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COMMENTARY

The Indirect Antiviral Potential of Long Noncoding RNAs Encoded by IFITM Pseudogenes

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ABSTRACT The interferon-induced transmembrane (*IFITM*) gene family performs multiple functions in immunity, including inhibition of virus entry into cells. The *IFITM* repertoire varies widely between species and consists of protein-coding genes and pseudogenes. The selective forces driving pseudogenization within gene families are rarely understood. In this issue, the human pseudogene *IFITM4P* is characterized as a virus-induced, long noncoding RNA that contributes to restriction of influenza A virus by regulating mRNA levels of *IFITM1*, *IFITM2*, and *IFITM3*.

KEYWORDS IFITM, interferons, lncRNA, miRNA, pseudogene, retrogene

Innate immunity plays a critical role in the initial detection and restriction of virus infections at the level of individual cells. Upon pathogen invasion, pattern recognition receptors, such as retinoic acid-inducible gene I (RIG-I), recognize pathogen-associated molecular patterns (PAMPs) and initiate a cascade of signaling that leads to the production of type I interferons (IFN-α and IFN-β) (1). These cytokine mediators interact with specific cellular receptors and activate the transcription of a distinct set of genes known as IFN-stimulated genes (ISGs) that collectively confer an antiviral state to cells (2). Regulation of ISG functions by transcriptional and posttranscriptional mechanisms is a blossoming area of research at the interface of immunology and virology. In this issue of the *Journal of Virology*, Xiao et al. (3) report that the interferon-inducible transmembrane (IFITM) proteins are regulated by a long noncoding RNA (lncRNA) encoded by a pseudogene known as *IFITM4P*.

IFITM proteins are a group of small transmembrane proteins known to regulate various cellular processes, including virus entry into cells (4). The human genome contains five *IFITM* genes (*IFITM1*, *IFITM2*, *IFITM3*, *IFITM5*, and *IFITM10*). *IFITM1-3* are upregulated by interferons and are the family members ascribed with immune functions (5). IFITM1-3 broadly inhibit infection by diverse enveloped viruses, including orthomyxoviruses, coronaviruses, flaviviruses, filoviruses, paramyxoviruses, and retroviruses (5, 6). All three immune-related IFITM proteins have been shown to remodel cellular membranes in a manner that disfavors virus-cell fusion. The functions of IFITM3 are best characterized. IFITM3 dimers increase membrane lipid order (rigidity) (7) and curvature (8) in order to disfavor virus-cell membrane fusion (9) and traffic endocytosed virions toward lysosomes for degradation (10, 11). IFITM3 exhibits the most potent antiviral activity against most viruses studied in cell culture, and it is required for control of influenza A virus *in vivo* (12–14). As components of the cell's first line of antiviral defense, there is much interest in the spatiotemporal regulation of IFITM proteins. Most human tissues contain cell types that express one or more IFITM proteins constitutively (15), including tissue-resident memory T cells (16, 17), respiratory epithelial cells (13), and hematopoietic stem cell progenitors (18–20). Beyond the level of transcription, posttranslational modifications play important roles in the stability and subcellular localization of IFITM proteins (21). For example, the E3 ligase NEDD4 ubiquitinates IFITM2 and IFITM3 and promotes their degradation in lysosomes (21–23). On the other hand, there is relatively little known about pathways that regulate the fate of *IFITM* mRNAs.

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In addition to the five protein-coding *IFITM* genes found in humans, there are multiple *IFITM*-like loci, which are designated pseudogenes due to apparent truncation of the open reading frame (ORF) and/or lack of an intron. At least 12 *IFITM*-derived pseudogenes, including *IFITM4P*, exist in the human genome, but functional information for their biological roles is lacking. Xiao et al. (3) used a cDNA microarray approach to identify RNAs that are up- or downregulated in lung epithelial cells during influenza A virus infection and chose to focus on the RNA encoded by *IFITM4P* due to its relatedness to the antiviral IFITM protein family. They showed that *IFITM4P* expression was induced 10 to 14 h following infection by multiple strains of influenza A virus and was also upregulated by another RNA virus (Sendai virus) and a DNA virus (herpes simplex virus 1). This observation was maintained in many, but not all, additional cell lines tested. Due to the authors' inability to detect a protein product, the *IFITM4P* mRNA (which is 300 bp long) was established as an lncRNA with potential functional roles played during virus infections. The authors went on to show that *IFITM4P* expression was triggered by purified viral RNA or poly(I·C), which represent the natural and synthetic ligand, respectively, of the pathogen recognition receptor RIG-I. Accordingly, the induction of *IFITM4P* by influenza A virus was lost in lung epithelial cells in which RIG-I was depleted. Furthermore, type I interferon treatment elevated *IFITM4P* levels, indicating that it may be an ISG. These findings suggested that *IFITM4P* may contribute to the antiviral state activated in response to virus infection.

The antiviral functions of *IFITM4P* were revealed by assessing the effect of *IFITM4P* knockdown or overexpression on influenza A virus, which promoted or inhibited infection, respectively. Importantly, levels of *IFITM4P* were inconsequential for infection by Sendai virus, which was previously shown to be insensitive to restriction by IFITM1-3 (24). These results indicated that *IFITM4P* may function similarly to the known antiviral effectors IFITM1-3. Alternatively, since *IFITM4P* is an lncRNA, it may exhibit indirect antiviral activity by regulating the expression of IFITM1-3. Indeed, Xiao et al. (3) show that knockdown of *IFITM4P* resulted in reduced levels of IFITM3 protein, which was accompanied by reduced levels of mRNA corresponding to *IFITM3*, *IFITM2*, and *IFITM1*. Conversely, overexpression of *IFITM4P* resulted in increased levels of *IFITM1*, *IFITM2*, and *IFITM3* mRNAs. These data suggested that *IFITM4P* lncRNA promotes the stability of *IFITM* mRNAs and provided an explanation for its observed anti-Influenza activity.

The fact that *IFITM4P* lncRNA stabilized mRNAs from the related *IFITM1-3* raised the possibility that it interferes with a process that negatively regulates these mRNAs. The authors used prediction software to identify microRNAs (miRNAs) capable of engaging *IFITM4P* lncRNA and identified miR-24-3p as one that is functionally capable of decreasing levels of *IFITM4P* as well as mRNA levels of *IFITM1-3*. Mutagenesis of *IFITM4P* or *IFITM1-3* mRNAs at nucleotides complementary to miR-24-3p rendered the transcripts resistant to miR-24-3p-mediated suppression.

Therefore, *IFITM4P* promotes the production of IFITM proteins by interfering with the silencing activity of miRNAs targeting *IFITM* transcripts. This mechanism of action led the authors to designate *IFITM4P* as a competing endogenous RNA (ceRNA). By acting as a decoy for miR-24-3p, *IFITM4P* augments the abundance of *IFITM1-3* mRNAs available for translation (Fig. 1). Furthermore, the regulatory relationship between *IFITM4P* and *IFITM1-3* mRNAs is bidirectional—increased levels of *IFITM1-3* mRNAs also augment the levels of *IFITM4P*, and this is due to the shared miR-24-3p-binding sequence they possess.

Given the importance of *IFITM4P* in the regulation of antiviral immunity, we decided to investigate the structure, origin, and evolutionary conservation of this gene to better understand its functions and to assess similarities to other *IFITM*-derived pseudogenes. lncRNAs are generally poorly conserved among various species relative to other well-studied noncoding RNAs, such as miRNAs and small nucleolar RNAs (snoRNAs) (25–27), implying that lncRNAs may perform species-specific functions. A previous publication stated that *IFITM4P* is found in mice (28). However, our genomics analyses in Ensembl (ensembl.org) found *IFITM4P* orthologs in 31 of 90 eutherian mammal species, including some rodent and bat species, but no such gene was identified in the mouse

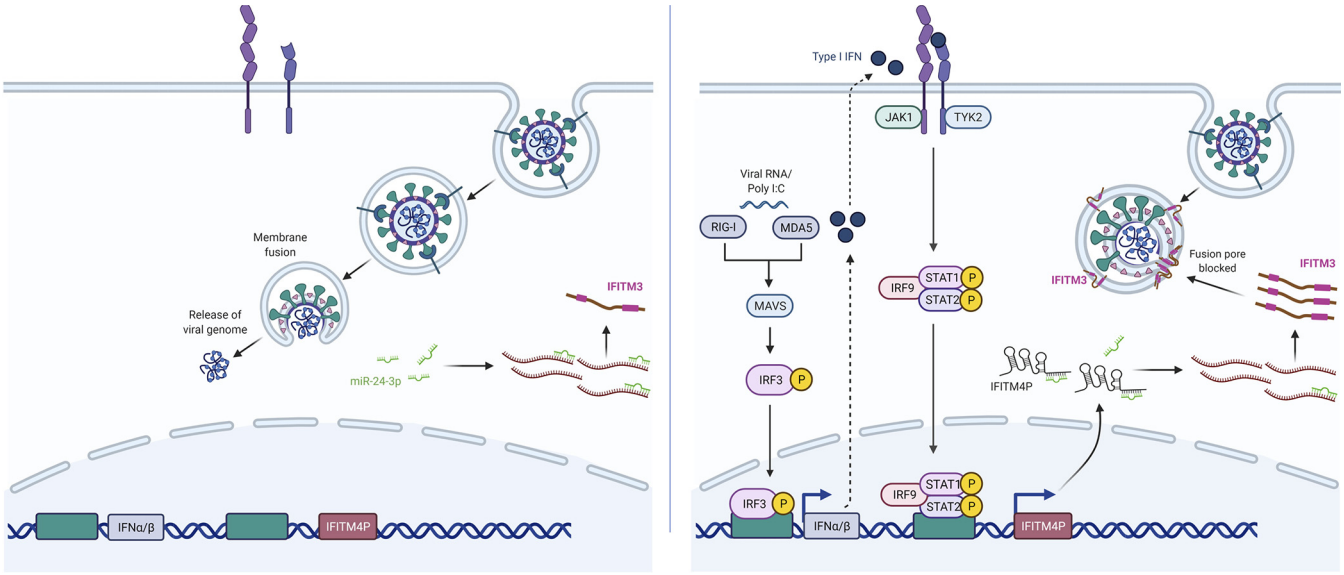

FIG 1 *IFITM4P*-mediated regulation of innate immunity to curb virus infection. (Left panel) The entry pathway exhibited by influenza A virus and other endocytic viruses is shown. Following internalization by endocytosis, membrane fusion between virus and endosome enables release of the viral ribonucleoprotein complex and initiation of virus replication. Binding of miR-24-3p to *IFITM1-3* mRNAs suppresses the production of IFITM1-3 proteins. (Right panel) Viral RNA or poly(I·C) is recognized by RIG-I or MDA5 and initiates the production of type I interferons (IFNs). IFN binds to its cognate receptor in an autocrine fashion (and in a paracrine fashion [not shown]), leading to induction of interferon-stimulated genes and *IFITM4P*. *IFITM4P* encodes a long noncoding RNA that acts as a decoy for miR-24-3p, releasing *IFITM1-3* mRNAs from a suppressed state and augmenting IFITM1-3 protein levels. Elevated IFITM proteins, particularly IFITM3, inhibit formation of the fusion pore during virus-cell membrane fusion. Figure created with BioRender.

genome. Mammalian *IFITM4P* orthologs exhibited various degrees of sequence conservation, with *IFITM4P* from chimpanzees, bonobos, and pig-tailed macaques most closely resembling the human gene. Elsewhere, including in other primate species, the *IFITM4P* locus has diverged or decayed. Phylogenetic analysis suggests that *IFITM4P* may have descended from *IFITM3* (Fig. 2). Overall, *IFITM4P* may act as a functional lncRNA in some, but not all, mammalian species. Furthermore, its role as a ceRNA impacting antiviral immunity may be confined to a select number of primates.

The sequence architecture of *IFITM4P* indicates that it is a processed pseudogene because it lacks introns and contains a poly(A) tail in its 3′ untranslated region (UTR) (Table 1). Processed pseudogenes, also known as retrogenes, are genes produced from mRNA transcripts that have been spliced, reverse transcribed into DNA by an endogenous retroelement, and integrated into a new genomic location (29). During pseudogenization, enhancers and promoter elements that were once required for gene expression are lost but may be reacquired following sequence evolution and natural selection. In that light, in contrast to the parental locus *IFITM3*, we did not detect a canonical interferon response element (ISRE) motif upstream of *IFITM4P*. This raises the possibility that the interferon inducibility of *IFITM4P* observed by Xiao et al. (3) is actually the result of interferon-induced *IFITM1*, *IFITM2*, and/or *IFITM3* mRNA transcripts binding to miR-24-3p, releasing *IFITM4P* from a silenced state.

lncRNAs have previously been found to participate in cellular functions by acting as decoys, guides, or scaffolds, but the demonstration that *IFITM4P* regulates the expression of *IFITM3* indicates that pseudogenes can be functionally selected to regulate the parental loci from which they were derived. We and others previously found that *IFITM3* has undergone recurrent gene duplication in a lineage-specific manner (23, 30). As such, the number of *IFITM* genes carried by vertebrates varies widely by species. Gene duplication and subsequent sequence divergence at the protein level can alter the subcellular localization of antiviral effectors or provide new functional modalities, a process known as neofunctionalization. However, this description of *IFITM4P* as a ceRNA reveals that RNA-based functions may also be a selective driving force for the rampant proliferation of *IFITM* genes in vertebrates.

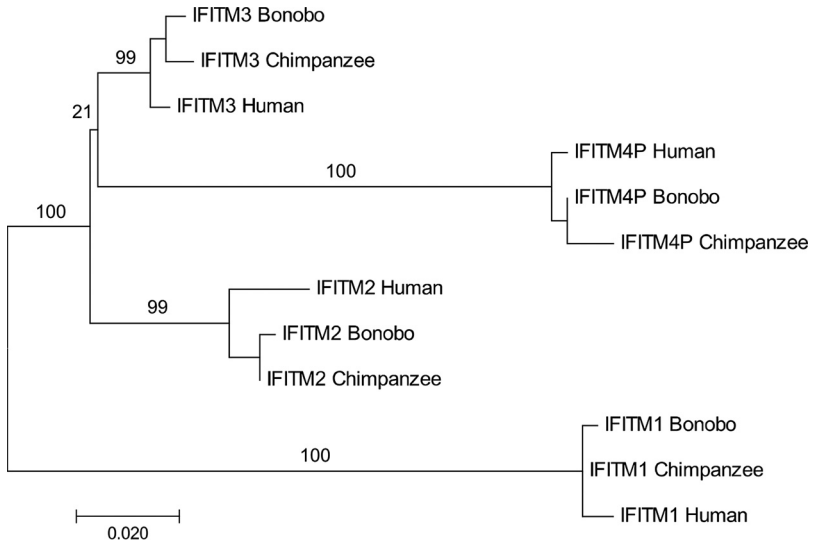

FIG 2 Phylogenetic reconstruction of *IFITM4P*, *IFITM1*, *IFITM2*, and *IFITM3* in great apes. Using MEGA7, open reading frames were aligned and gaps were removed such that a total of 335 nucleotides per sequence were obtained. Phylogenetic analysis was inferred by maximum likelihood, and the consensus tree with the highest log likelihood is shown. Initial trees for the heuristic search were obtained automatically by applying neighbor-joining and BioNJ algorithms to a matrix of pairwise distances estimated using the maximum composite likelihood (MCL) approach, and the topology with the superior log likelihood value was selected. The tree branches are drawn to scale, with branch lengths measured in number of substitutions per site. Confidence levels were determined using the bootstrapping method (500 iterations), and the numbers above branches indicate the percentage of trees in which the associated taxa clustered together.

The human genome contains at least 12 *IFITM*-derived pseudogenes, including *IFITM4P* (Table 1). It is possible that other *IFITM* pseudogenes share a complementary or redundant function with *IFITM4P*, such that multiple lncRNAs act on *IFITM* mRNAs simultaneously to further amplify mRNA stability and boost the antiviral protection conferred to cells. Alternatively, other *IFITM* pseudogenes may perform roles that are distinct from that of *IFITM4P*. Several contain an ISRE in their promoter, suggesting that they are interferon inducible and that this capacity may be the result of natural selection. In addition, four of them (*IFITM3P1*, *IFITM3P2*, *IFITM3P5*, and *IFITM8P*) contain intact open reading frames (with start and stop codons) that are as long as *IFITM3*, hinting that they may perform functions at the protein level (see Fig. S1 in the supplemental material). Apart from *IFITM4P*, the functional potential of these loci remains uncharacterized. However, a recent study on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients suggested that a potent and early induction of ISGs across

TABLE 1 Properties of human IFITM pseudogenes

Gene name	Ensembl ID	Genomic location	ISRE	Poly(A) tail	ORF length relative to IFITM3 (aa)
IFITM3P1	ENSG00000236562	Chr4(+)	No	Yes	22–133
IFITM3P2	ENSG00000223722	Chr12(+)	Yes	Yes	1–133
IFITM3P3	ENSG00000196114	Chr6(−)	Yes	Yes	22–45
IFITM3P4	ENSG00000230191	Chr7(+)	Yes	Yes	1–42
IFITM3P5	ENSG00000238168	Chr12(+)	Yes	Yes	22–147
IFITMP6	ENSG00000258352	Chr12(−)	No	Yes	1–97
IFITM3P7	ENSG00000233419	Chr1(−)	No	Yes	1–24
IFITM3P8	ENSG00000271377	Chr8(+)	No	Yes	1–31
IFITM3P9	ENSG00000271134	Chr2(−)	Yes	Yes	1–69
IFITM4P	ENSG00000235821	Chr6(−)	No	Yes	1–113
IFITM8P	ENSG00000215096	Chr8(+)	Yes	Yes	1–131
IFITM9P	ENSG00000213275	Chr11(−)	Yes	Yes	1–20

immune cell subtypes was associated with successful containment of virus and avoidance of COVID-19 (31). This protective gene signature included the likes of *IFITM3P1*, *IFITM3P2*, *IFITM3P3*, *IFITM3P6*, and *IFITM3P9*. Therefore, studies addressing the antiviral activities of *IFITM* pseudogenes against SARS-CoV-2 and other viruses are warranted. Particularly, it would be interesting to assess whether they perform indirect (lncRNA-based) or direct (protein-based) antiviral activities.

Prior to the demonstration that it bound to *IFITM4P*, miR-24-3p was known to target other cellular transcripts. miR-24-3p has been shown to play an antiviral role against influenza A virus by negatively regulating the expression of cellular furin, a protease required for the cleavage and activation of the viral fusion protein (32). In addition, miR-24-3p may downregulate neuropilin-1, which promotes the internalization of SARS-CoV-2 into cells (33, 34). These targets of miR-24-3p suggest that high levels of *IFITM4P*, through its actions as a ceRNA, may also promote infection by respiratory viruses. Therefore, the overall impact of *IFITM4P* on virus infections may result from the net effect of its antiviral and proviral effects.

The positive regulation of IFITM1-3 via the ceRNA activity of *IFITM4P* has implications beyond antiviral immunity. IFITM proteins are known to be upregulated in various cancers, and at least in some cases, they are believed to play a direct role in promoting tumorigenic phenotypes, such as cell proliferation, migration, and invasion (35). miR-24-3p expression is also associated with cancers and was previously reported to influence cell proliferation and migration by regulating SOX7 and ING1 (36–38). By competing for miR-24-3p binding, *IFITM4P* represents a previously unrecognized link (lnc!) between IFITM proteins and miR-24-3p and may impact cancer pathogenesis through multiple pathways. Detailing the functional crossroads between tumorigenesis and the antiviral state of cells is an important priority for biomedical research.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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