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Review Article

The Host Signaling Pathways Hijacked by Oncogenic Viruses

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Abstract

Oncogenic viruses are able to induce malignant tumors during their infection. In general, host signaling pathways are classified into three categories: (1) growth stimulatory pathways such as PI3K-Akt, MAPK, NF-κB and Jak-STAT pathways; (2) growth inhibitory pathways such as DNA damage response and p53-mediated pathways; (3) immune response pathways such as TLR and IFN pathways. Upon virus infections, there are numerous factors to regulate a cascade of events ranging from cell proliferation and survival to apoptosis and other types of cell death. In this review, we give an overview of the impact that eight oncogenic viruses and their oncoproteins have on the host cell signaling pathway, providing an outline of their interactions with the major cascade molecules. Several of these associations of viral oncoproteins with member of the cellular signaling pathway may be essential for determining the oncogenecity of oncogenic viruses. Prospectively, further understanding these interactions will help reveal the potential roles of these molecules as therapeutic targets both for viral infections and tumorigenesis.

Introduction

Viruses can only reproduce by infecting live cells. During their replication, some viruses manipulate the host cell machinery in such a way that may cause the host cell to reproduce out of control and become carcinogenesis. These viruses are known as oncogenic viruses, also named as "tumor viruses" or "cancer viruses". In 1909, Francis Peyton Rous showed that cancer could be transmitted through cell-free tumor extracts and thus viruses must be responsible for transmitting the tumor [1,2]. A new epoch began after that, the first human tumor virus Epstein-Barr virus (EBV) was identified from Burkitt's lymphoma in 1964 [3]. Currently, more than eight human tumor viruses are known. Human oncogenic viruses are classified into two categories according to their genomes, DNA viruses and RNA viruses. Most human tumor viruses belong to DNA viruses, including Epstein - Barr virus (EBV), Human Herpes Virus (HHV4), Hepatitis B Virus (HBV), Human Papilloma Viruses (HPV), Kaposi's Sarcoma Herpes Virus (KSHV), and Merkel cell polyomavirus (MCV). Human T-Lymphotropic Virus-I (HTLV-I) and Hepatitis C Virus (HCV) belong to human RNA tumor viruses (Table 1). Similarly, there are also some important animal oncogenic viruses that greatly affect the development of the livestock industry. For examples, Marek's Disease Virus (MDV) and Jaagsiekte Sheep Retrovirus (JSRV) can induce serious T cell lymphoma in chicken and lung cancer in sheep, respectively.

Since viruses cannot replicate independently, they have to exploit the host cell machinery to make new progeny. In order to produce a conducive environment, they take advantages of cellular signaling pathways by activating growth promoting pathways such as Jak-STAT, MAPK pathway and inhibiting growth suppression pathways, such as the DNA damage response. In addition, viruses also need to take measures to evade immune surveillance and utilize inflammation properly. DNA damage and misreplication cannot be fixed immediately due to inappropriate DNA repair system, resulting in tumor induction. In this way, tumorigenesis can be considered to be a by-product of virus replication. However, the mechanisms of oncogenic virus-induced tumors are diverse. Some viruses encode oncoproteins, which can mutate pro-oncogene or repress anti-oncoproteins, such as p53 and caspases. HBV and HCV induce chronic infection and inflammation and subsequently contribute to tumorigenesis. Besides, some DNA viruses cause cancers during their latent infection; this may be related to reduce immune responses [4]. This review will discuss four major pathways that are frequently regulated by tumor viruses during their infection, and suggest the possible relationships between oncogenic viruses and host cell signaling molecules.

DNA Damage Response and p53 Pathway

DNA Damage Response (DDR) acts as a surveillance mechanism during cell replication in detecting damaged DNA, initiating DNA repair, apoptosis and senescence depending on the strength and duration of the damage signals. DDR and repair pathways are controlled by the Ataxia-Telangiectasia Mutated (ATM) and RAD3-related (ATR), and DNA-dependent Protein Kinase (DNA-PK) [5]. ATM and ATR kinases are activated by DNA Double-Stranded Breaks (DSBs)

and DNA Single Strand Breaks (SSBs) respectively, subsequently initiate the activation of multiple downstream effectors, including Chk2, Chk1, p53, and γH2AX that lead to DNA repair, apoptosis or senescence [6]. DNA-PK is able to recognize DSBs and initiate Non-Homologous End Joining Repair (NHEJ) [7].

Viruses induce DDR through two different mechanisms: 1) activation of cellular oncogenes or 2) inappropriate expression of viral oncoproteins [8]. Most viruses infect and drive cells from the G0 phase to re-enter into the cell cycle to promote an environment conducive for viral replication. Due to frequent replication, DDR occurs along with accumulated replicative stress. Thus, all known human oncogenic viruses can induce DDR. For some DNA viruses, DDR may be beneficial in their lytic infection phase. For example, in EBV-infected nasopharyngeal epithelial cells, induction of lytic infection of EBV triggers ATM activation and localization of DDR proteins at the viral replication compartments, whereas suppression of ATM activity significantly suppressed replication of EBV DNA and production of infectious virions [9]. DDR induced apoptosis may help virions to release from infected cells. Similarly, a recent study showed that KSHV activates ATM and H2AX for the establishment and maintenance of its latency during *de novo* infection of primary endothelial cells [10]. HPV encoded oncoproteins E6 and E7 can also independently induce ATM or ATR pathways [11] and then increase the frequency of foreign DNA integration into the host genome [12]. High-risk E7 has been shown to activate the ATM and its downstream target Chk2 in undifferentiated and differentiated keratinocytes [13]. Since triggering this pathway suppresses tumor formation in some ways, DDR can be considered as a self-defense mechanism of host cells. In this case, tumor viruses have also evolved strategies to impair DDR in order to survive, such as abnormal expression of certain viral oncoproteins to antagonize the function of DDR downstream signaling components, or to target upstream checkpoint kinases.

Although the tumor suppressor p53 can be induced by various DNA damage, the proteasomal degradation and cytoplasmic sequestration of p53 can be also regulated by various viral proteins [14]. The latent oncoprotein EBNA3C of EBV has also been shown to attenuate the EBV-induced DDR through modulating p53 and Chk2 activities [15-17]. Similarly, KSHV encoded latent protein LANA can also directly associate with p53 to suppress its apoptotic activity [18,19]. HPV encoded E6 has been shown to bind p53 and stimulate ubiquitin-dependent degradation of p53 [20,21]. A recent study also suggests that β-HPV E6 proteins can attenuate p53 stability in response to aberrant mitosis and dysregulated centrosome duplication, resulting in an unstable genome condition and thereby promoting tumorigenesis [22]. HBV oncoproteins HBx can antagonise p53 function through binding to the p53 c-terminus to block its transactivation activity and sequestering p53 in the cytoplasm to suppress apoptosis [23-25]. For RNA viruses, HTLV-1 oncoprotein Tax induces p53 dysfunction through both NF-κB-dependent and -independent pathways [26-29].

p53 is an important tumor suppressor that guards against cellular DNA damage and transformation [29]. It has been termed "the guardian of genome integrity". There are multiple downstream targets of p53 that function in cell senescence, cell cycle arrest and apoptosis, such as p21, PUMA and NOXA [30,31]. And the depletion or inactivation of p53 by virus proteins leads to an accumulation of point mutations, genomic instability and DNA damage. As mentioned above, some of virus-encoded proteins can suppress p53 as a downstream target of DDR. The EBV-encoded EBNA3C is involved in transcriptional regulation and disruption of the cell cycle at the G1/S transition via direct interaction with p53 or via a p53-mediated pathway [32].

Kinase Signaling Pathways (PI3K/Akt pathway, ERK/MAPK pathway etc)

PI3K/Akt pathway

Phosphatidylinositol 3-kinase (PI3K)/Akt is an important intracellular signaling pathway, which responds to a wide range of stimuli such as growth factors, cytokines, nutrients, and hormones. These stimuli can play a significant role in cell survival, cell proliferation and cell motility [30-32]. PI3K has various downstream targets, including protein kinase B (PKB/c-Akt), Tec kinases, protein kinase C (PKC) isoforms, and Guanine Nucleotide Exchange Factors (GEFs) [33]. Among those downstream targets of PI3K, the recent focus has been on PKB/c-Akt because of its anti-apoptotic activity, which might be linked to oncogenic virus replication and tumorigenesis (Figure 1). The PI3K/Akt pathway is activated in HTLV-I-transformed cells, and its activation has been linked to apoptotic resistance [34-36]. Inhibition of Akt in HTLV-I-transformed cells down-regulates phosphorylation of Bad, which activates caspase-9 leading to apoptosis [37]. The PI3K pathway is also found to reduce telomerase activity in HTLV-I cells by decreasing cytoplasmic retention of the Wilms Tumor (WTI) protein, which strongly suppresses the hTERT promoter [38]. Another RNA oncogenic virus, HCV, can cause persistent infection in patients eventually progressing to tumors. It has been shown that NS5A, the core protein of HCV, activates PI3K by directly binding to its regulatory subunit p85, which results in enhanced Akt activity [39,40]. Akt phosphorylates NS5A *in vitro*, while NS5A phosphorylation has been shown to inversely correlate with HCV RNA replication [41-43]. These data suggest that activation of PI3K/Akt pathway by HCV not only protects cells against apoptosis but also contributes to the maintenance of steady-state levels of HCV replication. These effects may contribute to the establishment of persistent infection by HCV [44].

It was found that apoptosis of hepatocytes might be suppressed by Akt activation in HBV infected cells [45,46]. However, HBV encoded multifunctional protein HBx has also been shown to activates Akt to decrease overall levels of HBV replication through transcription factor hepatocyte nuclear factor 4α (HNF4α) in an *ex vivo* model of cultured primary hepatocytes. A number of studies showed that HBx is a multifunctional protein which is required for HBV replication in multiple experimental systems, including cultured primary rat and human hepatocytes, liver cells lines, as well as *in vivo* in livers of normal mice and chimeric mice with humanized livers [47-52]. Thus, we speculate that HBx can play a fine-tuning role in the balance between HBV replication and hepatocyte survival.

Recent studies showed that DNA oncogenic virus HPV-16 E6 and E7 oncoproteins promote the activation of Akt, mTOR, JNK, and c-Jun in non-small cell lung cancer cells [53]. In addition, the PI3K/Akt pathway is also activated and has the potential to enhance oncogenic transformation and cancer development. The activated stromal Akt can induce tumorigenesis and invasion through regulating Keratinocyte Growth Factor (KGF) levels in

HPV16 positive keratinocytes expressing E6 and E7 [54]. EBV encoded LMP1 and LMP2A can also activate the PI3K/Akt pathway, resulting in modulation of cell survival, apoptosis, proliferation and genomic stability via its downstream target proteins to cause cancer [55-58]. Moreover, JSRV Env protein upregulates Akt causing cell transformation by both PI3K-dependent and -independent pathways [59].

MAPK pathways

The Mitogen-Activated Protein Kinase (MAPK) pathways involve a core cascade of events in which an upstream MAPK Kinase Kinase (MAPKKK) is activated by extracellular stimuli or intracellular effector molecules, such as growth factors, cytokines and stress signals, subsequently phosphorylating MAPKK and eventually activating MAPK [60]. The MAPK family includes the ERK1/2, p38 and JNK, which play an important role in regulating cell proliferation, differentiation, apoptosis and immune responses [61-64] (Figure 1).

Among these, the MEK-ERK and JNK pathway are capable of stimulating cell growth and differentiation. These pathways can be utilized by viruses to aid their replication. Indeed, HBx protein promotes cell proliferation and rapid progression through the cell cycle by up-regulation of AP-1 and cyclin D1 via activation of the MEK/ERK and PI3K/Akt signaling pathways [65,66]. JNK and p38 pathways can induce host innate antiviral responses and oncogene-mediated transformation.LMP1 expression is associated with activation of a number of MAPKs, including JNK, AP-1, and p38, which might be responsible for IL-6, -8 expressions [61,67]. In addition, MAPK pathways play a key role in regulating the life cycle of KSHV. During early infection, KSHV induces the ERK1/2, JNK and p38 to facilitate its entry into the cells and modulate the initiation of viral gene expression [68,69]. During latent infection of KSHV, ERK1/2, JNK and p38 are required for the activation of lytic replication [69]. However, HCV encoded NS5A inhibits the activity of the mitogenic- and stress-activated transcription factor AP-1 through the Ras-ERK signaling, resulting in a slow-transition of infected hepatocytes from the G1 phase to S phase cell cycle [70].

The Ras-MEK-ERK pathway has also been shown to play critical roles in anti-apoptosis and transformation. For example, Ras-ERK signaling is relevant to protect cells against Tax-induced apoptosis protection and to enhance P-CREB levels, implying a potential role for Ras in HTLV-I-induced diseases [71]. Maeda et al. showed that selective inhibition of MEK1 and Ras can specifically prevent JSRV Env-induced transformation of NIH 3T3 and RK3E rat cells, indicating that the Ras-Raf-MEK-ERK pathway might be involved in JSRV Env-mediated transformation [72]. However, how JSRV Env proteins activate this pathway and why ERK phosphorylation is not detected in Env-transformed cells remain unclear.

Jak-STAT pathway

The Jak/STAT pathway consists of three main components: a receptor, Janus Kinase (Jak), and Signal Transducer and Activator of Transcription (STAT) [73]. Once outside signals such as interferon, interleukins, growth factors, or other chemical messengers, bind to their cognate receptors, receptor associated Jaks become activated. Subsequently, STAT proteins are activated, dimerized and translocated into the cell nucleus [74]. In the nucleus, STATs regulate cell growth, survival and differentiation through modulating the expression of target genes.

Most oncogenic viruses encode proteins that can activate the Jak/STAT pathway (Figure 1). For instance, the EBV encoded LMP1 has been shown to activate the Jak/STAT pathway through directly interacting with Jak3 and activating STAT1/3 in EBV-immortalized B cells [75]. Jak-STAT and NF-κB pathways are significantly activated by EBV infection in diffuse large B-cell lymphoma (DLBCL) cell lines [76]. HBV encoded HBx and HCV encoded NS5A induce Jak-STAT pathway through activation of STAT3 to promote HCC development [77-80]. In HTLV-1-transformed cells, Jak1, Jak3, and STAT5 are hyper-activated which promote cell proliferation of T cells [81,82]. MDV, an avian oncogenic virus, encoded oncoproteins Meq can up-regulate the expression of oncogenic protein, STAT3, and down-regulate the inhibitory signal like SHP-1, SOCS2, and PIAS [83].

However, STAT1 and STAT3 appear to play opposite roles in tumorigenesis. STAT1 induces pro-apoptotic and anti-proliferative genes in tumor cells and then enhances innate and adaptive immunity, while STAT3 is considered an oncogene due to its ability of promoting cell survival and virus-mediated transformation [84,85]. HPV E6 alone can inhibit STAT1 protein, decrease IFN expression and promote virus amplification and maintenance, but the inhibitory effects are greatly enhanced in the presence of E7 coexpression [86,87]. KSHV encoded RIF has been reported to form inhibitory complex with Jak1, Tyk2, and STAT2, resulting in impaired STAT1 and STAT2 activity and type I IFN signaling [88]. Thus, it is likely that viruses might employ different strategies in regulating transcription factors to promote viral replication.

TLR and IFN pathways

TLR: Viral infection triggers an early host immune response through activation of Pattern Recognition Receptors (PRR), such as Toll-Like Receptors (TLR). TLRs are transmembrane proteins that recognize Pathogen-Associated Molecular Patterns (PAMPs) and initiate innate and adaptive immune responses against pathogens [89,90]. Current studies have identified TLR2, -3, -4, -7, -8, and -9 that are involved in the recognition of viruses through binding to DNA, RNA, or viral glycoproteins [91-93]. All TLRs, except TLR3, recruit IL-1R-Associated Protein Kinases (IRAK) via adaptor MyD88, and subsequently activate MAPK and NF-κB pathways, finally inducing immune responses, inflammation, and cell survival [94]. TLR3 is the only one that relies on TRIF instead of MyD88 to activate IRF3, IRF7 and to induce the production of type I IFN.

Viruses have evolved different strategies to block the anti-viral effects of IFN in this pathway (Figure 1). EBV Rta suppresses IRF3 and IRF7 expression during the viral reactivation period and thereby inhibits Type I IFN responses to virus infection [95]. HTLV-I p30 protein abrogates the interferon response during viral replication through counteracting TLR3 and TLR4 signaling in human monocytes and dendritic cells [96]. KSHV-encoded Replication and Transcription Activator (RTA) protein can attenuate host defenses through specifically degrading TRIF by the ubiquitin-proteasome pathway [97]. Furthermore, KSHV is able to use the TLR3-TRIF pathway to enhance the expression of RTA, to expedite the degradation process of TRIF, and to block the TLR3-mediated inhibitory effects on KSHV replication [98]. Recent study showed that infection with KSHV efficiently inhibited TLR2-mediated NF-κB activation in THP-1 monocytes through RTA [99].

TLRs can also induce JNK, p38 and NF-κB pathways to regulate cell survival and proliferation. In this case, TLR can be enhanced by some viruses. For example, HTLV-I Tax induces TLR expression and synergistically activates NF-κB with wild-type MyD88, which contribute to cell proliferation and survival [100]. During primary infection, KSHV upregulates TLR3 expression and induces TLR3-specific cytokines and chemokines, including beta 1 interferon (IFN-β1) and CXCL10 (IP-10) in human monocytes [101]. This may be beneficial for viruses to establish latency. Moreover, activation of TLR7/8 can reactivate latent KSHV and induce viral lytic gene transcription and replication [102].

IFN pathway: Interferons (IFNs) are pleiotropic cytokines that exhibit important biologic activities, including antiviral, antiproliferative, antitumor and immunomodulatory effects [103,104]. IFNs are classified into two categories: type I IFNs contains the IFN−α, −β, −ω, −τ, −κ, −λ and -ζ; type-II IFN contains only IFN-γ [105,106]. IFNs bind to IFNR and initiate the IFN pathway depending on Jak-STAT activation. Activated STAT1 and STAT2 can form transcriptional complexes such as ISG Factor-3 complex (ISGF3) that translocate to the nucleus to induce genes expression [103,106] (Figure 1).

Viruses have evolved different strategies to block this pathway. For instance, HTLV-I-infected dendritic cells have an impaired ability to secrete type 1 IFN [107]. HTLV-I evades IFN signaling by decreasing the phosphorylation level of Tyk2 and STAT2 and inducing the Suppressor of Cytokine Signaling 1 (SOCS1) [108,109]. HPV oncoproteins E6 and E7 disrupt the type I IFN pathway through interacting with p48/IRF and inhibiting the formation of ISGF3 [110-112]. Silencing HPV-18 E1 mRNA in HeLa cells showed that E1 can mitigate the host defense against infection via inducing transcriptional repressors that coordinately inhibit TLR, IFN and apoptosis signaling pathway and inducing transcriptional activators involved in viral replication [113].

NF-κB: NF-κB consists of five subunits: RelA (p65), c-Rel, RelB, p50/NF-κB1 and p52/NF-κB2 [114]. In the canonical NF-κB signaling pathway, stimuli bind to receptors and activate the IκB kinase (IKK) complex, which is composed of two catalytic subunits (IKKα and

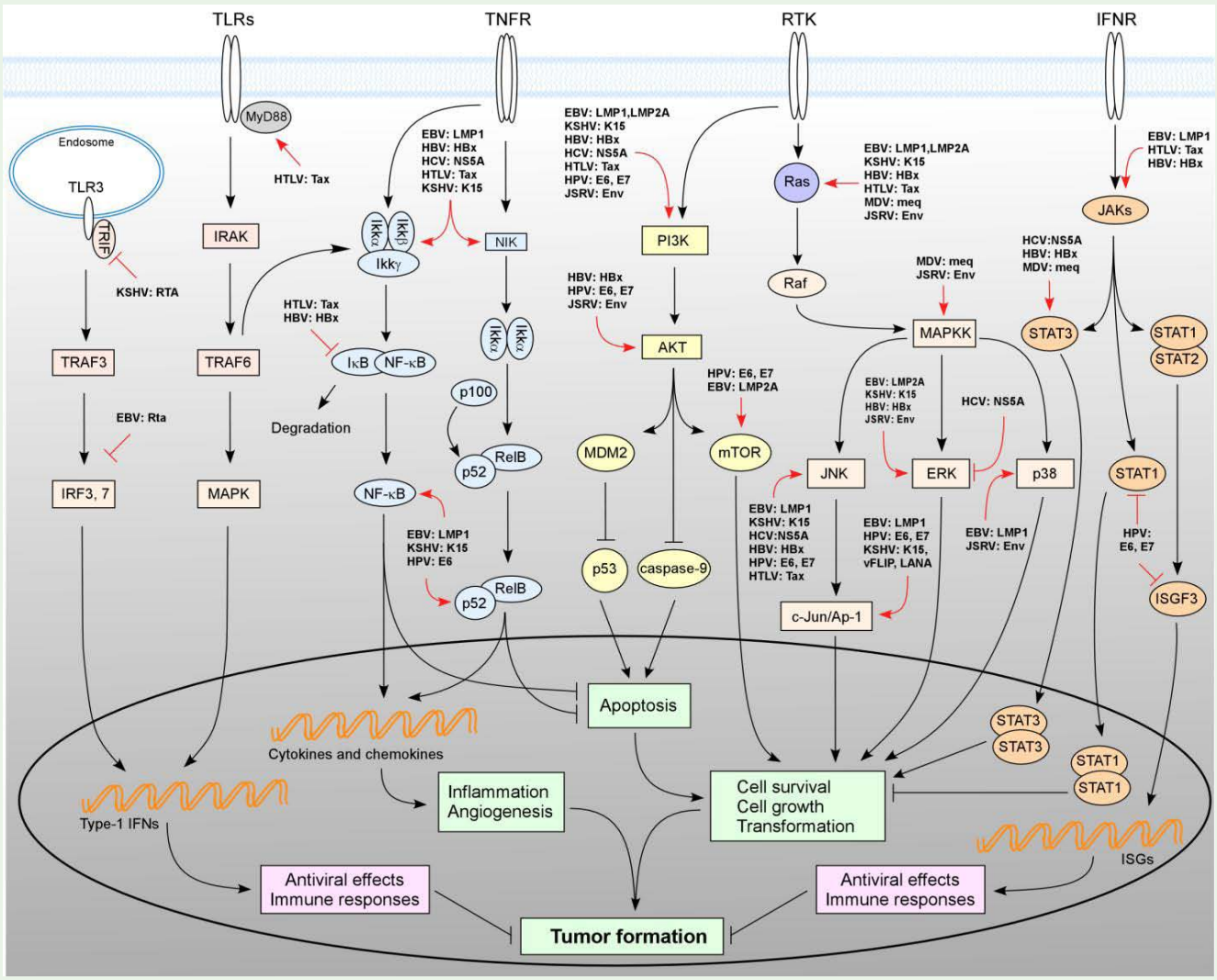

Figure 1: Common cellular signaling factors for oncogenic viral proteins.

Table 1: The oncogenic viruses.

Virus	Cancers	Hereditary substance	References
Epstein-Barr virus (EBV) Human herpesvirus (HHV4)	Burkitt's lymphoma, Nasopharyngeal carcinoma, non-Hodgkin's lymphoma, gastrointestinal lymphoma	dsDNA	[3]
Hepatitis B virus (HBV)	Hepatocellular carcinoma	ssDNA and dsDNA	[131]
Human T-lymphotrophic virus-I (HTLV-I)	T cell leukemia	+ssRNA	[132]
High-risk human papillomavirus (HPV 16, 18)	Cervical and penile cancers, head and neck cancers	dsDNA	[133,134]
Hepatitis C virus (HCV)	Hepatocellular carcinoma, lymphoma	+ssRNA	[135]
Kaposi's sarcoma herpesvirus (KSHV, HHV8)	Kaposi's sarcoma	dsDNA	[136]
Merkel cell polyomavirus (MCV)	Merkel cell carcinoma	dsDNA	[137]

IKKβ) and a regulatory subunit (IKKγ/NEMO) [115]. Without stimulation, NF-κB binds with IκBs in the cytoplasm. Once IKK is activated, it can target IκBs for polyubiquitination and proteasomal degradation. Freed NF-κB dimers translocate to the nucleus where they act as a transcription factor to induce multiple target genes. In the alternative NF-κB pathway, stimulation of the kinase NIK activates an IKKα homodimer and then IKKα activates a non-canonical NF-κB pathway in which p100 is process to p52, which translocates as p52/RELB hetero dimers into the nucleus to perform its trans-activation activity [116-118].

NF-κB is a major activator of anti-apoptotic gene expression and oncogenesis, thus, it is frequently activated during oncogenic virus infection to promote cell growth (Figure 1). Anti-apoptotic proteins Bcl-2, Bfl-1, and A20 can be upregulated by LMP1-mediated NF-κB activation [119,120]. Suppressing NF-κB activation causes spontaneous apoptosis in EBV-transformed LCLs providing further clues for its role in LMP1 signaling [121]. Similar to LMP1, transmembrane protein K15 of KSHV activates the NF-κB pathway depending on phosphorylation of tyrosine residue 481 in a C-terminal YEEVL motif [122]. It was found that KSHV K15 plays a role in NIK/IKK recruitment and results in the phosphorylation of p65/RelA [123]. In addition, HBx-induced NF-κB activation is mediated by direct interaction with TNFR1 and thereby induces hepatic steatosis and apoptosis [124,125]. Recently, a novel mechanism of HBx-induced NF-κB activation is discovered, forming a ternary complex among HBx, p22-FLIP and NEMO can greatly enhance NF-κB activation [126]. Moreover, HTLV-I Tax is able to activate NF-κB in both the cytoplasm and nucleus to promote proliferative effect on lymphocytes [82]. Tax binds the IKKγ/NEMO complex in the cytoplasm to affect IKK complex activity [127]. Up-regulation of NF-κB can be considered as a powerful weapon for preventing host cell apoptosis and then accomplishing transformation [128]. A Tax mutant that activates CREB/ATF but cannot activate NF-κB is able to immortalize human primary T-lmphocytes. This indicates that Tax can transform cells through NF-κB-independent pathway [129].

In addition to effects on cell survival, NF-κB can also activate multiple downstream targets that may enhance inflammatory responses and angiogenesis, such as cytokines and chemokines. LMP can promote the expression of proinflammatory cytokines such as IL-6 and IL-8, and angiogenesis factors such as COX2 and VEGF via the NF-κB-dependent pathway [61,130]. IL-6 and IL-8 play an important role in initiation and maintenance of acute inflammatory responses. COX2 and VEGF are related with angiogenesis and enhanced tumor metastasis.

Conclusion and Remarks

In the past decades, our knowledge of oncogenic virus-mediated modification of host cell signaling pathways has been growing rapidly. It is a battle between the virus and the host. Viruses hijack host growth stimulatory pathways to aid their replication and evade the host immune surveillance to make a conducive environment for tumor formation. We summarized an overview of common characteristics among oncogenic viruses (Table 1) and Figure 1 generally illustrates the dynamic processes of host signaling pathways affected by activation or inhibition of viral oncogenic factors. Actually, most signaling pathways are like double-edged swords for viruses. Their mutual interaction is to take advantage of the good side and repress the bad one. For example, DDR is mainly responsible for gene repair and clearance of damaged cells; thereby viruses encode proteins to counteract the effect of its downstream targets. But during certain period of infection, DDR is beneficial for virus replication and establishing latency. Over last a few decades, a significant amount of efforts have been invested by numerous researchers in order to clarify the function of host cell signaling pathways during infection of oncogenic viruses, but there are still mysteries to be discovered, e.g. the precise role of viruses in tumorigenesis. The new development of anti-viral vaccines/drugs and modulators of host signaling factors against oncogenic virus elements are attainable goals that have not yet been accomplished in animal/human cancer research fields. Although many mechanisms have been revealed in cell signaling cascades, given the number and diversity of the yet-to-be-studied oncogenic viral pathogens, much more is left to be discovered.

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