Immune Netw. 2018 Oct;18(5):e33
https://doi.org/10.4110/in.2018.18.e33
pISSN 1598-2629·eISSN 2092-6685

IMMUNE NETWORK

Review Article

Check for updates

Direct Antiviral Mechanisms of Interferon-Gamma

Soowon Kang [1], **Hailey M. Brown** [2], **Seungmin Hwang** [1,2,3,4,*]

[1]Department of Pathology, The University of Chicago, Chicago, IL 60637, USA
[2]Committee on Immunology, The University of Chicago, Chicago, IL 60637, USA
[3]Committee on Microbiology, The University of Chicago, Chicago, IL 60637, USA
[4]Committee on Cancer Biology, The University of Chicago, Chicago, IL 60637, USA

OPEN ACCESS

Received: Aug 31, 2018
Revised: Sep 25, 2018
Accepted: Sep 27, 2018

***Correspondence to**
Seungmin Hwang
Department of Pathology, Committee on Immunology, Committee on Microbiology, Committee on Cancer Biology, The University of Chicago, Chicago, IL 60637, USA.
E-mail: shwang@bsd.uchicago.edu

ORCID iDs
Soowon Kang
https://orcid.org/0000-0003-3451-9882
Hailey M. Brown
https://orcid.org/0000-0003-0872-7119
Seungmin Hwang
https://orcid.org/0000-0003-0846-5462

Conflicts of Interest
The authors declare no potential conflicts of interest.

Abbreviations
2-AP, 2-aminopurine; BKV, BK virus; cccDNA, covalently closed circular DNA; CHX, cycloheximide; CLDN1, claudin-1; DDX60, DEAD box polypeptide 60; DDX60L, DExD/H box helicase DEAD box polypeptide 60-like;

ABSTRACT

Interferon-gamma (IFNG) is a pleiotropic cytokine that modulates both innate and adaptive immune networks; it is the most potent activator of macrophages and a signature cytokine of activated T lymphocytes. Though IFNG is now appreciated to have a multitude of roles in immune modulation and broad-spectrum pathogen defense, it was originally discovered, and named, as a secretory factor that interferes with viral replication. In contrast to the prototypical type I interferons produced by any cells upon viral infection, only specific subsets of immune cells can produce IFNG upon infection or stimulation with antigen or mitogen. Still, virtually all cells can respond to both types of interferons. This makes IFNG a versatile anti-microbial cytokine and also gives it a unique position in the antiviral defense system. The goal of this review is to highlight the direct antiviral mechanisms of IFNG, thereby clarifying its antiviral function in the effective control of viral infections.

Keywords: Interferon-gamma; Antiviral agents; Defense mechanisms

INTRODUCTION

Interferon-gamma (IFNG) was first discovered as a soluble macromolecule with antiviral activity (1). In contrast to virally induced interferon (IFN) (2), it was produced from leukocytes upon stimulation with phytohemagglutinin, a mitogenic plant lectin (1). IFNG is now known to be produced by antigen-activated T lymphocytes and cytokine-activated group 1 innate lymphoid cells (ILC1) (3,4). Secreted IFNG stimulates adaptive antigen-specific immunity and activates innate cell-mediated immunity, particularly through the activation of macrophages (5-7). In fact, IFNG is a well-known broad-spectrum anti-microbial agent and a crucial regulator of overall inflammatory responses to pathogens (3). Ironically, despite its prominence, the original antiviral functions of IFNG remain poorly understood.

Interferons were originally named after their interfering effect on viral replication (2). Depending on the cellular receptor, three types of IFNs have been identified: types I, II, and III (8). Virtually all cells have the receptor for prototypical type I IFNs (e.g., IFN-α, IFN-β) and can produce them upon detection of viral or microbial invasion. Type II IFN receptors are also ubiquitously expressed, though only the aforementioned limited subsets of immune cells

IMMUNE NETWORK

DRG, dorsal root ganglia; EBOV, Ebola virus; EC, epidermal cell; GILT, interferon-gamma-inducible lysosomal thiolreductase; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; hpi, hour-post-infection; HPIV-3, human parainfluenza virus type 3; HPV, human papillomavirus; HSV-1, herpes simplex virus type 1; IDO, indoleamine 2,3-dioxygenase; IE, immediate-early; IFN, interferon; IFNG, interferon-gamma; ILC1, group 1 innate lymphoid cells; JAK/STAT, Janus kinase/signal transducer and activator of transcription; JCV, JC virus; LC3, microtubule associated protein 1 light chain 3; MCMV, murine cytomegalovirus; MHV-68, murine gamma-herpesvirus 68; MLV, murine leukemia virus; MNV, murine norovirus; NO, nitric oxide; NOS, nitric oxide synthase; pgRNA, pre-genome RNA; PKR, protein kinase R; PRRSV, porcine reproductive and respiratory syndrome virus; RC, replication complex/compartment; rcDNA, relaxed circular DNA; SINV, sindbis virus; SR-BI, scavenger receptor class B type I; TAg, T-antigen; VSV, vesicular stomatitis virus; VV, vaccinia virus

Author Contributions

Conceptualization: Hwang S, Kang S; Formal analysis: Kang S; Funding acquisition: Hwang S; Supervision: Hwang S; Visualization: Brown HM; Writing - original draft: Hwang S, Kang S; Writing - review & editing: Hwang S, Kang S, Brown HM.

produce IFNG, the type II IFN. In contrast, type III IFN receptors are only expressed in certain types of cells, such as mucosal epithelial cells, but most cells can produce type III IFNs (e.g., IFN-lambda) (9). In antiviral defense, type I IFNs are predominant, yet many viruses have multiple ways to evade their actions (10). Other IFNs can complement or synergize with type I IFNs, without the significant pathogenic risk associated with a type I IFN response (11,12).

Antiviral mechanisms of IFNG have not been well characterized. This is partly due to its overlapping antiviral effect with type I IFNs (8,13). IFNs activate an overlapping set of genes via similar Janus kinase/signal transducer and activator of transcription (JAK/STAT) protein signal transduction pathways, and thus antiviral activities of IFNs are somewhat redundant (14). In addition, type I IFNs can even be induced by IFNG and can contribute to the antiviral activity of IFNG (15). Certainly, IFNG possesses type I IFN-independent antiviral activity (16-18). Gene expression analysis of virus-infected cell lines and organisms, revealed overlapping yet not identical gene induction patterns between type I IFNs and IFNG (19).

Another contributing factor to the poor characterization of antiviral IFNG is its broad immunomodulatory activity. IFNG from ILC1s can confer prompt host protection at the initial site of viral infection (20). IFNG from antigen-activated T lymphocytes plays crucial roles in establishing an antiviral state and coordinating immune responses for the long-term control of viral infection (21-23). Functionally, IFNG can exert direct antiviral effects on infected cells and neighboring cells (17,24). It can also activate local immune cells, like tissue-resident dendritic cells, macrophages and NK cells, for augmented inflammation and antiviral functions (20,25-27). Moreover, IFNG can control the antiviral state by modulating the differentiation and maturation of T cells and B cells (28-31). In most cases, it is not easy to separate the direct antiviral function of IFNG from indirect antiviral function through its immunomodulatory activity (32-34).

Furthermore, several well-known antiviral functions of IFNG mostly lack a specific antiviral mechanism. For instance, IFNG is a potent inducer of indoleamine 2,3-dioxygenase (IDO) and nitric oxide synthase (NOS) (35,36). The resultant depletion of tryptophan and production of nitric oxide (NO) due to IDO and NOS expression, respectively, show strong antiviral effects. However, the molecular details are mostly unclear (37-45). IFNG can also exert non-cytolytic antiviral activity against several viruses, including hepatitis B virus (HBV) (46), Measles virus (47), Sindbis virus (SINV) (48), and West Nile virus (49). Nevertheless, the specific targets and effector proteins of the IFNG-mediated antiviral responses are largely unknown (50-52).

The goal of this review is to highlight the specific antiviral mechanisms of IFNG, thereby clarifying the antiviral function of IFNG in the effective control of viral infections. Principally, our focus here is to delineate the step of viral life cycle specifically inhibited by IFNG and to illuminate the antiviral effector proteins utilized by IFNG, whenever possible. We will discuss them along each step of the viral life cycle in the following sections (**Table 1**).

ENTRY

Viral infection starts with the attachment of a virus to its host cell surface, specifically via its receptor and/or non-specifically via cell surface molecules like glycans. Some viruses release their genomes directly into the cell after fusing its envelope with the plasma membrane, while some viruses enter the cells through cellular endocytosis (53,54). In the case of

Table 1. Viral life cycle targeted by IFNG

Targeted life cycle	Virus	Class of virus*	References
Entry	HCV	IV	(56)
	HPV 16 pseudovirus	I	(60)
	MLV	VI	(63)
Replication	SINV	IV	(48,65)
	PRRSV	IV	(66)
	HCV	IV	(68)
	VV	I	(38)
	MNV	IV	(18,71)
Gene expression	BKV	I	(72)
	HSV-1	I	(73)
	MCMV	I	(15)
	HPIV-3	V	(74)
	EBOV	V	(75)
Stability of gene expression and genome maintenance	HBV	VII	(45,78,79,81)
Release and transmission	HIV-1	VI	(63)
	HSV-1	I	(83,84)
Reactivation	HHV-8	I	(89,92)
	MHV 68	I	(90,91)
	HSV-1	I	(93,94)
	JCV	I	(95)

*Baltimore classification: Class I, double-stranded DNA viruses; Class IV, positive-sense single-stranded RNA viruses; Class V, negative-sense single-stranded RNA viruses; Class VI, positive-sense single-stranded RNA viruses that replicate through a DNA intermediate; Class VII, double-stranded DNA viruses that replicate through a single-stranded RNA intermediate.

endocytosis, the virus is sequestered inside the endosome until appropriate conditions (e.g., acidification of the organelle) are established, allowing the virus to release its core virion, containing the viral genome, or its genome directly into the cytoplasm (54). The released genome, either naked or still associated with viral proteins, then moves to specific sites in the cytoplasm or nucleus for its replication (53).

IFNG can directly inhibit viral invasion by controlling the expression and/or distribution of receptors required for virus entry (55,56) (**Fig. 1**). Hepatitis C virus (HCV) enters cells via a multistep process involving several receptors: CD81, scavenger receptor class B type I (SR-BI), claudin-1 (CLDN1), and occludin (OCLN) (57). IFNG hinders the entry of HCV by reducing the expression of CLDN1, a necessary HCV receptor that is particularly upregulated in the HCV-infected liver (58). Furthermore, IFNG alters the surface distribution of HCV receptors, like CD81 and SR-BI, thereby reducing the susceptibility of the cells to HCV infection (56). Similarly, IFNG inhibits the entry of human immunodeficiency virus (HIV) by downregulating the surface expression of its entry receptor CD4 in human monocytes (55,59).

IFNG can also inhibit viral entry at the transfer step of the invading virus from the endosome into the cytoplasm (**Fig. 1**). For the infection of human papillomavirus (HPV), the minor capsid protein (L2)/viral genome complexes need to be dissociated from major capsid proteins (L1) in the late endosome. Subsequently the dissociated L2/genome complexes translocate into the nucleus for genome replication (60,61). IFNG can obstruct this dissociation step by reducing the proteolysis of L1, leading to retention of L2/genome complex in the late endosome (60). In addition, IFNG-inducible lysosomal thiolreductase (GILT) localizes specifically to the endosomal/lysosomal compartments. GILT can break disulfide bonds within the envelope protein of several endocytosed viruses, including murine leukemia virus (MLV), vesicular stomatitis virus (VSV), and HIV-1 HXB2 strain. Since the Env protein is critical for the endosome-to-cytoplasm transition, the action of GILT inhibits viral entry and subsequent viral replication (62,63).

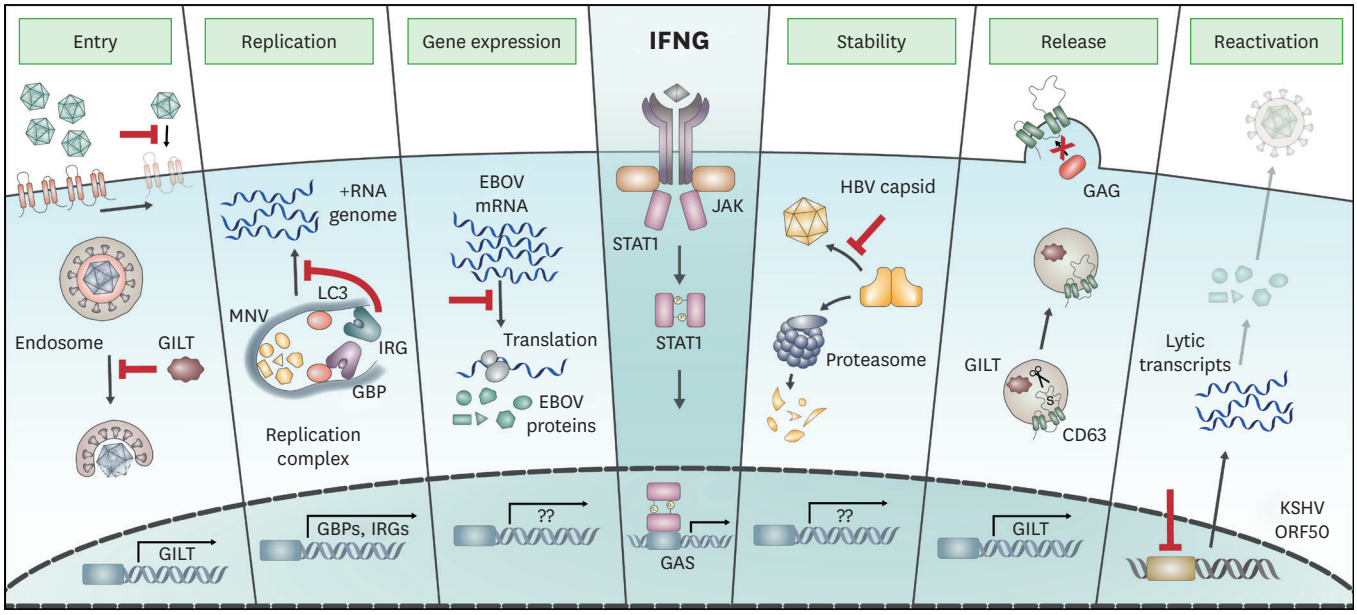

Figure 1. Antiviral mechanisms of IFNG. IFNG obstructs the various stages of viral life cycle in the cells stimulated with IFNG. Representative examples are depicted here: IFNG inhibits viral entry at both extracellular and intracellular stages, replication by disrupting replication niche, gene expression by hindering translation, stability by impeding nucleocapsid assembly, release by breaking the disulfide bond of a necessary cellular interaction partner, and reactivation by suppressing the transcription of a viral master regulator. Refer to the main text for the details of the antiviral mechanism. Red color bars signify inhibiting function of IFNG.

In sum, IFNG can inhibit viral entry at both extracellular and intracellular stages. In most cases, however, the downstream effectors are unclear, a frequent theme regarding the antiviral activity of IFNG.

REPLICATION

Viral replication is the fundamental goal of the virus life cycle (64). Inhibiting any step of the life cycle could result in the inhibition of viral genome replication during viral infection. Accordingly, it is difficult to pinpoint which steps of replication are specifically targeted by IFNG-mediated antiviral mechanisms. Here, we focus on the reports that showed viral genome replication as the most likely target of IFNG action.

The process of viral genome replication is tailored to the type of viral genome. The expression and function of viral proteins is an integral part of viral genome synthesis. Viruses with positive-sense RNA genomes express viral proteins from the incoming genome immediately upon entry using the translation machinery of the host cell. In contrast, viruses with negative-sense RNA genomes must transcribe positive-sense RNAs first from the incoming viral genome using viral polymerases packaged together in infectious virions. In both cases, a polyprotein is translated from a positive-sense viral RNA and then processed into individual proteins that function during viral replication (64). While most RNA viruses replicate in the cytoplasm, most DNA viruses replicate in the nucleus of the host cell. Cellular RNA polymerases are used to synthesize viral mRNAs, but genomic DNA synthesis is usually performed via viral proteins (8).

IFNG inhibits the genomic and sub-genomic RNA syntheses of SINV (48). A neuronal cell line (dCSM14.1) can be persistently infected with SINV, but IFNG treatment results in viral

https://doi.org/10.4110/in.2018.18.e33

clearance and improved survival of the cells (48,65). Viral RNA synthesis is transiently increased by 6 hour-post-infection (hpi) but markedly decreases after 18 hpi in the IFNG treated cells. As expected, the anti-SINV activity of IFNG in different types of neurons is dependent on the JAK/STAT signaling pathway (65). However, effector proteins working downstream of the JAK/STAT pathway were not identified. IFNG also decreases the level of genomic and sub-genomic RNA of porcine reproductive and respiratory syndrome virus (PRRSV) (66). This inhibitory effect is exerted at both the single cell and population levels, reducing the virion production and the cytopathic effect of PRRSV. The decrease in viral RNA accumulation is partially restored by protein kinase R (PKR) inhibitor, 2-aminopurine (2-AP). PKR is a common antiviral effector protein against many viruses, used by both type I IFNs and IFNG (67). The restoration of PRRSV replication upon 2-AP treatment suggests that IFNG utilizes PKR to inhibit viral RNA synthesis, but the incomplete restoration indicates the existence of another effector mechanism involved in this inhibition (66).

HCV replication, as well as entry, is also highly inhibited by IFNG in the human hepatocellular carcinoma cell line, Huh-7 (68); even in a Huh-7 derived HCV replicon cell line, where entry is bypassed, viral RNA and protein expressions are reduced upon IFNG treatment. Likewise, HCV replication in Huh-7 cells, as measured by a transiently transfected reporter plasmid, is inhibited by IFNG. Intriguingly, this antiviral effect of IFNG functions in Huh-7, but not in the hepatoblastoma cell line, Huh6 (68,69). Microarray-based gene expression analysis identified DExD/H box helicase DEAD box polypeptide 60-like (*DDX60L*) as an effector molecule responsible for the different antiviral activity of IFNG in Huh-7 and Huh6 cells (68). Gene expression of *DDX60L* is about three-times higher in IFNG-treated Huh-7 than in IFNG-treated Huh6 cells, whereas expression of other general ISGs is not altered. Consistently, knockdown of *DDX60L* attenuates the IFNG effect on HCV replication in Huh-7 cells (68). Further studies revealed that *DDX60L* exerts an antiviral effect specifically on viral RNA synthesis but not on internal ribosome entry site-mediated translation, assembly, release, or RNA stability of HCV (68).

IFNG can also inhibit viral replication by disrupting the replication niche of viruses (**Fig. 1**). Recently, this was exemplified by the effect of IFNG on the replication complex/compartment (RC) of positive-sense RNA viruses. Characteristic of all known positive-sense RNA viruses, the vesicle-like structure of the RC is created by the reorganization of cellular membranes and serves to provide a favorable microenvironment for viral RNA synthesis and protein translation/processing (70). Upon activation of macrophages by IFNG, the entry and pilot protein expression of murine norovirus (MNV) is not affected, but its replication is blocked at the step of RC formation (17). Consistently, the expression of the MNV capsid protein, which is translated from the sub-genomic RNA of MNV after genome replication, is also blocked by IFNG treatment (17). Unexpectedly, this anti-RC function of IFNG depends on a noncanonical function of autophagy proteins (17,71). Microtubule associated protein 1 light chain 3 (LC3) is a ubiquitin-like autophagy protein, normally conjugated to the growing autophagosome by a set of core proteins known as the LC3-conjugation system of autophagy. Remarkably, independent of its canonical function of sequestering and delivering cytoplasmic materials to the lysosome for degradation, the LC3-conjugation system marks the RC of MNV with LC3. This in turn recruits IFN-inducible GTPases, such as immunity related GTPases and guanylate binding proteins, to the MNV RC. These recruited GTPases are essential to disrupt the RC of MNV and consequently to inhibit MNV replication *in vitro* and *in vivo* (71). The RC of another positive-sense RNA virus, encephalomyocarditis virus, is also tagged with LC3 and the IFN-inducible GTPases. However, the general applicability

to other positive-sense RNA virus RCs and the exact mechanism of RC inhibition needs further investigation.

IFNG inhibits the genome replication of vaccinia virus (VV) (38). VV infection proceeds sequentially in the order of early gene expression, DNA replication, late gene expression, and virion production, while shutting down the expression of cellular proteins (38). Treatment of murine macrophage-like RAW 264.7 cells with IFNG does not significantly inhibit the expression of VV early gene products. However, viral DNA synthesis, subsequent expression of late gene proteins and viral particle production are completely suppressed by IFNG (38). Shut down of cellular protein expression by VV infection is also completely blocked by IFNG. Induction of iNOS by IFNG and consequent production of NO was shown to mediate this blocking of VV replication after early gene expression, although the functional target of NO is elusive (38). Remarkably, IFNG-mediated production of NO also inhibits the replication of VV in bystander cells.

GENE EXPRESSION

Inhibition of viral gene transcription is an effective antiviral strategy used by IFNG against many viruses. IFNG treatment effectively inhibits the acute infection of BK virus (BKV) regardless of its strains (72). The transcription of early gene, T-antigen (TAg), and subsequent expression of TAg protein is suppressed by IFNG. Consequently, expression of viral late genes and virion production are reduced by IFNG. Treatment of IFNG before or after viral infection leads to a similar inhibition in viral protein expression and virion production, indicating that the antiviral mechanism of IFNG against BKV is independent of viral entry (72). Accumulation of mRNAs during herpes simplex virus type 1 (HSV-1) infection is also inhibited by IFNG (73). Consequently, subsequent steps of viral life cycle including early and late gene expression, viral DNA synthesis and viral replication, are also inhibited. However, IFNG does not inhibit the stages of HSV-1 infection after its genome replication, such as virion maturation or release.

In the case of murine cytomegalovirus (MCMV) infection, IFNG inhibits the immediate-early (IE) gene transcription directly by controlling the activity of the MCMV major IE gene promoter (15). IFNG blocks the expression of MCMV IE transcripts and proteins much more efficiently in primary bone marrow derived macrophage than in mouse embryonic fibroblasts (15). This inhibitory effect appears very rapidly within an hour of IFNG treatment and is reversible upon removal of the stimulus. Remarkably, when type I IFN signaling is impaired, IFNG does not have a significant antiviral effect on MCMV (15). Thus, functional type I IFN signaling is required for the establishment of a full IFNG-induced antiviral state against MCMV. In contrast, IFNG inhibits the transcription of mRNAs from the negative-sense RNA genome of human parainfluenza virus type 3 (HPIV-3) without cross-talk with the type I IFN signaling pathway (74). The corresponding inhibitory mechanism is unknown, but a well-known viral RNA degradation mechanism via the 2-5A synthetase/RNase L pathway is not involved in this antiviral action of IFNG against HPIV-3 (74).

Viral protein synthesis is also an effective target of IFNG (**Fig. 1**). The pilot transcription of positive-sense RNA from the negative-sense RNA genome of Ebola virus (EBOV) does not need new viral protein expression; however, subsequent viral genome replication requires viral protein synthesis (75). EBOV replication is inhibited upon blocking of protein synthesis

by cycloheximide (CHX) treatment, and IFNG shows CHX-like effects on EBOV genome replication (75). Co-treatment of CHX and IFNG results in a similar effect to the single treatment of either CHX or IFNG, suggesting that IFNG blocks the life cycle of EBOV through the inhibition of protein synthesis after its entry and before its genome replication. This inhibitory effect of IFNG is identical in the peritoneal macrophages from type I IFN receptor knock-out mouse, indicating a type I IFN-independent antiviral activity of IFNG (75).

STABILITY OF GENE EXPRESSION AND GENOME MAINTENANCE

Weakening the stability of expressed viral genes is an effective antiviral mechanism used by IFNG. HBV is a double-stranded DNA virus that replicates through a single-stranded RNA intermediate (76). Upon HBV infection of hepatocytes, the viral capsid containing its genome is transported to the nucleus and the genome of HBV is released (77,78). Subsequently the HBV genome transforms from a relaxed circular DNA (rcDNA) into a covalently closed circular DNA (cccDNA) in the nucleus. This cccDNA functions as a template to transcribe viral mRNAs and pre-genome RNA (pgRNA). Interestingly, the HBV RNAs released to the cytoplasm are degraded faster than their nuclear counterpart (79). This is mediated by the IFNG-induced DEAD box polypeptide 60 (DDX60), which is involved in a viral RNA degradation pathway (79,80). Knockdown of DDX60 delays the degradation of cytoplasmic HBV RNA but not nuclear viral RNA (79).

Produced pgRNA of HBV is further encapsidated and acts as a template for viral reverse transcriptase to synthesize the DNA genome (76). This HBV genome replication is post-transcriptionally suppressed by IFNG in human hepatoma cells (45,81) (**Fig. 1**). Expression of pgRNA itself is not decreased by IFNG, but subsequent synthesis of single-stranded DNA (ssDNA) intermediate and rcDNA genome are reduced upon IFNG treatment (81). The expression of HBV capsid proteins to form the capsid assembly is modestly reduced. However, assembled capsids, encapsidated pgRNA, and capsid-associated intermediate DNAs are dramatically reduced by IFNG (81). A subsequent study found that IFNG inhibits the process of HBV capsid assembly, resulting in the degradation of the capsid protein and consequent decrease of pgRNA encapsidation and DNA replication.

IFNG-induced IDO expression and proteasomal degradation were suggested as the mechanism by which IFNG inhibits HBV encapsidation and core protein expression. IDO is a well-known IFNG-inducible effector molecule, which catalyzes tryptophan degradation (45). The reduction of HBV DNAs in cells expressing IDO is caused by a decrease in capsid protein synthesis, an essential component for the formation of HBV nucleocapsids. In addition, proteasome activity is altered by IFNG and associated with the antiviral state induced by IFNG (81,82). The IFNG-mediated reduction of HBV capsids and capsid-associated viral DNA is restored by the treatment of epoxomicin, a proteasome inhibitor (81), indicating a crucial role of proteasome activity in the antiviral function of IFNG against HBV.

IFNG can also decrease nuclear HBV cccDNA, the persistent form of the HBV genome, in the HBV-infected cell line (78). After encapsidation, rcDNA-containing capsids are either enveloped and released as progeny virions or reimported to the nucleus, resulting in the accumulation of cccDNA (77,78). The accumulation of cccDNA is very important for maintaining HBV persistence in infected cells. IFNG-induced intracellular pathways reduce

the amount of this nuclear HBV cccDNA as well as the maturation of HBV capsids (78). The IFNG-induced reduction of cccDNA is due to the destabilization of cccDNA through DNA deamination, which is promoted by the IFNG-induced APOBEC3A or APOBEC3B (78).

As demonstrated in the inhibition of HBV by IFNG, IFNG can decrease the stability of viral DNA, RNA, and proteins by degrading them through IFNG-induced effectors directly and indirectly.

RELEASE AND TRANSMISSION

After genome replication and virion assembly, progeny virions are released out of the originally infected host cell. IFNG can directly inhibit viral shedding and transmission to the next host cell (63,83,84) (**Fig. 1**). Induction of GILT by IFNG significantly restricts enveloped viruses, like MLV and VSV (63). However, some strains of HIV-1 are resistant to the IFNG-mediated restriction, because their Env protein can inhibit the signal transduction pathway of IFNG (63,85). Interestingly, even these HIV-1 strains, of which Env protein hinders IFNG signals, can be inhibited by GILT at the step of virion release (63). HIV-1 is released out of the cell through the formation of Gag-CD63 complexes. IFNG-induced GILT can significantly decrease the amount of HIV-1 Gag protein and virion production by breaking the disulfide bonds in cellular CD63 (63). Upon the cleavage of disulfide bonds in CD63 by GILT, HIV-1 Gag protein is unable to make a complex with CD63, and therefore is not released.

IFNG also attenuates neuronal transmission of HSV-1 (83,84). HSV-1 and other alpha-herpesviruses establish latency in the sensory nervous system (86). Periodical reactivation prompts the production of infectious virus in sensory ganglia, leading to the transport of virions to the axon of the neurons and subsequently to surrounding epithelial tissue (86). Thus, movement from neuronal cell bodies to axon termini, called anterograde transport, is an essential characteristic of alpha-herpesviruses for survival and propagation to other hosts. The action of IFNG on epidermal cells strongly inhibits HSV-1 during the initial transmission and subsequent spread via anterograde transport (84). Mikloska and Cunningham (84) and Mikloska et al. (87) developed an *in vitro* dual-chamber model consisting of human dorsal root ganglia (DRG) neurons and autologous epidermal cells (ECs) (DRG-EC model) in 2 separate compartments to study the anterograde axonal transport of HSV-1. IFNG treatment to the EC compartment, after axonal transmission of HSV-1 infection, inhibits infection and spread of HSV-1 (84). Both the number and size of viral cytopathic plaques in ECs are dramatically decreased by IFNG treatment in an outer chamber of the DRG-EC model when HSV-1 is transported as cell-free viruses or thru axon termini (84). These results suggest that IFNG can impede HSV-1 infection after axonal transmission and the subsequent spread of HSV-1 in ECs by its direct antiviral effect on the virus, although the nature of the IFNG-mediated change to the virus is unknown.

REACTIVATION

Reactivation is the mechanism by which a latently infected virus shifts its life cycle to a lytic replication, leading to productive replication and viral spreading (88). IFNG acts as a reactivation regulator for several viruses (89-94). The reactivation of human gamma-herpesvirus, human herpesvirus 8 (HHV-8; also known as Kaposi's Sarcoma-associated herpesvirus) is inhibited by IFNG (89,92). IFNG suppresses the expression of lytic transcripts

and consequent reactivation of HHV-8 by inhibiting the promoter activity of ORF50, which is necessary and sufficient to drive the lytic replication of HHV-8 in human microvascular endothelial cells (92) (**Fig. 1**). IFNG treatment also inhibits the reactivation of murine gammaherpesvirus 68 (MHV-68) from the peritoneal cells of latently infected mice, although IFNG is not involved in the inactivation of the infectious virus itself produced through the reactivation process (91). Peritoneal macrophages are mainly responsible for this IFNG-mediated reduction of MHV-68 reactivation (90). Interestingly, IFNG fails to control the reactivation from latently infected B cell reservoirs, indicating a cell-type dependent anti-reactivation effect of IFNG (90).

The inhibitory effect on HSV-1 reactivation by IFNG is composed of both direct and indirect mechanisms (93,94). IFNG inhibits viral reactivation indirectly through the protective mechanism of $CD8^+$ T cells (94). However, even in the absence of $CD8^+$ T cells, IFNG still can block HSV-1 reactivation from its latency in trigeminal ganglia cells (93,94). This blockade of HSV-1 reactivation from latency in neurons is related to the inhibitory effect of IFNG on IE gene expression, which is required for reactivation and viral structural gene expression (93). Similarly, IFNG also plays an important regulatory role in regulating JC virus (JCV) reactivation by limiting viral gene expression and replication (95). IFNG controls the gene expression of JCV by downregulating the major viral regulatory protein, TAg, in the glial cells (95). IFNG cannot inhibit viral DNA replication directly but can inhibit it indirectly via post-transcriptional suppression of TAg expression. Since TAg is essential for transactivation of viral promoters and genome replication, suppression of TAg by IFNG can negatively regulate JCV reactivation from latency.

CONCLUDING REMARKS

In general, the antiviral mechanisms of IFNG are poorly understood, especially in comparison to the immunomodulatory and overall anti-microbial functions of IFNG. However, a lesson may be learned from recent studies identifying a parallel function of IFNG in the defense against a protozoan parasite *Toxoplasma gondii* and a positive-sense single-stranded RNA virus MNV (71,96-99). Despite the dissimilarity of these 2 pathogens, a common IFNG-dependent mechanism underlies both the anti-protozoan and antiviral response (100). In this line of thinking, well-known anti-pathogen and immunomodulatory mechanisms of IFNG may guide the discovery of lesser-known antiviral mechanisms of IFNG.

Presently, there is no doubt that IFNG is more than a simple antiviral signaling molecule; it is also a crucial immunomodulatory cytokine. Based on its prominent role in the immune network, one might even name IFNG an interleukin if it were discovered today (3). However, over the decades, it has become clear that even the type I IFNs are not just antiviral cytokines (101-104). Fundamentally, IFNs can collaborate and complement each other for effective antiviral defense as well as immune modulation. Understanding the specific antiviral mechanisms of IFNG will help us to find the best antiviral strategy and thus effective therapeutic strategies against viral diseases, especially critical against viruses evolved to evade the prominent type I IFN-mediated antiviral responses (10).

https://doi.org/10.4110/in.2018.18.e33

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health (NIH) R01AI127518 and NIH DP2CA225208. H.M.B. was supported in part by NIH T32 AI007090.

REFERENCES

1. Wheelock EF. Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin. *Science* 1965;149:310-311.
CROSSREF
2. Isaacs A, Lindenmann J. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 1957;147:258-267.
PUBMED | CROSSREF
3. Billiau A, Matthys P. Interferon-gamma: a historical perspective. *Cytokine Growth Factor Rev* 2009;20:97-113.
PUBMED | CROSSREF
4. McKenzie AN, Spits H, Eberl G. Innate lymphoid cells in inflammation and immunity. *Immunity* 2014;41:366-374.
PUBMED | CROSSREF
5. Mackaness GB. The influence of immunologically committed lymphoid cells on macrophage activity *in vivo*. *J Exp Med* 1969;129:973-992.
PUBMED | CROSSREF
6. Douvas GS, Looker DL, Vatter AE, Crowle AJ. Gamma interferon activates human macrophages to become tumoricidal and leishmanicidal but enhances replication of macrophage-associated mycobacteria. *Infect Immun* 1985;50:1-8.
PUBMED
7. Nathan CF, Murray HW, Wiebe ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. *J Exp Med* 1983;158:670-689.
PUBMED | CROSSREF
8. Hoffmann HH, Schneider WM, Rice CM. Interferons and viruses: an evolutionary arms race of molecular interactions. *Trends Immunol* 2015;36:124-138.
PUBMED | CROSSREF
9. Lazear HM, Nice TJ, Diamond MS. Interferon-lambda: immune functions at barrier surfaces and beyond. *Immunity* 2015;43:15-28.
PUBMED | CROSSREF
10. García-Sastre A. Ten strategies of interferon evasion by viruses. *Cell Host Microbe* 2017;22:176-184.
PUBMED | CROSSREF
11. Diamond MS, Harris E. Interferon inhibits dengue virus infection by preventing translation of viral RNA through a PKR-independent mechanism. *Virology* 2001;289:297-311.
PUBMED | CROSSREF
12. Wack A, Terczyńska-Dyla E, Hartmann R. Guarding the frontiers: the biology of type III interferons. *Nat Immunol* 2015;16:802-809.
PUBMED | CROSSREF
13. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: an overview of signals, mechanisms and functions. *J Leukoc Biol* 2004;75:163-189.
PUBMED | CROSSREF
14. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu Rev Immunol* 2001;19:65-91.
PUBMED | CROSSREF
15. Kropp KA, Robertson KA, Sing G, Rodriguez-Martin S, Blanc M, Lacaze P, Hassim MF, Khondoker MR, Busche A, Dickinson P, et al. Reversible inhibition of murine cytomegalovirus replication by gamma interferon (IFN-γ) in primary macrophages involves a primed type I IFN-signaling subnetwork for full establishment of an immediate-early antiviral state. *J Virol* 2011;85:10286-10299.
PUBMED | CROSSREF
16. Sun B, Skjæveland I, Svingerud T, Zou J, Jørgensen J, Robertsen B. Antiviral activity of salmonid gamma interferon against infectious pancreatic necrosis virus and salmonid alphavirus and its dependency on type I interferon. *J Virol* 2011;85:9188-9198.
PUBMED | CROSSREF

17. Hwang S, Maloney NS, Bruinsma MW, Goel G, Duan E, Zhang L, Shrestha B, Diamond MS, Dani A, Sosnovtsev SV, et al. Nondegradative role of Atg5-Atg12/ Atg16L1 autophagy protein complex in antiviral activity of interferon gamma. *Cell Host Microbe* 2012;11:397-409.
PUBMED | CROSSREF
18. Prestwood TR, Morar MM, Zellweger RM, Miller R, May MM, Yauch LE, Lada SM, Shresta S. Gamma interferon (IFN-γ) receptor restricts systemic dengue virus replication and prevents paralysis in IFN-α/β receptor-deficient mice. *J Virol* 2012;86:12561-12570.
PUBMED | CROSSREF
19. Wieland SF, Vega RG, Müller R, Evans CF, Hilbush B, Guidotti LG, Sutcliffe JG, Schultz PG, Chisari FV. Searching for interferon-induced genes that inhibit hepatitis B virus replication in transgenic mouse hepatocytes. *J Virol* 2003;77:1227-1236.
PUBMED | CROSSREF
20. Weizman OE, Adams NM, Schuster IS, Krishna C, Pritykin Y, Lau C, Degli-Esposti MA, Leslie CS, Sun JC, O'Sullivan TE. Ilc1 confer early host protection at initial sites of viral infection. *Cell* 2017;171:795-808.e12.
PUBMED | CROSSREF
21. Lu B, Ebensperger C, Dembic Z, Wang Y, Kvatyuk M, Lu T, Coffman RL, Pestka S, Rothman PB. Targeted disruption of the interferon-gamma receptor 2 gene results in severe immune defects in mice. *Proc Natl Acad Sci U S A* 1998;95:8233-8238.
PUBMED | CROSSREF
22. Müller U, Steinhoff U, Reis LF, Hemmi S, Pavlovic J, Zinkernagel RM, Aguet M. Functional role of type I and type II interferons in antiviral defense. *Science* 1994;264:1918-1921.
PUBMED | CROSSREF
23. Huang S, Hendriks W, Althage A, Hemmi S, Bluethmann H, Kamijo R, Vilcek J, Zinkernagel RM, Aguet M. Immune response in mice that lack the interferon-gamma receptor. *Science* 1993;259:1742-1745.
PUBMED | CROSSREF
24. Changotra H, Jia Y, Moore TN, Liu G, Kahan SM, Sosnovtsev SV, Karst SM. Type I and type II interferons inhibit the translation of murine norovirus proteins. *J Virol* 2009;83:5683-5692.
PUBMED | CROSSREF
25. Senik A, Stefanos S, Kolb JP, Lucero M, Falcoff E. Enhancement of mouse natural killer cell activity by type II interferon. *Ann Immunol (Paris)* 1980;131C:349-361.
PUBMED
26. Nathan CF, Murray HW, Wiebe ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. *J Exp Med* 1983;158:670-689.
PUBMED | CROSSREF
27. Lee CK, Rao DT, Gertner R, Gimeno R, Frey AB, Levy DE. Distinct requirements for IFNs and STAT1 in NK cell function. *J Immunol* 2000;165:3571-3577.
PUBMED | CROSSREF
28. Gajewski TF, Fitch FW. Anti-proliferative effect of IFN-gamma in immune regulation. I. IFN-gamma inhibits the proliferation of Th2 but not Th1 murine helper T lymphocyte clones. *J Immunol* 1988;140:4245-4252.
PUBMED
29. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. Interleukin 17-producing $CD4^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;6:1123-1132.
PUBMED | CROSSREF
30. Leibson HJ, Gefter M, Zlotnik A, Marrack P, Kappler JW. Role of gamma-interferon in antibody-producing responses. *Nature* 1984;309:799-801.
PUBMED | CROSSREF
31. Sidman CL, Marshall JD, Shultz LD, Gray PW, Johnson HM. Gamma-interferon is one of several direct B cell-maturing lymphokines. *Nature* 1984;309:801-804.
PUBMED | CROSSREF
32. He XS, Draghi M, Mahmood K, Holmes TH, Kemble GW, Dekker CL, Arvin AM, Parham P, Greenberg HB. T cell-dependent production of IFN-gamma by NK cells in response to influenza A virus. *J Clin Invest* 2004;114:1812-1819.
PUBMED | CROSSREF
33. Hurgin V, Novick D, Werman A, Dinarello CA, Rubinstein M. Antiviral and immunoregulatory activities of IFN-gamma depend on constitutively expressed IL-1alpha. *Proc Natl Acad Sci U S A* 2007;104:5044-5049.
PUBMED | CROSSREF

34. Pak-Wittel MA, Yang L, Sojka DK, Rivenbark JG, Yokoyama WM. Interferon-γ mediates chemokine-dependent recruitment of natural killer cells during viral infection. *Proc Natl Acad Sci U S A* 2013;110:E50-E59.
PUBMED | CROSSREF

35. Takikawa O, Habara-Ohkubo A, Yoshida R. IFN-gamma is the inducer of indoleamine 2,3-dioxygenase in allografted tumor cells undergoing rejection. *J Immunol* 1990;145:1246-1250.
PUBMED

36. Karupiah G, Xie QW, Buller RM, Nathan C, Duarte C, MacMicking JD. Inhibition of viral replication by interferon-gamma-induced nitric oxide synthase. *Science* 1993;261:1445-1448.
PUBMED | CROSSREF

37. Kane M, Zang TM, Rihn SJ, Zhang F, Kueck T, Alim M, Schoggins J, Rice CM, Wilson SJ, Bieniasz PD. Identification of interferon-stimulated genes with antiretroviral activity. *Cell Host Microbe* 2016;20:392-405.
PUBMED | CROSSREF

38. Harris N, Buller RM, Karupiah G. Gamma interferon-induced, nitric oxide-mediated inhibition of vaccinia virus replication. *J Virol* 1995;69:910-915.
PUBMED

39. Komatsu T, Bi Z, Reiss CS. Interferon-gamma induced type I nitric oxide synthase activity inhibits viral replication in neurons. *J Neuroimmunol* 1996;68:101-108.
PUBMED | CROSSREF

40. Lin YL, Huang YL, Ma SH, Yeh CT, Chiou SY, Chen LK, Liao CL. Inhibition of Japanese encephalitis virus infection by nitric oxide: antiviral effect of nitric oxide on RNA virus replication. *J Virol* 1997;71:5227-5235.
PUBMED

41. Guidotti LG, McClary H, Loudis JM, Chisari FV. Nitric oxide inhibits hepatitis B virus replication in the livers of transgenic mice. *J Exp Med* 2000;191:1247-1252.
PUBMED | CROSSREF

42. Terajima M, Leporati AM. Role of indoleamine 2,3-dioxygenase in antiviral activity of interferon-gamma against vaccinia virus. *Viral Immunol* 2005;18:722-729.
PUBMED | CROSSREF

43. Jarasch N, Martin U, Kamphausen E, Zell R, Wutzler P, Henke A. Interferon-gamma-induced activation of nitric oxide-mediated antiviral activity of macrophages caused by a recombinant coxsackievirus B3. *Viral Immunol* 2005;18:355-364.
PUBMED | CROSSREF

44. Becerra A, Warke RV, Xhaja K, Evans B, Evans J, Martin K, de Bosch N, Rothman AL, Bosch I. Increased activity of indoleamine 2,3-dioxygenase in serum from acutely infected dengue patients linked to gamma interferon antiviral function. *J Gen Virol* 2009;90:810-817.
PUBMED | CROSSREF

45. Mao R, Zhang J, Jiang D, Cai D, Levy JM, Cuconati A, Block TM, Guo JT, Guo H. Indoleamine 2,3-dioxygenase mediates the antiviral effect of gamma interferon against hepatitis B virus in human hepatocyte-derived cells. *J Virol* 2011;85:1048-1057.
PUBMED | CROSSREF

46. Suri D, Schilling R, Lopes AR, Mullerova I, Colucci G, Williams R, Naoumov NV. Non-cytolytic inhibition of hepatitis B virus replication in human hepatocytes. *J Hepatol* 2001;35:790-797.
PUBMED | CROSSREF

47. Patterson CE, Lawrence DM, Echols LA, Rall GF. Immune-mediated protection from measles virus-induced central nervous system disease is noncytolytic and gamma interferon dependent. *J Virol* 2002;76:4497-4506.
PUBMED | CROSSREF

48. Burdeinick-Kerr R, Griffin DE. Gamma interferon-dependent, noncytolytic clearance of sindbis virus infection from neurons *in vitro*. *J Virol* 2005;79:5374-5385.
PUBMED | CROSSREF

49. Zhang M, Daniel S, Huang Y, Chancey C, Huang Q, Lei YF, Grinev A, Mostowski H, Rios M, Dayton A. Anti-West Nile virus activity of *in vitro* expanded human primary natural killer cells. *BMC Immunol* 2010;11:3.
PUBMED | CROSSREF

50. Rodriguez M, Pavelko K, Coffman RL. Gamma interferon is critical for resistance to Theiler's virus-induced demyelination. *J Virol* 1995;69:7286-7290.
PUBMED

51. Selin LK, Varga SM, Wong IC, Welsh RM. Protective heterologous antiviral immunity and enhanced immunopathogenesis mediated by memory T cell populations. *J Exp Med* 1998;188:1705-1715.
PUBMED | CROSSREF

52. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, Chisari FV. Determinants of viral clearance and persistence during acute hepatitis C virus infection. *J Exp Med* 2001;194:1395-1406.
PUBMED | CROSSREF

53. Mudhakir D, Harashima H. Learning from the viral journey: how to enter cells and how to overcome intracellular barriers to reach the nucleus. *AAPS J* 2009;11:65-77.
PUBMED | CROSSREF

54. Mercer J, Schelhaas M, Helenius A. Virus entry by endocytosis. *Annu Rev Biochem* 2010;79:803-833.
PUBMED | CROSSREF

55. Dhawan S, Heredia A, Wahl LM, Epstein JS, Meltzer MS, Hewlett IK. Interferon-gamma-induced downregulation of CD4 inhibits the entry of human immunodeficiency virus type-1 in primary monocytes. *Pathobiology* 1995;63:93-99.
PUBMED | CROSSREF

56. Wei X, Jia ZS, Lian JQ, Zhang Y, Li J, Ma L, Ye L, Wang JP, Pan L, Wang PZ, et al. Inhibition of hepatitis C virus infection by interferon-gamma through downregulating claudin-1. *J Interferon Cytokine Res* 2009;29:171-178.
PUBMED | CROSSREF

57. Douam F, Lavillette D, Cosset FL. The mechanism of HCV entry into host cells. *Prog Mol Biol Transl Sci* 2015;129:63-107.
PUBMED | CROSSREF

58. Reynolds GM, Harris HJ, Jennings A, Hu K, Grove J, Lalor PF, Adams DH, Balfe P, Hübscher SG, McKeating JA. Hepatitis C virus receptor expression in normal and diseased liver tissue. *Hepatology* 2008;47:418-427.
PUBMED | CROSSREF

59. Rongcun Y, Maes H, Corsi M, Dellner F, Wen T, Kiessling R. Interferon gamma impairs the ability of monocyte-derived dendritic cells to present tumour-specific and allo-specific antigens and reduces their expression of CD1A, CD80 AND CD4. *Cytokine* 1998;10:747-755.
PUBMED | CROSSREF

60. Day PM, Thompson CD, Lowy DR, Schiller JT. Interferon gamma prevents infectious entry of human papillomavirus 16 via an l2-dependent mechanism. *J Virol* 2017;91:pii: e00168-17.
PUBMED | CROSSREF

61. Popa A, Zhang W, Harrison MS, Goodner K, Kazakov T, Goodwin EC, Lipovsky A, Burd CG, DiMaio D. Direct binding of retromer to human papillomavirus type 16 minor capsid protein L2 mediates endosome exit during viral infection. *PLoS Pathog* 2015;11:e1004699.
PUBMED | CROSSREF

62. Kamiyama H, Kakoki K, Yoshii H, Iwao M, Igawa T, Sakai H, Hayashi H, Matsuyama T, Yamamoto N, Kubo Y. Infection of XC cells by MLVs and Ebola virus is endosome-dependent but acidification-independent. *PLoS One* 2011;6:e26180.
PUBMED | CROSSREF

63. Kubo Y, Izumida M, Yashima Y, Yoshii-Kamiyama H, Tanaka Y, Yasui K, Hayashi H, Matsuyama T. Gamma-interferon-inducible, lysosome/endosome-localized thiolreductase, GILT, has anti-retroviral activity and its expression is counteracted by HIV-1. *Oncotarget* 2016;7:71255-71273.
PUBMED | CROSSREF

64. Li D, Wei T, Abbott CM, Harrich D. The unexpected roles of eukaryotic translation elongation factors in RNA virus replication and pathogenesis. *Microbiol Mol Biol Rev* 2013;77:253-266.
PUBMED | CROSSREF

65. Burdeinick-Kerr R, Govindarajan D, Griffin DE. Noncytolytic clearance of sindbis virus infection from neurons by gamma interferon is dependent on Jak/STAT signaling. *J Virol* 2009;83:3429-3435.
PUBMED | CROSSREF

66. Rowland RR, Robinson B, Stefanick J, Kim TS, Guanghua L, Lawson SR, Benfield DA. Inhibition of porcine reproductive and respiratory syndrome virus by interferon-gamma and recovery of virus replication with 2-aminopurine. *Arch Virol* 2001;146:539-555.
PUBMED | CROSSREF

67. García MA, Gil J, Ventoso I, Guerra S, Domingo E, Rivas C, Esteban M. Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. *Microbiol Mol Biol Rev* 2006;70:1032-1060.
PUBMED | CROSSREF

68. Grünvogel O, Esser-Nobis K, Reustle A, Schult P, Müller B, Metz P, Trippler M, Windisch MP, Frese M, Binder M, et al. *DDX60L* is an interferon-stimulated gene product restricting hepatitis c virus replication in cell culture. *J Virol* 2015;89:10548-10568.
PUBMED | CROSSREF

69. Windisch MP, Frese M, Kaul A, Trippler M, Lohmann V, Bartenschlager R. Dissecting the interferon-induced inhibition of hepatitis C virus replication by using a novel host cell line. *J Virol* 2005;79:13778-13793.
PUBMED | CROSSREF

70. den Boon JA, Diaz A, Ahlquist P. Cytoplasmic viral replication complexes. *Cell Host Microbe* 2010;8:77-85.
PUBMED | CROSSREF

71. Biering SB, Choi J, Halstrom RA, Brown HM, Beatty WL, Lee S, McCune BT, Dominici E, Williams LE, Orchard RC, et al. Viral replication complexes are targeted by lc3-guided interferon-inducible GTPases. *Cell Host Microbe* 2017;22:74-85.e7.
PUBMED | CROSSREF

72. Abend JR, Low JA, Imperiale MJ. Inhibitory effect of gamma interferon on BK virus gene expression and replication. *J Virol* 2007;81:272-279.
PUBMED | CROSSREF

73. Pierce AT, DeSalvo J, Foster TP, Kosinski A, Weller SK, Halford WP. Beta interferon and gamma interferon synergize to block viral DNA and virion synthesis in herpes simplex virus-infected cells. *J Gen Virol* 2005;86:2421-2432.
PUBMED | CROSSREF

74. Choudhary S, Gao J, Leaman DW, De BP. Interferon action against human parainfluenza virus type 3: involvement of a novel antiviral pathway in the inhibition of transcription. *J Virol* 2001;75:4823-4831.
PUBMED | CROSSREF

75. Rhein BA, Powers LS, Rogers K, Anantpadma M, Singh BK, Sakurai Y, Bair T, Miller-Hunt C, Sinn P, Davey RA, et al. Interferon-gamma inhibits ebola virus infection. *PLoS Pathog* 2015;11:e1005263.
PUBMED | CROSSREF

76. Morikawa K, Suda G, Sakamoto N. Viral life cycle of hepatitis B virus: host factors and druggable targets. *Hepatol Res* 2016;46:871-877.
PUBMED | CROSSREF

77. Beck J, Nassal M. Hepatitis B virus replication. *World J Gastroenterol* 2007;13:48-64.
PUBMED | CROSSREF

78. Xia Y, Stadler D, Lucifora J, Reisinger F, Webb D, Hösel M, Michler T, Wisskirchen K, Cheng X, Zhang K, et al. Interferon-gamma and tumor necrosis factor-alpha produced by t cells reduce the HBV persistence form, cccDNA, without cytolysis. *Gastroenterology* 2016;150:194-205.
PUBMED | CROSSREF

79. Kouwaki T, Fukushima Y, Daito T, Sanada T, Yamamoto N, Mifsud EJ, Leong CR, Tsukiyama-Kohara K, Kohara M, Matsumoto M, et al. Extracellular vesicles including exosomes regulate innate immune responses to hepatitis b virus infection. *Front Immunol* 2016;7:335.
PUBMED | CROSSREF

80. Oshiumi H, Miyashita M, Okamoto M, Morioka Y, Okabe M, Matsumoto M, Seya T. DDX60 is involved in RIG-I-dependent and independent antiviral responses, and its function is attenuated by virus-induced EGFR activation. *Cell Reports* 2015;11:1193-1207.
PUBMED | CROSSREF

81. Xu C, Guo H, Pan XB, Mao R, Yu W, Xu X, Wei L, Chang J, Block TM, Guo JT. Interferons accelerate decay of replication-competent nucleocapsids of hepatitis B virus. *J Virol* 2010;84:9332-9340.
PUBMED | CROSSREF

82. Robek MD, Wieland SF, Chisari FV. Inhibition of hepatitis B virus replication by interferon requires proteasome activity. *J Virol* 2002;76:3570-3574.
PUBMED | CROSSREF

83. Song R, Koyuncu OO, Greco TM, Diner BA, Cristea IM, Enquist LW. Two modes of the axonal interferon response limit alphaherpesvirus neuroinvasion. *MBio* 2016;7:e02145-15.
PUBMED | CROSSREF

84. Mikloska Z, Cunningham AL. Alpha and gamma interferons inhibit herpes simplex virus type 1 infection and spread in epidermal cells after axonal transmission. *J Virol* 2001;75:11821-11826.
PUBMED | CROSSREF

85. Rihn SJ, Foster TL, Busnadiego I, Aziz MA, Hughes J, Neil SJ, Wilson SJ. The envelope gene of transmitted HIV-1 resists a late interferon gamma-induced block. *J Virol* 2017;91:pii: e02254-16.
PUBMED | CROSSREF

86. Lahiri Mukhopadhyay S, Bahubali VH, Manjunath N, Swaminathan A, Maji S, Palaniappan M, Parthasarathy S, Chandrashekar N. Central nervous system infection due to *Cryptococcus gattii sensu lato* in India: analysis of clinical features, molecular profile and antifungal susceptibility. *Mycoses* 2017;60:749-757.
PUBMED | CROSSREF

87. Mikloska Z, Sanna PP, Cunningham AL. Neutralizing antibodies inhibit axonal spread of herpes simplex virus type 1 to epidermal cells *in vitro*. *J Virol* 1999;73:5934-5944.
PUBMED

88. Traylen CM, Patel HR, Fondaw W, Mahatme S, Williams JF, Walker LR, Dyson OF, Arce S, Akula SM. Virus reactivation: a panoramic view in human infections. *Future Virol* 2011;6:451-463.
PUBMED | CROSSREF

89. Pozharskaya VP, Weakland LL, Offermann MK. Inhibition of infectious human herpesvirus 8 production by gamma interferon and alpha interferon in BCBL-1 cells. *J Gen Virol* 2004;85:2779-2787.
PUBMED | CROSSREF

90. Steed A, Buch T, Waisman A, Virgin HW 4th. Gamma interferon blocks gammaherpesvirus reactivation from latency in a cell type-specific manner. *J Virol* 2007;81:6134-6140.
PUBMED | CROSSREF

91. Steed AL, Barton ES, Tibbetts SA, Popkin DL, Lutzke ML, Rochford R, Virgin HW 4th. Gamma interferon blocks gammaherpesvirus reactivation from latency. *J Virol* 2006;80:192-200.
PUBMED | CROSSREF

92. Milligan S, Robinson M, O'Donnell E, Blackbourn DJ. Inflammatory cytokines inhibit Kaposi's sarcoma-associated herpesvirus lytic gene transcription in *in vitro*-infected endothelial cells. *J Virol* 2004;78:2591-2596.
PUBMED | CROSSREF

93. Decman V, Kinchington PR, Harvey SA, Hendricks RL. Gamma interferon can block herpes simplex virus type 1 reactivation from latency, even in the presence of late gene expression. *J Virol* 2005;79:10339-10347.
PUBMED | CROSSREF

94. Liu T, Khanna KM, Carriere BN, Hendricks RL. Gamma interferon can prevent herpes simplex virus type 1 reactivation from latency in sensory neurons. *J Virol* 2001;75:11178-11184.
PUBMED | CROSSREF

95. De-Simone FI, Sariyer R, Otalora YL, Yarandi S, Craigie M, Gordon J, Sariyer IK. IFN-gamma inhibits JC virus replication in glial cells by suppressing t-antigen expression. *PLoS One* 2015;10:e0129694.
PUBMED | CROSSREF

96. Choi J, Park S, Biering SB, Selleck E, Liu CY, Zhang X, Fujita N, Saitoh T, Akira S, Yoshimori T, et al. The parasitophorous vacuole membrane of *Toxoplasma gondii* is targeted for disruption by ubiquitin-like conjugation systems of autophagy. *Immunity* 2014;40:924-935.
PUBMED | CROSSREF

97. Park S, Choi J, Biering SB, Dominici E, Williams LE, Hwang S. Targeting by AutophaGy proteins (TAG): targeting of IFNG-inducible GTPases to membranes by the LC3 conjugation system of autophagy. *Autophagy* 2016;12:1153-1167.
PUBMED | CROSSREF

98. Choi J, Biering SB, Hwang S. Quo vadis? Interferon-inducible GTPases go to their target membranes via the lc3-conjugation system of autophagy. *Small GTPases* 2017;8:199-207.
PUBMED | CROSSREF

99. Biering SB, Choi J, Brown HM, Hwang S. LC3s hire membrane breakers to attack viral shelters. *Autophagy* 2017;13:2010-2012.
PUBMED | CROSSREF

100. Brown HM, Biering SB, Zhu A, Choi J, Hwang S. Demarcation of viral shelters results in destruction by membranolytic GTPases: antiviral function of autophagy proteins and interferon-inducible GTPases. *BioEssays* 2018;40:e1700231.
PUBMED | CROSSREF

101. Ng CT, Mendoza JL, Garcia KC, Oldstone MB. Alpha and beta type 1 interferon signaling: passage for diverse biologic outcomes. *Cell* 2016;164:349-352.
PUBMED | CROSSREF

102. Kim BH, Chee JD, Bradfield CJ, Park ES, Kumar P, MacMicking JD. Interferon-induced guanylate-binding proteins in inflammasome activation and host defense. *Nat Immunol* 2016;17:481-489.
PUBMED | CROSSREF

103. Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G. Type I interferons in anticancer immunity. *Nat Rev Immunol* 2015;15:405-414.
PUBMED | CROSSREF

104. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. *Nat Rev Immunol* 2015;15:87-103.
PUBMED | CROSSREF