S2-2

VIRAL INHIBITION OF INTERFERON SIGNAL TRANSDUCTION

Daniel D. Sedmak, Colleen M. Cebulla, Brian Rahill, and Daniel M. Miller

The Department of Pathology, The Ohio State University College of Medicine; Columbus, OH 43210, USA

Introduction

Type I and II interferons are major lines of defense against viral infections. IFNs, through activation of diverse antiviral pathways, block multiple steps of viral replication including entry of the virus into the cell, transcription, translation, maturation, assembly, and virion release. IFNs also augment immune recognition and lysis of virally infected cells through upregulation of MHC class I and II protein expression, and through upregulation of antigen processing machinery such as subunits of the proteasome. There is increasing evidence that IFN-mediated anti-viral effects have led multiple viruses to evolve mechanisms of blocking IFN-signaling in infected cells. Herein, we will review in greater detail the role of IFNs in antiviral activity, the IFN signal transduction pathways, and new information regarding specific mechanisms utilized by viruses to inhibit IFN signaling.

Antiviral mechanisms of IFN:

IFNs, through activation of diverse antiviral pathways, block multiple steps of viral replication including entry of the virus into the cell, transcription, translation, maturation, assembly, and virion release [1, 2]. Three main proteins mediate these IFN-induced direct antiviral effects. (1) 2',5'-oligoadenylate synthetase (2',5'-OAS) interacts with double stranded (ds)-RNA to activate a ribonuclease (RNAse L) which degrades mRNA, preventing viral products from being synthesized [1, 2]. (2) dsRNA-dependent protein kinase (PKR) also inhibits translation of viral products by phosphorylating translation initiation factor eIF-2 [1, 2]. (3) Mx proteins disrupt influenza, VSV, and HSV replication, working through an unknown mechanism [1, 2].

In addition to inhibiting viral replication, IFNs augment immune recognition and lysis of virally-infected cells [2]. Virally-infected cells are recognized by T cells via viral peptides presented in the context of major histocompatibility complex (MHC) class I and II molecules. Type I IFNs upregulate MHC class I protein expression, and type II IFNs upregulate both MHC

class I and II [3, 4]. Moreover, IFNs upregulate other antigen processing machinery, such as subunits of the proteasome [5].

To underscore the importance of IFNs in controlling viral infections, *in vivo* studies, with a few exceptions, show that experimentally disrupting IFN action enhances viral disease. In studies with neutralizing antibodies to IFN-α/β, mice infected with mouse hepatitis virus-3, influenza, Sindbis, encephalomyocarditis (EMC) virus, murine cytomegalovirus (MCMV), or herpes simplex virus (HSV)-1 were more susceptible to viral infection and pathology than non-IFN-α/β depleted controls [2]. In addition, symptomatic infections with Semliki Forest virus, EMC, HSV-1 and -2, Moloney sarcoma, Friend leukemia virus, or polyoma virus in naturally sensitive mice were exacerbated by IFN-α/β depletion. Similar results were generated in experiments using IFN-α/β receptor knockout mice [2]. Analyses of the role of IFN-γ in viral infection have produced analogous results, demonstrating that IFN-γ promotes recovery from and clearance of lymphocytic choriomeningitis and vaccinia viruses [2].

Several studies demonstrate the importance of IFNs in controlling HCMV disease. Intramuscular IFN-α reduces the replication of MCMV in the spleen and liver of mice and IFN-α receptor knockout mice are 800-fold more susceptible to MCMV infection than their wild type litter mates [6, 7]. Numerous *in vitro* studies demonstrate that pretreating cells with IFN-α inhibits human HCMV replication by decreasing transcription of the immediate-early (IE) HCMV gene products [8, 9]. The antiviral effects of IFN also extend to clinical therapy, as IFN-α treatment significantly reduces the incidence of serious HCMV infections in seropositive renal transplant recipients [10].

In addition to the type I interferons, studies of IFN-γ in MCMV models demonstrate that IFN-γ is a critical cytokine in controlling acute and chronic CMV infection [7, 11]. *In vivo* it has been documented that (1) IFN-γ accounts for the majority of natural killer (NK) cell-mediated antiviral effects during acute infection [12, 13]; (2) Neutralization of IFN-γ prevents MCMV

clearance from the salivary gland and prevents control of MCMV infection [14, 15]; and (3) IFN-γ depletion increases MCMV titers in the liver and spleen [13]. *In vitro* it has been documented that (1) Pretreatment of diverse cell types with IFN-γ inhibits HCMV replication [9, 16-19]; and (2) IFN-γ pretreatment restores HCMV antigen processing and presentation to HCMV specific $CD8^+$ T lymphocyte clones [20, 21]. Recently, it has been reported that MCMV infection in IFN-γ receptor knockout mice leads to an uncontrolled persistent infection resulting in a severe vasculitis of large arterial vessels [7]. In contrast, there are very few studies demonstrating that IFN-γ positively influences CMV replication [22].

Furthermore, two animal models demonstrate that the IFN stimulated JAK/STAT signal transduction pathway is critical for controlling CMV infections. STAT1 knockout mice and IFN-α receptor/IFN-γ receptor double knockout mice, which are deficient in IFN stimulated signal transduction and biological responses, are exquisitely sensitive to viral infection [7, 23]. In these mice, acute MCMV infection proceeds unchecked and rapidly leads to death [7, 23].

IFN Signal Transduction:

The diverse biological activities of the IFNs are mediated by a conserved signal transduction pathway [4]. IFN-α binds to its receptor (IFNAR1 and IFNAR2), which stimulates the activation of kinases JAK1 and Tyk2 [24]. JAK1 and Tyk2 phosphorylate each other, the cytoplasmic tail of IFNAR1, STAT1 and STAT2 (signal transducers and activator of transcription). STAT1/STAT2 heterodimers unite with DNA-binding protein p48 to form the transcription factor complex ISGF3, which binds to the IFN stimulated response element (ISRE) sites in many IFN-α responsive promoters [4, 25-27]. Alternatively, phosphorylated STAT1 homodimers and STAT1/STAT2 heterodimers can move to the nucleus and bind to elements such as the inverted repeat (IR) element of the interferon regulatory factor-1 (IRF-1) gene to activate transcription in an ISGF3-*independent* manner [28, 29].

In the IFN-γ signal transduction pathway, the receptor (IFN-γR1 and IFN-γR2) binds IFN-γ; associated JAK1 and JAK2 unite, triggering tyrosine phosphorylation [4, 30]. Phosphorylated STAT1α forms a homodimer called IFN-γ activating factor (GAF) that binds to the IFN-γ activated sequence (GAS) elements in the promoters of IFN-γ stimulated genes to activate transcription [31, 32].

Viral disruption of IFN signaling:

Recent work demonstrates that viruses have evolved means of disrupting IFN stimulated JAK/STAT signal transduction. Adenovirus E1A gene products inhibit IFN-α and IFN-γ signal transduction, thereby protecting E1A expressing cells from IFN stimulated antiviral and immunoregulatory responses; and E1A enhances replication by distinct viruses in IFN-treated adenovirus-infected cells [33-38]. Adenovirus E1A gene products decrease p48, and overexpression of p48 can restore IFN-α signal transduction in E1A transfected cells [35]. In addition, in some cell types (HeLa and 3Y1 rat fibroblasts but not HT1080 cells), E1A also decreases STAT1 levels, further preventing IFN-α and IFN-γ induced signaling [34, 35, 39]. However, the mechanisms which mediate these decreases are unknown.

The ability of human papilloma virus (HPV) to inhibit IFN signal transduction, has also been recently investigated since IFN-α treatments of HPV-infected patients have yielded only marginal clinical benefits [40]. The HPV E7 oncoprotein was a candidate for disrupting IFN signaling since (1) HPV-transformed cells disrupted IFN-α stimulated responses, (2) patients responding well to IFN-α treatment had lower levels of E7 oncoprotein, and (3) E7 shares sequence and functional homology with the IFN-α-signal-transduction-blocking adenovirus E1A protein [40]. Cells transfected with HPV E7 inhibited the induction of IFN-α inducible genes, but not IFN-γ inducible genes. Moreover, these cells lost ISGF3 formation and p48 nuclear translocation, without decreasing p48 levels. The E7 protein could potentially play a direct role in inactivating p48, since it binds p48 [40].

Mumps disrupts IFN-induced gene expression in infected cells through inhibition of the signaling pathway [41-44]. One recent study demonstrated that the lesion in the signaling pathway was an absence of STAT1α, mediated by a post-transcriptional mechanism [44]. This signaling defect prevented the antiviral effects of IFN against VSV superinfection [42].

Filoviruses, including the lethal Ebola virus, have proved resistant to IFN prophylaxis in infected monkeys [45, 46]. Recently, Ebola virus was shown to inhibit the induction of IFN induced genes including MHC class I, IRF-1, and 2',5'-OAS. Gel shift experiments demonstrated that both IFN-α and IFN-γ signal transduction was blocked in Ebola-infected endothelial cells (EC); signaling complexes did not bind the ISRE, and only very low levels of GAS-binding complexes were formed [46]. The precise site of inhibition has not been determined, but likely candidates include JAK1, STAT1, or STAT2. This disruption of IFN signaling could contribute to the severe immunosuppression and high viral titers seen in Ebola infection.

The Hepatitis B virus (HBV) terminal protein was demonstrated to block the signaling response to IFN-α and IFN-γ by interfering with the formation of active ISGF3 complexes [47]. It is hypothesized that enough terminal protein may be generated in chronic HBV infections which could make IFN-α therapy less effective and antagonize infected hepatocyte antigen presentation to cytotoxic T lymphocytes.

The Epstein-Barr virus (EBV) nuclear antigen 2 (EBNA-2) gene similarly prevents activation of IFN stimulated genes by IFN-α, however, this inhibition appears to occur downstream of the activation of ISGF3 [48]. Moreover, unlike other viruses which interfere with IFN signaling, this inhibition of signaling prevents the antiproliferative effect of IFN-α, yet it does not prevent the antiviral actions of IFN [49].

HCMV employs many mechanisms enabling it to evade immunosurveillance and persist in the host [50]. Inhibiting IFN-γ and IFN-α signal transduction are some of those important strategies. HCMV is the first virus identified as inhibiting IFN-γ stimulated JAK/STAT signal

transduction by targeting JAK1. This lesion results in blocked IFN-γ stimulated signal transduction and gene expression including the induction of MHC class II, class I, and associated antigen processing genes in EC and fibroblasts [51, 52]. HCMV immediate early (IE) and/or early (E) genes decrease JAK1 expression through a post-translational mechanism involving the proteasome [52].

JAK1 is an essential component of type I IFN signaling, suggesting that HCMV could similarly inhibit IFN-α responsiveness by targeting JAK1. However, recent reports that a HCMV virion protein is capable of upregulating a subset of IFN-α responsive genes, *independent* of IFN treatment and signal transduction, cast doubt upon the ability of HCMV to block IFN-α responsiveness [53, 54]. Our experiments determined, however, that IFN-α–induced ISGF3-dependent signaling was blocked, since IFN-α treatment was unable to upregulate MHC class I, 2',5'-OAS, or MxA RNA levels in HCMV infected cells [55]. Further, ISGF3- *independent* IFN-α induced signaling was inhibited, since IRF-1 mRNA induction was blocked in CMV infected cells [55]. Gel shift experiments revealed that both ISGF3 and STAT1 homodimer formation, were inhibited [55]. These findings could be explained by the discoveries that JAK1 as well as p48, an essential component of ISGF3, are both significantly decreased by HCMV [55]. Thus, CMV induces lesions in multiple levels of the IFN-α JAK/STAT signal transduction pathway, decreasing both JAK1 and p48. The ability for CMV to evade the type I and II IFN-stimulated antiviral and immunoregulatory responses in EC probably contributes to EC "reservoirs" of infectious virus.

It is increasing evident that multiple mechanisms for viral disruption of IFN signaling by a virus, will be discovered. Recently, Le Roy et al. discovered a distinct mechanism for HCMV-mediated disruption of IFN-γ inducible MHC class II expression utilizing an *in vitro* model where cells are infected with HCMV and treated with IFN-γ simultaneously. Their studies show a repression of CIITA mRNA expression as early as 6 hours after infection suggesting that a

HCMV protein or HCMV-induced signal inhibits IFN-γ stimulated CIITA expression at the level of the CIITA promoter [56].

In summary, recent findings suggest that the intense selection pressure of cell mediated antiviral immune responses have led several viruses to evolve strategies for inhibiting IFN signaling. Studies directed toward identification of viral proteins and mechanisms involved in disrupting IFNs may lead to therapies which will thwart these responses and ameliorate the complications associated with persistent stages of infection.

References:

1 Samuel CE: Antiviral actions of interferon interferon-regulated cellular proteins and their surprisingly selective antiviral activities. Virol 1991;183: 1-11.

2 Vilcek J, Sen GC: Interferons and other cytokines; in Fields BN, Knipe DM and Howley PM (eds): Fields Virology. Philadelphia, PA, Lippincott-Raven Publishers, 1996, pp 341-365.

3 Boss JM: Regulation of transcription of MHC class II genes. Curr Opin Immunol 1997;9: 107-113.

4 Darnell JE, Kerr IM, Stark GR: Jak-Stat pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 1994;264: 1415-1421.

5 Martin B, Chin K, Olsen J, Skinner C, Dey A, Ozato K, Ting J: Induction of MHC class I expression by the MHC class II transactivator CIITA. Immunity 1997;6: 591-600.

6 Yeow W-S, Lawson CM, Beilharz MW: Antiviral activities of individual murine IFN-(alpha) subtypes in vivo: intramuscular injection of IFN expression constructs reduces cytomegalovirus replication. J Immunol 1998;160: 2932-2939.

7 Presti RM, Pollock JL, Dal Canto AJ, O'Guin AK, Virgin HW: Interferon-γ regulates acute and latent murine cytomegalovirus infection and chronic disease of the great vessels. J Exp Med 1998;188: 577-588.

8 Martinotti MG, Gribaudo G, Gargiglio M, Caliendo A, Lembo D, Angeretti A, Cavallo R, Landolfo S: Effect of interferon-α on immediate early gene expression of murine cytomegalovirus. J Interferon Res 1993;13: 105-109.

9 Gribaudo G, Ravaglia S, Caliendo A, Cavallo R, Gariglio M, Martinotti MG, Landolfo S: Interferons inhibit onset of murine cytomegalovirus immediate-early gene transcription. Virol 1993;197: 303-311.

10 Hirsch MS, Schooley RT, Cosimi AB, Russell PS, Delmonico FL, Tolkoff-Rubin NE, Herrin JT, Cantell K, Farrell M-L, Rota TR, Rubin RH: Effects of interferon-alpha on cytomegalovirus reactivation syndromes in renal-transplant recipients. New Engl J Med 1983;308: 1489-1493.

11 Biron CA: Cytokines in the generation of immune responses to, and resolution of, virus infection. Curr Opin Immunol 1994;6: 530-538.

12 Kawaguchi Y, Bruni R, Roizman B: Interaction of herpes simplex virus 1 alpha regulatory protein ICP0 with elongation factor 1 delta: ICP0 affects translational machinery. J Virol 1997;71: 1019-1024.

13 Orange JS, Wang B, Terhorst C, Biron CA: Requirement for natural killer cell-produced interferon γ in defense against murine cytomegalovirus infection and enhancement of this defense pathway by interleukin 12 administration. J Exp Med 1995;182: 1045-1056.

14 Jonjic S, Mutter W, Weiland F, Reddehase MJ, Koszinowski UH: Site-restricted persistent cytomegalovirus infection after selective long-term depletion of CD4 T lymphocytes. J Exp Med 1989;169: 1199-1212.

15 Lucin P, Pavic I, Polic B, Jonjic S, Koszinowski UH: Gamma interferon-dependent clearance of cytomegalovirus infection in salivary glands. J Virol 1992;66: 1977-1984.

16 Davignon J-L, Castanie P, Yorke JA, Gautier N, Clement D, Davrinche C: Anti-human cytomegalovirus activity of cytokines produced by CD4+ T-cell clones specifically activated by IE1 peptides in vitro. J Virol 1996;70: 2162-2169.

17 Heise MT, Virgin HW: The T-cell-independent role of gamma interferon and tumor necrosis factor alpha in macrophage activation during murine cytomegalovirus and herpes simplex virus infections. J Virol 1995;69: 904-909.

18 Lucin P, Jonjic S, Messerle M, Polic B, Hengel H, Koszinowski U: Late phase inhibition of murine cytomegalovirus replication by synergistic action of interferon-gamma and tumour necrosis factor. J Gen Virol 1994;75: 101-110.

19 Schut RL, Gekker G, Hu S, Chao CC, Pomeroy C, Jordan MC, Peterson PK: Cytomegalovirus replication in murine microglial cell cultures: suppression of permissive infection by interferon-γ. J Infect Dis 1994;169: 1092-1096.

20 Hengel H, Eblinger C, Pool J, Goulmy E, Koszinowski UH: Cytokines restore MHC class I complex formation and control antigen presentation in human cytomegalovirus-infected cells. J Gen Virol 1995;76: 2987-2997.

21 Hengel H, Lucin P, Jonjic S, Ruppert T, Koszinowski UH: Restoration of cytomegalovirus antigen presentation by gamma interferon combats viral escape. J Virol 1994;68: 289-297.

22 Haagmans BL, van der Meide PH, Stals FS, van der Eertwegh AJM, Claassen E, Bruggeman CA, Horzinek MC, Schijns VECJ: Suppression of rat cytomegalovirus replication by antibodies against gamma interferon. J Virol 1994;68: 2305-2312.

23 Durbin JE, Hackenmiller R, Simon MC, Levy DE: Targeted disruption of the mouse STAT1 gene results in compromised innate immunity to viral disease. Cell 1996;84: 443-450.

24 Lew DJ, Decker T, Strehlow I, Darnell JE: Overlapping elements in the guanylate-binding protein gene promoter mediate transcriptional induction by alpha and gamma interferons. Mol Cell Biol 1992;1991: 182-191.

25 Schindler C, Shuai K, Prezioso VR, Darnell JE: Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. Science 1992;257: 809-813.

26 Ghislain JJ, Fish EN: Application of genomic DNA affinity chromatography identifies multiple interferon-alpha-regulated Stat2 complexes. J Biol Chem 1996;271: 12408-12413.

27 Li X, Leung S, Kerr IM, Stark GR: Functional subdomains of STAT2 required for preassociation with the alpha interferon receptor and for signaling. Mol Cell Biol 1997;17: 2048-2056.

28 Haque SJ, Williams BRG: Identification and characterization of an interferon (IFN)-stimulated response element-IFN-stimulated gene factor 3-independent signaling pathway for IFN-alpha. J Biol Chem 1994;269: 19523-19529.

29 Li X, Leung S, Qureshi S, Darnell JE, Stark GR: Formation of Stat1-Stat2 heterodimers and their role in the activation of IRF-1 gene transcription by interferon-alpha. J Biol Chem 1996;271: 5790-5794.

30 Hibino Y, Kumar CS, Mariano TM, Lai D, Pestka S: Chimeric interferon-γ receptors demonstrate that an accessory factor required for activity interacts with the extracellular domain. J Biol Chem 1992;267(6): 3741-3749.

31 Shuai K, Stark GR, Kerr IM, Darnell JEJ: A single phosphotyrosine residue of stat91 required for gene activation by interferon-gamma. Science 1993;261: 1744-1746.

32 Schindler C, Darnell JE: Transcriptional responses to polypeptide ligands: The Jak-Stat pathway. Ann Rev Biochem 1995;64: 621-651.

33 Gutch MJ, Reich NC: Repression of the interferon signal transduction pathway by the adenovirus E1A oncogene. Proc Natl Acad Sci, USA 1991;88: 7913-7917.

34 Leonard GT, Sen GC: Effects of adenovirus E1A protein on interferon-signaling. Virol 1996;224: 25-33.

35 Leonard GT, Sen GC: Restoration of interferon responses of adenovirus E1A-expressing HT1080 cell lines by overexpression of p48 protein. J Virol 1997;71: 5095-5101.

36 Kalvakolanu DVR, Bandyopadhyay SK, Harter ML, Sen GC: Inhibition of the interferon inducible gene expression by adenovirus E1A proteins: block in transcriptional complex formation. Proc Natl Acad Sci, USA 1991;88: 7459-7463.

37 Mahr JA, Gooding LR: Immune evasion by adenoviruses. Immunol Rev 1999;168: 121-130.

38 Anderson KP, Fennie EH: Adenovirus early region 1A modulation of interferon antiviral activity. J Virol 1987;61: 787-795.

39 Takeda T, Nakajima K, Kojima H, Hirano T: E1A repression of IL-6-induced gene activation by blocking the assembly of IL-6 response element binding complexes. J Immunol 1994;153: 4573-4582.

40 Barnard P, McMillan NAJ: The human papillomavirus E7 oncoprotein abrogates signaling mediated by interferon-α. Virol 1999;259: 305-313.

41 Fujii N, Oguma K, Kimura K, Yamashita T, Ishida S, Fujinaga K, Yashiki T: Oligo-2',5'-adenylate synthetase activity in K562 cell lines persistently infected with measles or mumps virus. J Gen Virol 1988;69: 2085-2091.

42 Fujii N, Kimura K, Murakami T, Indoh T, Ishida S, Fujinaga K, Oguma K: Suppression of interferon-induced oligo-2',5'-adenylates synthetase induction in persistent infection. J Gen Virol 1990;71: 3071-3074.

43 Fujii N, Yokosawa N, Ishida S, Shirakawa S, Kubota T, Indoh T, Fujinaga K, Yashiki T: Investigation of IFN type-I receptor and IFN regulatory factor expression relating to induction of 2',5'-oligoadenylate synthetase in cells persistently infected with the mumps virus. Microbiol Immunol 1996;40: 777-781.

44 Yokosawa N, Kubota T, Fujii N: Poor induction of interferon-induced 2',5'-oligoadenylate synthetase (2-5 AS) in cells persistently infected with mumps virus is caused by decrease of STAT-1α. Arch Virol 1998;143: 1985-1992.

45 Peters CJ, Sanchez A, Rollin PE, Ksiazek TG, Mruphy FA: Filoviridae: marburg and ebola viruses; in Fields BN, Knipe DM and Howley PM (eds): Fields Virology. New York, Lippincott-Raven, 1996, vol 1, pp 1161-1176.

46 Harcourt BH, Sanchez A, Offermann MK: Ebola virus selectively inhibits responses to interferons, but not to interleukin-1β, in endothelial cells. J Virol 1999;73: 3491-3496.

47 Foster GR, Ackrill AM, Goldin RD, Kerr IM, Thomas HC, Stark GR: Expression of the terminal protein region of hepatitis B virus inhibits cellular responses to interferons α and γ and double-stranded RNA. Proc Natl Acad Sci, USA 1991;88: 2888-2892.

48 Kanda K, Decker T, Aman P, Wahlstrom M, von Gabain A, Kallin B: The EBNA2-related resistance towards alpha interferon in Burkitt's lymphoma cells effects induction of IFN-induced genes but not the activation of transcription factor ISGF3. Mol Cell Biol 1992;12: 4930-4936.

49 Aman P, von Gabain A: An Epstein-Barr virus immortalization associated gene segment interferes specifically with the IFN-induced anti-proliferative response in human B-lymphoid cell lines. EMBO J 1990;9: 147-152.

50 Miller DM, Sedmak DD: Viral effects on antigen processing. Curr Opin Immunol 1999;11: 94-99.

51 Miller DM, Zhang Y, Rahill BM, Kazor K, Rofagha S, Eckel JJ, Sedmak DD: Human cytomegalovirus blocks interferon-gamma stimulated upregulation of MHC class I expression and the class I antigen processing machinery. Transplantation; *In Press.*

52 Miller DM, Rahill BM, Boss JM, Lairmore MD, Durbin JE, Waldman WJ, Sedmak DD: Human cytomegalovirus inhibits major histocompatibility complex class II expression by disruption of the Jak/Stat pathway. J Exp Med 1998;187: 675-683.

53 Zhu H, Cong JP, Shenk T: Use of differential display analysis to assess the effect of human cytomegalovirus infection on the accumulation of cellular RNAs: Induction of interferon-responsive RNAs. Proc Natl Acad Sci, USA 1997;94: 13985-13990.

54 Navarro L, Mowen K, Rodems S, Weaver B, Reich N, Spector D, David M: Cytomegalovirus activates interferon immediate-early response gene expression and an interferon regulatory factor 3-containing interferon-stimulated response element-binding complex. Mol Cell Biol 1998;18: 3796-3802.

55 Miller DM, Zhang Y, Rahill BM, Waldman WJ, Sedmak DD: Human Cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. J Immunol 1999;162: 6107-6113. 1999;168: 143-156.

56 Le Roy E, Muhlethaler-Mottet A, Davrinche C, Mach B, Davignon JL: Escape of human cytomegalovirus from HLA-DR-restricted CD4+ T-cell response is mediated by repression of γ interferon- induced class II transactivator expression. J Virol 1999;73(8): 6582-6589.