

Review



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Tumour viruses and innate immunity

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Host cells sense viral infection through pattern recognition receptors (PRRs), which detect pathogen-associated molecular patterns (PAMPs) and stimulate an innate immune response. PRRs are localized to several different cellular compartments and are stimulated by viral proteins and nucleic acids. PRR activation initiates signal transduction events that ultimately result in an inflammatory response. Human tumour viruses, which include Kaposi's sarcoma-associated herpesvirus, Epstein–Barr virus, human papillomavirus, hepatitis C virus, hepatitis B virus, human T-cell lymphotropic virus type 1 and Merkel cell polyomavirus, are detected by several different PRRs. These viruses engage in a variety of mechanisms to evade the innate immune response, including downregulating PRRs, inhibiting PRR signalling, and disrupting the activation of transcription factors critical for mediating the inflammatory response, among others. This review will describe tumour virus PAMPs and the PRRs responsible for detecting viral infection, PRR signalling pathways, and the mechanisms by which tumour viruses evade the host innate immune system.

This article is part of the themed issue 'Human oncogenic viruses'.

1. Introduction

The detection of microbial pathogens is an essential first step in mounting an innate immune response to infection. Cells sense invading pathogens through germline-encoded pattern recognition receptors (PRRs) that recognize molecular signatures conserved across many microbes, known as pathogen-associated molecular patterns (PAMPs). Viral PAMPs include viral proteins and nucleic acids, such as single-stranded RNA, double-stranded RNA, CpG unmethylated DNA and 5' triphosphorylated RNA.

PRR recognition of PAMPs triggers a signalling cascade that ultimately results in the activation of transcription factors, NF-κB and IRF3/7 (reviewed in [1]). NF-κB is responsible for upregulating pro-inflammatory cytokines and chemokines, which attract immune cells to the site of infection, while IRF3/7 upregulates the type I interferons (IFNs). Type I IFNs signal in an autocrine and paracrine manner to induce an antiviral state through the upregulation of interferon-stimulated genes (ISGs) such as PRRs, proteins involved in antigen presentation, transcription factors, pro-inflammatory cytokines and chemokines, and proteins that are directly antiviral. NF-κB activation occurs when PRR signalling results in degradation of IκB, a protein that sequesters NF-κB in the cytoplasm, which allows NF-κB to translocate to the nucleus. IRF3/7 activation also results in nuclear translocation, and occurs when PRR signalling activates kinases that phosphorylate these transcription factors.

2. Pattern recognition receptors and signalling

Toll-like receptors (TLRs) are one family of PRRs that sense PAMPs at the cell surface or in endosomes (reviewed in [2]). Eleven mammalian TLRs have been identified, and although their expression is cell-type dependent, most cells express a subset of these receptors. The plasma membrane localized TLRs that are relevant to viral infection are TLRs 2 and 4, which recognize viral proteins [3,4]. The endosomal TLRs recognize nucleic acid and include TLR3, which recognizes

double-stranded RNA, TLR7/8, which recognizes single-stranded RNA, and TLR9, which recognizes CpG unmethylated DNA, a common motif in DNA virus genomes [5–9].

TLRs recognize their substrates through leucine-rich repeat (LRR) motifs in their Ig-like ectodomains (reviewed in [2]). TLRs signal through their Toll/interleukin-1 receptor (TIR) domains, found on the cytoplasmic side of the endosomal or plasma membrane, by interacting with the TIR domain-containing adaptor proteins MyD88 or TRIF. TLR3 is the only TRIF-dependent TLR, while TLRs 2, 7/8 and 9 signal through MyD88, and TLR4 can signal through either adaptor protein [10–20]. Signalling from these adaptors leads to IRF3/7 and NF- κ B activation, resulting in upregulation of pro-inflammatory cytokines, chemokines and type I IFN. In some cell types, TLR activation can also result in upregulation of type III IFNs, the IFN λ family of cytokines [21]. Like type I IFNs, type III IFNs are upregulated by IRFs and combat viral infection by upregulating ISGs.

While some TLRs detect viral nucleic acid in endosomes, another family of PRRs called the RIG-I-like receptors (RLRs) sense non-self RNAs in the cytoplasm (reviewed in [22]). RLR signalling results in the activation of NF- κ B and IRF3/7, and thus upregulation of pro-inflammatory cytokines, chemokines and type I IFN. The three RLR family members, RIG-I, MDA5 and LGP2, are expressed at a low level in most cell types, and are upregulated upon exposure of cells to IFN [23–26]. RIG-I and MDA5 are both activated by double-stranded RNAs with blunt ends, which are signatures of foreign RNA (reviewed in [27]). RIG-I is activated by short double-stranded RNAs bearing a 5' triphosphate moiety, another signature of non-self RNAs, while MDA5 is activated by long double-stranded RNAs. RIG-I may also be activated by single-stranded RNAs bearing a 5' triphosphate.

RLRs are composed of two N-terminal tandem caspase activation and recruitment (CARD) domains, a central DExD/H box RNA helicase domain, and a C-terminal repressor domain (reviewed in [22]). When no RNA is present, RIG-I remains in a closed conformation where the CARD domains are bound by the repressor domain and cannot signal [28]. RNA binding stimulates a conformational change that releases the CARD domains from the repressor domain, allowing for RIG-I multimerization and CARD domain association with the RLR adaptor protein, MAVS [29–32]. On the other hand, MDA5 lacks a functional repressor domain and does not shield its CARD domains, and instead relies on multimerization along double-stranded RNA for MAVS recruitment [33]. The third member of the RLR family, LGP2, lacks a CARD domain and may act as a regulator of RIG-I and MDA5 signalling [26].

The RLR adaptor protein, MAVS, is a CARD domain-containing transmembrane protein that is localized to the outer membrane of mitochondria, to mitochondria-associated membranes and to peroxisomes [29–32]. Upon RLR activation, relocalization to MAVS-containing membranes occurs, and CARD-CARD interactions between RLRs and MAVS leads to activation of kinases. These kinases can then phosphorylate and activate NF- κ B and IRF3/7 to induce type I IFNs. Like TLRs, RLRs can also induce IFN λ .

While RLRs are cytosolic sensors of foreign RNA, there are also cytosolic sensors of foreign DNA. The central regulator of DNA sensing is stimulator of interferon genes (STING), an endoplasmic reticulum-resident transmembrane protein that also localizes to mitochondria and mitochondria-associated

membranes [34–38]. Upon STING activation, either through direct sensing of DNA or by an upstream DNA sensor, STING dimerizes and translocates to the perinuclear region, where TBK1 is then recruited. TBK1 can then phosphorylate STING and IRF3, resulting in the induction of type I IFN.

There are multiple DNA sensors that can activate STING (reviewed in [39]). These include DAI, the first DNA sensor to be identified, DDX41, which is a dendritic cell-specific DNA sensor, and IFI16, which can recognize both cytoplasmic and nuclear DNA, among several others. cGAS is the most recently identified cytoplasmic DNA sensor, where binding of DNA to cGAS stimulates the catalysis of cGAMP from ATP and GTP [40–42]. cGAMP then acts as a second messenger to activate STING. cGAS can also be activated by RNA:DNA hybrid molecules, and there is some evidence that STING can be activated by fusion of viral and host membranes [43,44].

Nucleotide binding oligomerization domain (NOD)-like receptors (NLRs) are another class of PRRs that recognize PAMPs in the cytoplasm (reviewed in [45]). There are 22 mammalian NLRs, several of which can form inflammasomes, which are comprised of an NLR, procaspase 1 and ASC. NLR oligomerization results in activation of caspase 1, which can then cleave and mature pro-IL-1 β and pro-IL18 to their active forms, IL-1 β and IL18. These pro-inflammatory cytokines are secreted and can then bind their cognate receptors, resulting in downstream activation of NF- κ B. Inflammasomes can also be formed by non-NLR proteins like AIM2 and RIG-I, an RLR.

NLRs consist of an N-terminal effector domain, a central NOD domain and variable numbers of LRR domains [46]. The effector domain can be either a CARD or PYD domain, which can form homotypic interactions with adaptor proteins and caspases. The NOD domain is responsible for NLR oligomerization, which is an ATP-dependent process. As is the case for TLRs, the LRR domains of NLRs are responsible for PAMP sensing. These domains may also function to auto regulate NLR activation by binding the NOD domain and preventing spontaneous NLR oligomerization [47,48]. NLRs can recognize several PAMPs, as well as damage-associated molecular patterns (DAMPs), and direct binding of NLRs to bacterial components has been demonstrated [49,50]. It is possible that NLRs sense cellular changes induced by viral infection, rather than viral proteins or nucleic acids [51,52].

3. Detection of tumour viruses by pattern recognition receptors

(a) DNA tumour viruses

(i) Kaposi's sarcoma-associated herpesvirus

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8, is the etiologic agent of three human cancers, Kaposi's sarcoma, primary effusion lymphoma and multicentric Castlemann's disease [53]. KSHV is a gammaherpesvirus with a large, double-stranded DNA genome. Like other herpesviruses, KSHV primarily establishes latent infection where only a few viral genes are expressed, but can be reactivated from latency to a lytic state where genome replication and production of progeny virions occur. KSHV infection is detected by a variety of PRRs. In primary monocytes, KSHV infection activates TLR3, which may be recognizing viral RNA transcripts packaged in the tegument, resulting in TLR3

upregulation and induction of IFN [54]. In plasmacytoid dendritic cells (pDCs), the major IFN-producing cells in the human body, KSHV DNA activates TLR9 [55,56]. TLR signaling can also stimulate reactivation from latency in infected B cells, as reactivation can be triggered by treatment with a TLR7/8 agonist or by infection with vesicular stomatitis virus [57]. Furthermore, *de novo* KSHV infection and reactivation from latency are detected by RIG-I and MAVS [58], as well as the cGAS-STING pathway [59]. Mice deficient for cGAS have higher viral titres following infection with MHV68, a virus related to KSHV, providing further evidence for the importance of the cGAS-STING pathway in detecting and suppressing KSHV infection [60]. KSHV infection is also detected by IFI16 and NLRP1, which form inflammasomes that stimulate IL-1 β secretion [61,62].

(ii) Epstein–Barr virus

Epstein–Barr virus (EBV), also known as human herpesvirus 4, infects more than 90% of the world's population [63]. EBV is associated with Burkitt's lymphoma, Hodgkin lymphoma and post-transplant lymphoma, as well as nasopharyngeal carcinoma [63,64]. Like KSHV, EBV is a gammaherpesvirus with a large double-stranded DNA genome, and latent and lytic phases of the viral life cycle. EBV infection is detected by TLRs 2 and 7, which do not require viral replication for stimulation, as both wild-type and UV-inactivated virus can activate these TLRs [65]. Surprisingly, TLR2 can also be activated by a nonstructural protein, the EBV dUTPase [66]. In B cells, the natural reservoir of EBV, infection results in TLR7 upregulation and TLR9 activation [67–69]. Likewise, EBV stimulates TLRs 7 and 9 in pDCs [70,71]. TLR7 can be activated by EBV-encoded RNAs (EBERs), which may be released from infected cells in exosomes, activating PRRs in neighbouring cells and stimulating IFN production [71,72]. EBERs are also detected by RIG-I, as they are RNA polymerase III-derived transcripts which contain a 5' triphosphate moiety [73].

(iii) Human papillomavirus

Human papillomavirus (HPV), a non-enveloped virus with a small, double-stranded DNA genome, infects the basal keratinocytes of skin or mucous membranes. High-risk HPV subtypes are the causative agents of cervical cancer and are also associated with anogenital, oropharyngeal, and head and neck cancers [74]. In keratinocytes, HPV DNA is detected by TLR9 [75]. Additionally, there is some circumstantial evidence to support a role for STING in detection of HPV in that HPV E2 downregulates STING [76], and HPV E7 interacts with and inhibits this sensor [77], although sensing of HPV primary infection by STING has not yet been demonstrated.

(iv) Hepatitis B virus

Hepatitis B virus (HBV) currently infects approximately 240 million people worldwide, and chronic HBV infection can lead to liver cancer [78]. An estimated 73% of liver cancer deaths worldwide are attributable to hepatitis viruses. HBV is an enveloped virus with a partially double-stranded DNA genome. When HBV-infected cells are transfected to overexpress the TLR adaptor proteins MyD88 or TRIF, the RLR adaptor protein MAVS, or the DNA sensor DAI, the quantity of HBV DNA and RNA in those cells decreases [79,80]. Treatment of HBV transgenic mice with TLR3, 4, 5, 7 or 9

agonists, but not TLR2 agonists, reduced HBV replication [81]. A TLR7 agonist also decreased HBV DNA in the liver of infected chimpanzees [82]. Additionally, in transfected cells or in mice hydroponically injected with HBV genomes, MDA5 is upregulated and is activated by HBV, and HBV-infected mice heterozygous for MDA5 have increased HBV DNA compared to wild-type mice [83]. Taken together, these data indicate that both TLRs and RLRs are responsible for detecting HBV infection.

(v) Merkel cell polyomavirus

Merkel cell polyomavirus (MCV) is a small, non-enveloped virus with a double-stranded DNA genome. MCV is the causative agent of Merkel cell carcinoma, a rare type of skin cancer [84]. The interaction between MCV and the innate immune system is largely unknown. However, TLR9 may play a role in the detection of MCV infection given that MCV large T antigen downregulates TLR9 expression [85].

(b) RNA tumour viruses

(i) Hepatitis C virus

Hepatitis C virus (HCV) is a flavivirus that currently infects approximately 170 million people worldwide [86]. HCV is capable of establishing chronic infection, which can result in liver damage and hepatocellular carcinoma [87]. HCV is an enveloped virus with a single-stranded, positive sense RNA genome. The HCV core protein and non-structural protein 3 activate TLR2 at the cell surface [88]. In endosomes, HCV RNA is detected by TLR3 and by TLR7/8 [89,90]. HCV RNA is also sensed in the cytoplasm by RIG-I, which recognizes several features of the HCV genome such as a 3' polyU sequence, short regions of dsRNA, and the 5' triphosphorylated end of the genome [91–93]. Surprisingly, the HCV 3'UTR can also stimulate STING [94]. HCV infection also activates NLRP3, which may sense cellular changes induced by infection, as the production of reactive oxygen species during infection is important for NLRP3 activation [95,96].

(ii) Human T-cell lymphotropic virus type 1

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that currently infects an estimated 15–20 million people worldwide [97]. HTLV-1 is associated with adult T-cell leukaemia/lymphoma, a proliferation of CD4+ T cells caused by integration of the HTLV-1 provirus. HTLV-1 is predominantly detected in CD4+ T cells, but has also been found in other immune cells including pDCs [98,99]. In pDCs, HTLV-1 RNA is detected by TLR7 [100]. Currently, no other PRRs have been described as important for innate immune detection of HTLV-1.

4. Evasion of host innate immunity by tumour viruses

Tumour viruses employ a variety of mechanisms to evade the host innate immune response. These strategies include downregulation of sensors, inhibition of signal transduction pathways and disruption of transcription factor activation, among others. The following section will describe tumour virus-encoded proteins that antagonize the innate immune response. Figure 1 summarizes tumour virus inhibition of TLR

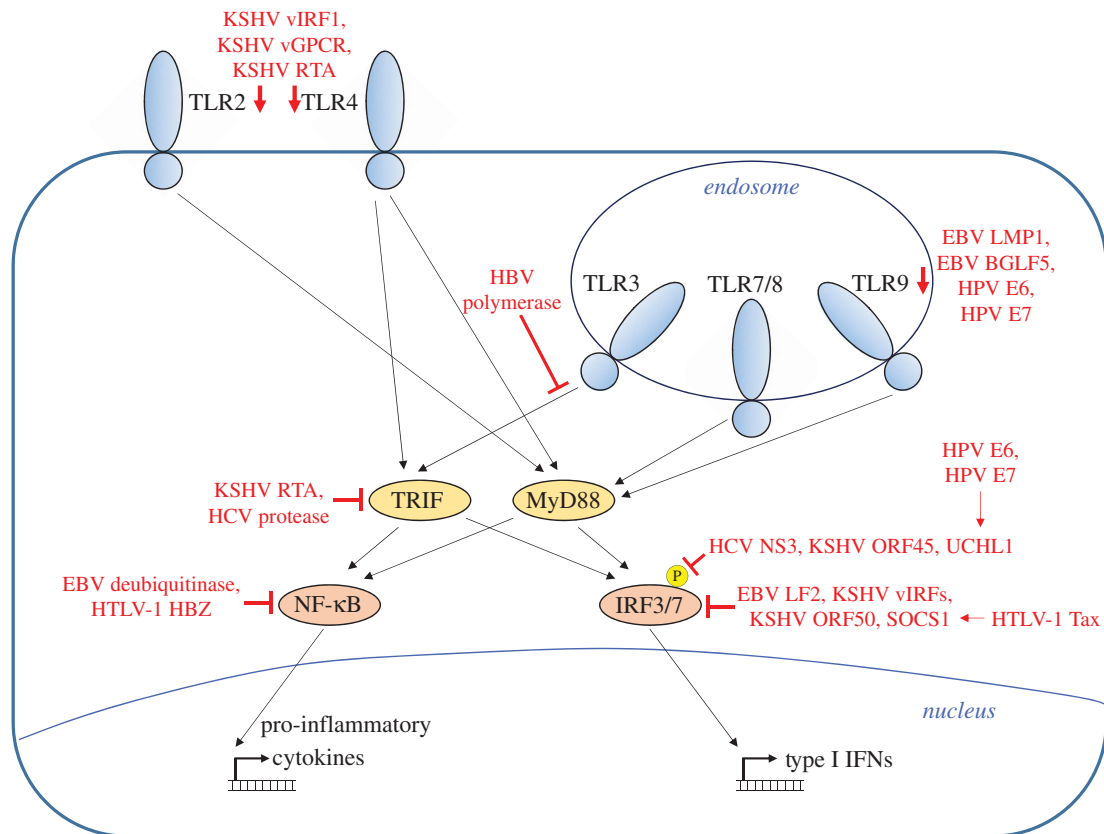


Figure 1. Inhibition of TLR signalling by tumour viruses. TLRs 2 and 4, which are responsible for detecting viral proteins at the plasma membrane, are down-regulated by KSHV vIRF1, vGPCR and RTA. The endosomal TLRs are responsible for detecting nucleic acid and include TLR3, TLR7/8 and TLR9. TLR9 is downregulated by EBV LMP1, EBV BGLF5, HPV E6 and HPV E7. TLRs signal through the adaptor proteins TRIF and MyD88. TLR3 signalling is inhibited by the HBV polymerase, and TRIF is inhibited by KSHV RTA and by the HCV protease. TRIF and MyD88 activate the transcription factors IRF3/7 and NF- κ B, which is inhibited by the EBV deubiquitinase and by HTLV-1 HBZ. IRF phosphorylation is inhibited by HCV NS3, KSHV ORF45 and the cellular protein UCHL1, which is induced by HPV E6 and E7. IRFs are inhibited by EBV LF2, KSHV vIRFs, KSHV ORF50 and the cellular protein SOCS1, which is induced by HTLV-1 Tax.

signalling pathways, and figure 2 summarizes inhibition of cytoplasmic PRRs.

(a) DNA tumour viruses

(i) Kaposi's sarcoma-associated herpesvirus

KSHV encodes several proteins that antagonize the innate immune response. For example, KSHV vIRF1, vGPCR and RTA downregulate TLRs 2 and 4 [101,102]. Additionally, the adaptor protein responsible for mediating TLR3 and some TLR4 signalling, TRIF, is degraded by KSHV RTA [103]. RIG-I signalling is also disrupted by KSHV, as the KSHV deubiquitinase ORF64 prevents RIG-I ubiquitination, a modification essential for RIG-I activity [104]. In addition to inhibiting TLR and RLR signalling, KSHV blocks STING signalling. KSHV ORF52 disrupts cGAS binding to DNA and inhibits the enzymatic activity of cGAS to prevent STING activation [105]. Furthermore, there is evidence that cytoplasmic localized isoforms of LANA (latency-associated nuclear antigen) bind cGAS and prevent cGAS-mediated IFN production [106]. Additionally, KSHV vIRF1 blocks STING activation by disrupting STING interactions with TBK1 [59]. Inflammasome signalling can also be inhibited by KSHV ORF63, which blocks the NLRP1 inflammasome to prevent caspase activation and IL1 β and IL18 processing, thereby reducing NLRP1-mediated cell death [62]. Finally, KSHV can disrupt transcription factor activation. Three of the four KSHV vIRF proteins interact with cellular IRFs and prevent their transcriptional activity (reviewed in [107]). KSHV ORF45 prevents IRF7 phosphorylation, and

ORF50 can stimulate IRF7 ubiquitination and degradation [108,109]. Lastly, KSHV LANA competes with IRF3 to bind the IFN promoter, thereby reducing IFN transcription [110].

(ii) Epstein–Barr virus

Like KSHV, EBV inhibits the innate immune response at several points in PRR signalling pathways. The EBV proteins LMP1 and BGLF5 reduce TLR9 expression through inhibition of TLR9 transcription or degradation of TLR9 transcripts, respectively [69,111]. EBV encodes a deubiquitinase that prevents TLR signalling-mediated NF- κ B activation [112]. Additionally, EBV ORF52 blocks cGAS binding to DNA [105]. Finally, the EBV tegument protein LF2 disrupts IRF7-mediated IFN expression [113], and EBV infection induces the expression of a dominant negative form of IRF5 [67].

(iii) Human papillomavirus

HPV employs similar innate immune evasion strategies to KSHV and EBV. For example, the E6 and E7 proteins from high-risk HPV subtypes reduce TLR9 expression, and the TLR3 adaptor, TICAM1, is downregulated in HPV-positive cells [75,114]. Additionally, HPV E7 blocks cGAS-STING signalling [77]. HPV-positive keratinocytes have reduced NLRP2 expression compared to uninfected cells, and the E6 protein from high-risk HPV subtypes can mediate degradation of the immature form of IL-1 β , thereby reducing the impact of inflammasome signalling [114,115]. HPV also disrupts transcription factor activation, as the E6 and E7 proteins from

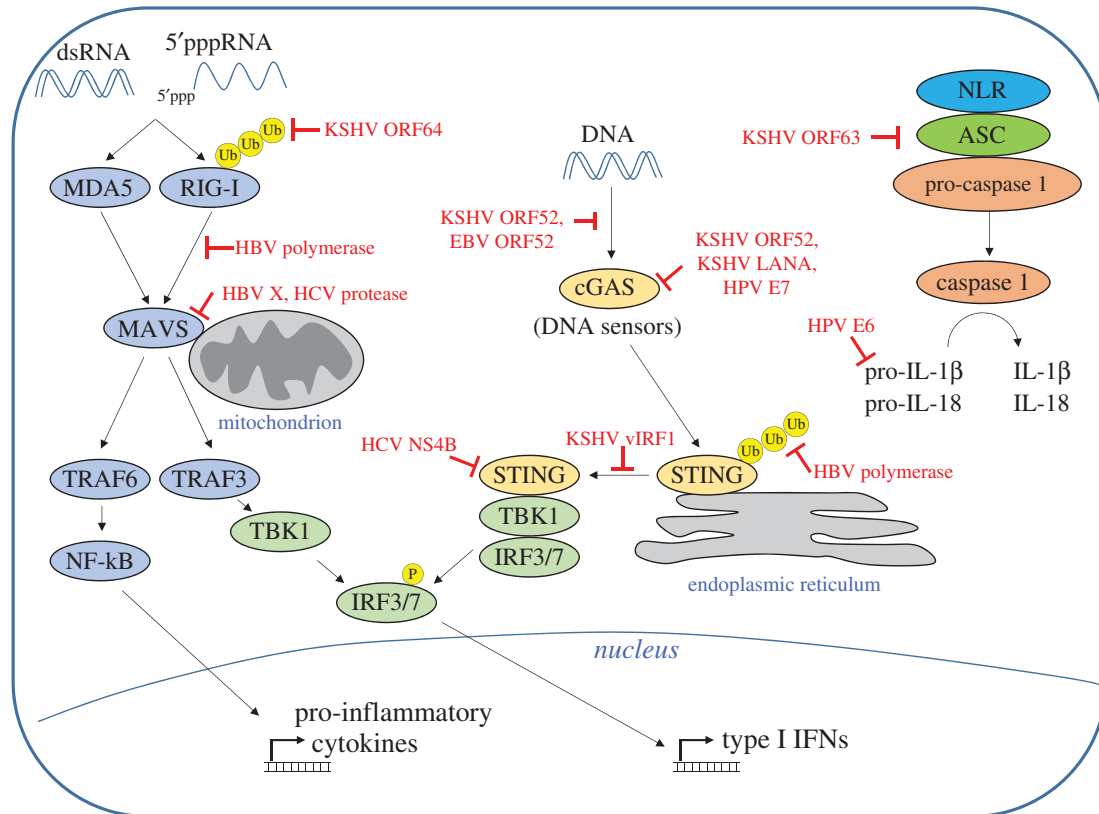


Figure 2. Inhibition of cytoplasmic PRRs by tumour viruses. Cytosolic double-stranded RNA is detected by the RLRs RIG-I and MDA5. RIG-I ubiquitination is inhibited by KSHV ORF64, and RIG-I signalling is inhibited by the HBV polymerase. RLRs signal through the adaptor protein MAVS, which is inhibited by HBV X and the HCV protease. Cytosolic DNA is detected by a variety of DNA sensors, including cGAS. Binding of DNA to cGAS is inhibited by KSHV ORF52 and EBV ORF52. cGAS activity is inhibited by KSHV ORF52, KSHV LANA and HPV E7. DNA sensors activate STING. STING ubiquitination is inhibited by the HBV polymerase, KSHV vIRF1 prevents STING association with TBK1, and HCV NS4B disrupts STING signalling complexes. The NLRP1 inflammasome is inhibited by KSHV ORF63, and HPV E6 mediates degradation of pro-IL-1 β .

high-risk HPVs downregulate genes involved in NF- κ B activation, and upregulate UCHL1, a disruptor of TLR signalling that inhibits IRF3 phosphorylation [116]. UCHL1 also blunts NF- κ B activation by destabilizing NF- κ B essential modulator, a scaffolding protein that coordinates the degradation of I κ B to allow for NF- κ B nuclear translocation. HPV E2 downregulates IFN κ , a type of IFN secreted exclusively by epithelial cells [76]. Furthermore, the E6 protein from high-risk HPVs prevents phosphorylation of STAT transcription factors, which are critical for mediating signalling from the IFN receptor and upregulating ISGs [117]. This disruption is essential for HPV replication and long-term maintenance of HPV episomes. The E6 and E7 proteins from high-risk HPVs are also capable of downregulating some IFN-stimulated genes, and can counteract the effects of the ISG PKR, a kinase that blocks all translation by phosphorylating the translation initiation factor EIF2 α [118,119]. E6 and E7 prevent PKR phosphorylation and activation, allowing translation to occur [119].

(iv) Hepatitis B virus

HBV is also capable of disrupting the innate immune response. Purified HBV virions inhibit signalling from TLRs 3 and 4, and the HBV polymerase inhibits both TLR3 and RIG-I signalling [120–122]. Signal transduction through the RLR adaptor protein MAVS is also disrupted by an interaction with the HBV X protein [123]. Additionally, the HBV polymerase interacts with STING and blocks STING K63-linked polyubiquitination, a modification essential for STING-mediated IFN induction [124].

(v) Merkel cell polyomavirus

The mechanisms of MCV evasion of the innate immune response remain largely unknown. However, it has been reported that MCV small T antigen binds to and disrupts NF- κ B essential modulator, thereby inhibiting NF- κ B activation and signalling [125].

(b) RNA tumour viruses

(i) Hepatitis C virus

HCV also encodes proteins that disrupt innate immune signalling. The HCV protease cleaves the TLR3 and TLR4 adaptor protein TRIF, as well as the RLR adaptor MAVS [30,126]. Additionally, the HCV NS4B protein is a STING homologue that interacts with STING and disrupts STING signalling complexes [94]. Finally, HCV NS3 prevents IRF3 phosphorylation [127].

(ii) Human T-cell lymphotropic virus type 1

HTLV-1 uses several mechanisms to disrupt IRF and NF- κ B signalling. HTLV-1 induces expression of microRNAs that downregulate mediators of PRR signalling, like the kinase responsible for phosphorylating IRF3 [128,129]. Additionally, HTLV-1 Tax induces SOCS1 expression, a protein responsible for IRF3 ubiquitination and degradation [130,131]. Furthermore, the HTLV1 HBZ protein interacts with NF- κ B and blocks NF- κ B DNA binding activity, and can also stimulate NF- κ B ubiquitination and degradation [132]. HTLV-1 also

blunts STAT signalling, possibly through Tax competing with STAT2 for co-activating proteins [133,134].

In summary, cells encode an array of PRRs that can detect viral infection by recognizing PAMPs. These PRRs can sense viral proteins at the surface of the cell, or viral nucleic acid in endosomes, in the cytoplasm, or in the nucleus. Tumour virus infection is detected by these receptors, which results in activation of transcription factors that upregulate pro-inflammatory cytokines, chemokines and IFN. These molecules are responsible for attracting immune cells to the site of infection, and for inducing an antiviral state in infected and neighbouring cells. However, tumour viruses have several mechanisms for confounding the innate immune

response, including downregulating PRRs, preventing PRR recognition of their substrates, blocking transcription factor activation, disrupting signalling from IFN receptors, and inhibiting the effects of antiviral proteins.

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Competing interests. We declare we have no competing interests.

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