Mini-Review

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Interferon-stimulated gene 20-kDa protein (ISG20) in infection and disease: Review and outlook

Zhiwei Zheng[1,2,3,4], Lin Wang[1,2,3], Jihong Pan[1,2,3,*]

[1] *Shandong Medicinal Biotechnology Center, Ji'nan, China;*
[2] *Key Laboratory for Rare & Uncommon Diseases of Shandong Province, Ji'nan, China;*
[3] *Key Laboratory for Biotech-drugs of the Ministry of Health, Ji'nan, China;*
[4] *School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Ji'nan, China.*

Summary **Interferon-stimulated exonuclease gene 20 (ISG20) is an RNA exonuclease in the yeast RNA exonuclease 4 homolog (REX4) subfamily and the DEDDh exonuclease family, and this gene codes for a 20-kDa protein. Those exonucleases are involved in cleaving single-stranded RNA and DNA. ISG20 is also referred to as HEM45 (HeLa estrogen-modulated, band 45). Expression of ISG20 can be induced or regulated by both type I and II interferons (IFNs) in various cell lines. ISG20 plays a role in mediating interferon's antiviral activities. In addition, ISG20 may be a potential susceptibility biomarker or pharmacological target in some inflammatory conditions. Exonucleases are useful components of many physiological processes. Despite recent advances in our understanding of the functions of ISG20, much work remains to be done with regard to uncovering the mechanism of action of ISG20 in specific diseases and adapting ISG20 for use as a biomarker of disease. This review describes current information on ISG20 and its potential use in marking disease. This review describes several research achievements thus far and it seeks to provide some new ideas for future related research.**

Keywords: ISG20, interferon-stimulated gene, antiviral, exonuclease, clinical use

1. Introduction

Interferons comprise a family of secretory proteins characterized chiefly by their ability to induce cellular antiviral proteins (*1*). The 20-kDa protein of interferon-stimulated exonuclease gene 20 (ISG20) is a protein induced by interferons or double-stranded RNA (*2,3*). Its involvement in antiviral mechanisms was elucidated in a recent study (*4*), where overexpression of recombinant ISG20 in cultured cells was found to increase cellular resistance to infection by some RNA genomic viruses (*1*). ISG20 is an exonuclease that can cleave single-stranded RNA and DNA (*5,6*). It plays a role in mediating interferon's antiviral activities. Levels of ISG20 expression differ in some diseases (such as rheumatoid arthritis) in comparison to those in healthy individuals (*7*). In addition, interferons, estrogens, and polyIC can increase the expression of ISG20 in several cell lines (*2,8,9*). However, the specific functions and mechanisms of ISG20 in different diseases need to be explored further. The current review provides an overview of the current understanding of the clinical significance of ISG20.

2. ISG20: Molecular characterization

The initial discovery of ISG20 occurred in 1997 (*2*). When Gongora *et al*. used differential screening to search for as-yet unidentified IFN-regulated genes, they identified interferon-regulated genes after treating cultured human lymphoblastoid Daudi cells with 500 IU of human α/β-interferon (IFN). One of those genes is induced by both type I and II IFNs in various cell lines. Designated interferon-stimulated exonuclease gene 20 (ISG20), this gene codes for a 20-kDa protein (*2*). A separate study identified this protein around the same

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**Address correspondence to:*
Dr. Jihong Pan, Shandong Medicinal and Biotechnology Center, Shandong Academy of Medical Sciences, 18877 Jingshi Road, Ji'nan, Shandong 250062, China.
E-mail: pjh933@sohu.com

time. Pentecost used differential display PCR on mRNA from a human cervical cancer cell line (UP1) stably transfected with an estrogen receptor (ER) expression construct (*8*). An mRNA was widely expressed at low levels in cell lines and was up regulated by E2 in ER-positive breast cancer lines; this was named HeLa estrogen-modulated, band 45 (HEM45) (*8*).

ISG20 is localized to human chromosome 15q26 (*10*). Further, the encoded amino acid sequence shares homology with other species (*11*). *ISG20* encodes a 181-amino acid protein of 20.4 kDa with a theoretical isoelectric point (pI) of 9.5. The optimum pH for ISG20 is about 7.0, and the protein prefers Mn^{2+} as a metal cofactor (*5*). These properties help to explain the optimal conditions for the exonuclease activity of ISG20. This exonuclease preferentially degrades RNA at a rate 35-fold higher than it degrades single-stranded DNA (*5,6*). ISG20 also belongs to the DEDDh exonuclease family, which is defined by four conserved acidic residues, three aspartates (D), and one glutamate (E), distributed among three separate sequence motifs (Exo I–III) (*6,12*) and with a fifth conserved residue of histidine (H). The protein also shares striking homology with the product of the *Xenopus laevis XPMC2* gene (*2*).

2.1. *Expression*

Expression of ISG20 can be induced in cell lines through exposure to both type I (IFN-α/β) and type II (IFN-γ) IFNs; HuIFN-α/β is a stronger inducer of that expression than IFN-γ (*2*). ISG20 expression can also be induced by poly IC (an authentic double-stranded RNA that mimics viral infections when applied to cells) in human vascular endothelial cells (HUVEC) (*9*). The upregulation of ISG20 following IFN exposure occurs at the transcriptional level, in keeping with the majority of IFN-induced genes (*2*). Further, the constitutive transcriptional activity of ISG20 following IFN exposure may be attributable to the interferon-stimulated response element (ISRE).

Zeng *et al*. found that the levels of ISG20 mRNAs were significantly upregulated *in vivo* in the spleen and lungs of goats infected with goatpox virus (GTPV) (*13*). However, ISG20 can also be expressed at high levels in peripheral blood leukocytes, lymphoid tissues (such as spleen or thymus), the colon, and the lungs without exogenous IFN treatment (*2*). When the location of ISG20 protein was assessed immunohistochemically in human HeLa and lymphoblastoid Daudi cells, diffuse cytoplasmic and nucleoplasmic localization was observed, but ISG20 also appeared in the nucleus, including the nucleolus and Cajal bodies (CBs) (*14*). Further, electron microcopy analysis revealed that ISG20 was principally concentrated in the dense fibrillar component of the nucleolus, the major site for rRNA processing (*14*). Similarly, laser confocal microscopy detected porcine ISG20 primarily in the nucleus, with only a small amount in the cytoplasm (*15*). ISG20 localizes in spherical nuclear particles termed promyelocytic leukemia protein oncogenic domains (PODs), which are also known as nuclear domain 10 or the Kr body. Gongora *et al*. also reported that ISG20 is distributed diffusely throughout the nucleoplasm in 30% of the positive CCL13 cells. This finding strongly suggests that progression of the cell cycle may change the distribution of ISG20 in the intranuclear compartment (*16*).

2.2. *Function and mechanism*

Along with ribonuclease (RNase) L, ISG20 is the second known RNase that is regulated by interferon. RNases may play an important role in protection against various pathogens, including viruses and bacteria, in both cellular and extracellular regions (*17*). Like other exonucleases, ISG20 may play a role in cleaving both DNA and RNA. However, ISG20 has distinctive residues, Met14 and Arg53, to accommodate hydrogen bonds with the 2'-OH group of the UMP ribose, which promotes a preference for RNA substrates (*1*). Further, a stem-loop structure at the 3' end of RNA substrates leads to a strong reduction in the activity of ISG20 RNase, and ISG20 operates poorly on double-stranded regions (*5*). Interestingly, substitution of a single conserved aspartic acid with a glycine or using an aspartate to replace an alanine mutation at the structurally equivalent residue may cause a significant decrease in the 3'-5' exonuclease activity of ISG20 (*5*). Eliminating the exonuclease activity of ISG20 through use of a single amino acid substitution in the conserved exonuclease motif ExoII verified the relationship between ISG20's antiviral activities and its functioning as an exonuclease (*4*).

Evidence also suggests that ISG20 is a promyelocytic leukemia (PML) nuclear body (NB)-associated protein (*2*). A PML NB is a subnuclear structure in mammalian cells that participates in various cellular events including transcription regulation, maintenance of genomic stability, antiviral activity, cell apoptosis, and tumor inhibition (*15*). Gongora *et al*. concluded that PML NBs may play a role in the viral infection process (*2*). PML NBs are also known sites of hormone-dependent RNA polymerase II transcription and oncogenic DNA viral transcription and replication.

ISG20 (HEM45) is reported to play a role in controlling cellular proliferation and differentiation by mediating estrogen (*8*), and the human gene was identified independently on the basis of its increased level of expression in response to either interferon or estrogen hormone (*2,8*). Further, ISG20 degrades viral RNAs as part of the interferon-regulated antiviral response and/or cellular mRNAs as a regulatory component of interferon and estrogen signaling (*5*). Although ISG20 is important for cellular function,

Table 1. List of viruses associated with ISG20-mediated antiviral activity

Name of Virus	Main Biological Mechanism	Experimental Host Cells	*Ref.*
Hepatitis A virus (HAV)	ISG20 exonuclease activity	Huh7.5, HEK293 FLP-IN T-Rex	*23*
Hepatitis virus (HBV)		HepG2	*36,37*
Hepatitis C virus (HCV)	ISG20 exonuclease activity	HEK293	*38*
		Huh7.5	*23*
Yellow fever virus (YFV)		HEK293	*23*
Bovine viral diarrhea virus (BVDV)		MBDK	*23*
Vesicular stomatitis virus (VSV)	ISG20 exonuclease activity	HeLa	*4*
Encephalomyocarditis virus (EMCV)	ISG20 exonuclease activity	HeLa	*4*
Influenza virus	ISG20 exonuclease activity	HeLa	*4*
		293T/A549	*39*
Human immunodeficiency virus (HIV)	ISG20 exonuclease activity	CEM, Peripheral blood mononuclear cells	*40*
Sindbis virus (SB)		Tet-off MEF	*24*
West Nile virus		HEK293	*19*
Dengue virus		HEK293	*19*
Kaposi's sarcoma-associated herpesvirus (KSHV)		PDLF /HGF	*30*
Porcine reproductive and respiratory syndrome virus (PRRSV)		SJPL	*15*
Rabies virus (RABV)		Neuronal	*41*
Epstein-Barr virus (EBV)		B cell	*42*
Cytomegalovirus		Fibroblast	*43*

overexpression of exogenous ISG20 is detrimental to cell survival (*17*) Thus, the activity of ISG20 must be tightly regulated (*17*). In addition, ISG20 may be a biomarker of some diseases and it represents a potential new target for drug screening.

3. Physiological and pathological roles of ISG20

3.1. *ISG20 and viruses*

Interferons (IFNs) are a family of secreted proteins that provide the front line of defense against viral infections (*4*). The antiviral activities of IFNs are generally regarded to operate through three pathways: the double-stranded RNA-dependent protein kinase R (PKR), the 2-5A/RNase L system, and the Mx proteins (*4*). However, in fibroblasts of mice triply deficient in PKR, RNase L (ribonuclease L), and Mx (myxovirus resistance), IFN still protected against viral infections. This finding indicates the existence of additional IFN-induced antiviral pathway(s) (*18*).

ISG20 can inhibit the replication of RNA viruses. Some hypotheses propose that ISG20 affects the development of viruses by degrading viral RNA, but it may also act indirectly on cellular factors required for viral replication or transcription (*17*). The mechanism underlying this activity remains unclear, but the 3'-5'exonuclease activity of ISG20 is believed to be the effector mechanism through which ISG20 mediates IFN-antiviral activity against viral RNAs (2). Indeed, a number of viruses are reported to be susceptible to ISG20-mediated antiviral activity (see Table 1) *in vitro*.

Studies of viral susceptibility to the antiviral effects of ISG20 provide insight that will prove helpful to future research. Espert *et al*. found that the expression of an inactive form of ISG20 has no effect on the ability of IFN to fight against the influenza virus and encephalomyocarditis virus (EMCV). This finding suggests that the contribution of ISG20 is likely minor in the presence of these viruses, in comparison to other IFN-induced pathways (*4*). Similarly, ISG20 only partly mediates the antiviral action of IFN against the vesicular stomatitis virus (VSV) (*4*). A study screened 29 types of ISGs that are induced in Huh7 cells by IFN-α and/or up-regulated in HCV-infected livers, and results revealed that viperin, ISG20, and PKR inhibited the replication of hepatitis C virus (HCV) replicons in a non-cytolytic manner (*19*). This means that many interferon-stimulated genes are mediated by the products of specific but usually overlapping sets of cellular genes induced in target cells in diverse biological processes (*2*).

Zhou *et al*. (*20*) and Espert *et al*. (*4*) failed to find that ISG20 had any significant role in inhibiting the replication of the DNA genomic adenovirus. However, ISG20 is effective against the hepatitis virus (HBV), which is a DNA virus. Lu *et al*. suggested that adenoviruses are a special type of DNA virus, so a failure to inhibit adenovirus does not preclude a general DNase function for this protein (*21*). In addition, Jiang *et al*. found that level of HCV RNA was significantly reduced but β-actin mRNA was not apparently affected even in the same wild-type ISG20-expressing cells, indicating that ISG20 selectively attacks viral RNA but not cellular mRNA (*22*). Further studies on the molecular mechanism of the substrate selection of ISG20 exonuclease are clearly warranted (*22*).

Interestingly, ISG20 exhibits no demonstrable effect on yellow fever virus (YFV) in Huh7.5-derived cells but it potently inhibits YFV replication in HEK293 cells (*23*). In addition, assay data for some gene products, including ISG20, display differing antiviral activity *in vitro* versus *in vivo* (*24*). These findings suggest that caution must be used when interpreting results obtained

from different cell types and in different settings (*24*).

In addition to these antiviral actions, ISG20 can participate in other processes related to viral infection. For example, Zeng *et al*. found that GTPV infection can significantly induce mRNA expression of type I IFN, inflammatory cytokines, signal paths, Toll-like receptors, and some critical interferon-stimulated genes, including *ISG20* (*13*). This indicates that GTPV infection could activate host innate immune signaling, leading to cytokine response and antiviral defense (*13*). In the liver, ISG20 acts to prevent chronic liver disease caused by infections with the hepatitis A, B, or C virus. The protein functions downstream of IFN signaling in the innate defense of the liver, exhibiting broad antiviral activities against multiple, distinct hepatitis viruses (*23*).

Although progress has been made, many of the specific mechanisms by which ISG20 inhibits different viruses still need to be explained.

3.2. *ISG20 and potential biomarkers*

ISG20 has generated interest as a potential biomarker for certain diseases. Biomarkers are important because they can reduce costs to patients, eliminate the incidence of adverse reactions, and avoid the risk of causing further damage. Many studies involving the use of miRNAs as biomarkers to diagnose disease, predict prognosis, and facilitate treatment are ongoing. Biomarkers can also help to study disease.

Fertility in dairy cattle Microarray analysis and statistical validation of selected genes using qRT-PCR revealed that nine genes, including *ISG20*, were differentially expressed between repeat breeder (a normal estrous cycling animal that did not become pregnant after three inseminations despite the absence of clinically detectable reproductive disorders) and normally fertile Holstein Friesian heifers (*25*). This finding is interesting given the low heritability of traditional fertility traits, which are based on phenotype observation, and the recent trend toward an increasing use of genomic selection tools in dairy cattle breeding programs (*25*). The results of that study identified genes that are potential markers of fertility in dairy cattle, and those genes would prove useful when incorporated in genomic selection tools in dairy cattle breeding programs.

Mature and activated dendritic cells Many genes, including ISG20 (*HEM45*), are differentially expressed between mature and activated dendritic cells (MADCs) and immature dendritic cells (IMDCs) (*26*). The comprehensive identification of specific genes expressed in human IMDCs and MADCs should identify potential genes to define heterogeneous subsets as well as the function and stage of maturation of dendritic cells (DCs) (*26*). This stratification can contribute to further understanding of the function of DCs in the host defense system and it may also be useful in diagnosing or monitoring human diseases in which DCs play a role.

Multiple sclerosis Multiple sclerosis (MS) is a chronic, progressive, and disabling immune-mediated disorder of the central nervous system. In the pursuit to develop treatments for MS, IFN-β, a type I IFN, was the first agent to show clinical efficacy in treating relapsing–remitting (RR) MS and it is still the most commonly used agent. Expression of ISG20 can be induced in cell lines with IFN-β (*2*). Is there some relationship between ISG20 and MS? Martire *et al*. analyzed the baseline level of expression of a panel of 25 genes (potential biomarkers to predict the response to IFN-beta treatment) including ISG20 in whole blood of 20 patients with RR MS (10 responders and 10 non-responders) to verify the ability of those genes to predict the clinical response to the drug. However, the levels of *ISG20* expression were not correlated with clinical features such as the duration of disease, relapse frequency before treatment, and the baseline Expanded Disability Status Scale score (*27*). No statistically significant differences in levels of expression were observed for any of the genes analyzed. Sensitive and specific biomarkers for diagnosis of MS, prediction of its prognosis, and prediction of treatment efficacy are being identified (*28*). However, about 40% of patients respond poorly or not at all to IFN-β treatment. Could ISG20 be a perfect replacement for IFN-β? Several studies have suggested that patterns of IFN-stimulated genes in RR MS can predict a clinical response to treatment, but most of the suggested biomarkers have not been confirmed in a completely independent analysis. Further insight into ISG20 as a potential biomarker will depend on increasing the number of patients, while maintaining rigor in patient selection, and providing a sufficiently long follow-up (*27*).

Rheumatoid arthritis Chang *et al*. used the Illumina Human HT-12 v4 Expression BeadChip to examine expression of *ISG20* in synovial tissues of patients with rheumatoid arthritis (RA) compared to patients with osteoarthritis, and they verified their results using qRT-PCR (*7*). Results revealed that expression of *ISG20* was upregulated in synovial tissues of patients with RA and findings suggested that ISG20 may play a role in RA pathogenesis. Recombinant IFN-γ has been reported to be effective in RA treatment (*29*). However, no study has examined the specific contribution of ISG20 to RA. Thus, further research is needed. In recent studies, the current authors found that some inflammatory cytokines, including IL-6 and IL-10, are upregulated when ISG20 is overexpressed in RA fibroblast-like synoviocytes (unpublished data). Dai *et al*. reported that some genes, and particularly *ISG15* and *ISG20*, are required for maintenance of virus latency through regulation of specific Kaposi's sarcoma-associated herpesvirus (KSHV) microRNAs (*30*). MicroRNA (miRNA) regulation is an emerging field to understand

the mechanisms regulating a variety of inflammation-mediated diseases. miRNAs play important roles in cell physiology and the pathogenesis of human diseases. miRNAs may regulate gene expression at the posttranscriptional level. In addition, miRNAs exhibit tissue-specific or developmental stage-specific patterns of expression and are associated with diverse biological events such as cell growth, apoptosis, cell differentiation, cancer, and autoimmune arthritis (*31*).

Some microRNAs downregulate the expression of inflammatory cytokines (*31*). ISG20 may regulate some putative microRNA(s) that possibly inhibit inflammatory cytokines in RA. Further, several microRNAs are associated with the pathogenesis of RA through chronic inflammation and hyperplasia in synovial lining cells (*32*). Thus, future studies are needed to verify whether ISG20 is a potential biomarker or an important target in the pathogenesis of RA and whether ISG20 can be used in drug screening or immunotherapy related to RA.

3.3. *Other progress*

ISG20 has also been mentioned in other studies. Imaizumi *et al*. reported that ISG20 may be involved in innate immunity against viral infection in vascular endothelial cells (*9*). Additionally, some evidence indicates that ISG20 plays a role in the innate immune response against various pathogens, including bacteria and parasites (*17*). For example, ISG20 may be a major effector of innate immune response against Listeria infection in macrophage cells or Mycobacterium tuberculosis and Toxoplasma gondii in DCs (*33,34*).

Finally, chronic stress can affect genes involved in the functioning of the vascular system, injury response, and inflammation, and ISG20 is a gene involved in this inflammatory process (*35*). The transcription of ISG20 is induced by chronic stress and possible vascular injury due to increased blood pressure. Findings suggest that stress may affect brain functions as a result of the stress-induced dysfunction of the vascular system.

4. Conclusions and outlook

Great progress has been in understanding ISG20. Indeed, much is known about the structure, expression, and function of ISG20. Current efforts are focused on the antiviral activity of ISG20. Recent studies describing the role of ISG20 in other types of inflammatory responses, beyond its antiviral activity, will likely lead to more work on its potential as a biomarker, drug target, or immunotherapy option for diseases like MS and RA. However, the biological activities of ISG20 and specific mechanisms of action of ISG20 in these diseases remain unclear. Future studies must attempt to uncover the specific mechanisms of ISG20's action in a variety of diseases and to explore its potential in as-yet-unexplored settings.

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