Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Viral suppression of the interferon system

Friedemann Weber*, Otto Haller

Abteilung Virologie, Institut für Medizinische Mikrobiologie und Hygiene, Universität Freiburg, D-79008 Freiburg, Germany

Received 29 November 2006; accepted 19 January 2007
Available online 27 January 2007

Abstract

Type I interferons (IFN-α/β) were originally discovered by their strong and direct antiviral activity [A. Isaacs, J. Lindenmann, Virus interference. I. The interferon, Proc. R. Soc. Lond. B Biol. Sci. 147 (1957) 258–267] (see review by J. Lindenmann on p. 719, in this issue). Nevertheless, only very recently it was entirely realized that viruses would not succeed without efficient tools to undermine this potent host defense system. Current investigations are revealing an astonishing variety of viral IFN antagonistic strategies targeting virtually all parts of the IFN system, often in a highly specific manner. Viruses were found to interfere with induction of IFN synthesis, IFN-induced signaling events, the antiviral effector proteins, or simply shut off the host cell macromolecule synthesis machinery to avoid booting of the antiviral host defense. Here, we will describe a few well-characterized examples to illustrate the sophisticated and often multi-layered anti-IFN mechanisms employed by viruses.

Keywords: Virus; Interferon; Interferon escape mechanism; Interferon antagonism

1. Interference with interferon induction

In most nucleated body cells, viral infections activate transcription of the "classic" IFN-β gene [1] by a signaling chain which is initiated by the RNA sensors RIG-I and MDA-5, which in turn act through the adaptor IPS-1 and the kinases TBK-1 and IKK-α to activate the transcription factor IRF-3 (see reviews by P. Pitha and by T. Fujita on pages 744 and 754 this issue respectively). A parallel pathway involves the dsRNA-binding kinase PKR, the TRAF adaptor molecules and the NF-κB kinase IKKζ/β (see review by García et al., on p. 799 this issue). Most viruses investigated so far interfere with one or several steps in these important signaling chains [2–6]. Fig. 1 provides a schematic overview over the IFN induction pathway and some selected viral counterparts.

Until very recently, it was thought that the only IFN-inducing molecule which clearly distinguishes viruses from their host (i.e. self vs. non-self) is double-stranded RNA (dsRNA). Many RNA and DNA viruses therefore express proteins which bind this key molecule to avoid IFN induction and activation of dsRNA-dependent antiviral enzymes [7,8]. Well-investigated examples are the NS1 protein of influenza A virus [9–12], the E3L protein of poxviruses [13,14], the VP35 protein of Ebola virus [15,16], the sigma3 protein of reoviruses [17], and the US11 protein of herpes simplex virus [18,19]. The murine cytomegalovirus encodes two proteins, m142 and m143 which together block dsRNA-mediated signaling pathways [20,21]. However, in the case of the influenza virus NS1 and the Ebola virus VP35 dsRNA-binding appears only to contribute to the IFN antagonism without being essential [15,22,23]. In addition, we have recently shown that some viruses do not produce detectable amounts of dsRNA at all [24], indicating that in these cases other molecules IFN-eliciting molecules are important. Indeed, viral ssRNAs bearing a 5’triphosphate group are a potent trigger of IFN induction, acting through RIG-I [25,26]. In line with this, it was shown that the NS1 of influenza A virus can bind ssRNA as well, and is able to form complexes with RIG-I [26,27]. Similarly, a dsRNA-binding defective VP35 mutant can still block IFN induction [15], suggesting a similar mode of action. Thus, RNA binding by these viral IFN antagonists appears to be contributing to their IFN antagonism without being sufficient. An IFN induction antagonist devoid of any RNA-binding activity

* Corresponding author. Tel.: +49 761 203 6614; fax: +49 761 203 6634.
E-mail address: friedemann.weber@uniklinik-freiburg.de (F. Weber).

© 2007 Elsevier Masson SAS. All rights reserved.

doi:10.1016/j.brio.2007.01.005
is the V protein of the paramyxovirus SV5. This small protein inhibits IFN induction by sequestering the RIG-I-related RNA sensor MDA-5 [28,29], raising the question how SV5 deals with the parallel RIG-I pathway. This paramyxovirus-specific problem can be avoided by blocking components of the signaling pathway which are situated further downstream and therefore needed by both RIG-I and MDA-5. The next in line, the adaptor protein IPS-1, connects the RNA sensors with the IFN-activated signaling factors NF-κB which in turn are activated by RIG-I and MDA5 via IPS-1. NF-κB is mainly activated by the PKR pathway. Examples of viral IFN antagonists interfering with different steps in the IFN induction pathways are the NS1 of influenza viruses, the V protein of paramyxoviruses, the NS3-4A protein of hepatitis C virus, the P protein of Rabies virus, the G1 protein of hantavirus NY-1, the NPpro protein of classical swine fever virus and bovine viral diarrhea virus, the E6 protein of human papilloma virus 16, the viral IRF homologs (vIRFs) of human herpesvirus 8, the NSs proteins of bunyaviruses, the M protein of vesicular stomatitis virus, and the proteases of Picornaviruses.

2. Interference with interferon-activated signaling

IFN-β and the multiple IFN-α subspecies activate a common type I IFN receptor (IFNAR) which signals to the nucleus through the so-called JAK-STAT pathway (Fig. 2). The STAT proteins are latent cytoplasmic transcription factors which become phosphorylated and activated by the Janus kinases JAK-1 and TYK-2 [67]. Phosphorylated STAT-1 and STAT-2 recruit a third factor, IRF-9, to form a complex known as IFN-stimulated gene factor 3 (ISGF-3) which translocates to the nucleus and binds to the IFN-stimulated response element (ISRE) in the promoter region of interferon-stimulated genes (ISGs).

The IFN signal transduction pathway represents another important target of viruses (Fig. 2). Members of the paramyxovirus family, which contains mainly important pathogens, encode two different (but genetically related) proteins named C and V which interfere with STAT function. Depending on the virus species, these IFN antagonists act either by binding the STAT proteins, by inducing their degradation, or by inhibiting the JAK kinases [68–82]. The P protein of Rabies virus binds to activated STAT1 and STAT2 and retains them in the cytoplasm [83]. Thus, the paramyxoviral V protein as well as the rabies virus P protein have a dual anti-IFN function as they block both IFN induction (see above) and STAT signaling.

Ebola virus, by contrast uses a different protein, VP24, to block nuclear import of STAT by interacting with the transporter protein karyopherin alpha1 [84]. STAT signaling is also disturbed by viruses causing persistent infections, such as Hepatitis C virus [85,86], herpes simplex virus [87,88], HHV-8 [41], or cytomegalovirus [89,90]. Poxviruses inhibit simply impose a general block on host cell transcription and translation. For example, the non-structural NSs proteins of the Rift Valley Fever virus and Bunyamwera virus interfere with the basic cellular transcription machinery [46–48]. Although this strategy appears to be unspecific, in vivo experiments clearly demonstrated that the biological purpose of this broad-band shut-off is to inhibit IFN synthesis [49,50]. The matrix (M) protein of vesicular stomatitis virus (VSV) is also a potent host cell shutoff factor which inhibits basal transcription [51], impairs nuclear-cytoplasmic transport of RNAs and proteins [52], and inactivates translation factors [53]. As is the case with bunyavirus NSs, the biological significance of VSV M-mediated shutoff is to suppress IFN induction [54,55]. Also, proteinases of Picornaviruses (e.g. Foot and Mouth disease virus, Theiler’s virus, Polio virus) and Pestiviruses (e.g. Classical Swine fever virus) cause a shutoff-of the host cell metabolism to interfere with the IFN response [37,56–60].

Interestingly, the non-structural protein NS1 of influenza A virus also impairs the post-transcriptional processing and nuclear export of cellular pre-mRNAs [61–63] in order to counteract the antiviral host response [64,65]. Thus, NS1 is a versatile protein with the ability to prevent IFN induction both by IFN pathway-specific and by less specific means, and recent studies suggest that there is a surprisingly great strain-specific variation in these activities [66].
Herpes simplex virus triggers the dephosphorylation of eIF-2α in HIV- and Picornavirus-infected cells [104, 105]. This is achieved by the ICP0 protein of herpes simplex virus [103] [12, 14]. dsRNA-independent inhibition of the RNaseL system and ADAR, although this has only been shown in a few cases, can be achieved either by “inventing” one or several specialized factors or by expanding the function of existant gene products. For example, tumor cells express soluble IFN-binding proteins to neutralize secreted IFN molecules [91–94].

3. Inhibition of with interferon effector proteins

The dsRNA-binding proteins mentioned above also serve a second purpose, namely the inhibition of the dsRNA-activated antiviral enzymes. This has been demonstrated for the influenza virus NS1 [11, 12, 95–99], the poxvirus E3L [97], the reovirus sigma3 [100], the herpesvirus US11 [19, 101], and the dsRNA-binding proteins of human and murine cytomegaloviruses [20, 21, 102]. Importantly, also for this anti-IFN effector function more that just dsRNA binding appears to be necessary, since in many cases a direct interaction with e.g. PKR has been demonstrated (reviewed in Ref. [7]). Sequensting dsRNA may also inhibit the 2–5OAS pathway and ADAR, although this has only been shown in a few cases [12, 14]. dsRNA-independent inhibition of the RNaseL system is achieved by the ICP0 protein of herpes simplex virus [103] and by upregulation of RLI, a cellular inhibitor of RNaseL, in HIV- and Picornavirus-infected cells [104, 105].

PKR is also attacked by other means. The γ34.5 protein of Herpes simplex virus triggers the dephosphorylation of eIF-2α, thus reverting the translational block established by PKR [106]. The E2 protein of Hepatitis C virus [107], the Tat protein of HIV [108] and the K3L protein of Vaccinia virus [109] act as pseudosubstrates for PKR. Another strategy is to encode small, highly structured RNAs which compete with dsRNA and inactivate PKR. This was demonstrated for adenoviruses [110], Hepatitis C virus [111], Epstein-Barr virus [112], and HIV [113]. However, for Epstein-Barr virus it was shown that the PKR inhibition by the so-called EBER RNAs observed in vitro does not occur in vivo [114], suggesting that EBERs are important for other activities such as inhibition of apoptosis.

It is obvious from the listings above that viruses have evolved multiple means to disrupt the IFN response. In some cases, there are specialized anti-IFN factors such the non-structural proteins of influenza viruses. In many other cases, however, viral gene products with a defined function in virus replication cycle can additionally acquire the ability to block the IFN system. Important examples include the V, W and C proteins of paramyxoviruses [79, 115], the P protein of rabies virus [32, 83] and the VP35 protein of Ebola virus [116], which are regulators of the viral polymerase. Also, the matrix proteins of Thogoto virus [117] and vesicular stomatitis virus [58], the nucleoprotein of arenaviruses [118], and the glycoprotein of hantaviruses [33] not only have structural functions, but are IFN antagonists as well. Some viruses such as Dengue virus or SARS-coronavirus encode a multitude of anti-IFN factors which together may strongly contribute to an enhanced virulence [119–121]. Apparently, modulating the IFN system can be achieved either by “inventing” one or several specialized factors or by expanding the function of existant gene products.

4. Outlook

Understanding the interplay between viruses and the IFN response can help to design new strategies for prevention and therapy. Viruses unable to counteract the IFN response are excellent candidates for live virus vaccines. They can be grown to high titers in IFN-deficient cell cultures but are attenuated in vivo since they elicit a robust innate and adaptive immune responses. This concept has been proven for influenza viruses [122–125], human parainfluenza virus type 1 [126], human and bovine respiratory syncytial viruses [127–129], and may likewise apply to other viruses.

Oncolytic viruses designed for the targeted destruction of tumors is another promising application. Tumor cells often eliminate one or several parts of the IFN system during the transformation process [130–133]. For example, tumor cells were shown to acquire specific mutations leading to resistance of cellular translation to inhibition by PKR [134]. The payoff is an increased susceptibility to infection [131, 134, 135], and the tumor selectivity of viruses can be further increased by using mutants with defective IFN antagonists. The inability of these mutant viruses to fight the IFN response is complemented by the IFN-deficiency of the tumor cells. At the same time, these viruses are unable to infect the IFN-competent body cells. This concept is proven by an IFN-inducing VSV mutant [55] and a herpes simplex virus lacking the...
anti-PKR gene γ34.5 [136,137] which specifically destroyed tumors in immunocompetent hosts.

Thus, unravelling the strategies by which viruses counteract the IFN system not only helps to better understand viral pathogenesis but can also result in novel vaccination strategies and therapies.

Acknowledgments

Our own work described in the text was supported by grants from the Deutsche Forschungsgemeinschaft.

References

[1] A. Isaacs, J. Lindenmann, Virus interference. I., The interferon, Proc. R. Soc. Lond, B Biol. Sci. 147 (1957) 258–267.
[2] C.F. Basler, A. Garcia-Sastre, Viruses and the type I interferon antiviral system: induction and evasion, Int. Rev. Immunol. 21 (2002) 305–337.
[3] K.K. Conzelmann, Transcriptional activation of alpha/beta interferon genes: interference by nonsegmented-strand RNA viruses, J. Virol. 79 (2005) 5241–5248.
[4] A. Garcia-Sastre, C.A. Biron, Type 1 interferons and the virus-host relationship: a lesson in detente, Science 312 (2006) 879–882.
[5] O. Haller, F. Weber, The interferon response circuit: Induction and suppression by pathogenic viruses, Virology 344 (2006) 119–130.
[6] F. Weber, F. Kochs, O. Haller, Inverse interference: how viruses fight the interferon system, Viral Immunol. 17 (2004) 498–515.
[7] J.O. Langland, J.M. Cameron, M.C. Heck, J.K. Jancovich, B.L. Jacobs, Inhibition of PKR by RNA and DNA viruses, Virus Res. 119 (2006) 100–110.
[8] B.L. Jacobs, J.O. Langland, T. Brandt, Characterization of viral double-stranded RNA-binding proteins, Methods 15 (1998) 225–232.
[9] A. Garcia-Sastre, A. Egorov, D. Matassov, S. Brandt, D.E. Levy, J.E. Durbin, F. Palese, T. Muster, Influenza A virus lacking the NS1 gene replicates in interferon- deficient systems, Virology 252 (1998) 324–330.
[10] A. Garcia-Sastre, Inhibition of interferon-mediated antiviral responses by influenza A viruses and other negative-strand RNA viruses, Virology 279 (2001) 375–384.
[11] Y. Lu, M. Wambach, M.G. Katze, R.M. Krug, Binding of the influenza virus NS1 protein to double-stranded RNA inhibits the activation of the protein kinase that phosphorylates the eIF-2 translation initiation factor, Virology 214 (1995) 222–228.
[12] J.Y. Min, R.M. Krug, The primary function of RNA binding by the influenza A virus NS1 protein in infected cells: Inhibiting the 2‘-5’ oligo (A) synthetase/RNase L pathway, Proc. Natl. Acad. Sci. USA 103 (2006) 7100–7105.
[13] S. Homemann, O. Harlin, C. Staub, S. Kising, V. Erfre, B. Kaspers, G. Haeker, G. Satter, Replication of modified vaccinia virus Ankara in primary chicken embryo fibroblasts requires expression of the interferon resistance gene E3L, J. Virol. 77 (2003) 8394–8407.
[14] Y. Xiang, R.C. Condit, S. Vijayasri, B. Jacobs, B.R. Williams, R.H. Silverman, Blockade of interferon induction and action by the E3L double-stranded RNA binding proteins of vaccinia virus, J. Virol. 76 (2002) 5251–5259.
[15] W.B. Cardenas, Y.M. Loo, M. Gale Jr., A.L. Hartman, C.R. Kimberlin, L. Martinez-Sobrido, E.O. Saphire, C.F. Basler, Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-I signaling, J. Virol. 80 (2006) 5168–5178.
[16] A.L. Hartman, J.E. Dover, J.S. Towner, S.T. Nichol, Reverse genetic generation of recombinant Zaire Ebola viruses containing disrupted IRF-3 inhibitory domains results in attenuated virus growth in vitro and higher levels of IRF-3 activation without inhibiting viral transcription or replication, J. Virol. 80 (2006) 6430–6440.
[17] B.L. Jacobs, J.O. Langland, Reovirus sigma 3 protein: dsRNA binding and inhibition of RNA-activated protein kinase, Curr. Top. Microbiol. Immunol. 233 (1998) 185–196.
[18] I. Mohr, Neutralizing innate host defenses to control viral translation in HSV-1 infected cells, Int. Rev. Immunol. 23 (2004) 199–220.
[19] J. Poppers, M. Mulvey, D. Khoo, I. Mohr, Inhibition of PKR activation by the proline-rich RNA binding domain of the herpes simplex virus type 1 Us11 protein, J. Virol. 74 (2000) 11215–11221.
[20] S.J. Child, L.K. Hanson, C.E. Brown, D.M. Janzen, A.P. Geballe, Double-stranded RNA binding by a heterodimeric complex of murine cytomegalovirus m142 and m143 proteins, J. Virol. 80 (2006) 10173–10180.
[21] R.S. Valchanova, M. Picard-Maureau, M. Bduit, W. Brune, Murine cytomegalovirus m142 and m143 are both required to block protein kinase R-mediated shutdown of protein synthesis, J. Virol. 80 (2006) 10181–10190.
[22] N.R. Donelan, B. Dauber, X. Wang, C.F. Basler, T. Wolff, A. Garcia-Sastre, The N- and C-terminal domains of the NS1 protein of influenza B virus can independently inhibit IRF-3 and beta interferon promoter activation, J. Virol. 78 (2004) 11574–11582.
[23] N.R. Donelan, C.F. Basler, A. Garcia-Sastre, A recombinant influenza A virus expressing an RNA-binding-defective NS1 protein induces high levels of beta interferon and is attenuated in mice, J. Virol. 77 (2003) 13257–13266.
[24] F. Weber, V. Wagner, S.B. Rasmussen, R. Hartmann, S.R. Paludan, Double-stranded RNA is produced by positive-strand RNA viruses and DNA viruses but not in detectable amounts by negative-strand RNA viruses, J. Virol. 80 (2006) 5059–5064.
[25] V. Hormung, J. Ellegast, S. Kim, K. Brzozka, A. Jung, H. Kato, H. Poesch, S. Akira, K.K. Conzelmann, M. Schlee, et al., 5‘-Triphosphate RNA is the ligand for RIG-I, Science 314 (2006) 994–997.
[26] A. Pichlmair, O. Schulz, C.P. Tan, T.J. Naslund, P. Liljestrom, F. Weber, E.S.C. Reis, RIG-I-mediated antiviral responses to single-stranded RNA bearing 5‘-phosphates, Science 314 (2006) 997–1001.
[27] M. Mibayashi, L. Martinez-Sobrido, Y.M. Loo, W.B. Cardenas, M. Gale Jr., A. Garcia-Sastre, Inhibition of retinoic acid-inducible gene-1-mediated induction of interferon-β by the NS1 protein of influenza A virus, J. Virol. 81 (2007) 514–524.
[28] J. Andrejeva, K.S. Childs, D.F. Young, T.S. Carlos, N. Stock, S. Goodbourn, R.E. Randall, The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter, Proc. Natl. Acad. Sci. USA 101 (2004) 17264–17269.
[29] K. Childs, N. Stock, C. Ross, J. Andrejeva, L. Hilton, M. Skinner, R. Randall, S. Goodbourn, mda-5, but not RIG-I, is a common target for paramyxovirus V proteins, Virology 359 (2007) 190–200.
[30] R. Lin, J. Lacoste, P. Nakhaei, Q. Sun, L. Yang, S. Paz, P. Wilkinson, J. Julkunen, D. Vitour, E. Meurs, J. Hiscott, Dissociation of a MAVS/IPS-1/VISA/Cardif-IKKepsilon molecular complex from the mitochondrial outer membrane by hepatitis C virus NS3-4A proteolytic cleavage, J. Virol. 80 (2006) 6072–6083.
[31] E. Meylan, J. Curran, K. Hofmann, D. Moradpour, M. Binder, R. Bartenschlager, J. Tschopp, Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus, Nature 437 (2005) 1167–1172.
[32] K. Brzozka, S. Finke, K.K. Conzelmann, Identification of the rabies virus alpha/beta interferon antagonist: phosphorylating P interferes with phosphorylation of interferon regulatory factor 3, J. Virol. 79 (2005) 7673–7681.
[33] P.J. Alff, I.N. Gavrilovskaya, E. Gorburnova, K. Endriss, Y. Chong, E. Geimonen, N. Sen, N.C. Reich, B.R. Mackow, The pathogenic NY-1 hantavirus G1 cytoplasmic tail inhibits RIG-I- and TBK-1-directed interferon responses, J. Virol. 80 (2006) 9676–9686.
[34] O. Baulofer, A. Summervield, K.C. McCullough, N. Ruggli, Role of double-stranded RNA and Npro of classical swine fever virus in the activation of monocyte-derived dendritic cells, Virology 343 (2005) 93–105.
Inhibition of interferon signaling by the Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor-3 (vIRF-3) inhibits transcription from the human beta interferon promoter, J. Virol. 71 (1997) 371–377.

D. F. Stojdl, B. D. Lichty, B. R. ten Oever, J. M. Paterson, A. T. Power, S. Knowles, R. Marius, J. Reynard, L. Poliquin, H. Atkins et al., VSV strains with defects in their ability to shutdown innate immune responses are potent systemic anti-cancer agents, Cancer Cell 4 (2003) 263–275.

S. Delhaye, V. van Pesch, T. Michiels, The leader protein of Theliers’ virus interferes with nucleocytoplasmic trafficking of cellular proteins, J. Virol. 78 (2004) 4357–4362.

T. de Los Santos, S. de Avila Botto, R. Weiblen, M. J. Grubman, The leader proteinase of foot-and-mouth disease virus inhibits the induction of beta interferon mRNA and blocks the host innate immune response, J. Virol. 80 (2006) 1906–1914.

D. S. Lyles, Cytopathogenesis and inhibition of host gene expression by RNA viruses, Microbiol. Mol. Biol. Rev. 64 (2000) 709–724.

N. Ruggli, J. D. Tratschin, M. Schweizer, K. C. McCullough, M. A. Hofmann, A. Summerfield, Classical swine fever virus interferes with cellular antiviral defense: evidence for a novel function of N(pro), J. Virol. 77 (2003) 7645–7654.

V. van Pesch, O. van Eyll, T. Michiels, The leader protein of Theliers’ virus inhibits immediate-early alpha/beta interferon production, J. Virol. 75 (2001) 7811–7817.

Z. Chen, Y. Li, R. M. Krug, Influenza A virus NS1 protein targets poly(A)-binding protein II of the cellular 3′-end processing machinery, Embo J 18 (1999) 2273–2283.

P. Fortes, A. Beloso, J. Ortin, Influenza virus NS1 protein inhibits pre-mRNA splicing and blocks mRNA nucleocytoplasmic transport, Embo J 13 (1994) 704–712.

Y. Li, Z. Y. Chen, W. Wang, C. C. Baker, R. M. Krug, The 3′-end-processing factor CPSF is required for the splicing of single-intron pre-mRNAs in vivo, Rna 7 (2001) 920–931.

M. J. Kim, A. G. Latham, R. M. Krug, Human influenza viruses activate an interferon-independent transcription of cellular antiviral genes: outcome with influenza A virus is unique, Proc. Natl. Acad. Sci. USA 99 (2002) 10096–10101.

D. L. Noah, K. Y. Twu, R. M. Krug, Cellular antiviral responses against influenza A virus are countered at the posttranscriptional level by the viral NS1A protein via its binding to a cellular protein required for the 3′ end processing of cellular pre-mRNAs, Virology 307 (2003) 386–395.

A. Hayman, S. Comely, A. Lackenby, S. Murphy, J. McCauley, S. Goodbourn, W. Barclay, Variation in the ability of human influenza A viruses to induce and inhibit the IFN-beta pathway, Virology 347 (2006) 52–64.

D. E. Levy, J. E. Darnell Jr., Stats: transcriptional control and biological impact, Nat. Rev. Mol. Cell Biol. 3 (2002) 651–662.

J. Andrejeva, D. F. Young, S. Goodbourn, R. E. Randall, Degradation of STAT1 and STAT2 by the V proteins of simian virus 5 and human parainfluenza virus type 2, respectively: consequences for virus replication in the presence of alpha/beta and gamma interferons, J. Virol. 76 (2002) 2159–2167.

L. Didcock, D. F. Young, S. Goodbourn, R. E. Randall, The V protein of simian virus 5 inhibits interferon signalling by targeting STAT1 for proteasome-mediated degradation, J. Virol. 73 (1999) 9928–9933.

D. Gardin, J. C. Marq, L. Strahle, P. le Mercier, D. Kolakofsky, All four Sendai Virus C proteins bind Stat1, but only the larger forms also induce its mono-ubiquitination and degradation, Virology 295 (2002) 256–265.

J. P. Parisien, J. F. Lau, J. J. Rodriguez, B. M. Sullivan, A. Moscona, G. D. Parks, R. A. Lamb, C. M. Horvath, The V protein of human parainfluenza virus 2 antagonizes type I interferon responses by destabilizing signal transducer and activator of transcription 2, Virology 283 (2001) 230–239.

C. M. Ulane, J. J. Rodriguez, J. P. Parisien, C. M. Horvath, STAT3 ubiquitylation and degradation by mumps virus suppress cytokine and oncogene signaling, J. Virol. 77 (2003) 6385–6393.
B. Gotoh, K. Takeuchi, T. Komatsu, J. Yokoo, The STAT2 activation process is a crucial target of Sendai virus C protein for the blockade of alpha interferon signaling, J. Virol. 77 (2003) 3360–3370.

S.K. Nanda, M.D. Baron, Rinderpest virus blocks type I and type II interferon action: role of structural and nonstructural proteins, J. Virol. 80 (2006) 7555–7568.

H. Palosaari, J.P. Parisien, J.J. Rodriguez, C.M. Horvath, STAT protein interference and suppression of cytokine signal transduction by measles virus V protein, J. Virol. 77 (2003) 7635–7644.

M.S. Park, M.L. Shaw, J. Munoz-Jordan, J.F. Cros, T. Nakaya, N. Bouvier, P. Palese, A. Garcia-Sastre, C.F. Basler, Newcastle disease virus (NDV)-based assay demonstrates interferon-antagonist activity for the NDV V protein and the Nipah virus V, W, and C proteins, J. Virol. 77 (2003) 1501–1511.

J.J. Rodriguez, J.P. Parisien, C.M. Horvath, Nipah virus V protein evades alpha and gamma interferons by preventing STAT1 and STAT2 activation and nuclear accumulation, J. Virol. 76 (2002) 11476–11483.

J.J. Rodriguez, L.F. Wang, C.M. Horvath, Hendra virus V protein inhibits interferon signaling by preventing STAT1 and STAT2 nuclear accumulation, J. Virol. 77 (2003) 11842–11845.

M.L. Shaw, A. Garcia-Sastre, P. Palese, C.F. Basler, Nipah virus V and W proteins have a common STAT1-binding domain yet inhibit STAT1 activation from the cytoplasmic and nuclear compartments, respectively, J. Virol. 78 (2004) 5633–5641.

M.L. Shaw, W.B. Cardenas, D. Zamarin, P. Palese, C.F. Basler, Nuclear localization of the Nipah virus W protein allows inhibition of both virus- and toll-like receptor 3-activated signaling pathways, J. Virol. 79 (2005) 6078–6088.

K. Takeuchi, T. Komatsu, J. Yokoo, A. Kato, T. Shioda, Y. Nagai, B. Gotoh, Sendai virus C protein physically associates with Stat1, Genes Cells 6 (2001) 545–557.

S. Yokota, H. Saito, T. Kubota, N. Yokosawa, K. Amano, N. Fujii, Measles virus suppresses interferon-alpha signaling pathway: suppression of Jak1 phosphorylation and association of viral accessory proteins, C and V, with interferon-alpha receptor complex, Virology 306 (2003) 135–146.

K. Brzozka, S. Finke, K.K. Conzelmann, Inhibition of interferon signaling by rabies virus phosphoprotein P: activation-dependent binding of STAT1 and STAT2, J. Virol. 80 (2006) 2675–2683.

S.P. Reid, L.W. Leung, A.L. Hartman, O. Martinez, M.L. Shaw, C. Carbonnel, F. Van Volckh, S.T. Nichol, C.F. Basler, Ebola virus Vp24 binds karyopherin alpha1 and blocks STAT1 nuclear accumulation, J. Virol. 80 (2006) 5156–5167.

C. Francois, G. Duverlie, D. Rebouillat, H. Khorsi, S. Castelain, H.E. Blum, A. Gaignon, C. Wychowski, D. Moradpour, E.F. Meurs, Expression of hepatitis C virus proteins interferes with the antiviral action of interferon independently of PKR-mediated control of protein synthesis, J. Virol. 74 (2000) 5857–5859.

M.H. Heim, D. Moradpour, H.E. Blum, Expression of hepatitis C virus proteins inhibits signal transduction through the Jak-STAT pathway, J. Virol. 73 (1999) 8469–8475.

A.V. Chee, B. Roizman, Herpes simplex virus 1 gene products occlude the interferon signaling pathway at multiple sites, J. Virol. 78 (2004) 4185–4196.

S. Yokota, Y. Yokosawa, T. Okabayashi, T. Suzutani, S. Miura, K. Jimbow, N. Fujii, Induction of suppressor of cytokine signaling-3 by herpes simplex virus type 1 contributes to inhibition of the interferon signaling pathway, J. Virol. 78 (2004) 6282–6286.

S. Khan, A. Zimmermann, M. Basler, M. Groenert, H. Hengel, A cytomegalovirus inhibitor of gamma interferon signaling controls immunoproteasome induction, J. Virol. 78 (2004) 1831–1842.

A. Zimmermann, M. Trilling, M. Wagner, M. Wilborn, I. Bubic, S. Jonic, U. Koszinowski, H. Hengel, A cytomegaloviral protein reveals a dual role for STAT2 in IFN-γ signaling and antiviral responses, J. Exp. Med. 201 (2005) 1543–1553.

A. Alcamì, G.L. Smith, Vaccinia, cowpox, and camelpox viruses encode soluble gamma interferon receptors with novel broad species specificity, J. Virol. 69 (1995) 4633–4639.

A. Alcamì, J.A. Symons, G.L. Smith, The vaccinia virus soluble alpha/ beta interferon (IFN) receptor binds to the cell surface and protects cells from the antiviral effects of IFN, J. Virol. 74 (2000) 11230–11239.

F. Puehler, K.C. Weining, J.A. Symons, G.L. Smith, P. Staeheli, Vaccinia virus-encoded cytokine receptor binds and neutralizes chicken interferon-gamma, Virology 248 (1998) 231–240.

J.A. Symons, A. Alcamì, G.L. Smith, Vaccinia virus encodes a soluble type I interferon receptor of novel structure and broad species specificity, Cell 81 (1995) 551–560.

M. Bergmann, A. Garcia-Sastre, E. Carnero, H. Pehamberger, K. Wolff, P. Palese, T. Muster, Influenza virus NS1 protein counteracts PKR-mediated inhibition of replication, J. Virol. 74 (2000) 6203–6206.

E. Hatada, S. Saiki, P. Palese, Mutant influenza viruses with a defective NS1 protein cannot block the activation of PKR in infected cells, J. Virol. 73 (1999) 2425–2433.

J.O. Langland, B.L. Jacobs, Inhibition of PKR by vaccinia virus: role of the N- and C-terminal domains of E3L, Virology 324 (2004) 419–429.

S. Li, J.Y. Min, R.M. Krug, G.C. Sen, Binding of the influenza A virus NS1 protein to PKR mediates the inhibition of its activation by either PACT or double-stranded RNA, Virology 349 (2006) 13–21.

B. Dauber, J. Schneider, T. Wolff, Double-stranded RNA binding of influenza A virus nonstructural NS1 protein inhibits protein kinase R but is not essential to antagonize production of alpha/beta interferon, J. Virol. 80 (2006) 11667–11677.

F. Imani, B.L. Jacobs, Inhibitory activity for the interferon-induced protein kinase is associated with the reovirus serotype 1 sigma 3 protein, Proc. Natl. Acad. Sci. USA 85 (1988) 7887–7891.

G.A. Peters, D. Kho, I. Mohr, G.C. Sen, Inhibition of PACT-mediated activation of PKR by the herpes simplex virus type 1 Us11 protein, J. Virol. 76 (2002) 11054–11064.

M. Hakki, A.P. Gehale, Double-stranded RNA binding by human cytoplasmic poly(A)binding protein interacts with cell surface, J. Virol. 79 (2005) 7311–7318.

P.T. Sobol, K.L. Mossman, ICP0 prevents RNase L-independent rRNA cleavage in herpes simplex virus type 1-infected cells, J. Virol. 80 (2006) 218–225.

C. Martinand, C. Montavon, T. Salehzada, M. Silh0, B. Lebleu, C. Bisbal, RNase L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 2–5A/RNase L pathway in human T cells, J. Virol. 73 (1999) 290–296.

C. Martinand, T. Salehzada, M. Silh0, B. Lebleu, C. Bisbal, RNase L inhibitor (RLI) antisense constructions block partially the down regulation of the 2–5A/RNase L pathway in encephalomyocarditis-virus (EMCV)-infected cells, Eur. J. Biochem. 254 (1998) 248–255.

B. He, M. Gross, B. Roizman, The gamma(1)34.5 protein of herpes simplex virus 1 complexes with protein phosphatase 1alpha to dephosphorylate the alpha subunit of eukaryotic initiation factor 2, J. Virol. 66 (1992) 1943–1950.

M.B. Mathews, T. Shenk, Adenovirus virus-associated RNA and translation control, J. Virol. 65 (1991) 5657–5662.

J.Vyas, A. Elia, M.J. Clemens, Inhibition of the protein kinase PKR by the internal ribosome entry site of hepatitis C virus genomic RNA, RNA 9 (2003) 858–870.

A. Elia, K.G. Laing, A. Schofield, V.J. Tilleray, M.J. Clemens, Regulation of the double-stranded RNA-dependent protein kinase PKR by RNAs encoded by a repeated sequence in the Epstein—Barr virus genome, Nucleic Acids Res. 24 (1996) 4471–4478.
[113] S. Gunnery, A.P. Rice, H.D. Robertson, M.B. Mathews, Tat-responsive region RNA of human immunodeficiency virus 1 can prevent activation of the double-stranded-RNA-activated protein kinase, Proc. Natl. Acad. Sci. USA 87 (1990) 8687–8691.

[114] I.K. Ruf, K.A. Lackey, S. Warudkar, J.T. Sample, Protection from interferon-induced apoptosis by Epstein–Barr virus small RNAs is not mediated by inhibition of PKR, J. Virol. 79 (2005) 14562–14569.

[115] S. Goodbourn, L. Didcock, R.E. Randall, Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures, J. Gen. Virol. 81 (2000) 2341–2364.

[116] C.F. Basler, A. Mikulasova, L. Martinez-Sobrido, J. Paragas, E. Muhlberger, M. Bray, H.D. Klenk, P. Palese, A. Garcia-Sastre, The Ebola virus VP35 protein inhibits activation of interferon regulatory factor 3, J. Virol. 77 (2003) 7945–7956.

[117] A. Pichlmair, J. Buse, S. Jennings, O. Haller, G. Kochs, J. Paragas, S. Goodbourn, L. Didcock, R.E. Randall, Interferon antagonist NS2 protein of respiratory syncytial virus is an important virulence determinant for humans, J. Infect. Dis. 193 (2006) 573–581.

[118] M.N. Teng, S.S. Whitehead, A. Bermpinghum, M. St Claire, W.R. Elkins, B.R. Murphy, P.L. Collins, Recombiant respiratory syncytial virus that does not express the NS1 or M2-2 protein is highly attenuated and immunogenic in chimpanzees, J. Virol. 74 (2000) 9317–9321.

[119] S.M. Batcock, T.W. Collier, D. Zu, K. Hirasawa, Negative regulation of the alpha interferon-induced antiviral response by the Ras/Raf/MEK pathway, J. Virol. 80 (2006) 4422–4430.

[120] S. Krishnamurthy, T. Takimoto, R.A. Scroggs, A. Portner, Differentially regulated interferon response determines the outcome of Newcastle disease virus infection in normal and tumor cell lines, J. Virol. 80 (2006) 5145–5155.

[121] D.F. Stojdl, B. Lichty, S. Knowles, R. Marius, H. Atkins, N. Sonenberg, J.C. Bell, Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus, Nat. Med. 6 (2000) 821–825.

[122] J.E. Strong, M.C. Coffey, D. Tang, P. Sabinin, P.W. Lee, The molecular basis of viral oncology: usurpation of the Ras signaling pathway by reovirus, Embo J 17 (1998) 3351–3362.

[123] S. Balkachandran, G.N. Barber, Defective translational control facilitates vesicular stomatitis virus oncology, Cancer Cell 5 (2004) 51–65.

[124] M.C. Coffey, J.E. Strong, P.A. Forsyth, P.W. Lee, Reovirus therapy of tumors with activated Ras pathway, Science 298 (1992) 1332–1334.

[125] W.D. Hunter, R.L. Martuza, F. Feigenbaum, T. Todo, T. Mineta, T. Yazaki, M. Toda, J.T. Newsome, R.C. Platenberg, H. Atkins, N. Sonenberg, S.D. Rabbkin, Attenuated, replication-competent herpes simplex virus type 1 mutant G207: safety evaluation of intracerebral injection in non-human primates, J. Virol. 73 (1999) 6319–6326.

[126] T. Mineta, S.D. Rabbkin, T. Yazaki, W.D. Hunter, R.L. Martuza, Attenuated multi-mutated herpes simplex virus-1 for the treatment of malignant gliomas, Nat. Med. 1 (1995) 938–943.