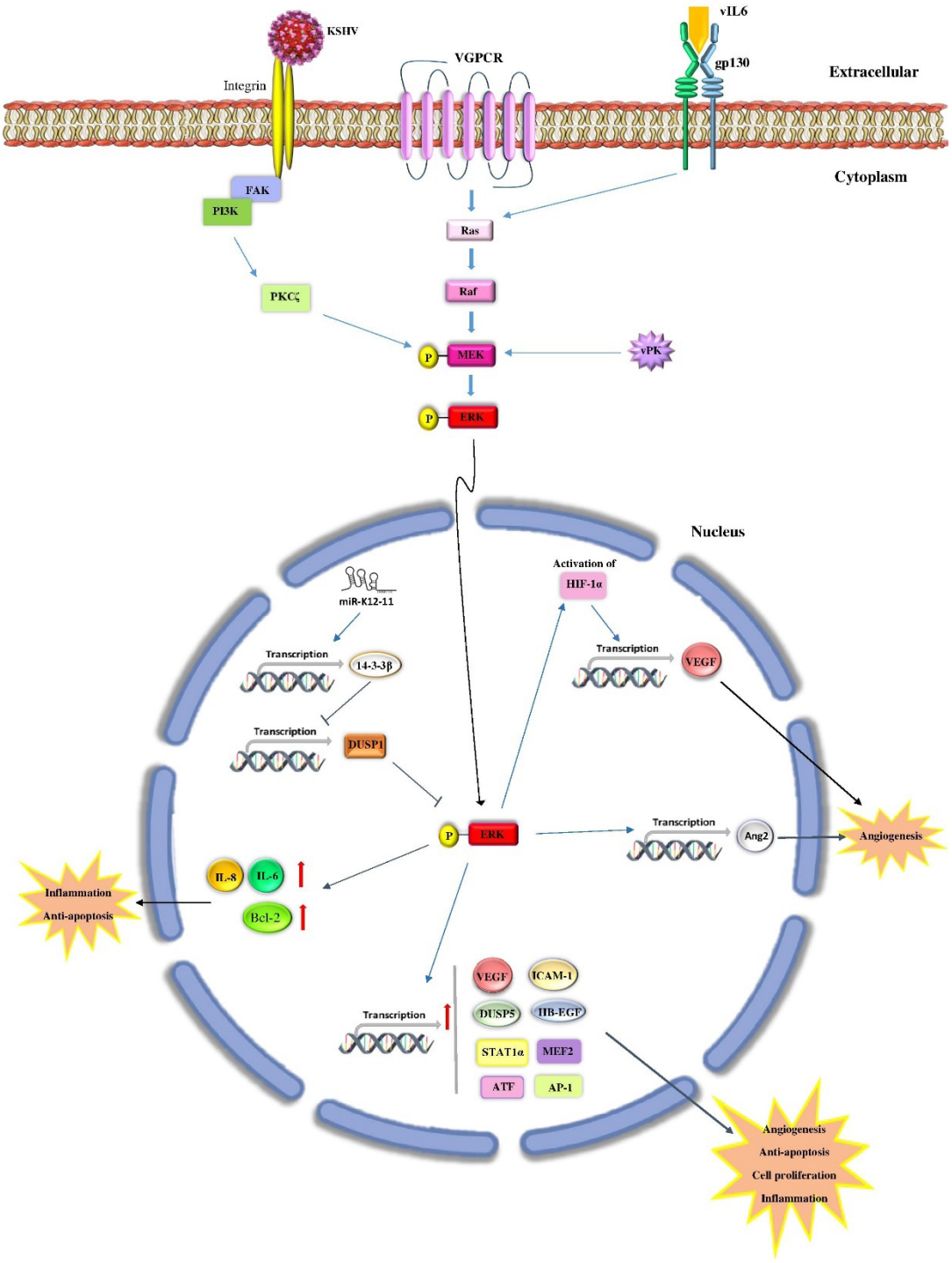

Figure 3. Schematic model of the KSHV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: KSHV oncoproteins vPK, GPCR, and vIL6, as well as KSHV-encoded miR-K12-11, drive cancer progression by hijacking cellular signaling pathways. ERK activation mediated by vPK can regulate the expression of ATF2, ATF3, AP-1, IL-8, and Bcl-2, causing inflammation and affecting anti-apoptotic factors. Viral GPCR stimulates the Ras→Raf→MEK→ERK→HIF-1α→VEGF pathway and induces angiogenesis. vIL6 activates the Ras→Raf→MEK→ERK→Ang2 pathway through gp130 and induces angiogenesis. By suppressing DUSP1 expression, KSHV-encoded miR-K12-11 increases ERK activation and secretion of IL-6, IL-8, and VEGF, and induces angiogenesis and inflammation. Interactions of KSHV envelope glycoproteins with integrins activate the FAK→PI-3K→PKCζ→MEK→ERK pathway, which leads to increased expression of AP-1, STAT1α, MEF2, ATF, DUSP5, HB-EGF, VEGF, and ICAM-1, affecting angiogenesis, inflammation, anti-apoptosis, and cell proliferation.

Stabilization and nuclear accumulation of cyclin D1 in a GSK-3β dependent pathway by HBx protein was also confirmed by Chen et al [89]. HBx can also stimulate the transcription of cyclin genes by activating the Ras/Raf/MAPK signaling pathway, as phosphorylation and activation of Elk-1 and CREB have been observed in HBV-positive cells [44]. A study by Xia and colleagues confirmed that HBx promotes the activation of ERK1/2, which enhances CREB binding to the promoter region of the forkhead box M1 (*FOXM1*) gene, leading to its increased expression. FOXM1, in turn, drives liver cell invasion and metastasis by upregulating matrix metalloproteinase-7 (MMP-7), RhoC, and Rho-associated kinase 1 (ROCK1) [45]. As a result, abnormal expression of RhoC/ROCK—key regulators of cell shape and movement—and MMP-7, which can disrupt E-cadherin, contributes significantly to the metastatic process [45].

HBx activates Ras, Raf, and MAP kinases, which subsequently increase expression of the transcriptional regulator AP-1 [12], NF-kB [13] and MMP-9 [14]. Additionally, HBx induces the ERK/NF-κB pathway, leading to increased expression of TNF-α and subsequent cell proliferation [90]. HBx also modulates regulation of Ras/MEK/MAPK pathway through other mechanisms. For instance, it has been shown to downregulate hepatocyte nuclear factor 4α (HNF4α) through activation of the ERK pathway [46]. HNF4α, recognized as a tumor suppressor in specific tissues, modulates genes integral to cell cycle regulation, programmed cell death, and genomic integrity maintenance [91]. Additionally, HBx-mediated stimulation of the Ras/MEK/MAPK axis has been documented in HBV-positive cancer cells, leading to centrosome proliferation and mitotic aberrations [92]. Notch1 is another molecule that is upregulated in HBV-positive cancerous cells. HBx activates the Notch1 pathway and suppresses the expression of DUSP1, an inhibitor of p-ERK. Consequently, the Notch1 pathway enhances ERK activity by decreasing the expression of DUSP1 [15]. Furthermore, research has indicated that the HBx protein stimulates the expression of special AT-rich sequence-binding protein 1 (SATB1) through the activation of the ERK and p38 MAPK pathways (Figure 4) [47].

Overall, HBV promotes cancer by producing the HBx protein, which activates oncogenic pathways such as AKT/mTOR, ERK, and MAPK. This leads to enhanced transcription of genes implicated in cell proliferation and metastatic progression, including c-Myc, cyclin D1, and MMP-7. HBx also enhances these pathways by downregulating inhibitors such as HNF4α and DUSP1. The drug sirolimus, an mTOR inhibitor, can suppress these effects and is considered a potential therapeutic option for HBV-related liver cancer.

3.5. HCV

HCV is a single-stranded RNA virus categorized within the Flaviviridae family and, unlike some other viruses, it remains extrachromosomal and does not integrate into the host genome [93]. It is linked to several diseases, including HCC, type III immune complex-mediated cryoglobulinemia, and non-Hodgkin lymphoma [93]. Key viral proteins such as core, NS3, NS5A, and NS5B are known to interfere with cell cycle regulation, lipid metabolism, apoptosis, transcriptional signaling, and cellular proliferation [93]. HCV is highly genetically diverse, comprising seven primary genotypes and multiple subtypes; among them, genotype 1b is most strongly associated with an elevated risk of HCC [93].

Research has shown that HCV activates regulatory proteins including c-Fos and c-Jun, and increases cyclin D1 expression by triggering the ERK signaling pathway [48]. Interestingly, HCV exhibits a biphasic regulatory effect on AP-1 transcriptional activity. On one hand, it enhances AP-1 activation via the MAPK/ERK pathway; on the other hand, it can suppress AP-1 activity. The NS5A protein of HCV interacts with proteins belonging to the Src family of non-receptor tyrosine kinases, leading to reduced apoptosis by inhibiting AP-1 via suppression of the mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway [49]. Additionally, the HCV core protein binds to 14-3-3 proteins and activates Raf-1 kinase by preventing dephosphorylation at the S621 site [50]. Notably, the core protein alone is sufficient to activate the MAPK/ERK cascade via Raf-1-mediated signaling [50]. This activation promotes the expression of HB-EGF, which subsequently initiates anti-apoptotic signaling via the Akt and IKK pathways [50].

Additionally, expression of the HCV NS3 protein is capable of initiating the ERK1/2 signaling cascade, resulting in elevated levels of NF-κB, COX-2, and MMP-9 [51]. The E2 envelope protein present in the HCV virion also plays a key role in mediating viral attachment and entry into host cells. Notably, E2 is a potent stimulator of the MAPK/ERK pathway through interaction with CD81 surface receptor and LDL receptor (LDLR) on target cells [52]. This activation of MAPK/ERK signaling, along with the subsequent activation of the downstream the transcriptional regulator ATF-2, significantly promotes cellular proliferation [52]. HCV binding to the EGFR is capable of upregulating proteins involved in angiogenesis, fibrogenesis, and inflammatory responses, including AREG, IL8, CCL20, CSF1, GDF15, IGFBP1, VNN3, thrombospondin-1, and PAI-1, which play im-

portant roles in malignant processes [54]. EGFR kinase inhibitors mainly prevent HCV infection by blocking EGFR endocytosis, while monoclonal antibodies or small molecule antagonists that obstruct EGFR ligand engagement or downstream signaling targeting downstream EGFR signaling do not affect HCV entry [94]. Studies have shown that inhibition of EGFR using drugs such as erlotinib, gefitinib, and sorafenib can reduce viral entry and inhibit the inflammatory and angiogenic effects induced by HCV. These drugs prevent viral replication by inhibiting EGFR-related signaling pathways [95, 96].

It is important to mention that normal cells attempt to inhibit cancer pathways by expressing various tumor suppressors, notably bromodomain-containing protein

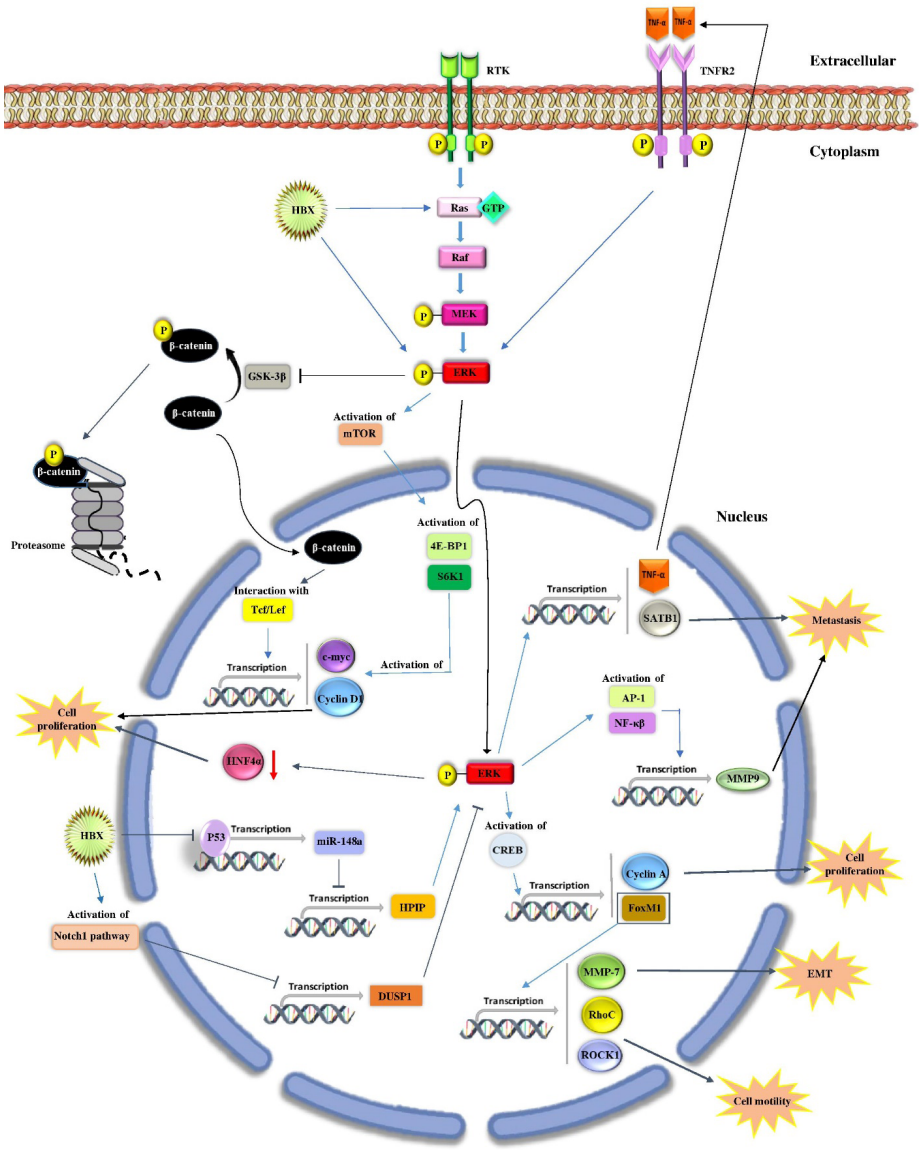

Figure 4. Schematic model of HBV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: HBV oncoprotein HBx drives cancer progression by hijacking cellular signaling pathways. HBx increases MMP-9 expression by stimulating Ras→ Raf→MEK→ERK→AP-1 and NF-kB pathway and affects metastasis. This protein also stimulates HPIP expression by suppressing miR-148a expression, which enhances ERK→mTOR→S6K1 and 4E-BP1→cyclin D1 and c-myc pathway and increases cell proliferation. c-myc and cyclin D1 are also increased by HBx→ERK→β-catenin→Tcf/Lef pathway and affect cell proliferation. ERK activated by HBx also plays a role in increasing TNF-α and SATB1 expression and decreasing HNF4 expression in HBV-positive cancer cells, thereby affecting metastasis. HBx activates Ras→ Raf→MEK→ERK→CREB→cyclin A and FoxM1 pathway and affects cell proliferation. This leads to FoxM1-mediated expression of MMP-7, RhoC, and ROCK1, promoting metastasis. This HBV protein increases ERK activities by inducing the Notch1 pathway, causing anti-apoptotic activity and cell proliferation.

7 (BRD7) [53]. BRD7 is classified within the family of bromodomain-containing proteins and plays roles in chromatin remodeling, regulation of the cell cycle, and transcriptional activity [53]. As a component of the PBAF complex, BRD7 acts as a tumor suppressor in cancers such as nasopharyngeal, ovarian, osteosarcoma, and colorectal cancer. It is crucial for the transcription of genes regulated by well-known tumor suppressors like p53 and BRCA1 [53]. However, HCV disrupts this tumor-suppressive role by lowering BRD7 expression or promoting its degradation, which interferes with BRD7's negative feedback on the Ras/Raf/MEK/ERK pathway, thereby encouraging cell proliferation (Figure 5) [53].

Overall, HCV promotes cell proliferation, inhibits apoptosis, and activates inflammatory and angiogenic pathways by disrupting cellular signaling pathways such as MAPK/ERK and downregulating tumor suppressors

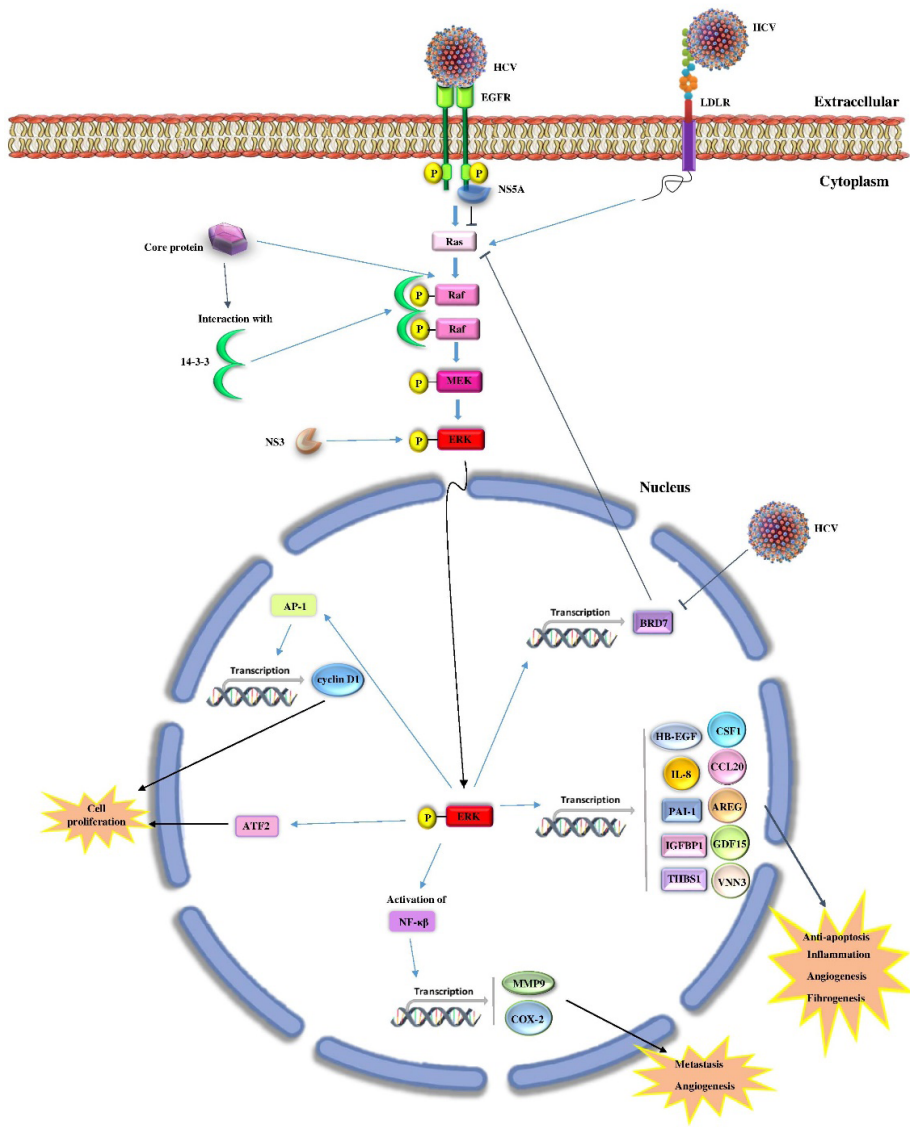

Figure 5. Schematic model of HCV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: HCV oncoproteins NS5A, core protein, NS3, and E2 drive cancer progression by hijacking cellular signaling pathways. HCV-activated ERK increases cyclin expression. Unlike other oncoproteins, NS5A reduces cell apoptosis by downregulating the Ras→Raf→MEK→ERK pathway and suppressing AP1 activity. The core protein can activate Raf alone or through interaction with 14-3-3 proteins, leading to increased HB-EGF expression and activation of anti-apoptotic signaling pathways. In addition, NS3 activates ERK→NF-κB→COX-2 and MMP-9 signaling, which affect angiogenesis and metastasis. The envelope protein E2, by binding to LDLR, activates the Ras→Raf→MEK→ERK→ATF-2 pathway and significantly increases cell proliferation. While HCV binding to EGFR leads to the expression of angiogenic, profibrotic, and proinflammatory proteins, activation of the Ras→Raf→MEK→ERK pathway can also influence BRD7 expression. By suppressing BRD7, HCV reduces the negative feedback regulation of BRD7 in the Ras/Raf/MEK/ERK signaling pathway, thereby facilitating cell proliferation.

like BRD7. These mechanisms contribute to liver cancer development. EGFR inhibitors such as erlotinib and sorafenib can block these pathways, thereby preventing HCV entry and replication.

3.6. HTLV

One of the most important retroviruses with high prevalence in some parts of the world is the Human T-lymphotropic virus, since it can cause approximately 5% of adult T-cell leukemia cases [97, 98]. HTLV can encode an oncoprotein called Tax that plays important roles in numerous pathways, especially Ras/MAPK, in promoting leukemogenesis [98].

The most recognized oncoprotein of HTLV is Tax, which interferes with the GTP/GDP switch by interacting with GTPase-activating protein (GAP1m), leading to an increase in the active Ras form (GTP-Ras) [55, 99]. This activation stimulates the Ras/Raf-1/MEK/ERK1/2 signaling pathway, leading to increased phosphorylation levels of CREB. CREB functions as a DNA-binding transcriptional regulator involved in gene expression modulation and can inhibit the mitochondrial apoptosis pathway [55, 99]. These effects establish a milieu con-

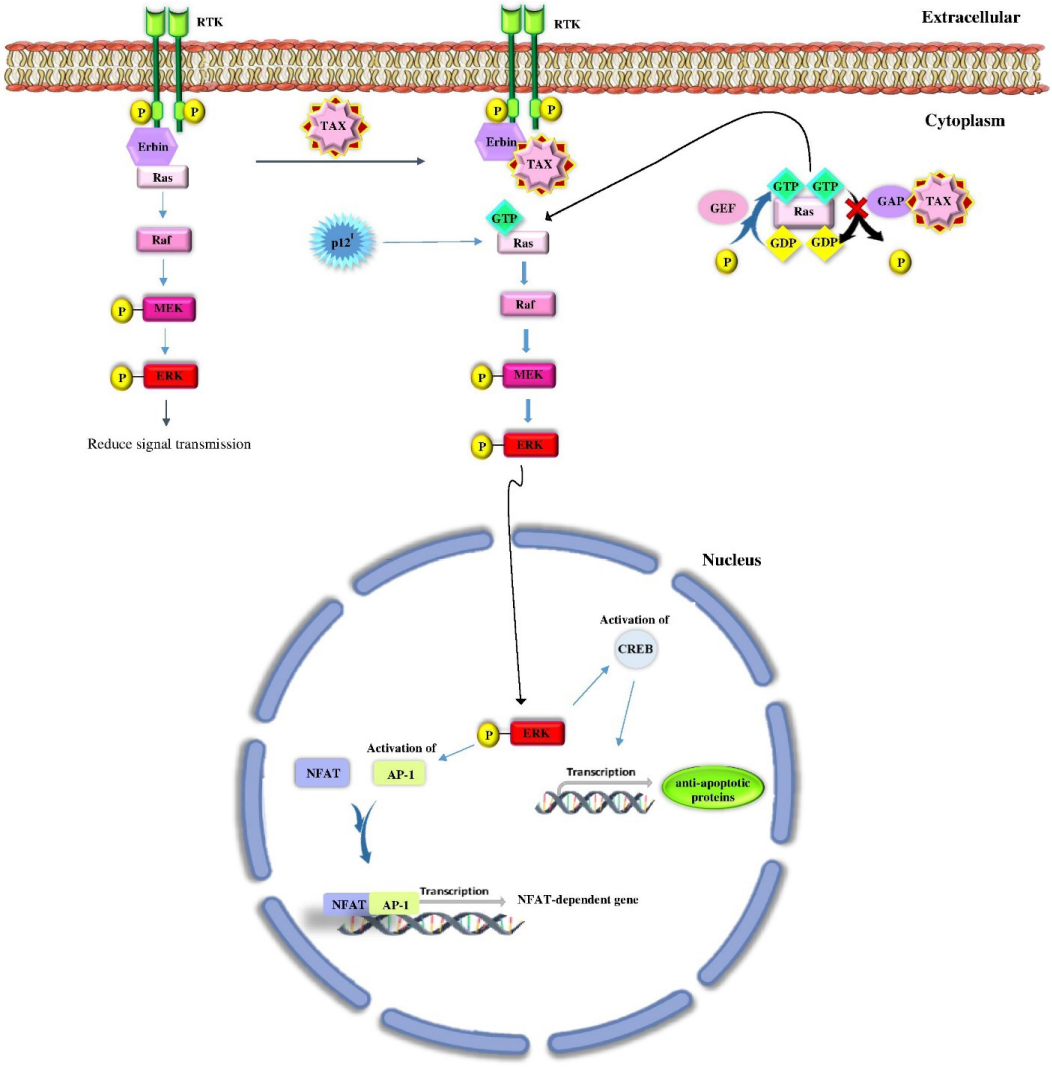

Figure 6. Schematic model of the HTLV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: HTLV oncoproteins Tax and p12I drive cancer progression by hijacking cellular signaling pathways. The Tax oncoprotein increases GTP-Ras levels, which leads to inhibition of the mitochondrial apoptosis pathway through CREB activation. In addition, Tax activates the Ras→Raf→MEK→ERK signaling pathway through interaction with Erbin, affecting anti-apoptotic and proliferative activity. p12I of HTLV-1 can also activate the Ras→Raf→MEK→ERK→AP-1 pathway, which leads to the formation of the NFAT/AP-1 complex and NFAT-dependent gene expression, affecting cell proliferation.

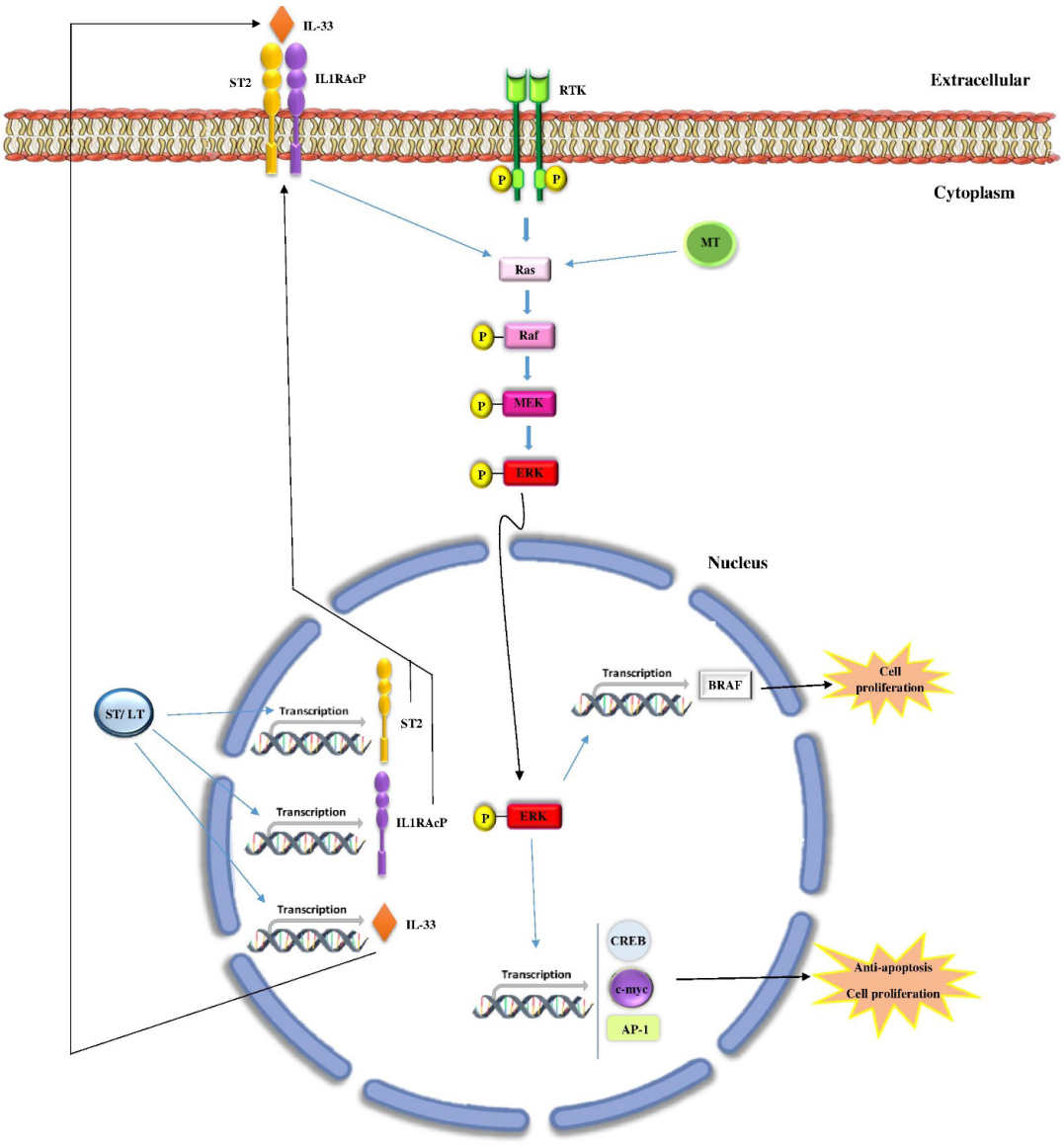

Figure 7. Schematic model of the MCPyV carcinogenesis mechanisms through the MAPK/ERK pathway

Note: MCPyV oncoproteins LT, sT, and MT drive cancer progression by hijacking cellular signaling pathways. LT and sT oncoproteins, through the stimulation of IL-33 expression and its receptors ST2 and IL1RAcP, increase the MAPK→ERK→AP-1, CREB, and c-MYC pathways, and cause anti-apoptotic activity and cell proliferation. While MT can activate the Ras→Raf→MEK→ERK→BRAF pathway and affect cell proliferation.

ducive to viral genome replication and promote carcinogenesis. Studies analyzing Tax mutations in lymphocytes have found that Tax-induced activation of p53 is associated with its capacity to stimulate the NF-κB signaling axis, but not with its interaction with p300 or CREB activation. Furthermore, expression of a mutant IκBα (S32,36A), which blocks NF-κB activation, also reduces Tax's capacity to activate p53 [100]. Similarly, just as Erbin reduces the transforming activity of Tax1 in cell proliferation through interaction with Ras, Tax1 is likewise competent in initiating the Ras–Raf–MEK–ERK signaling cascade [56].

To inhibit this pathway, farnesylthiosalicylic acid (FTS or Salirasib) is suggested as a therapeutic option. This drug works by inhibiting the membrane localization of Ras proteins, reducing their activity, and can have antitumor effects in HTLV-1 infected cells [101].

In another study, it is mentioned that the synergistic function of NFAT and AP-1 is critical for initiating transcription and peripheral lymphocyte proliferation. HTLV-1 p12I can activate the Ras/MAPK pathway and AP-1 phosphorylation (Figure 6) [57].

Overall, the HTLV virus can cause adult T-cell leukemia. The oncoprotein Tax facilitates viral replication and carcinogenesis by activating the Ras/MAPK pathway and preventing apoptosis. The drug FTS can inhibit Ras activity, showing anti-tumor effects. Moreover, the p12I protein stimulates the Ras/MAPK signaling pathway and contributes to the clonal expansion of lymphocytes.

3.7. MCPyV

MCPyV belongs to the Polyomaviridae family as a part of the skin microbiota, and it is the only oncogene-related polyomavirus in humans. Indeed, this virus is responsible for Merkel cell carcinoma (MCC), especially in immunocompromised individuals [102]. The transformation of Merkel cells is associated with the expression of small, large, and middle T antigens (sT-Ag, LT-Ag, and MT-Ag, respectively) [102].

Research on the link between MCPyV and the Ras/MAPK pathway is limited; however, a 2022 study reported that the LT and sT proteins of MCPyV promote the expression of IL-33 and its surface-bound receptors, including ST2 (IL1RL1) and IL1RacP [58]. Secreted IL-33 binds to ST2 and IL1RacP, triggering receptor-mediated cell-surface engagement andMAPK/ERK1/2 pathway activation. This activation leads to the induction of transcriptional regulators regulated by ERK1/2, such as AP-1, ATF/CREB, and c-MYC [58]. Moreover, MT stimulates ERK through the Ras/Raf pathway, leading to upregulation of BRAF and ultimately uncontrolled cell proliferation (Figure 7) [59].

4. Conclusion

Oncoviruses induce the activation of transcription factors, and the Ras/MAPK pathway is one of the main targets of oncoviruses during tumorigenesis. Overviewing the relation between the Ras/MAPK pathways and numerous oncoviruses in cancers can give researchers the opportunity to identify the best treatment for patients suffering from oncoviral infections.

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Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and study design: Ebrahim Faghihloo; Data analysis, interpretation, and writing the original draft: Shaian Tavakolian, Fariba Rafiei, and Mohammad Javad Roustaye gourabi; Review and editing: Ebrahim Faghihloo and Hossein Goudarzi.

Conflict of interest

The authors declared no conflict of interest.

Data availability

The datasets used during the current study are available from the corresponding author upon reasonable request.

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