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Virus-cell interactions: impact on cytokine production, immune evasion and tumor growth

Abstract

The outcome of a viral infection ranges from benign to fatal with the clinical pictures being very diverse. This is largely due to the virus-cell interactions that occur in the infected organism. Rapidly after infection, cells initiate a first line of defense against the virus. The cells sense viruses through several mechanisms. Among these the ability to respond to accumulation of double-stranded RNA has been particularly well studied and seems to be of importance. On the other hand, the close co-existence of virus and host has allowed viruses to develop

mechanisms to down-modulate the initial reaction or to exploit this proinflammatory response in its own advance. This review describes how virus infections affect cellular signal transduction and the mechanisms through which certain viruses modulate this response to dampen the immune response or prevent cell death.

Full text

INTRODUCTION

The establishment of a viral infection is a battle bet-ween the virus and the host. Since virus and host have co-evolved, the organism is armed with mechanisms to defeat the intruder and, likewise, the virus has adapted strategies to circumvent the host response. To be able to respond rapidly to virus infections cells are armed with various latent mechanisms that are able to sense viral components and initiate intracellular signal transduction, thus mounting an antiviral host response. In parallel an overwhelming number of viral tactics to evade or down-regulate the host response have been described. Appropriation of the cellular machinery for macromolecular biosynthesis is also a common event utilized by many viruses. Some viruses exploit this to tune the cell to selectively produce viral products, whereas for other viruses this leads to cell transformation and tumorigenesis. By focusing on selected human pathogenic viruses this review highlights the current understanding of virus-cell interactions and how this affects the host immune response and may influence normal cellular growth.

VIRUS-INDUCED SIGNAL TRANSDUCTION

The ability of the organism to mount a strong first line of antiviral defense is highly dependent on the cells being able to activate signal transduction cascades that bring about production of *e.g.* proinflammatory cytokines, free radicals, pro-apoptotic proteins and antigen-presentation-associated proteins [1, 2]. The best-described virus-activated signal transduction pathways are illustrated in Figure 1 and described in more details below.

Nuclear factor kappaB (NF-kappaB), is the cardinal cellular proinflammatory transcription factor. It is a homo- or hetero-dimeric complex present in the

cytoplasm in a latent form associated with an inhibitory subunit, IkappaB [3, 4]. Following the appropriate stimulus, IkappaB is serine phosphorylated by the IkappaB kinase (IKK), ubiquitinated, and eventually degraded by the 26S proteasome. Released from IkappaB, the nuclear localization signal of NF-kappaB is exposed and the transcription factor migrates to the nucleus and activates transcription. Viruses are able to activate NF-kappaB through many different mechanisms [2], but common to many infections is the pathway dependent on accumulation of double-stranded RNA (dsRNA). The dsRNA-activated protein kinase (PKR) becomes active upon dsRNA-binding and activates IKK, which in turn mediates NF-kappaB activation [5].

The interferon (IFN) regulatory factor (IRF) family of transcription factors is involved in many aspects of the immune response [6]. For instance, IRF-1 deficient mice fail to develop natural killer cells and are hyporesponsive to IFN-gamma. With respect to virus-induced signal transduction IRF-3 and IRF-7 have been shown to be activated in a virus-specific manner and to play crucial roles in clearance of virus infections [7]. Like NF-kappaB, the two IRFs require post-translational modification to become activated. Upon infection, the proteins are serine/threonine phosphosphorylated, which allow the proteins to adapt a conformation compatible with homo- or heterodimerization. The dimers migrate to the nucleus and activate transcription. There is evidence that IRF-3 and -7 are essential for the ability of virus-infected cells to produce IFN-alpha/beta [7] as well as the CC chemokine RANTES [8].

A third group of transcription factors activated by many viruses include activator protein-1 (AP-1) and activating transcription factor 2 (ATF2)/Jun. Activation of these transcription factors is dependent on up-stream kinases of the mitogen-activated protein (MAP) kinase family, *e.g.* p38 and Jun N-terminal kinase (JNK) [9]. The transcription factors are active as dimers with Jun family members being part of both the ATF2/Jun complex and AP-1 (Figure 1). The involvement of AP-1 and ATF2/Jun in virus-induced cytokine and chemokine-induction is well documented. For example herpes simplex virus (HSV) type 2-induced TNF-alpha production relies on ATF2/Jun [10] and HIV-1 upregulates production of monocyte chemoattractant protein 1 via AP-1 [11].

Another transcription factor activated in response to virus infection is nuclear factor of activated T cells (NF-AT). NF-AT is constitutively present in the cytoplasm of some cell types, notably T cells, in a latent phosphorylated form.

Increasing levels of cytoplasmic calcium activates the calmodulin-dependent phosphatase calcineurin, which activates NF-AT by dephosphorylation [12].

In addition to the above-described examples, other cellular transcription factor activities have been reported to be affected by virus infection. These include CCAAT enhancer-binding proteins (C/EBPs), selective promoter factor (Sp1), and cAMP response element binding protein (CREB) [13, 14]. In conclusion, virus-cell interactions lead to activation of a range of cellular signal transduction pathways. Below we discuss how this impacts on host defense and normal cellular growth and describe how viruses have evolved strategies to interfere with the cellular response to infection.

MOLECULAR INTERACTIONS GOVERNING CYTOKINE PRODUCTION BY VIRUS-INFECTED CELLS

Concerning the virus-cell interactions responsible for the above-described findings, much can be learned from what is currently known about virus-induced cytokine production. For many virus infections the first wave of cytokine production is important for the eventual outcome of the infection [15, 16]. Moreover, given the well-described role of cytokines in virus-mediated immunopathology [17, 18], it is no surprise that in-depth understanding of virus-induced cytokine production has received much attention recently.

Viruses can trigger cells to produce cytokines through a number of mechanisms, which are summarized in Figure 2. First, interactions between viral surface proteins and cellular receptors can trigger signaling from the cytoplasmic region of the receptor and thus stimulate cytokine production. To illustrate, the Epstein-Barr virus (EBV) glycoprotein gp350 interacts with the cellular surface protein CD21 and triggers cells to produce *e.g.* tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta and IL-6 (for a more comprehensive list see ref. 2). At the level of intracellular signaling this involves CD21-dependent activation of NF-kappaB, p38 and the phosphatidylinositol 3-kinase (PI-3K) [19-21]. Other viral surface proteins able to stimulate cytokine production include the HIV-1 gp120 protein [22-24] and gD of HSV-1 [25, 26].

Second, proteins packed into the virus particle and released into the cell upon infection may also affect signal transduction in a manner that stimulates cytokine production. This is best documented for the HIV-1 viral protein R (Vpr),

which is able to trigger production of at least IL-6, IL-8, IL-10, TNF-alpha, and IFN-gamma in certain cell types [27]. Concerning the mechanisms employed by Vpr to bring about cytokine production, there is evidence that NF-kappaB and C/EBPbeta are involved but the upstream signals remain to be elucidated [27]. Studies with HSV-1 and -2 suggest that as yet unidentified virion-associated (tegument) proteins play a role in induction of TNF-alpha production in macrophages [26].

Third, accumulation of viral dsRNA during viral replication may lead to production of a number of cytokines. This is due to the ability of the cell to sense dsRNA and subsequently activate stress-induced signaling by PKR and the IRF-3/7 pathway, as well as by yet unidentified pathways [28-31]. The examples of dsRNA-induced cytokine production are numerous with the process of IFN-alpha/beta induction being the first discovered and best described [32]. Other examples of cytokine production through dsRNA-dependent pathways include induction of IL-6 expression by HSV and the murine picornavirus encephalomyocarditis virus [31, 33]. Recently it has been shown that EBV triggers cells to produce IL-10 through a mechanism dependent on viral poly(A)-negative RNAs (EBERs) but independent of any known RNA-dependent signaling [30].

Fourth, overload of viral proteins in the endoplasmic reticulum (ER) activates cellular stress signaling and may subsequently activate cytokine production. It is known that influenza virus hemagglutinin and the E3/19K protein of adenovirus activate NF-kappaB through the ER pathway [34], but cytokines being the endpoint of this pathway have not been described. However, given the well-established role of NF-kappaB as inducer of proinflammatory mediators, it seems likely that influenza virus hemagglutinin and the E3/19K protein of adenovirus may activate cytokine production through this pathway.

Finally, production of cytokines and chemokines by infected cells can be brought about by viral proteins produced during latency or productive life cycle of the virus. The mechanisms are very diverse and depend on the nature of the specific protein [2]. The latent membrane protein 1 (LMP1) of EBV stimulates production of at least IL-6, IL-8 and IL-10 [21, 35]. LMP1 is a membrane-spanning protein with a cytoplasmic domain activating signal transduction. There is evidence that LMP1 activates NF-kappaB, ATF2 and IRF-7, which are responsible for the ability of this protein to stimulate cytokine production [21, 36, 37]. The Tax protein of human T-lymphotropic virus type 1 (HTLV-1) is also a potent inducer of cytokine

production. For instance, Tax brings about production of a whole array of cytokines, including IL-2, TNF-alpha and IFN-gamma [38, 39]. The mechanisms underlying this involve the ability of Tax both to stimulate the NF-kappaB, NF-AT and MAP kinase pathways in the cytoplasm [40-42] and to augment transcription factor activity directly through protein-protein interactions [43, 44].

Altogether, viruses induce cells to produce cytokines through multiple virus-cell interactions. This illu-strates that cells are in possession of many mechanisms to sense viruses and quickly mount an antiviral response. However, as will be described below, the virus-cell interaction is a constant battle and many viruses have evolved strategies to down-modulate the host response to infection.

VIRAL STRATEGIES TO COUNTERACT PROINFLAMMATORY SIGNAL TRANSDUCTION

Given the discussion above, it appears that proinflammatory signaling activated in infected cells helps the organism to mount an antiviral response. With the intimate nature of the virus-cell relationship in mind, it is therefore no surprise that many viruses have evolved mechanisms to counteract the cellular response to infection. This section presents selected examples and discusses the mechanisms of action.

Influenza virus infects and replicates in epithelial cells of the upper respiratory tract. To facilitate replication the virus has means to dampen the cellular defense against the virus. This is primarily mediated by the viral nonstructural protein 1 (NS1), which is able to inhibit activation of NF-kappaB, IRF-3 and PKR [45-47]. This function of NS1 strongly impairs the ability of the infected cell to produce IFN-alpha/beta in response to the infection and may thus contribute to the virulence of influenza virus.

Another elegant example of virus-mediated evasion of the host response is provided by the African swine fewer virus (ASFV). This virus primarily infects porcine macrophages and causes an often fatal hemorrhagic disease in susceptible pig populations. Interesting-ly, infection by ASFV is characterized by the absence of an adequate host response to the infection. Part of the explanation to this phenomenon seems to be associated with the fact that ASFV encodes an ankyrin motif-rich protein, A238L [48, 49], highly homologous to

IkappaBalpha. This homologue has now been found to be responsible for inhibition of NF-kappaB activation as well as cytokine production in infected cells [48, 49]. The ASFV A238L protein also inhibits NF-AT activation by interacting with the NF-AT-activating phosphatase calcineurin [50]. Although not a human pathogen, this virus provides a textbook example of how viral appropriation of cellular mechanisms may be exploited by viruses to inhibit virus-induced cellular proinflammatory signal transduction and hence the antiviral defense.

The mumps virus, a paramyxovirus, which causes parotitis, is also able to interfere with cellular signal transduction in a manner that may impair the immune response against the infection. Signal transduction by IFN-alpha/beta/gamma is dependent on signal transducer and activator of transcription (STAT)-1alpha [32, 51] and this transcription factor is the key mediator of antiviral responses by the three IFNs [52, 53]. Mumps virus causes a decrease in the cellular levels of STAT1alpha and thus renders cells less sensitive to IFNs [54].

Adenovirus employs a very cunning strategy to hamper the ability of infected cells to eradicate the virus. The E1A protein binds to the transcriptional co-activator CREB-binding protein (CBP)/p300 and hence impairs the ability of cells to trigger inducible transcription of antiviral products [55]. For instance, cells expressing E1A display impaired capacity to respond to IFN stimulation [56].

Above it was mentioned that influenza virus inhibits activation of PKR via its NS1 protein [47]. This virus also employs a second strategy to accomplish this goal, namely upregulation of the cellular inhibitor of PKR, p58IPK [57]. The important role of PKR in antiviral defense is now evidenced in the literature by the description of more than 10 different viruses that inhibit PKR function [58]. The mechanisms used include viral RNAs that bind but fail to activate PKR [59] and virus-activated phosphatases that dephosphorylate PKR target proteins [60].

In addition to the above-described inhibition of cellular signal transduction, some viruses exploit the proinflammatory signaling machinery to support virus replication. Replication of HIV-1 is driven by transcription of the viral genome from the long terminal repeat. This viral promoter contains multiple binding sites for transcription factors of the NF-kappaB, NF-AT, Sp1 and C/EBP families [61-65]. Thus, in addition to supporting antiviral defense, this group of

proinflammatory mediators aid viral replication and hence explains, why it may be beneficial for HIV to activate these transcription factors. Similar strategies are used by HSV, which displays reduced replication competence in cells unable to activate NF-kappaB and p38 [66, 67]. This is the case despite the essential roles of NF-kappaB and p38 in induction of the antiviral mediator TNF-alpha [26].

In summary, cells respond to viral infections by mounting a proinflammatory antiviral response. Viruses, on the other hand, have evolved mechanisms to either inhibit this response or to exploit the proinflammatory signal transduction in their own favor. This is accomplished by incorporation of binding sites for specific transcription factors into the promoter regions of their genomes, thereby promoting viral replication and spread.

VIRUSES AND TUMOR GROWTH

Many cell types respond to viral infections by undergoing apoptosis. This represents an efficient means to limit virus replication and spread. The molecular mechanisms of the pro-apoptotic response to virus infections involve IRF-3 and PKR [68, 69]. To counteract this, certain viruses are endowed with mechanisms to limit apoptosis [70, 71]. This prolongs the time window where the infected cell can produce new virus particles and hence supports viral replication. However, the interference with the apoptosis machinery of the cell may in some instances lead to transformation of the infected cells and tumorigenesis.

EBV plays a role in the pathogenesis of the lymphoproliferative disease Burkitt's lymphoma. The virus can also give rise to nasopharyngal carcinoma, where the tumor cells are of epithelial origin. The mechanism of cell transformation by EBV is very complex and detailed descriptions are beyond the scope of this review. For an updated description (see ref. 72). With respect to the discussion of the present review, it is of particular interest that transformation is dependent on LMP1 and its ability to activate NF-kappaB [72-74]. The basis for this seems to involve the anti-apoptotic activities of NF-kappaB [75], which include the cellular inhibitors of apoptosis (c-IAP1, c-IAP2 and IXAP), the TNF receptor-associated factors (TRAF1 and TRAF2) and Bcl-2 family proteins [76-78].

Another virus with oncogenic potential is hepatitis B virus (HBV). This virus can cause chronic hepatitis and hepatocellular carcinoma [79]. The HBV X protein

(HBx) has been found to be able to induce carcinomas in transgenic mice [80] and much research has thus focused on the role of this protein in cell transformation. One of the targets of HBx is the tumor suppressor p53. This transcription factor has multiple functions including modification of transcription, cell cycle arrest and control of pro-apoptotic pathways [79]. It has been demonstrated that HBx and p53 interact physically and that HBx inhibits p53-dependent apoptosis in primary human fibroblasts [81]. Another mechanism potentially involved in cell transformation by HBV is persistent activation of NF-kappaB [82]. However, at the same time there is evidence that HBx can stimulate apoptosis under certain conditions through induction of TNF-alpha and Myc proteins [83, 84]. Recently, Schneider and colleagues studied this apparent paradox in details and found that the balance between NF-kappaB and Myc proteins is important for whether HBx displays pro- or anti-apoptotic activities [85]. This finding reconciles previous discrepancies and furthermore defines an important parameter that may influence HBV pathogenesis.

HTLV-1 is a retrovirus with a well-documented oncogenic potential. HTLV-1 infections are normally asymptomatic, but after a long period of latency the virus can cause adult T cell lymphocytic leukemia (ATLL) or the non-oncogenic neurological disease HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Most described functions of HTLV-1, including its oncogenic potential, are ascribed to the viral protein Tax [38, 86]. The ability of HTLV-1 to cause cell transformation and leukemogenesis has been studied extensively and shown to involve multiple mechanisms including interference with cellular signal transduction [87]. First Tax activates NF-kappaB, which promotes cell survival through the anti-apoptotic activities of this transcription factor. NF-kappaB is also responsible for the observed elevation in IL-2 receptor alpha expression and autocrine secretion of IL-2 and IL-15 [39, 88]. Both of these cytokines are T lymphocyte growth factors and use the IL-2 receptor alpha chain. The role of NF-kappaB in tumorigenesis by HTLV-1 Tax is underscored by the finding that *in vivo* delivery of NF-kappaB anti-sense DNA rapidly leads to regression of Tax-induced fibrosarcomas [89]. Second, HTLV-1 Tax affects normal cellular control functions by repressing the function of a number of tumor suppressors [87]. Tax binds to the transcriptional co-activator CBP, in a manner incompatible with CBP-p53 interaction and thereby inhibits p53-dependent transcription [90]. Third, HTLV-1 Tax disrupts cell cycle control. This is done by counteraction of the activity of negative regulators of the cycline-dependent kinase (CDK) 4 through interactions with these proteins [91].

Consequently CDK will remain constitutively active and hence allow cell cycle progression and uncontrolled cell division.

The discussion above has focused on viruses with direct oncogenic activity. However, non-transforming viruses may also support tumor growth by indirect routs. Immunosuppressing viruses may do so by hampering tumor surveillance and anti-tumor immune mechanisms. Moreover, one virus may potentiate the activity of an oncogenic virus through trans-activation, this being best documented for HIV-1 [92]. There is now evidence that HIV-1 can promote the development of human herpes virus 8-dependent Kaposi's sarcoma. In addition, despite no etiologic association, HIV-1 can lead to a more aggressive tumor progression in human papilloma virus 16/18-associated cervical carcinoma.

In summary, this section has described how viruses can promote tumor growth. The virus may activate cellular signal transduction and interfere with various facets of normal cell cycle regulation, ultimately supporting cellular survival and neoplasia. Alternatively, certain non-oncogenic viruses can trans-activate oncogenic viruses or impair the organisms immune system, thus rendering normal tumor surveillance less efficient.

CONCLUSION

The outcome of a virus infection is determined by many factors. Early virus-cell interactions induce proinflammatory signal transduction in cells and initiate the first line of defense against the infection. For instance, production of cytokines and chemokines by virus-infected cells constitutes an early response against infection. This allows the infected organism to mount an efficient antiviral response. The viruses, on the other hand, have developed strategies to counteract the host response and hence facilitate viral replication. The mechanisms involved are numerous and include inhibition of proinflammatory cellular signal transduction. This balance between the ability of the organism to mount an antiviral response and the virus to develop counteracting measures is an important parameter in what determines the eventual outcome of an infection. Moreover, modulation of signal transduction may cause changes in the infected cells in a manner that leads to immortalization and cancer development with potential fatal outcome for the host.

Over the years, studies on virus-cell interactions have taught researchers important lessons about central aspects of immunology, cancer biology and basic cell biology. Future research will undoubtedly, yield even more interesting information about this fascinating virus-host interplay. Finally, and most importantly, there is hope that this knowledge will lead to drug developments that can be exploited in the clinic to develop more efficient treatment for patients.

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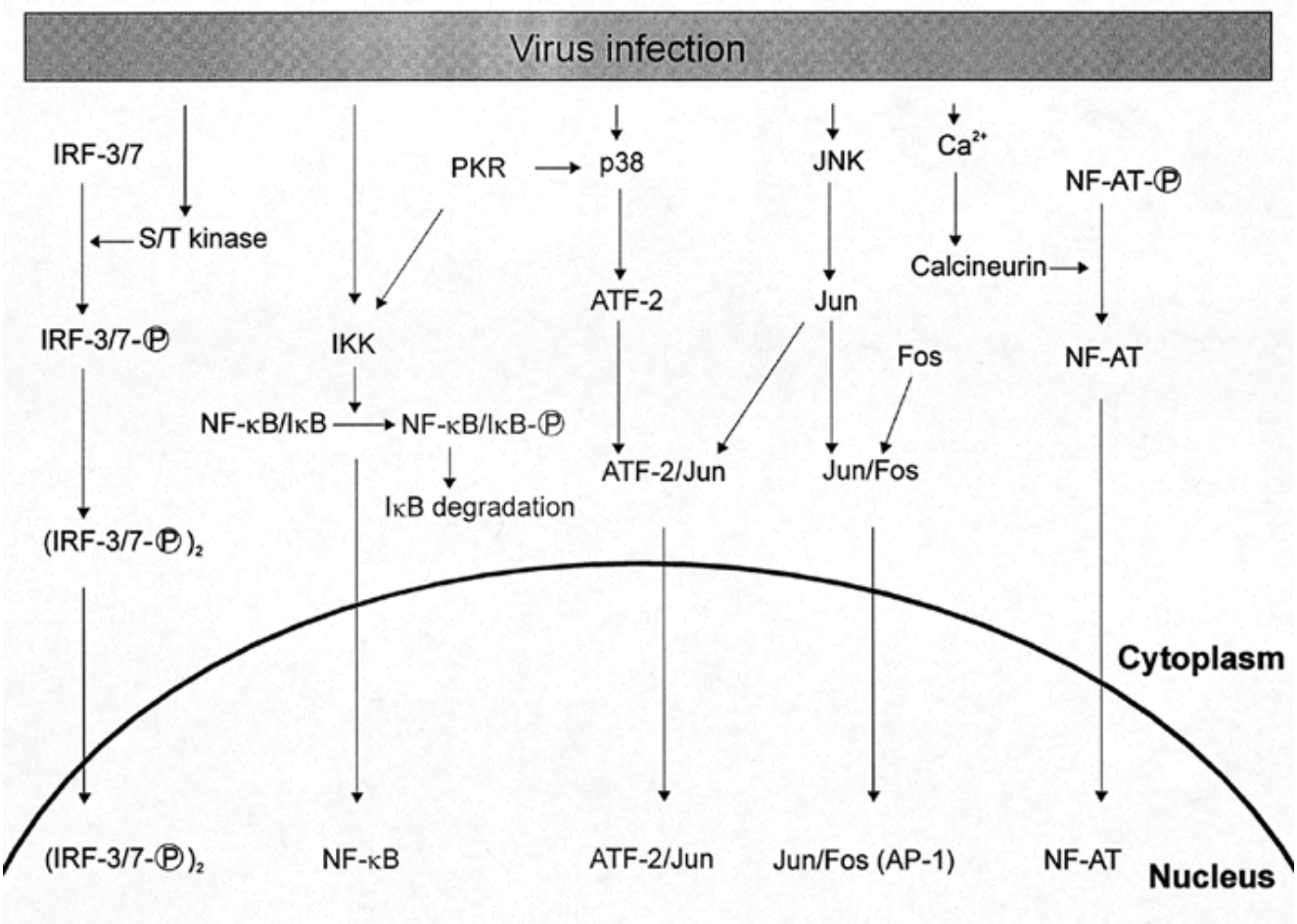


Figure 1

Signal transduction in virus-infected cells.

Cells respond to virus infection by activating a number of proinflammatory signaling cascades and transcription factors. The best described among these are IRF-3/7, NF-kappaB, ATF-2/Jun, AP-1 and NF-AT. Since these pathways contribute to establish the host response to infection,

some viruses have adapted strategies to interfere with cellular signal transduction. Yet other viruses exploit the proinflammatory cellular signaling machinery to support virus replication. For more detailed descriptions, see the text. S/T, serine/threonine kinase.

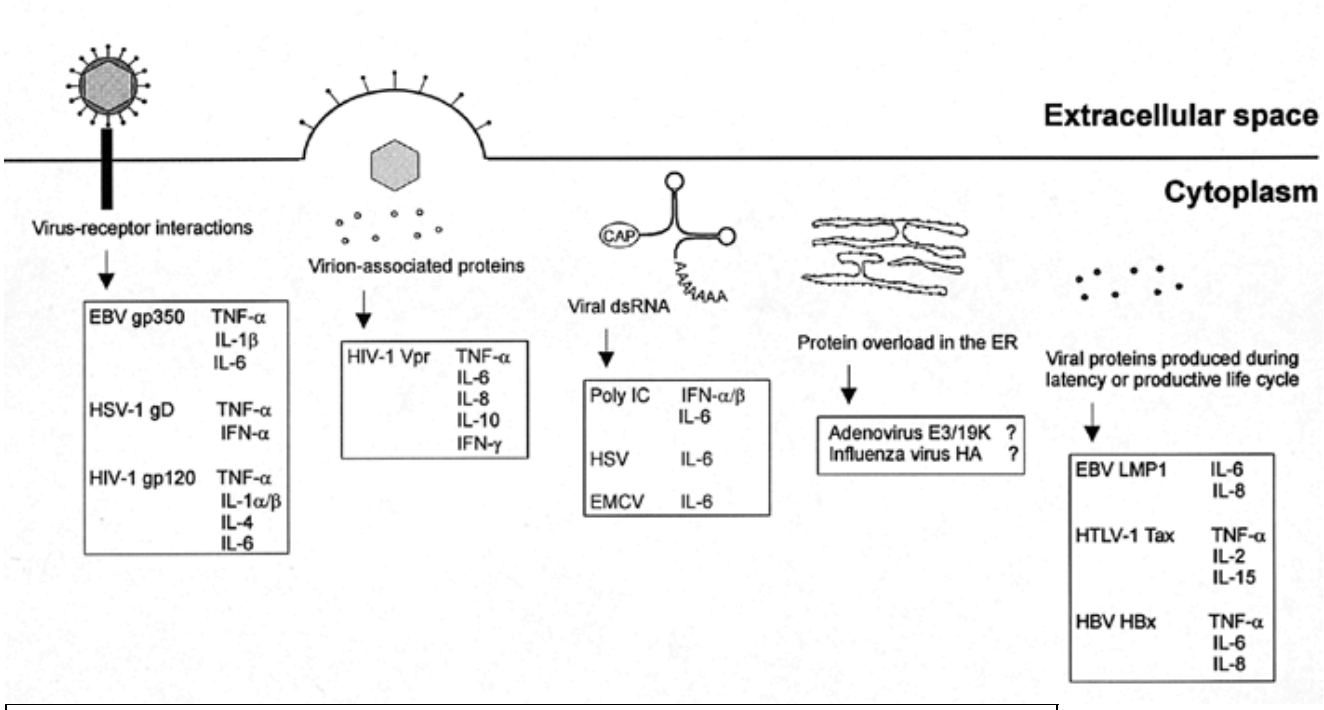


Figure 2

Virus-cell interactions regulating cytokine expression in virus-infected cells.

Viruses induce cells to produce cytokines by a number of mechanisms. First, virus-receptor interactions can induce intracellular signal transduction leading to cytokine expression. Second, virion-associated proteins released into the infected cell upon entry may stimulate cytokine production. Third, accumulation or viral dsRNA during viral replication is sensed by the cells through several mechanisms that support production of proinflamatory cytokines. Fourth, protein overload in the ER, due to massive production of viral proteins, activates cellular

stress signalling and can trigger cytokine production. Finally, virus-encoded proteins produced during latency or the productive replication cycle affect numerous cellular signal transduction pathways and hence support expression of cytokines. For each mechanism a few examples from the literature are given. EMCV, encephalomyocarditis virus. Other abbreviations used in the figure are defined in the text.

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