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Interferon-stimulated Antiviral Effectors against RNA Viruses: A Review

Lekshmi J. Das[1], Gnanavel Venkatesan[2]*, Sindhutai Bapurao Nagargoje[3] and Dechamma H.J.[4]

[1] Ph.D. Scholar, Foot-and-mouth Disease Research Laboratory,
Indian Veterinary Research Institute, Hebbal, Bengaluru (Karnataka), India.
[2]Senior Scientist, Foot-and-mouth Disease Research Laboratory,
Indian Veterinary Research Institute, Hebbal, Bengaluru (Karnataka), India.
[3]MVSc Scholar, Foot-and-mouth Disease Research Laboratory,
Indian Veterinary Research Institute, Hebbal, Bengaluru (Karnataka), India.
[4]Principal Scientist, Foot-and-mouth Disease Research Laboratory,
Indian Veterinary Research Institute, Hebbal, Bengaluru (Karnataka), India.

(Corresponding author: Gnanavel Venkatesan)*
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ABSTRACT: Interferon (IFN) production is the earliest cellular immune response to a virus infection. Interferon-stimulated genes (ISG) are induced in response to IFNs and confer an antiviral state to host cells. There are numerous interferon effector pathways, many of which are not fully described. ISGs can target various steps of the viral life cycle and the coordinated effect of ISGs imparts antiviral effects, adding to complications in understanding. Many recent efforts have been focused on characterizing the mode of action of ISGs. Insight into IFN signaling and effector pathways during RNA virus infection will broaden the knowledge of antiviral proteins against them. We review here the current understanding of a few ISGs and their antiviral pathways blocking various steps of RNA virus infection in humans and animals. ISG products take part in a diverse role and further advances will expose unanticipated areas of antiviral research and vaccine development.

Keywords: Interferon-stimulated genes (ISG), ISG-15, Mx, viperin, IRF-3, IRF-7.

INTRODUCTION

RNA virus populations, commonly known as quasi species due to their higher mutation rate, make them a difficult target for antiviral drugs and vaccines. This rapidly evolving nature of RNA viruses will bring about emerging and re-emerging diseases, highlighting the need to understand host-viral interactions further. The first line of host defense against the virus is the innate immune response, activated by recognizing pathogen-associated molecular patterns (PAMP) by pattern recognition receptors (PRRs). PAMPs are the unique molecules expressed by microbes, recognized by innate immune cells using a variety of receptors named PRRs. Activation of these receptors will commence downstream signaling pathways, and finally, cytokines, chemokines, and interferons (IFNs) are produced, the latter of which mediates early antiviral response. IFNs produced can transcriptionally induce hundreds of interferon-stimulated genes (ISGs) in surrounding cells, which can hinder viral replication and eventually lead to viral clearance (Fig. 1) (Owen *et al.*, 2013). Interferons are proteins transcriptionally induced by PRR that interfere with the production of new viral particles.

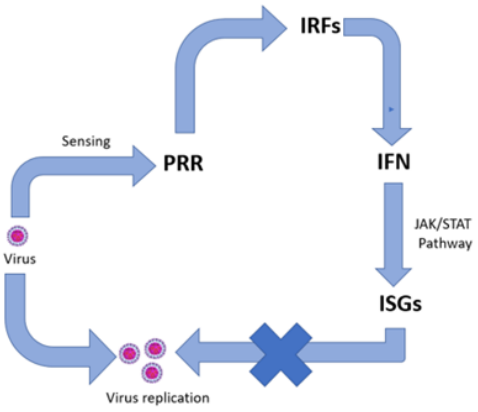

Fig. 1. Interferon pathway.

Type 1 interferons, major representatives are IFN-α and IFN-β, initiate antiviral effects by binding to specific receptors expressed by all cell types. Type I and III IFN are usually known for their antiviral action, even though type II IFN is also recognized for its antiviral properties (Borden *et al.*, 2007). IFN dimer binding to IFN receptors induces JAK/STAT signaling pathway and finally initiates the transcription of ISGs (Chanotra *et al.*, 2022). Genes turned on by IFN are called as ISGs (Owen *et al.*, 2013). Although the identification of hundreds of

ISGs dates back over 35 years ago, only a few have been characterized and described for their ability to combat antiviral activity (Knight *et al*., 1979; Schoggins *et al*., 2011). Overexpressed more than 380 human ISGs in human cells, which revealed the antiviral effects of those ISGs against various viruses. In this review, we provide an overview of our current understanding of the role of ISGs such as ISG-15, Mx1, viperin, IRF-3, and IRF-7 in host antiviral immune response, on the fact that these proteins have proven effects against RNA viruses. We are considering the antiviral mechanisms of these ISGs against disease-causing RNA viruses in humans and animals. Moreover, understanding the host mechanisms to battle virus evasion will enlighten much-needed research on antiviral effectors.

ISG-15: ISG-15, a ubiquitin-like protein, is one of the most strongly induced ISGs and can directly inhibit viral replication. ISG-15 belongs to the ubiquitin family, which comprises ubiquitin and ubiquitin-like modifiers. These two involve cellular activities such as intracellular trafficking, cell cycle control, protein stability, and immune modulation. Type 1 interferons are the primary inducer of ISG-15, and they can be covalently conjugated to target proteins by a process termed ISGylation or depart as an unconjugated form. This unconjugated ISG-15 protein can act as a cytokine (Perng and Lenschow 2018). Desai *et al.*(2006) reported that ISG-15 can compete with ubiquitin for the ubiquitin-binding sites of a protein, thereby indirectly modulating host protein degradation. The precursor form of ISG-15 is a 17-kDa protein that is proteolytically cleaved at the C terminus, exposing an LRLRGG amino acid sequence that can attach to lysine residues in target proteins. Usually, ISGylation of the target protein is carried out by an enzymatic cascade similar to ubiquitin conjugation that includes an activating enzyme (E1), a conjugating enzyme (E2), and a ligase (E3). Recent research has shown the antiviral properties of ISG-15, which impair viral replication by ISGylation of both host and virus proteins. A few of those instances are discussed below.

Coxsackievirus B3 (CVB3), a common causative agent for inflammatory cardiomyopathy in humans, possesses a viral protease (2A pro) which can cleave mammalian eukaryotic translation initiation factor 4G (eIF4G), results in the shutdown of cellular translation. Studies revealed that 2APro is a substrate for ISG-15 conjugation, and this modification prevents the cleavage of host eIF4G during the infection of CVB3. Furthermore,compared to ISG-15-ablated cardiomyocytes, ISG-15 suppressed viral copy number and titer in CVB3-infected cardiomyocytes (Rahnefeld *et al*., 2014). ISG-15 differentially regulates influenza A and B since the total lysine content of the influenza B virus is 35% higher than the influenza A virus. ISG-15 protects the host from mortality during influenza A virus infection by a mechanism that is distinct from influenza B virus infection; later, ISG-15 conjugation results in a drastic depletion of viral load *in vivo.* Studies revealed that influenza A viral proteins modified by ISG-15 have little role in viral replication. However, they are crucial to pathogenesis (Morales *et al*., 2015). Activation of ISG-15 by the E1 activating enzyme (UbE1L) is critical for initiating ISGylation of proteins. Mice lacking the ISG-15 E1 enzyme were highly susceptible to Sindbis virus infection supports its role in the antiviral effect of ISG-15(Giannakopoulos *et al*., 2009). ISG-15 expression inhibits Ebola virus matrix protein VP40 ubiquitination by host ubiquitin ligase enzyme. VP40 is crucial for viral egress. Therefore, ISG-15 inhibits the budding of the Ebola virus (Okumura *et al*., 2008). The effects of ISGylation on two vector-borne RNA viruses, dengue virus (DENV) and West Nile virus (WNV), were investigated and revealed that these viral infections drastically increased ISG-15-conjugated proteins in the infected cells. ISG-15 silenced cells gave significantly higher titer for DENV and WNV in quantitative PCR, suggesting that it impedes viral replication by altering viral or cellular proteins (Dai *et al.,* 2011). ISG-15 was not detectably produced in puppies deficient in subunit 1 of the type I IFN receptor after chikungunya virus (CHIKV) infection, proven ISG-15 is expressed as a part of the IFN response. There was no rise in CHIKV viral load in mice lacking ISG-15. However, a pronounced increase in the expression of proinflammatory cytokines was noticed, giving new insights into the mechanism of action of ISG-15 (Werneke *et al*., 2011). Many viruses elicit countermeasures against ISG-15, exemplified by the deconjugation of ISG-15 appears to be an approach used by coronavirus to interfere with ISG-15 conjugates (Gold *et al*., 2022).

Mx: Mx, a dominant resistance gene first identified in mice which provided an antiviral state towards the influenza virus (Horisberger *et al*., 1983). Mx proteins are type 1 interferon-induced dynamin-like GTPases found in most species in one to three isoforms. The structural features of Mx protein include the GTPase domain at N-terminal, a middle domain, and a GTPase effector domain at the C-terminal region common to dynamins but lacks a proline-rich domain and a pleckstrin homology domain (Cai *et al*., 2013; Haller *et al*., 2015). Purified Mx protein self-assembles into ring-like & helical structures, which seems critical for GTPase activity and recognition of viral target proteins (Haller *et al*., 2007). Most mammals possess two closely related Mx genes, similar to the human Mx1 (MxA) and Mx2 (MxB) lineage. In infected cells, MxA can recognize incoming vRNPs (viral ribonucleoprotein) along with newly synthesized NP (nucleoprotein) in the cytoplasm and inhibits the translocation of vRNPs and NP to the nucleus, thereby culminating in virus infection (Haller *et al*., 2015). MxA has broad antiviral action towards several viruses such as orthomyxoviruses, paramyxoviruses, togaviruses, rhabdo viruses, reoviruses, picornaviruses, and bunyavirus, but the mechanism of action is not fully elucidated (Haller

and Kochs, 2002).

The antiviral activity of Mx depends on where they are located within the cell. Mx1 localizes mainly in the nucleus and resists virus replication in the nucleus. During influenza virus infection, the NP of the influenza virus is the principal target for Mx and blocks the virus's primary transcription in the nucleus (Zimmermann *et al*., 2011). In contrast, Mx2 is a cytoplasmic protein that can prevent the multiplication of cytoplasmic viruses such as rhabdovirus and bunyavirus. This suggests that different Mx proteins work at different cell locations to resist viruses, which widens its spectrum of action (Haller *et al*., 2007). Human MxB targets the HIV-1 capsid immediately after the cell entry and inhibits the integration of the viral genome into host DNA (Goujon *et al*., 2013). MxA targets vesicular stomatitis virus and parainfluenza virus nucleocapsid and inhibits early viral mRNA synthesis (Schwemmle *et al*., 1995). Rift Valley fever virus, another member of *Bunyaviridae*, is blocked by cytoplasmic rat Mx2 protein since it replicates in the cytoplasm (Sandrock *et al*., 2001). Viral hemorrhagic septicemia virus (VHSV), which comes under the *Rhabdoviridae* family, causes mortality in freshwater and marine fishes and counteracts higher Mx gene expression by the non-virion (NV) gene (Kim and Kim, 2012). A double-stranded RNA virus, infectious pancreatic necrosis virus, remarkably induces Mx transcript expression in Atlantic halibut fish (Jensen and Robertsen 2000). Therefore, Mx isoforms play a crucial role in antiviral defense since they hamper viruses at various locations, where the virus accumulates more in the cell.

Viperin: Viperin is a well-studied antiviral effector, also known as RSAD2 (radical S-adenosyl-L methionine (SAM) domain-containing 2) because its central domain is homologous to the radical S-adenosyl-L-methionine family of enzymes. Viperin is a typical IFN-inducible gene expressed nominally in most cells but is significantly expressed during IFN signaling. It is induced by two different pathways like JAK-STAT signaling and direct activation of IRF1/3 (Indraccolo *et al*., 2007). Viperin is usually associated with the endoplasmic reticulum (ER) and ER-derived lipid droplets, which are involved in lipid metabolisms (Schneider *et al*., 2014). Like other members of the SAM superfamily of enzymes, they catalyze a wide variety of radical-mediated reactions. However, it is still unknown how exactly viperin functions. Hampering the viral transcription might be an effective mechanism for the viperin's mode of action. Structural studies on the active site of viperin suggest that its substrate may be nucleoside triphosphate (Fenwick *et al*., 2017). Viperin requires an additional protein crucial for its SAM activity: cytosolic iron-sulfur assembly component 1 (Upadhyay *et al*., 2017). It was demonstrated that viperin inhibits the budding of the influenza virus from the plasma membrane, as it disrupts lipid raft microdomains by inhibiting the enzyme FPPS, the enzyme involved in the synthesis of various isoprenoid-derived lipids (Wang *et al*., 2007). Viperin significantly inhibits Enterovirus A71 (EVA71), a major pathogen of human hand-foot-and-mouth disease, through interacting with EVA71 2C protein in the endoplasmic reticulum (Wei *et al*., 2018). When viperins role in CHIKV replication was investigated, mice lacking RSAD2 displayed higher viremia and symptoms during infection compared to wild-type mice. They identified the N-terminal amphipathic α-helical domain of viperin as essential for suppressing CHIKV replication. In contrast, mutation at the SAM domain resulted in a lack of confirmational stability, unfolding of protein leading to loss of its antiviral action (Teng *et al*., 2012). A recent study describes viperin inhibits RNA-dependent RNA polymerase responsible for its broad-spectrum antiviral action against RNA viruses. Viperin catalyses the conversion of cytidine triphosphate (CTP) to 3′-deoxy- 3′,4′-didehydro-CTP (ddhCTP) through SAM-mediated radicals. ddhCTP can act as a chain termination for RNA dependant RNA polymerase, directly reducing ZIKA virus release from Vero cells (Gizzi *et al*., 2018). Similarly, RSAD is reported to restrict measles virus infection at the stage of virus release (Kurokawa *et al*., 2019).

The molecular mechanism behind the inhibitory effect of viperin seems to be more related to the virus. For the hepatitis C virus, viperin interacts with non-structural protein 5A (NS5A) in lipid droplets, an essential component during viral replication. They hypothesize that viperin may promote the degradation of NS5A through ubiquitination similar to NS3 degradation in flavivirus (Panayiotou *et al*., 2018; Ghosh *et al*., 2019). Similarly, overexpressed viperin in PK-15 cells drastically reduced the viral copy number of classical swine fever due to its interaction with NS5A through the radical SAM domain (Xu *et al*., 2020). Occasionally viperin interact with structural proteins for its antiviral effect. In the case of Newcastle disease virus (NDV), chicken viperin is predicted to interact with matrix protein and reduces virus replication (Shah *et al*., 2019). Overexpression of viperin strongly inhibited Junín virus (JUNV), member of *Arenaviridae* family and causative agent of Argentine hemorrhagic fever (AHF). Two mechanisms were described by which infectious virus release was inhibited: mislocalization of virus glycoprotein preventing virus assembly and altered lipogenesis that could prevent virus budding. Even though RSAD inhibits a number of RNA viruses, some viruses take benefit from this antiviral host protein. It is reported that viperin-dependent lipogenesis will enhance infectious virion production and envelop formation in many viruses. Viruses possess countermeasures to overcome host immune responses by interfering with the viperin proteins. For example, bunyavirus non-structural protein S counteracts the regulatory action of viperin (Lerolle *et al*., 2021). In general, interaction with structural and non-structural viral proteins as well as involvement in lipid metabolism are the elucidated mechanisms of

viperin's antiviral effect.

IRF 3 and 7: During viral infection, cell-intrinsic immune response commences by recognition of PAMPs by the host cell leading to activation, dimerization, nuclear transport of IFN regulatory factor (IRF) 3/7, and in turn, IFN transcription in the nucleus. IFN induces the death of infected cells and prevents the spread of viral infection by activating ISGs (Flint *et al*., 2020). IRF-3 and IRF-7 are the two interferon regulatory factor family members, having the greatest structural and functional similarity. However, these molecules play distinct roles with a positive feedback mechanism between the two. IRF-3 is expressed constitutively in all tissue and is neither induced by viral infection. Unlike IRF-3, IRF-7 is mainly induced by type 1 IFN signaling. During a viral infection, the role of IRF-3 is primarily at the initial stage of the IFN cascade, whereas IRF-7 plays a crucial role in the later phase.

Constitutively expressing a fusion protein of porcine IRF-7 and -3 strongly induced type 1 IFN and prevented mortality in the FMD mouse model (Ramirez-Carvajal *et al*., 2014). In another study, pigs inoculated with an adenovirus vector expressing IRF-3 and 7 gave protection from FMD without even developing clinical signs and viremia during the challenge (Ramírez-Carvajal *et al*., 2016). IRF-3 & IRF-7 double deficient mice produced high levels of dengue viral load in the liver compared to wild-type mice. At the same time, single-knockout IRF3/7 mice revealed that IRF-7 plays a slightly more critical role than IRF-3 in restricting DENV replication (Chen *et al*., 2013). In line with this, influenza A virus infection in IRF3/7 double knockout mice resulted in the absence of production of IFN-α and IFN-β. While the absence of IRF-3 had a moderate effect on IFN expression, the deletion of IRF-7 completely inhibited IFN-α production after infection (Hatesuer *et al*., 2017). In contrast, the NDV replicated better in IRF-3 KO macrophages than in IRF-7 KO macrophages. This might explain why the secretion of type 1 interferon after IRF-3 knockout was delayed compared to IRF-7 KO & wild-type macrophages (Wilden *et al*., 2011). A unique relationship between the antiviral protein ISG-15 and IRF-3 was identified, where conjugation of ISG-15 to IRF-3 will antagonize the ubiquitination and degradation of IRF-3. This uncovers a novel positive feedback mechanism of the innate immune response (Shi *et al*., 2010). FMD virus leader proteinase is an interferon antagonist that reduces host cap-dependent mRNA translation demonstrated to be decreasing IRF3/7 expression (Wang *et al*., 2010). The FMD virus leader proteinase is known to function as an interferon antagonist by diminishing the translation of host cap-dependent mRNA. This action has been shown to result in reduced expression of IRF3/7, as demonstrated in the study by Wang *et al.* (2010). Similarly, the nucleocapsid protein (N) of the Peste des Petits Ruminants (PPR) virus antagonizes IRF-3 to evade the host defense mechanism. N protein interacts with IRF-3 to block its activation and inhibit type I IFN production (Zhu *et al*., 2019). IRF3/7 can act as positive regulators and final effectors of IFN signaling.

CONCLUSIONS

Interferon provides early immune defense against viral infection and imparts its action through ISGs, the final effectors of the interferon pathway. ISG-15, Mx, and viperin are the major ISGs against RNA virus infection, whereas IRF-3 and IRF-7 act as major regulators of IFN signaling. Antiviral effects of interferons reveal innate immune responses to inhibit viral infection and may help to elucidate effective strategies to treat viral disease.

FUTURE SCOPE

Strategies used by viruses to evade the antiviral mechanisms are important in giving insight into the virus-cell interaction and uncovering new antiviral targets. Further understanding of antiviral proteins has great potential in the area of diminishing undesirable autoimmune responses. Last but not least, insight into the broader role of the antiviral proteins will reveal more interesting developments in the field of the cellular immune response as well as virus immune evasion strategies.

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Conflict of Interest. None.

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