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Interferon, Mx, and viral countermeasures

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Abstract

The interferon system provides a powerful and universal intracellular defense mechanism against viruses. Knockout mice defective in IFN signaling quickly succumb to all kinds of viral infections. Likewise, humans with genetic defects in interferon signaling die of viral disease at an early age. Among the known interferon-induced antiviral mechanisms, the Mx pathway is one of the most powerful. Mx proteins belong to the dynamin superfamily of large GTPases and have direct antiviral activity. They inhibit a wide range of viruses by blocking an early stage of the viral replication cycle. Likewise, the protein kinase R (PKR), and the 2–5 OAS/RNaseL system represent major antiviral pathways and have been extensively studied. Viruses, in turn, have evolved multiple strategies to escape the IFN system. They try to go undetected, suppress IFN synthesis, bind and neutralize secreted IFN molecules, block IFN signaling, or inhibit the action of IFN-induced antiviral proteins. Here, we summarize recent findings about the astonishing interplay of viruses with the IFN response pathway.

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1. Starting point: interferon-mediated inborn resistance to viruses in mice

Historically, mouse models of genetically determined resistance against viruses were useful to find antiviral factors involved in innate immunity. Some inbred mouse strains proved to be less susceptible to infection by specific viruses than others. In most cases, the degree of antiviral resistance was controlled by several genes, but occasionally a single gene was found to be responsible [1]. A good example is the inborn resistance against influenza and influenza-like viruses found in wild mice and some inbred mouse strains [2–4]. Forty-five years ago, Jean Lindenmann, co-discoverer of interferon with Alick Isaacs, described an inbred mouse strain which was unusually resistant when infected with doses of influenza A virus (FLUA V) that were lethal to ordinary laboratory mice [4]. Subsequent work revealed that this unusual resistance is brought about by a single gene, Mx1 (for orthomyxovirus resistance gene 1), localized on mouse chromosome 16 [5], and that the Mx1 protein has intrinsic antiviral activity [6,7]. Unexpectedly, the Mx1 gene turned out to belong to the so-called interferon (IFN) responsive genes (ISGs) and is strictly regulated by type I (α and β) and type III (λ) IFNs [8,9]. Gene expression is rapidly induced in viral infections through the action of virus-induced IFNs. In the absence of IFNs, the Mx gene is silent, making Mx transcripts or protein an excellent marker for type I IFN activity [10,11].

In influenza virus-susceptible mice, the Mx1 gene is defective. Most inbred strains of mice carry nonfunctional Mx1 alleles [12]. Why intact Mx1 genes are absent in most inbred mouse strains remains unresolved. Most likely, the reason is a founder effect, suggesting that most laboratory mice share the distal part of chromosome 16 with a common ancestor mouse. Genetic defects present in laboratory mice but rarely in wild mice have been described for other gene loci. A single autosomal dominant gene locus, designated Flv/Wnv, is responsible for natural resistance of mice against infection with West Nile virus (WNV) and other flaviviruses. The gene was recently identified as Oas1b, a member of a large IFN-regulated gene family encoding 2'-5'-oligoadenylate synthetases (2–5 OAS) known to play an important role in antiviral defense [13,14]. The intact Oas1b gene is
again found in wild mice and some rare inbred strains but not in most laboratory strains which carry a nonsense mutation in the distal part of chromosome 5. In contrast to Mx1, comparisons of the mouse and human genomes did not reveal a direct equivalent of the mouse Oas1b gene in humans [15]. Additional examples of genetic resistance are known in mice in which single genes play a major role [16].

Here, we summarize recent advances in our understanding of some of these IFN-regulated defense mechanisms and discuss how viruses manage to counteract these restriction elements.

2. Transcriptional activation of IFN genes

Type I IFNs are produced by cells in direct response to virus infection and comprise a large number of IFN-α subspecies and a single IFN-β, as well as some additional family members [17,18]. The recently discovered IFN-λ1, IFN-λ2, and IFN-λ3 (also termed IL-28A, IL-28B, and IL-29) are functionally similar to the type I IFNs but use distinct receptors to mediate their antiviral activity [19]. Conserved molecular signatures of viruses serve as “danger signals” which are recognized by specialized receptors of the host cell. These receptors are collectively called pattern recognition receptors (PRRs) because they recognize a diverse range of conserved pathogen-associated molecular patterns (PAMPs) found in infectious disease agents (Fig. 1).

The main PAMP of viruses appear to be nucleic acids, such as double-stranded RNA (dsRNA) molecules [20] and specific structures at the 5′ end of certain viral ssRNA genomes which carry a 5′ triphosphate group [21,22]. dsRNA or 5′ triphosphate moieties are usually not present on host RNA species and appear to provide an ideal recognition pattern for non-self [23].

Induction of type I IFN gene expression is transcriptionally regulated and is best understood for IFN-β (Fig. 1). The IFN-β promoter has binding sites for several transcription factors which cooperate for maximal promoter activation. There is general agreement that interferon regulatory factor 3 (IRF-3) plays a central role [24]. IRF-3 needs to be phosphorylated to become active. The enzymes responsible for IRF-3 phosphorylation have recently been demonstrated to be the IKK-like kinases IKKe and TBK-1 [25,26]. These kinases are activated by the RNA helicase RIG-I and/or MDA5 [27,28] and, presumably, some Toll-like receptors (TLR) [29,30]. RIG-I and MDA5 bind dsRNA molecules and 5′ triphosphorylated ssRNAs in the cytoplasm of infected cells. Phosphorylated IRF-3 homo-dimerizes and moves into the nucleus where it recruits the transcriptional coactivator, CREB-binding protein (CBP), to initiate IFN-β mRNA synthesis [24]. In addition, NF-κB and ATF-2/cJUN (AP-1) are activated as a more general stress response. Together these transcription factors strongly upregulate IFN-β expression (Fig. 1).

A second IRF family member, IRF-7, is expressed in most cells at very low amounts. It needs to be induced by IFN to reach sufficient levels and is then activated by virus infection in much the same way as IRF-3 [31]. IRF-7 is part of a positive feedback loop leading to amplification of IFN gene expression. Activated IRF-7 cooperates with IRF-3 and stimulates expression of the numerous IFN-α genes leading to a broad IFN-α response [32]. In specialized IFN-α-producing cells, e.g. plasmacytoid dendritic cells, IRF-7 is constitutively present at high levels and is directly activated in response to signals from certain TLRs which stimulate immediate IFN-α synthesis [33,34].

3. Interferon-induced antiviral pathways

The various IFN-α subspecies and the single IFN-β bind to and activate a common type I IFN receptor (IFNAR), whereas type III (λ) IFNs activate their cognate type III receptor. Both receptors signal to the nucleus through the so-called JAK-STAT pathway (Fig. 2). This pathway is well characterized [35] and will not be described here in detail.

Type I and type III IFNs activate the expression of an overlapping set of more than 300 IFN-stimulated genes (ISGs) which have antiviral, antiproliferative, and immunomodulatory functions [36,37]. Three IFN-induced enzyme systems represent major antiviral pathways and have been extensively studied. These include protein kinase R (PKR) [38,39], the 2–5 OAS/RNaseL system [40] and the Mx GTPases [41]. Mice lacking one of these components...
show dramatically increased virus susceptibilities [42,43]. Interestingly, cells from so-called triple knock-out mice lacking PKR, RNaseL and Mx1 are still capable of mounting a limited IFN-induced antiviral state, indicating that additional antiviral pathways exist [43].

Additional proteins with potentially important antiviral activities are ISG20 [44], P56 [45,46], guanylate-binding protein-1 (GBP-1) [47], and promyelocytic leukemia protein (PML) [48]. ISG20 is an IFN-induced 3'-5' exonuclease that specifically degrades ssRNA in vitro. Expression of ISG20 leads to a reduction in vesicular stomatitis virus (VSV) gene expression and blocks viral replication in cell culture [44]. P56 binds the eukaryotic initiation factor 3e (eIF3e) subunit of the eukaryotic translation initiation factor eIF3 and is likely to suppress viral as well as cellular RNA translation [46,49]. GBP-1 belongs to the dynamin superfamily of large GTPases like Mx and has antiviral activity against VSV [47]. Finally, the PML protein is a TRIM family member (also called TRIM19) which shuttles between the cytoplasm and the nucleus where it forms a specialized subnuclear compartment known as ND10 or PML nuclear body. Overexpression of PML has been found to suppress replication of several viruses, including VSV, influenza A virus (FLUAV) [50], lymphocytic choriomeningitis virus [51] and human foamy retrovirus (HFV) [52]. Interestingly, cells from wild-type and PML knockout mice proved to be equally permissive for herpes simplex virus 1 (HSV-1) and FLUAV, suggesting that PML itself has no antiviral activity against these viruses [53,54]. Rather, IFN responsiveness of cells may be influenced by PML and PML nuclear bodies, as suggested by recent findings [53].

4. Mx is a major player in IFN-induced host defense

All available evidence indicates that recovery from influenza virus infection in mice requires a functional Mx1 defense system [7]. Numerous experiments using Mx1-congenic or Mx1-transgenic mice demonstrated that the Mx1 system is indispensable for recovery from infection with otherwise deadly influenza viruses [55]. Moreover, it became clear that the course of disease observed in Mx1-positive mice reflects quite well the characteristics of an uncomplicated acute influenza virus infection in man, indicating that these animals better mimic the innate immune system of humans than standard laboratory mice. The human ortholog, called MxA, has a broad antiviral activity against a range of different viruses. MxA-sensitive viruses include members of the bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, togaviruses, poxviruses, reoviruses and Hepatitis B virus, a DNA virus with a genomic RNA intermediate [41]. The mechanism of action has so far been studied for a small number of viruses only and is still incompletely understood. In general, Mx proteins were found to bind to essential viral components and to block their functions. For example, the human MxA protein accumulates in the cytoplasm of IFN-treated cells and blocks replication of the infecting virus soon after cell entry. It has been shown to target the viral capsids by recognizing the major capsid component, the viral ribonucleoprotein of some orthomyxo- and bunyaviruses [56–58]. The protective power of the human MxA GTPase is best demonstrated in MxA-transgenic mice. Human MxA was sufficient to turn susceptible Mx1-negative mice into resistant animals [59]. Moreover, even the constitutive expression of MxA in otherwise IFN-nonresponsive IFNAR−/− animals conferred full resistance against disease, thus highlighting the importance of the human Mx system for antiviral defense [59].

5. Viral countermeasures

Viruses are known to block the IFN system at different levels, and different approaches are used by different viruses to accomplish this. An efficient strategy is used by vaccinia and other poxviruses which express soluble IFN-binding proteins to neutralize secreted IFN molecules [60–63]. Most viruses have evolved multifunctional proteins which specifically target distinct components of the IFN signaling cascade. A large number of viral proteins with anti-IFN properties have been described in the past few years and have been extensively described in a number of recent reviews [64–66].

5.1. Viral subversion of IFN induction

To subvert innate immunity, many viruses interfere with one or several steps in the IFN induction pathway. The NS1 protein of influenza A virus binds to both dsRNA and ssRNA.
presumably by recognizing inter- or intramolecular dsRNA regions. Importantly, NS1 also associates with RIG-I in infected cells and seems to impair its signaling function [22,67]. In contrast, the V protein of paramyxovirus SV5 has no apparent RNA-binding activity. It inhibits IFN induction by targeting the RIG-I-related RNA sensor MDA-5 [27,68]. Next in line is the adaptor protein Cardif/IPS-1/MAVS/VISA which connects the RNA sensors RIG-I and MDA5 with the IRF-3 kinases TBK-1/IKK-ε [69–72]. It is specifically cleaved by the NS3-4A protease of hepatitis C virus (HCV) and additional flaviviruses [70,73,74] (see also contribution of Michael Gale in this volume). Activation of IRF-3 by TBK-1 is prevented by the phosphoprotein P of Rabies virus [75] and the G1 glycoprotein of the hantavirus NY-1 [76]. IRF-3 itself is degraded by the NPro proteins of pestiviruses such as classical swine fever virus and of bovine viral diarrhea virus [77–79] via the proteasomal pathway [80,81]. Also, the E6 protein of human papilloma virus 16 binds and inactivates IRF-3 [82], and the proteins ORF 3b, ORF 6 and N of SARS-coronavirus directly target IRF-3 [83] to inhibit IFN induction [84]. A sophisticated strategy to block IRF-3 is used by certain herpesviruses. Human herpes virus 8 (HHV-8), the causative agent of Kaposi sarcoma, expresses several IRF homologues, termed vIRFs, which exert a dominant-negative effect [85–91].

Many viruses which lytically infect the host cell simply prevent IFN synthesis by imposing a general block on host cell transcription. For example, the nonstructural NSs proteins of the Rift Valley Fever virus and Bunyamwera virus interfere with the basic transcription machinery [92–95].

5.2. Targeting the effector proteins of the antiviral state

An efficient way to escape the IFN response is to directly inhibit the proteins that mediate the antiviral state. IFN-regulated PKR and 2–5 OAS are expressed in a latent, inactive form in uninfected cells. Both enzymes need to be activated by viral dsRNA. This requirement makes them vulnerable to IFN antagonists found in many viruses. Some viruses express RNA-binding proteins which are able to prevent the activation of PKR or the 2–5 OAS/RNaseL system by sequestering dsRNA molecules [96–103]. An alternative strategy used by viruses is to encode small RNAs which compete with dsRNA for binding to PKR, thereby preventing activation. This is the case for adenoviruses [104], HCV [105], Epstein-Barr virus (EBV) [106], and HIV-1 [107]. Several viruses express proteins which either directly bind to or otherwise inactivate PKR. For example, the γ34.5 protein of HSV-1 triggers the dephosphorylation of eIF-2α, thus reverting the translational block established by PKR [108]. The E2 protein of HCV acts as pseudosubstrate for PKR [109], as does the Tat protein of HIV-1 [110] or the K3L protein of vaccinia virus [111]. Interestingly, FLUAV exploits a cellular pathway to block PKR in that it activates p58IPK, a cellular inhibitor of PKR [102] and NS1 to block PKR as well as the 2–5 OAS/RNaseL system [112,113]. Poliovirus induces the degradation of PKR [114]. Many viruses also block the RNaseL pathway, either by expressing dsRNA-binding proteins (see above), or by other, more direct means. Encephalomyocarditis virus as well as HIV-1 induce the synthesis of RLI, a cellular RNaseL inhibitor [115,116]. Infection with HSV-1 and HSV-2 activates the synthesis of 2′-5′-oligoadenylate derivatives which bind and prevent RNaseL activation [117]. The Poliovirus genome contains a conserved RNA structure which inhibits RNaseL [118]. The antiviral effect of IFN is inhibited in cells infected with RSV [119,120], an effect most probably mediated by the viral NS1 and the NS2 proteins [121–123].

Certain viruses induce the disruption of PML nuclear bodies (also called ND10) by proteasome-dependent degradation of PML and Sp100 [124]. In HSV-1 infected cells, viral ICP0 accumulates in ND10 and induces the degradation of PML and Sp100, an activity which requires the E3 ligase activity of ICP0 [125,126]. Similar disruptions of ND10 were observed in cells infected with CMV, EBV, HPV and adenoviruses [127]. It is conceivable that viruses disassemble these nuclear structures to get rid of antiviral components but sufficient data supporting this view are not yet available.

There is no evidence for a specific viral inhibitor of Mx proteins so far. Mx proteins are not posttranslationally modified and their activity is not modulated by dsRNA. Nevertheless, viruses have found means to subvert the Mx system.

6. Viral escape from the Mx response

The mouse Mx1 protein inhibits a very early step of the influenza virus multiplication cycle. It blocks primary transcription of the incoming viral genome, a process which is performed by the associated viral polymerase. Since the virus can not transcribe and replicate its genome in the presence of Mx, generation of Mx escape mutants is virtually impossible. Therefore, a prime strategy of Mx-sensitive orthomyxoviruses is to suppress IFN production in the vertebrate host, thereby avoiding Mx expression in potential target cells. The influenza-like Thogoto virus (THOV) was recently shown to have an accessory protein with IFN-antagonistic activity. The sixth genomic segment of THOV encodes two transcripts: a spliced mRNA that codes for the matrix (M) protein and an unspliced mRNA that encodes a C-terminally extended M protein, named ML [128]. Recombinant mutant viruses were generated that lacked ML. These ML-deficient viruses were strong IFN inducers but showed otherwise no obvious growth deficits in IFN-defective cells or animals [129]. In IFN-competent Mx1-positive mice, however, the mutant virus devoid of ML was highly attenuated. In contrast, wild-type virus expressing ML were able to grow in
such animals because ML was blocking IFN production [130]. Interestingly, ML inhibits the transcriptional activity of IRF-3 which is required for IFN gene expression. Recent data show that the ML protein of THOV interferes with IRF-3 dimerization and recruitment of the transcriptional coactivator CBP by activated IRF-3 [132]. The IFN-specific transcription factor IRF-3 is known to be a central player in IFN gene expression and, not surprisingly, is affected by viral proteins from many unrelated viruses (see above).

Another strategy of orthomyxoviruses is to escape from Mx by fast growth. In collaboration with Adolfo Garcia-Sastre at the Mount Sinai School of Medicine in New York, our group recently studied an exceptional influenza A virus strain that is highly pathogenic for Mx1-positive mice [131]. This virus acquired a number of virulence-enhancing mutations during passage in Mx1 mice. Interestingly, the highly virulent virus was still susceptible to the antiviral action of mouse Mx1 protein. Mx1-positive mice, but not Mx1-deficient mice were highly resistant to the virus if pretreated with IFN shortly before infection (Fig. 3). Also, the highly virulent virus was not a better inhibitor of IFN production than an ordinary influenza virus, indicating that the IFN antagonistic function of its NS1 protein did not make the difference. A series of experiments demonstrated that the highly virulent virus was able to replicate much faster in mouse lung than a normal mouse-adapted virus. It grew to about 1000 fold higher titers within the first 24 h post infection, as compared to standard virus. We concluded that the virus had a head start due to an unusually high virus multiplication speed and could outrun the establishment of the IFN-mediated antiviral Mx response. In other words, inducible host defense mechanisms can be overcome if the pathogen multiplies extremely fast. It is conceivable that highly pathogenic viruses may often profit from the fact that the IFN system requires time to become active. It remains to be seen whether a similar evasion strategy is used by other successful influenza A viruses such as the Asian H5N1 viruses or the pandemic strain of 1918.

7. Concluding remarks

The interplay between viruses and the IFN system is an interesting facet of the virus–host relationship and reflects an ongoing evolutionary race between the two genetic systems. Emerging viruses have to constantly adapt to guarantee successful trans-species transmission in new hosts. Pandemic influenza A viruses presumably display a number of evasion mechanisms, including the surprisingly simple measure of fast growth. Our present knowledge of the IFN system and viral escape strategies is still limited. Future research should provide a better insight into the intricate interplay between viruses and the innate immune defenses of the host.
Conflict of interest statement

None.

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References

[1] Guenet JL, Bonhomme F. Wild mice: an ever-increasing contribution to a popular mammalian model. Trends Genet 2003;19:24–31.
[2] Haller O. Inborn resistance of mice to orthomyxoviruses. Curr Top Microbiol Immunol 1981;92:25–52.
[3] Haller O, Acklin M, Staeheili P. Influenza virus resistance of wild mice: wild-type and mutant Mx alleles occur at comparable frequencies. J Interferon Res 1987;7:647–56.
[4] Lindenmann J. Resistance of mice to mouse-adapted influenza A virus. Virology 1962;16:203–4.
[5] Reeves RH, O’Hara BF, Pavan WJ, Gearhart JD, Haller O. Genetic mapping of the Mx influenza virus resistance gene within the region of mouse chromosome 16 that is homologous to human chromosome 21. J Virol 1988;62:4372–5.
[6] Arnheiter H, Skuntz S, Noteborn M, Chang S, Meier E. Transgenic mice with intracellular immunity to influenza virus. Cell 1990;62:51–61.
[7] Staeheili P, Haller O, Boll W, Lindenmann J, Weissmann C. Mx protein: constitutive expression in 3T3 cells transformed with cloned Mx cDNA confers selective resistance to influenza virus. Cell 1986;44:147–58.
[8] Haller O, Arnheiter H, Lindenmann J, Gresser I. Host gene influences sensitivity to interferon action selectively for influenza virus. Nature 1980;283:660–2.
[9] Holzinger D, Jorns C, Stertz S, et al. Induction of MxA gene expression by influenza virus requires type I or type III interferon signaling. J Virol 2007;81:7776–85.
[10] Antonelli G, Simeoni E, Turriani O, et al. Correlation of interferon-induced expression of MxA mRNA in peripheral blood mononuclear cells with the response of patients with chronic active hepatitis C to IFN-alpha therapy. J Interferon Cytokine Res 1999;19:243–51.
[11] Roers A, Hochkeppel HK, Horisberger MA, Hovanessian A, Haller O. MxA gene expression after live virus vaccination: a sensitive marker for endogenous type I interferon. J Infect Dis 1994;169:807–13.
[12] Staeheili P, Grob R, Meier E, Sutcliffe JG, Haller O. Influenza virus-susceptible mice carry Mx genes with a large deletion or a nonsense mutation. Mol Cell Biol 1998;8:4518–23.
[13] Perelygin AA, Scherbik S, Schulz O, Tan CP, et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5’ phosphates. Science 2006;314:997–1001.
[14] Bowie AG, Fitzgerald KA. RIG-I: tri-ing to discriminate between self and non-self RNA. Trends Immunol 2007;28:147–50.
[15] Hiscott J. Triggering the innate antiviral response through IRF-3 activation. J Biol Chem 2007;282:15325–9.
[16] Roers A, Hochkeppel HK, Horisberger MA, Hovanessian A, Haller O. MxA gene expression after live virus vaccination: a sensitive marker for endogenous type I interferon. J Infect Dis 1994;169:807–13.
[17] Roers A, Hochkeppel HK, Horisberger MA, Hovanessian A, Haller O. MxA gene expression after live virus vaccination: a sensitive marker for endogenous type I interferon. J Infect Dis 1994;169:807–13.
[18] Roberts RM, Ezashi T, Rosenfeld CS, Ealy AD, Kubisch HM. Evolution of the interferon tau genes and their promoters, and maternal-trophoblast interactions in control of their expression. Reprod Suppl 2003;61:239–51.
[19] Ank N, West H, Paludan SR. IFN-lambda: novel antiviral cytokines. J Interferon Cytokine Res 2006;26:373–9.
[20] Weber F, Wagner V, Rasmussen SB, Hartmann R, Paludan SR. 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 2006;80:5059–64.
[21] Homung V, Ellegast J, Kim S, et al. 5’-Triphosphate RNA Is the ligand for RIG-I. Science 2006;314:994–7.
[22] Scherbik S, Schulz O, Tan CP, et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5’ phosphates. Science 2006;314:997–1001.
[23] Bowie AG, Fitzgerald KA. RIG-I: tri-ing to discriminate between self and non-self RNA. Trends Immunol 2007;28:147–50.
[24] Hiscott J. Triggering the innate antiviral response through IRF-3 activation. J Biol Chem 2007;282:15325–9.
[25] Fitzgerald KA, McWhirter SM, Faia KL, et al. IKKEpsilon and TBK1 are essential components of the IRF3 signaling pathway. Nat Immunol 2003;4:491–6.
[26] Sharma S, TenOever BR, Grandvaux N, Zhou GP, Lin R, Hiscott J. Triggering the interferon antiviral response through an IKK-related pathway. Science 2003;300:1148–51.
[27] Andrejeva J, Childs KS, Young DF, et al. 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 2004;101:17264–9.
[28] Yoneyama M, Kikuchi M, Natsukawa T, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 2004;5:730–7.
[29] Beutler B. Inferences, questions and possibilities in Toll-like receptor signalling. Nature 2004;430:257–63.
[30] Uematsu S, Akira S. Toll-like receptors and type I interferons. J Biol Chem 2007;282:15319–23.
[31] tenOever BR, Sharma S, Zou W, et al. Activation of TBK1 and IKK epsilon kinases by vesicular stomatitis virus infection and the role of viral ribonucleoprotein in the development of interferon antiviral immunity. J Virol 2004;78:10636–49.
[32] Levy DE, Marie I, Prakash A. Ringing the interferon alarm: differential regulation of gene expression at the interface between innate and adaptive immunity. Curr Opin Immunol 2003;15:52–8.
[33] Honda K, Taniguchi T. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat Rev Immunol 2006;6:644–58.
[34] Kawai T, Sato S, Ishii KJ, et al. Interferon-alpha induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. Nat Immunol 2004.
[35] Levy DE, Darnell Jr JE. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol 2002;3:651–62.
[36] de Veer MJ, Holko M, Frevel M, et al. Functional classification of interferon-stimulated genes identified using microarrays. J Leukoc Biol 2001;69:912–20.
[37] Der SD, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon alpha, beta, or gamma, using oligonucleotide arrays. Proc Natl Acad Sci USA 1998;95:15623–8.
[38] Garcia MA, Gil J, Ventoso I, et al. Impact of protein kinase PKR in innate immune responses to single-stranded RNA viruses. J Virol 2006;80:5059–64.
[39] Brinton MA, Perelygin AA, Schulz O, Tan CP, et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5’ phosphates. Science 2006;314:997–1001.
[40] Silverman RH. Fascination with 2-5A-dependent RNase: a unique enzyme that functions in interferon action. J Biol Chem 2007;282:15325–9.
[41] de Veer MJ, Holko M, Frevel M, et al. Functional classification of interferon-stimulated genes identified using microarrays. J Leukoc Biol 2001;69:912–20.
[42] Der SD, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon alpha, beta, or gamma, using oligonucleotide arrays. Proc Natl Acad Sci USA 1998;95:15623–8.
[43] Garcia MA, Gil J, Ventoso I, et al. Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. Microbiol Mol Biol Rev 2006;70:1032–60.
[44] Williams BR, PKR; a sentinel kinase for cellular stress. Oncogene 1999;18:6112–20.
[45] Silverman RH. Fascination with 2-5A-dependent RNase: a unique enzyme that functions in interferon action. J Interferon Res 1994;14:101–4.
[46] Haller O, Kochs G. Interferon-induced mx proteins: dynamin-like GTPases with antiviral activity. Traffic 2002;3:710–7.
Alcami A, Paranjape J, Brown TL, et al. Interferon action and apoptosis are defective in mice devoid of 2',5'-oligoadenylate-dependent RNase L. EMBO J 1997;16:6355–63.

Zhou A, Paranjape JM, Der SD, Williams BR, Silverman RH. Interferon action in triply deficient mice reveals the existence of alternative antiviral pathways. Virology 1999;258:435–40.

Espert L, Degols G, Gongora C, et al. ISG20, a new interferon-induced RNase specific for single-stranded RNA, defines an alternative antiviral pathway against RNA genomic viruses. J Biol Chem 2003;278:16151–8.

Guo J, Hui DJ, Merrick WC, Sen GC. A new pathway of translational regulation mediated by eukaryotic initiation factor 3. EMBO J 2000;19:6891–7.

Hui DJ, Bhasker CR, Merrick WC, Sen GC. Viral stress-inducible protein p56 inhibits translation by blocking the interaction of eIF3 with the ternary complex eIF2.GTP.Met-tRNAi. J Biol Chem 2003;278:39477–82.

Anderson SL, Carton JM, Lou J, Xing L, Rubin BY. Interferon-induced guanylate binding protein-1 (GBP-1) mediates an antiviral effect against vesicular stomatitis virus and encephalomyocarditis virus. Virology 1999;256:8–14.

Regad T, Chelbi-Alix MK. Role and fate of PML nuclear bodies in interferon-induced antiviral state against a complex retrovirus via its association with the viral transactivator. EMBO J 2001;20:3495–505.

Chee AV, Lopez P, Pandolfi PP, Roizman B. Promyelocytic leukemia protein mediates interferon-based anti-herpes simplex virus 1 effects. J Virol 2003;77:7101–5.

Engelhardt OG, Sirma H, Pandolfi PP, Haller O. Mx1 GTPase accumulates in distinct nuclear domains and inhibits influenza A virus in cells that lack promyelocytic leukemia protein nuclear bodies. J Gen Virol 2004;85:2315–26.

Arnhite Her, Frese M, Kambadur R, Meier E, Haller O. Mx transgenic mice–animal models of health. Curr Top Microbiol Immunol 2005;294:1–14.

Chen Z, Benureau Y, Rijnbrand R, et al. RBV disrupts RIG-I signaling by NS3/4A-mediated cleavage of the adaptor protein MAVS. J Virol 2007;81:964–76.

Lin R, Lacoste J, Nakhaei P, et al. 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 2006;80:6072–83.

Brzozka K, Finke S, Conzelmann KK. Identification of the rabies virus alpha/beta interferon antagonist: phosphoprotein P interferes with phosphorylation of interferon regulatory factor 3. J Virol 2005;79:7673–81.

Alff PJ, Gavrilovskaya IN, Gorbunova E, et al. The pathogenic NY-1 hantavirus G1 cytoplasmic tail inhibits RIG-I and TBK-1-directed interferon responses. J Virol 2006;80:9676–86.

Bauhofer O, Summerfield A, McCullough KC. Ruggli N. Role of double-stranded RNA and Npro of classical swine fever virus in the activation of monocyte-derived dendritic cells. Virology 2005;343:93–105.

La Rocca SA, Herbert RJ, Crooke H, Drew TW, Wileman TE, Powell PP. Loss of interferon regulatory factor 3 in cells infected with classical swine fever virus involves the N-terminal protease. Npro. J Virol 2005;79:7239–47.

Ruggli N, Bird BH, Liu L, Bauhofer O, Tratschin JD, Hofmann MA. Npro of classical swine fever virus is an antagonist of double-stranded RNA-mediated apoptosis and IFN-alpha/beta induction. Virology 2005;340:265–76.

Bauhofer O, Summerfield A, Sakoda Y, Tratschin JD, Hofmann MA. Ruggli N. Role of double-stranded RNA virus interferes with interferon regulatory factor 3 and induces its proteasomal degradation. J Virol 2007;81:514–24.

Hilton L, Moganaraj KC, Zhang G, et al. The Npro product of bovine viral diarrhea virus inhibits DNA binding by interferon regulatory factor 3 and targets it for proteasomal degradation. J Virol 2006;80:11723–32.

Ronco LV, Karpova AY, Vidal M, Howley PM. Human papillomavirus 16 E6 oncoprotein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. Genes Dev 1998;12:2061–72.

Kopecky-Bromberg SA, Martinez-Sobrino L, Friesman M, Baric RA, Palese P. Sars coronavirus proteins Orf 3b, Orf 6, and nucleocapsid function as interferon antagonists. J Virol 2007;81:548–57.
Mathews MB, Pichlmair A, Martinez-Sobrido L, et al. Inhibition of Beta interferon induction by severe acute respiratory syndrome coronavirus suggests a two-step model for activation of interferon regulatory factor 3. J Virol 2005;79:2079–86.

Bursely K, Yeow WS, Lubyova B, et al. Functional analysis of human herpesvirus 8-encoded viral interferon regulatory factor 1 and its association with cellular interferon regulatory factors and p300. J Virol 1999;73:7334–42.

Bursely K, Yeow WS, Pitha PM. Unique properties of a second human herpesvirus 8-encoded interferon regulatory factor (vIRF-2). J Hum Virol 1999;2:19–32.

Fuld S, Cunningham C, Khucher A, Davison AJ, Blackbourn DJ. Inhibition of interferon signaling by the Kaposi’s sarcoma-associated herpesvirus full-length viral interferon regulatory factor 2 protein. J Virol 2006;80:3092–7.

Li M, Lee H, Guo J, et al. Kaposi’s sarcoma-associated herpesvirus viral interferon regulatory factor. J Virol 1998;72:5433–40.

Lubyova B, Pitha PM. Characterization of a novel human herpesvirus 8-encoded protein, vIRF-3, that shows homology to viral and cellular interferon regulatory factors. J Virol 2000;74:1819–201.

Lubyova B, Kellum MJ, Frisancho AJ, Pitha PM. Kaposi’s sarcoma-associated herpesvirus-encoded vIRF-3 stimulates the transcriptional activity of cellular IRF-3 and IRF-7. J Biol Chem 2004;279:7643–54.

Zimring JC, Goodbourn S, Offermann MK. Human herpesvirus 8 encodes an interferon regulatory factor (IRF) homolog that represses IRF-1-mediated transcription. J Virol 1998;72:701–7.

Boulou M, Janzen C, Vialat P, et al. Genetic evidence for an interferon-antagonistic function of rift valley fever virus nonstructural protein NSs. J Virol 2001;75:1371–7.

Billecocq A, Spiegel M, Vialat P, et al. NSs protein of Rift Valley Fever Virus blocks interferon production by inhibiting host gene transcription. J Virol 2004;78:9798–806.

Le May N, Dubael S, De Santis LP, Billecocq A, Bouloy M, Egly JM. TFIIF transcription factor, a target for the Rift Valley hemorrhagic fever virus. Cell 2004;116:541–50.

Thomas D, Blakgri G, Wagger V, et al. Inhibition of RNA polymerase II phosphorylation by a viral interferon antagonist. J Biol Chem 2004;279:31471–7.

Cardenas WB, Loo YM, Gale Jr M, et al. Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-I signaling. J Virol 2006;80:5168–78.

Child SJ, Hanson LK, Brown CE, Janzen DM, Geballe AP. Double-stranded RNA binding by a heterodimeric complex of murine cytoplasmic RNA helicase A and NS2. J Virol 1999;73:290–6.

Garcia-Sastre A, Egorov A, Matassov D, et al. Influenza A virus lacking the NS1 gene replicates in interferon-deficient systems. Virology 1998;252:324–30.

Garcia-Sastre A. Inhibition of interferon-mediated antiviral responses by influenza A viruses and other negative-strand RNA viruses. Virology 2001;279:375–84.

Hartman AL, Dover JE, Towner JS, Nichol ST. 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 induction without inhibiting viral transcription or replication. J Virol 2006;80:6430–40.

Langland JO, Cameron JM, Heck MC, Jancovich JK, Jacobs BL. Inhibition of PKR by RNA and DNA viruses. Virus Res 2006;119:100–10.

Lee TG, Tomita J, Hovanessian AG, Katze MG. Purification and partial characterization of a cellular inhibitor of the interferon-induced protein kinase of Mr 68,000 from influenza virus-infected cells. Proc Natl Acad Sci USA 1990;87:6208–12.

Valchanova RS, Picard-Maureau M, Bult M, Brune W. Murine cytomegalovirus m142 and m143 are both required to block protein kinase R-mediated shutdown of protein synthesis. J Virol 2006;80:10181–90.

Mathews MB, Shenk T. Adenovirus-associated RNA and translation control. J Virol 1991;65:5657–62.

Vyas J, Elia A, Clemens MJ. Inhibition of the protein kinase PKR by the internal ribosome entry site of hepatitis C virus genomic RNA. RNA 2003;9:858–70.

Elia A, Laing KG, Schofield A, Tillery AJ, Clemens MJ. 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 1996;24:4491–8.

Gunnery S, Rice AP, Robertson HD, Mathews MB. 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 1990;87:8067–91.

He B, Gross M, Reizman B. The gamma(1)34.5 protein of herpes simplex virus 1 complexes with polo protein phosphatase 1alpha to dephosphorylate the alpha subunit of the eukaryotic translation initiation factor 2 and preclude the shutoff of protein synthesis by double-stranded RNA-activated protein kinase. Proc Natl Acad Sci USA 1997:94:843–8.

Taylor DR, Shi ST, Romano PR, Barber GN, Lai MM. Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein. Science 1999;285:107–10.

Roy S, Katze MG, Parkin NT, Edery I, Hovanessian AG, Sonenberg N. Control of the interferon-induced 68-kilodalton protein kinase by the HIV-1 tat gene product. Science 1990;247:1216–9.

Davies MV, Elroy-Stein O, Jagus R, Moss B, Kaufman RJ. The vaccinia virus K3L gene product potentiates translation by inhibiting double-stranded-RNA-activated protein kinase and phosphorylation of the alpha subunit of eukaryotic initiation factor 2. J Virol 1992;66:1943–50.

Li S, Min YJ, Krug RM, Sen GC. Binding of the influenza A virus NS1 protein to PKR mediates the inhibition of its activation by either PACT or double-stranded RNA. Virology 2006;349:1–21.

Min YJ, Krug RM. 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 2006;103:7100–5.

Black TL, Barber GN, Katze MG. Degradation of the interferon-activated 68,000-M(r) protein kinase by poliovirus requires RNA. J Virol 1993;67:791–800.

Martindale C, Montavon C, Salezhada T, Silhol M, Lebleu B, Bisbal C. 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 1999;73:290–6.

Martindale C, Salezhada T, Silhol M, Lebleu B, Bisbal C. 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 1998;254:248–55.

Cayley PJ, Davies JA, McCullagh KG, Kerr IM. Activation of the pp(A2‘p)A3 system in interferon-treated, herpes simplex virus-infected cells and evidence for novel inhibitors of the pp(A2‘p)A3-dependent RNase. Eur J Biochem 1984;143:165–74.

Han JQ, Townsend HL, Jha BK, Paranjape JM, Silverman RH, Barton DJ. A phylogenetically conserved RNA structure in the poliovirus open reading frame inhibits the antiviral endoribonuclease RNase L. J Virol 2007;81:5561–72.

Atreya PL, Kulkarni S. Respiratory syncytial virus strain A2 is resistant to the antiviral effects of type I interferons and human MxA. Virology 1999;261:227–41.

Young DF, Didcock L, Goodbourn S, Randall RE. Paramyxoviridae use distinct virus-specific mechanisms to circumvent the interferon response. Virology 2000;269:383–90.

Schlenker J, Bossert B, Buchholz U, Conzelmann KK. Bovine respiratory syncytial virus nonstructural proteins NS1 and NS2 cooperatively antagonize alpha/beta interferon-induced antiviral response. J Virol 2000;74:8234–42.

Spann KM, Tran KC, Chi B, Rabin RL, Collins PL. Suppression of the induction of alpha, beta, and gamma interferons by the NS1 and NS2 proteins of human respiratory syncytial virus in human epithelial cells and macrophages. J Virol 2004;78:4363–9.
[123] Wright PF, Karron RA, Madhi SA, et al. The interferon antagonist NS2 protein of respiratory syncytial virus is an important virulence determinant for humans. J Infect Dis 2006;193:573–81.

[124] Moller A, Schmitz ML. Viruses as hijackers of PML nuclear bodies. Arch Immunol Ther Exp (Warsz) 2003;51:295–300.

[125] Boutell C, Sadis S, Everett RD. Herpes simplex virus type 1 immediate-early protein ICP0 and is isolated RING finger domain act as ubiquitin E3 ligases in vitro. J Virol 2002;76:841–50.

[126] Van Sant C, Hagglund R, Lopez P, Roizman B. The infected cell protein 0 of herpes simplex virus 1 dynamically interacts with proteasomes, binds and activates the cdc34 E2 ubiquitin-conjugating enzyme, and possesses in vitro E3 ubiquitin ligase activity. Proc Natl Acad Sci USA 2001;98:8815–20.

[127] Muller S, Dejean A. Viral immediate-early proteins abrogate the modification by SUMO-1 of PML and Sp100 proteins, correlating with nuclear body disruption. J Virol 1999;73:5137–43.

[128] Kochs G, Weber F, Gruber S, Delvendahl A, Leitz C, Haller O. Thogoto virus matrix protein is encoded by a spliced mRNA. J Virol 2000;74:10785–9.

[129] Hagmaier K, Jennings S, Buse J, Weber F, Kochs G. Novel gene product of Thogoto virus segment 6 codes for an interferon antagonist. J Virol 2003;77:2747–52.

[130] Pichlmair A, Buse J, Jennings S, Haller O, Kochs G, Staeheli P. Thogoto virus lacking interferon-antagonistic protein ML is strongly attenuated in newborn Mx1-positive but not Mx1-negative mice. J Virol 2004;78:11422–4.

[131] Grimm D, Staeheli P, Hufbauer M, et al. Replication fitness determines high virulence of influenza A virus in mice carrying functional Mx1 resistance gene. Proc Natl Acad Sci USA 2007;104:6806–11.

[132] Jennings S, Martinez-Sobrido L, Garcia-Sastre A, Weber F, Kochs G. Thogoto virus ML protein suppresses IRF3 function. Virology 2005;331:63–72.

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