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Review

Interferon Induced *IFIT* Family Genes in Host Antiviral Defense

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Abstract

Secretion of interferons (IFNs) from virus-infected cells is a hallmark of host antiviral immunity and in fact, IFNs exert their antiviral activities through the induction of antiviral proteins. The IFN-induced protein with tetratricopeptide repeats (*IFITs*) family is among hundreds of IFN-stimulated genes. This family contains a cluster of duplicated loci. Most mammals have *IFIT1*, *IFIT2*, *IFIT3* and *IFIT5*; however, bird, marsupial, frog and fish have only *IFIT5*. Regardless of species, *IFIT5* is always adjacent to *SLC16A12*. *IFIT* family genes are predominantly induced by type I and type III interferons and are regulated by the pattern recognition and the JAK-STAT signaling pathway. *IFIT* family proteins are involved in many processes in response to viral infection. However, some viruses can escape the antiviral functions of the *IFIT* family by suppressing *IFIT* family genes expression or methylation of 5' cap of viral molecules. In addition, the variants of *IFIT* family genes could significantly influence the outcome of hepatitis C virus (HCV) therapy. We believe that our current review provides a comprehensive picture for the community to understand the structure and function of *IFIT* family genes in response to pathogens in human, as well as in animals.

Key words: *IFIT* family, evolution, antiviral activities, regulation and signaling, therapy of infectious diseases.

Introduction

Interferons (IFNs) are a family of proteins secreted by host cells in response to various pathogens such as viruses, bacteria, fungi, or parasites, which trigger the protective defenses of the immune system [1]. There are three types of IFNs in host animals: type I (IFN-α, IFN-β and IFN-ω), type II (IFN-γ), and type III (IFN-λ1, IFN-λ2 and IFN-λ3). All IFNs are secreted ligands of specific cell surface receptors that elicit the expression of hundreds of interferon stimulated genes (ISGs) [2-3]. Among them, the interferon-induced protein with tetratricopeptide repeats (IFITs) family has been heavily studied. Basically, this family of proteins is characterized by multiple repeats of tetratricopeptide repeat helix-turn-helix motifs that mediate a variety of protein-protein interactions involved in translation initiation, virus replication, double-stranded RNA signaling, cell migration, and proliferation [4]. Here we review the family's evolutionary features, expression patterns, antivirus activities, and genetic variants. Understanding the structure and function of *IFIT* family genes will certainly help elucidate how the immune system combats pathogens,

thus improving therapy of infectious diseases in human, as well as in animals.

IFIT Family Genes and Evolution

Research has shown that the *IFIT* gene family is conserved in mammals, amphibians and fish, but does not exist in lower animals, like *Drosophila melanogaster* (fruit fly), *Caenorhabditis elegans* (nematode) and *Saccharomyces cerevisiae* (yeast), or in plants [5-6]. Based on the current reference genome assemblies, we collected data on the gene family in *Homo sapiens* (human), *Macaca mulatta* (rhesus monkey), *Callithrix jacchus* (common marmoset), *Pongo abelii* (sumatran orangutan), *Canis familiaris* (dog), *Sus scrofa* (pig), *Bos taurus* (cattle), *Equus caballus* (horse), *Nomascus leucogenys* (northern white-cheeked gibbon), *Mus musculus* (mouse), *Rattus norvegicus* (rat), *Monodelphis domestica* (gray short-tailed opossum), *Gallus gallus* (chicken), *Xenopus (Silurana) tropicalis* (western clawed frog) and *Danio rerio* (zebrafish). The first eight mammals have four members in the *IFIT* gene family: *IFIT1* (also known as *ISG56*), *IFIT2* (known as *ISG54*), *IFIT3* (known as *ISG60*), and *IFIT5* (known as *ISG58*) (Figure 1). However, *IFIT3* is absent in gibbons, while *IFIT5* does not exist in mice and rats. Opossums, chickens, frogs, and zebrafish possess *IFIT5* only. In addition to these four members, humans, marmosets, orangutans, dogs, gibbons, mice and rats have an *IFIT1*-like (*IFIT1L*) gene, while dogs and mice have an *IFIT3L* gene. Moreover, opossums, chickens, frogs, and zebrafish have multiple *IFIT5L* genes (Figure 1). Several *IFIT*-related pseudogenes were also identified in human (*IFIT6P*), orangutan (*IFIT1LP* and *IFIT2LP*), dog (*IFIT2LP* and *IFIT5LP*), pig (*IFIT3LP*), cattle, horse and gibbon (*IFIT2LP*), and frog and zebrafish (*IFIT5LP*), respectively. Phylogenetic relationships of *IFIT* family genes are complicated (Figure 2). In most cases, members 2, 3 and 5 are relatively close to each other, members 1 and 1L are clustered together, and *IFIT5L* genes are near one another. These data show that re-annotation of the gene family among different species is needed.

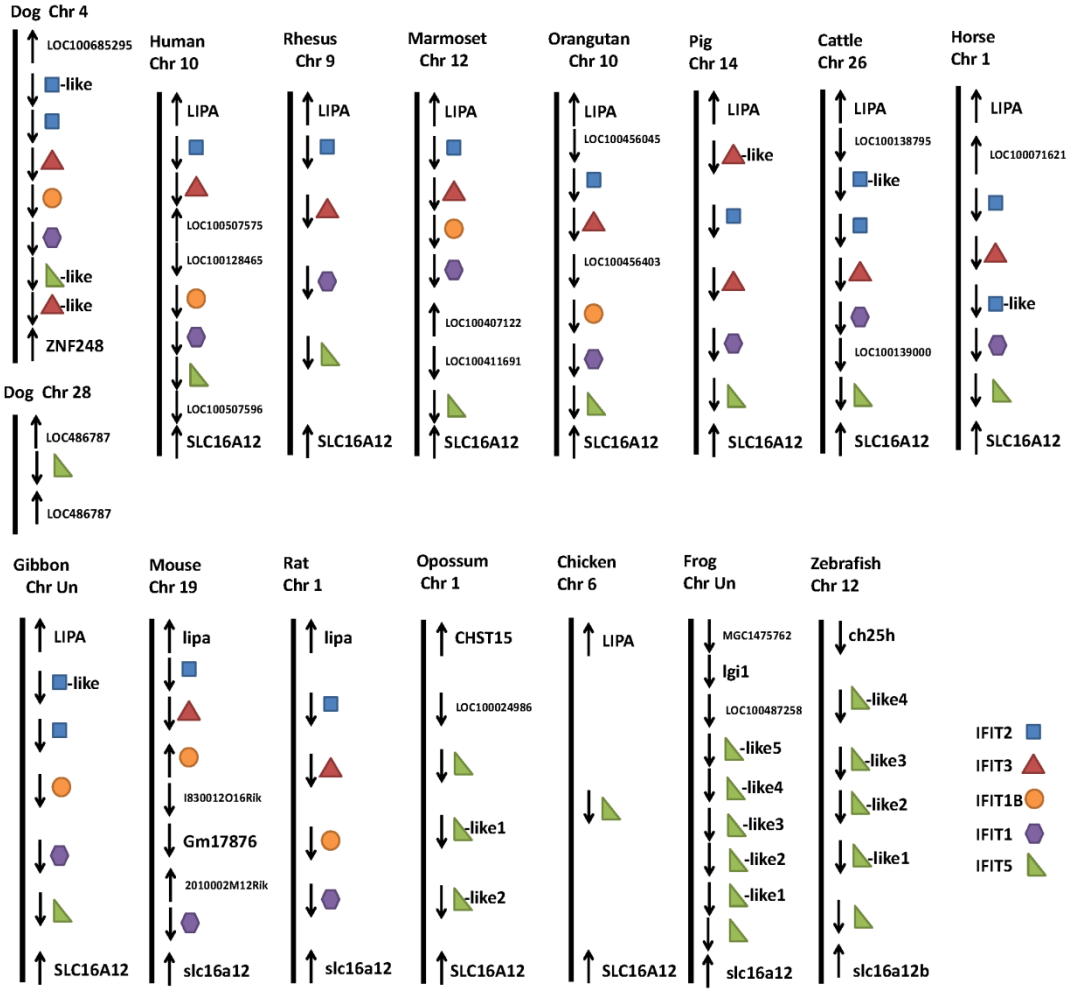

Figure 1. Genomic neighborhood surrounding the *IFIT* family duplicated genes. The relative locations and orientations of both *IFIT* family genes and their adjacent neighbor genes were collected from the NCBI database plus chromosome number if available.

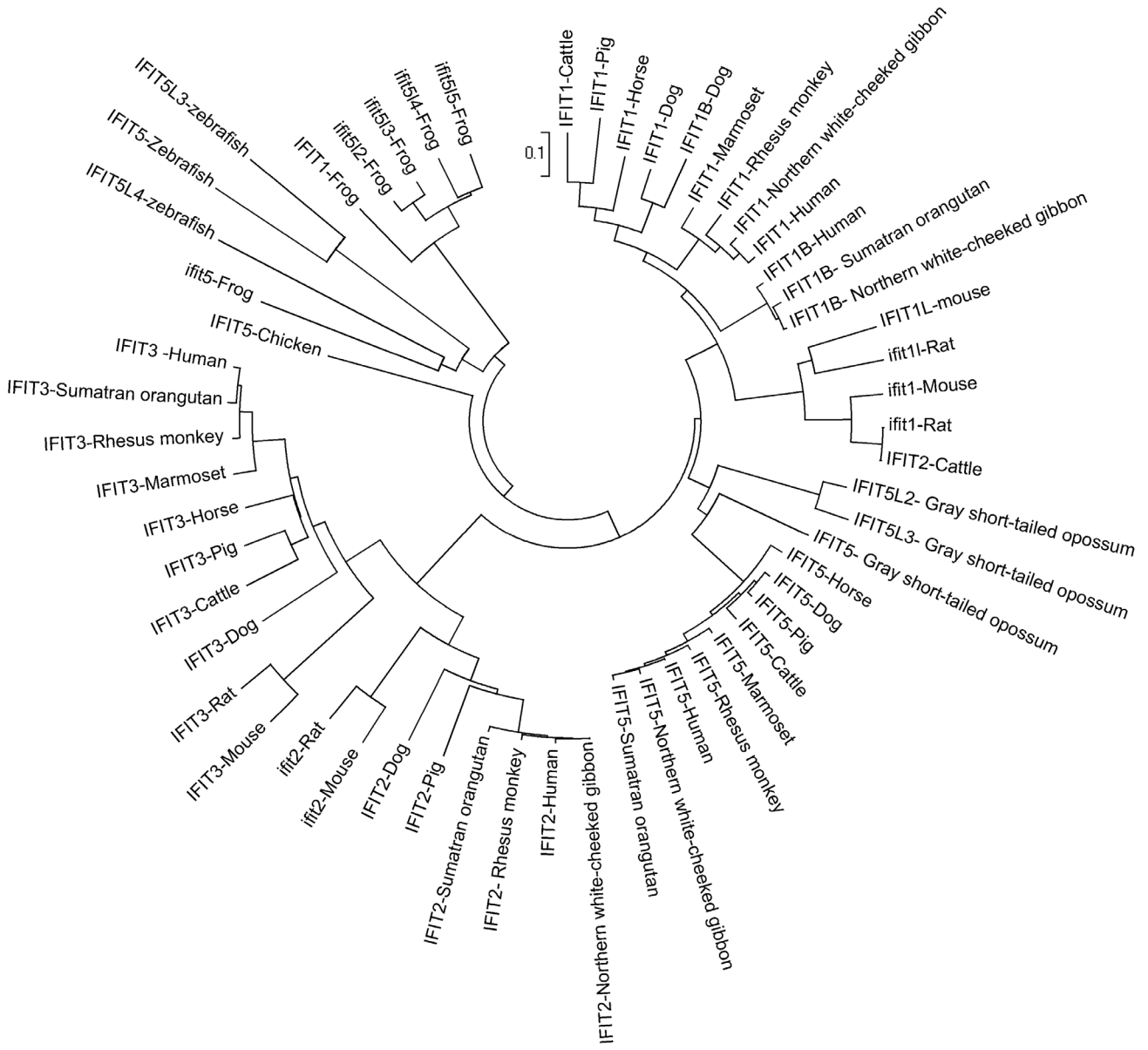

Figure 2. Phylogeny of IFIT family proteins. A neighbor-joining tree of IFIT family proteins was generated by MEGA4.0 [62].

The *IFIT* family is clustered on chromosomes 10 in human, 9 in rhesus, 12 in marmoset, 10 in orangutan, 14 in pig, 26 in cattle, 1 in horse, 19 in mouse, 1 in rat, 1 in opossum, 6 in chicken and 12 in zebrafish, but has not been placed on chromosomes in gibbon and frog. However, the *IFIT* family in the dog genome is split between two chromosomes: *IFIT1*, *IFIT2* and *IFIT3* on 4 and *IFIT5* on 28 (Figure 1). Among these fifteen species, only three species – dog, opossum and frog do not have the family confined in a region between *LIPA* (lipase A, lysosomal acid, cholesterol esterase) and *SLC16A12* (solute carrier family 16, member 12 (monocarboxylic acid transporter 12)) (Figure 1). However, *IFIT5* is always located adjacent to *SLC16A12,* regardless of species (Figure 1). Most of the *IFIT* family genes have two exons and contain two or three IFN-stimulated response elements (IRSE) in their promoter regions [7]. The IRSE are important cis-acting elements recognized by IFN-stimulated gene factor 3 (*ISGF3*) that are activated by IFN and various stimuli [8].

IFIT family expressions and cellular locations

Generally speaking, *IFIT* family genes are usually less abundantly expressed in the absence of stimuli. They are prominently induced by type I and type III interferons, especially IFN-α/β [9]. Various

pathogens, particularly viruses, induce *IFIT* family gene expression. Both DNA- and RNA- viruses efficiently elicit *IFIT* family genes transcription. Cytomegalovirus (CMV) is a DNA virus, which broadly infects human and animals. *IFIT2* was induced at 8 hours after infection with human CMV (HCMV)[10]. Adenovirus is a double-stranded linear DNA virus that causes upper respiratory infection in children. Zhao and colleagues [11] found that *IFIT1* and *IFIT2* were activated during the late stage of adenovirus type 12 infection in primary human fibroblasts. Other DNA viruses, like Simian virus 40 (SV40), a polyomavirus also stimulate *IFIT* family genes expression [12-13].

West Nile virus (WNV) is a positive-sense, single-stranded RNA virus with an extensive tropism that infects a broad number of species. In mouse, *Ifit1* and *Ifit2* are often induced after WNV infection [14]. Porcine reproductive and respiratory syndrome virus (PRRSV), an arterivirus that causes disease in all ages of swine, activates *IFIT1* and *IFIT3* expression in porcine alveolar macrophages (PAM), and *IFIT1* and *IFIT5* expression in lung [15-16]. Hantaviruses are negative-sense RNA viruses and include Hantaan virus (HTNV), Prospect Hill virus (PHV), Tula virus (TULV) and others. PHV and TULV infect human endothelial cells, resulting in strong induction of *IFIT3* expression [17]. The influenza A virus is a negative-sense, single-stranded RNA virus. The IFIT family proteins, IFIT1, IFIT2 and IFTI3 were up-regulated in human primary macrophages in response to influenza virus infection [18] and IFIT2 is strongly up-regulated in peripheral blood of pediatric patients during the acute stage of influenza infection [19]. The only *IFIT* family gene in birds, *IFIT5*, was significantly increased in duck lung at day 1 post-infection with highly pathogenic influenza A virus (VN1203) as compared with low pathogenic influenza A virus (BC500) [20]. Other RNA viruses, such as Japanese encephalitis virus (JEV), lymphocytic choriomeningitis virus (LCMV), and rabies viruses also induce *IFIT* family genes expression [14, 21-22].

Lipopolysaccharide (LPS) of bacteria is an important agent that stimulates *IFIT* family genes expression. *IFIT1*, *IFIT2*, *IFIT3* and *IFIT5* are transcribed when human moncytes are infected with wild-type *Neisseria meningitidis* compared with LPS-deficient *Neisseria meningitidis*. Stimulation of Raw246.7 macrophages with LPS also elicited *IFIT2* in a type I interferon dependent manner [23-24]. Chlamydia is another type of pathogen that activates *IFIT* gene family expression. During secondary infection of Chlamydia pneumonia in mouse mononuclear cells, *Ifit1* and *Ifit3* were up-regulated [25].

Protein functioning depends mainly on their subcellular locations. Generally speaking, IFIT family proteins function in the cytoplasm. IFIT1 is located in the cytosol. However, Li and co-workers found that IFIT1 interacted with mitochondrial membrane protein MAV1, indicating that IFIT1 is also located in mitochondria to regulate immune response [26]. Like IFIT1, IFIT3 is also located in the cytoplasm and mitochondria [27]. In addition to cytoplasm and mitochondria, IFIT2 also appears in microtubules. IFIT2 interacts with the cytoskeleton, which may play an important role in cell proliferation and microtubule dynamics [21]. IFIT5 is reported to reside in cytoplasm, but it does not interact with other IFIT family proteins [28].

Signaling associated with IFIT family member expression

IFIT family gene expression relies on pattern recognition and the JAK-STAT pathway. Pathogen-associated molecular patterns (PAMPs) are molecules associated with groups of pathogens including viruses, bacteria, fungi and others. Pattern recognition receptors (PRRs) recognize different PAMPs during pathogen infection and activate downstream signaling molecules [29]. As a result, Toll-like receptors (TLRs) signaling and RIG-like receptors (RLRs) signaling induce *IFIT* family gene expression [30]. TLR3 senses double-stranded RNA (dsRNA), TLR7 and TLR8 sense single-stranded RNA (ssRNA), and TLR9 recognizes CpG-DNA [31]. The TIR domain-containing adaptor inducing IFN-β (TRIF)-dependent signaling pathway or myeloid differentiation primary response gene (88) (MyD88)-dependent signaling pathway transfect the signal from the TLRs, which leads to the activation of IRF3 or IRF7 by phosphorylation. The activated IRF3 or IRF7 is then translocated to the nucleus, resulting in type I interferon gene expression (Figure 3) [32]. For example, *irf3*(-/-) mice lack expression of type I interferon and *IFIT* family genes in macrophages and cortical neurons during WNV infection [33]. In addition, secretory IFNs bind to IFN receptors at the cell surface, which then activate Janus kinase (JAK) and signal transducers and activators of transcription (STAT) pathways. The phosphorylated STAT1, STAT2, and IRF9 form the ISGF3 complex that translocates into the nucleus and binds to the ISRE elements in the promoter of *IFIT* family genes, thus stimulating *IFIT* family genes expression (Figure 3) [34]. RIG-I-like receptors (RLRs) are located in the cytoplasm and recognize dsRNA that originated from the genomic RNA of dsRNA viruses or is generated during replication of ssRNA viruses [35]. The adaptor

IFN-β-promoter stimulator 1 (IPS-1) located in mitochondria interacts with the caspase-recruitment domain (CARDs) of RLRs and triggers signaling cascades and enhances IFN expression, thus stimulating IFIT family gene expression though JAK-STAT signaling as a result of TLRs signaling (Figure 3) [36] .

Antivirus properties and immune regulation of IFIT family

IFIT family proteins are involved in many processes in response to viral infection, mainly by reducing virus replication. The IFIT family proteins contain a TPR (tetratricopeptide repeat) domain, a 34 amino acid motif folding in to a helix-turn-helix structure, which mediates protein interactions [4]. IFIT1 and IFIT2 are involved in a nonspecific antiviral program through their direct interactions with eIF3, which subsequently suppresses more than 60% of translation in cells and viruses during protein synthesis (Figure 4) [37-39]. The IFIT family, especially IFIT1 and IFIT3, restrict DNA and RNA virus replication, such as hepatitis B virus (HBV), human papillomavirus (HPV), hepatitis C virus (HCV), West Nile virus (WNV) and others [13, 17, 28, 40-41]. Knockdown of *IFIT1* though RNA interference in human hepatocytes enhanced HCV replication during infection [40]. Similar results were also observed in other *IFIT* family members during other viral infections [28]. Although, *IFIT* family genes commonly restrict virus replication through alternation of protein synthesis, more mechanisms need to be explored. An intriguing, newly found antiviral mechanism of *IFIT* family genes is the ability of IFIT family proteins to directly bind viral RNA. Viral RNA that carries 5'PPP-RNA is recognized by IFIT1, followed by sequestering with the IFIT complex that contains IFIT1, IFIT2 and IFIT3. IFIT5, which shares the highest sequence homology with IFIT1, is also associated with PPP-RNA, but has little interaction with IFIT2 and IFIT3 (Figure 4) [28]. These data provide evidence that the IFIT family members play an important role in killing invasive RNA. Working together with other ISGs, they are able to restrict virus replication. In addition, IFIT2 may limit replication of vesicular stomatitis virus (VSV) in brain. Virus titer was higher in *ifit2* (-/-) mice compared to wild-type mice during VSV infection. However, *ifit1* could not prevent VSV replication [42].

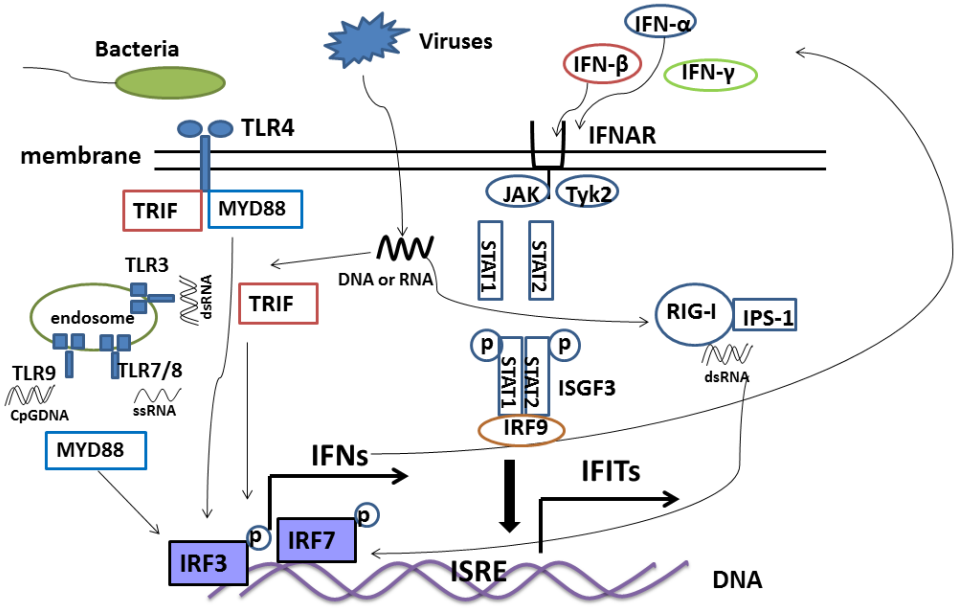

Figure 3. Signaling pathway of *IFIT* family genes. Toll-like receptors (TLRs) and RIG-like receptors (RLRs) are pattern recognition receptors (PRRs) families that recognize pathogen-associated molecular patterns (PAMPs) that trigger signaling. TLR3 and RIG-I sense dsRNA, while TLR4 senses LPS, TLR7/8 senses ssRNA and TLR9 senses CpG DNA. Adapter proteins MYD88, TRIF and ISP-1 are used by the receptor complex that activate IRF3 and IRF7 by phosphorylaton, which then bind the DNA to stimulate IFN expression. Secreted IFN binds the receptor IFNAR at the cell surface, followed by activation of STAT1 and STAT2. The phosphorylated STAT1, STAT2, and IRF9 form the ISGF3 complex, which is translocated into the nucleus, binds with the ISRE elements in the promoter of IFIT family genes, and thus stimulates IFIT family genes expression.

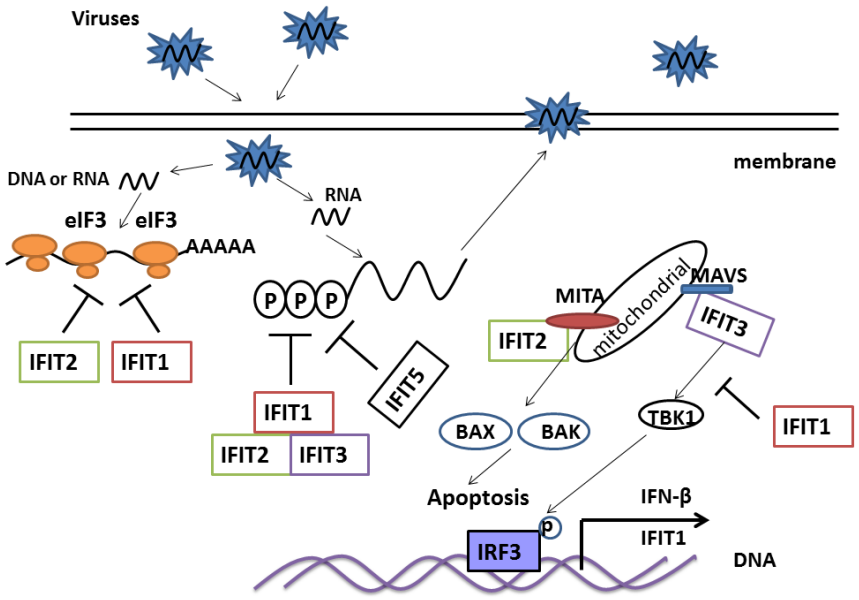

Figure 4. Antiviral and immune regulated function of IFIT family genes. IFIT1 and IFIT2 directly bind eIF3 and suppress transcription of virus genes. IFIT1, IFIT2 and IFIT3 form a complex in cytoplasm that recognizes and kills PPP-RNA. IFIT5 may also kill PPP-RNA directly. IFIT1 disrupts the interaction of MITA, MAVS and TBK1, which then negatively regulates the cellular antiviral response. IFIT2 interacts with MITA, and induces apoptosis via the mitochondrial pathway that is induced by the innate immune response. IFIT3 bridges TBK1 to MAVS in mitochondria, which synergizes the activation of IRF3 and NF-κB to activate the immune response.

Innate immunity is the first line of defense against invading pathogens. The *IFIT* family shows potent antiviral ability so it is conceivable that they also influence the innate immune response. IFIT1 negatively regulates cellular antiviral response by disrupting the interaction of the MITA (mediator of IRF3 activation), MAVS (mitochondrial antiviral signaling protein) and TBK1 (TANK-binding kinase 1), which transfer signaling from RLRs recognized pathogens. Over-expression of *IFIT1* could inhibit virus triggered activation of IFN-β, NF-κB and IRF3 (Figure 4) [26]. Furthermore, IFIT3, a new component of the MAVS complex located in mitochondria, could bridge TBK1 to MAVS on the mitochondrion which synergizes the activation of IRF3 and NF-κB (Figure 4) [27]. In addition, IFIT2 is also a MITA-associated protein, and induces apoptosis via the mitochondrial pathway that is induced by innate immune response. IFIT3 could block apoptosis by binding IFIT2 (Figure 4) [43].

Virus inference with host IFIT family members

Although the host immune response shows powerful antiviral capacity, viruses have evolved many processes to escape the host immune system, including inhibition of humoral response, interference with interferons and inhibition of cytokines and chemokines, for example [44]. When human hepatocytes were pretreated with IFN-α and then infected with HCV, IFN-induced *IFIT1* expression was inhibited [40]. Other researchers also confirmed that HCV infection blocks the ISGs or cytokine expression, resulting in persistent HCV infection [45]. Varicella-zoster virus (VZV) may down-regulate *IFIT1* and *IFIT2* mRNA expression through its immediate-early protein ORF61, which antagonizes the IFN-beta pathway [46]. The NSP1β (Nonstructural Protein 1β) of PRRSV inhibits *IFIT* family gene expression by blocking nuclear translocation of STAT1 [47]. The 42-residue C-terminal of the Tula virus Gn reduces *IFIT1* expression via unique interaction with TBK1 complex when TULV infects endothelial cells [17].

An interesting, newly identified strategy that viruses use to escape the antiviral activity of *IFIT* family genes is through 2′-*O* methylation of the 5' cap of viral RNA [48]. For example, C57BL/6 mice that were infected with the WNV mutant (WNV-E218A) strain that lacks 2′-*O* MTase showed 0% mortality compared with 40% mortality when mice were infected with wild-type WNV. Studies have shown that IFIT1 and IFIT2 play an important role in restricting infection of WNV lacking 2'-O methylation. In fact, transgenic expression of IFIT1 and IFIT2 in 3T3 cells strongly blocked the viruses which lacked 2'-O methylation [48]. Methylation in the 5′ cap structure of

RNA is considered as an essential process for RNA translation and stability [49], therefore, 2′-O methylation of the viral genome that imitates host mRNA greatly benefits its life cycle and survival.

Genetic variants of IFIT family genes

Variants in ISGs and interferon pathway genes (IPGs) are usually associated with many immune traits, such as blood parameters, antibody titer and total white blood cells (WBC) [50]. Immune traits provide measurements of individual immune capacity. No doubt, variants in ISGs and IPGs could also influence host response to various pathogens. Recent reports showed that polymorphisms in IPGs and ISGs influence the effect of therapy against HCV infection. A tag SNP (rs2278034) in intron 11 of *ACK1* was associated with IFN therapy outcome in patients infected with HCV. SNP (rs8099917) in *IL-28* influences its expression in patients, which interferes with drug therapy against HCV [51-52]. On the other hand, *IFIT* family genes are important ISGs, which play important roles in resisting HCV infection. The polymorphism (rs3004479) in the *IFIT1* gene is strongly associated with sustained virological response (SVR) in HCV-1 patients [53]. SVR is a clinical index measuring detectable HCV in patient blood six months after treatment with type I interferon and ribavirin [54]. Patients with the A/A genotype have higher SVR than those with the G/G genotype ($P<0.05$), and achieve a better therapy outcome [53].

Certainly genetic polymorphisms can be used to improve innate resistance to virus infection in livestock species. Infectious disease often causes economic loss in animal production. In 2006, an outbreak of highly pathogenic porcine reproductive and respiratory syndrome (HP-PRRS) affected more than 2 million pigs and decimated the Chinese swine industry [55]. Millions of chickens are slaughtered or die every year because of Marek's disease (MD), Avian influenza (AI) and other infectious diseases [56-57]. Genetic selection for disease resistance may improve the ability of animals to respond to disease challenge [58]. An increasing number of SNPs in innate immune response related-genes, such as TLRs genes, are associated with infectious disease susceptibility [59-61]. *IFIT* family genes contain many variants (Table 1). So this family should have great potential to be probed for improved resistance to infectious diseases.

Summary and perspectives

Innate immunity is the first line of defense against invading pathogens. As IFIT family genes are involved in regulating innate immune responses, they are important targets with potent antiviral activities. They could restrict various viruses, stimulate apoptosis, and regulate immune responses. Variants in *IFIT* family genes could influence therapy for infectious diseases. However, many questions remain. What stimulated the members of this clustered gene family to be duplicated during evolution? How have the genomic structures of duplicated genes diverged and how have structural divergences among the family members contributed to functional diversities associated with innate resistance to virus infection? These questions need to be explored further. We believe that additional understanding of the molecular and functional diversities of the *IFIT* members is imperative for developing more effective vaccines and inventing novel intervention strategies to combat viral outbreaks in both humans and animals.

Table 1. Numbers of SNPs in the IFITs family genes currently available in NCBI dbSNP Database for five species

Species	IFIT1	IFIT2	IFIT3	IFIT5
Human	267	151	351	210
Mouse	170	469	87	No
Dog	7	13	2	77
Cattle	16	44	89	38
Pig	2	2	4	2

Competing Interests

The authors have declared that no competing interest exists.

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