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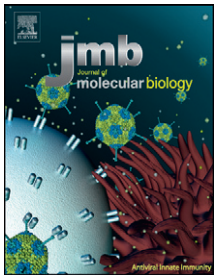

IFITMs Restrict the Replication of Multiple Pathogenic Viruses

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Abstract

The interferon-inducible transmembrane protein (IFITM) family inhibits a growing number of pathogenic viruses, among them influenza A virus, dengue virus, hepatitis C virus, and Ebola virus. This review covers recent developments in our understanding of the IFITM's molecular determinants, potential mechanisms of action, and impact on pathogenesis.

Introduction

To replicate, viruses must gain access to the resource-rich cytosol that lies beyond the cell's plasma membrane. Enveloped viruses breach this barrier by using specialized fusion proteins. Three major classes of viral fusion proteins exist, all similarly containing a fusion peptide that inserts into the cytolemma, thereby anchoring the two membranes side by side [1]. Once transfixed, the juxtaposed membranes are forcefully distorted as the viral envelope protein undergoes a profound conformational change; the two outer leaflets are welded together to form a hemifusion intermediate that rapidly converts into a fusion pore through which the viral contents enter the cytosol. Any means by which the host can block fusion would confer an advantage by preventing both the emergence of an escalating number of progeny viruses and the deployment of viral countermeasures.

Restriction factors are a diverse group of host proteins that are united in the common goal of antagonizing viral replication. Multiple mechanisms of restriction have evolved, with some factors having activity against one virus and others acting broadly across several viral families. The expression of many restriction factors is transcriptionally controlled by the antiviral cytokine, interferon (IFN). Among such IFN-stimulated genes, the related restriction factors, IFN-inducible transmembrane protein (IFITM)1, 2, and 3, inhibit the replication of multiple pathogenic viruses, including influenza A virus (IAV) and influenza B virus, West Nile virus, dengue virus (DENV), severe acute respiratory syndrome coronavirus (SARS CoV), hepatitis C virus (HCV) and the filoviruses, Ebola virus (EBOV) and Marburg virus (MARV; Table 1) [2,3,15]. The antiviral properties of the IFITMs were discovered using orthologous functional genomic strategies [2,8,13,32,41]. Early work showed that the IFITMs resided on the cytolemmal and endosomal membranes and specifically blocked viral pseudoparticles bearing the receptors of restricted viruses, demonstrating that they acted during an early envelope-dependent portion of the viral life cycle [2]. Further studies revealed that the IFITMs block viral replication by preventing viral-host membrane fusion subsequent to viral binding and endocytosis [3,4]. Imaging studies of these events revealed that the invading viruses were trapped by the IFITMs, leading to their ultimate destruction in the host cell's lysosomes and autolysosomes, both of which are expanded with IFITM expression (Fig. 1a and b) [4]. A range of viruses are restricted in this manner, including ones that exploit each of the host cell's endocytic pathways [42]. The kinetics of this entrapment are rapid, with viral entry usually occurring over a 5- to 30-min time span, requiring the IFITMs to already be in place or to rapidly mobilize to meet such threats.

Table 1. Viruses inhibited by IFITM proteins

Virus	Family	Host receptor	Endocytic pathway	Where the virus enters the host cell	pH Requirement[a]
IAV	Orthomyxovirus	α2,6-linked sialic acid (human)	Clathrin-mediated endocytosis, macropinocytosis	RAB7+ late endosomes	pH 5.5
DENV	Flavivirus	CD14	Clathrin-mediated endocytosis	RAB7+ late endosomes	pH 5.5
West Nile virus	Flavivirus	Unknown	Clathrin-mediated endocytosis	RAB7+ late endosomes	pH 5.5
Yellow fever virus	Flavivirus	Unknown	Clathrin-mediated endocytosis	RAB7+ late endosomes	pH 5.5
Omsk hemorrhagic fever virus	Flavivirus	Unknown	Clathrin-mediated endocytosis	RAB7+ late endosomes	pH 5.5
HCV	Flavivirus	CD81, Occludin, SB-RI, Claudin-1	Clathrin-mediated endocytosis	RAB5+ early endosomes	pH 6.5
SARS CoV	Coronavirus	Angiotensin-converting enzyme 2 (ACE2)	Clathrin-mediated endocytosis	Lysosomes (pH-dependent cleavage: cathepsins B and L)	pH 4.5
MARV	Filovirus	Neimann-Pick C1 (NPC1), T-cell immunoglobulin mucin domain-1 (TIM-1), C-type lectins	Macropinocytosis	NPC1+ lysosomes (pH-dependent cleavage: cathepsins B and L)	pH 4.5
EBOV	Filovirus	Neimann-Pick C1 (NPC-1), T-cell immunoglobulin mucin domain-1 (TIM-1), C-type lectins	Macropinocytosis	NPC1+ lysosomes (pH-dependent cleavage: cathepsins B and L)	pH 4.5
Rift Valley fever virus	Bunyavirus	Unknown	Dynamin II-dependent caveolin-1-mediated endocytosis	RAB7+ late endosomes	pH 5.5
La Crosse virus	Bunyavirus	Unknown	Clathrin-mediated endocytosis	RAB7+ late endosomes	pH 5.5
Andes virus	Bunyavirus	Unknown	Unknown	RAB7+ late endosomes	pH 5.5
Hantaan virus	Bunyavirus	Unknown	Clathrin-dependent endocytosis	RAB7+ late endosomes	pH 5.5
Vesicular stomatitis Indiana virus	Rhabdovirus	LDL receptor	Clathrin-mediated endocytosis	RAB5+ early endosomes	pH 6.5
Scophthalmus maximus rhabdovirus	Rhabdovirus	Unknown	Unknown	Unknown	Stable infectivity between pH 4 and pH 9
HIV-1	Lentivirus	CD4, CXCR4, or CCR5	Unknown	Cell surface, early endosomes	pH Independent
JSRV	Betaretrovirus	Hyaluronidase 2 (Hyal2)	Dynamin-associated endocytosis	RAB5+ early endosomes	pH 6.5
Reovirus	Reovirus	Proteinaceous receptor junction adhesion molecule A (JAM-A)	Clathrin-mediated endocytosis	RAB7+/RAB9+ late endosomes	pH 5.5
Rana grylio virus	Iridoviridae	Unknown	Caveolin-mediated endocytosis	Unknown	pH-dependent

[a] pH values provided have been standardized based on reports of the values found for the relevant endosomal compartments in the primary literature: early endosome, pH 6.5; late endosome, pH 5.5; lysosome, pH 4.5.

Table 1 (*continued*)

Virus	Cathepsin processing	IFITM specificity	References
IAV	No	IFITM3 > IFITM2 > IFITM1	[2–7]
DENV	No	K562: IFITM3/IFITM1 > IFITM2	[2,8–12]
West Nile virus	No	IFITM3 > IFITM1 > IFITM2	[2,8,11,13,14]
Yellow fever virus	No	IFITM3 > IFITM1 > IFITM2	[2,11,13,14]
Omsk hemorrhagic fever virus	No	IFITM3 > IFITM1 > IFITM2	[2,11,14]
HCV	No	IFITM1, not IFITM3	[2,13–16]
SARS CoV	Yes	A549: IFITM3/IFITM2 ≥ IFITM1 Vero E6: IFITM1 > IFITM2 > IFITM3	[3,17]
MARV	Yes	A549: IFITM3 > IFITM1 > IFITM2 Vero E6: IFITM1 > IFITM2/IFITM3 HUVEC: IFITM3 > IFITM1 > IFITM2 293T: IFITM3 > IFITM2 > IFITM1	[3,18]
EBOV	Yes	A549: IFITM1/IFITM3 > IFITM2 Vero E6: IFITM1 > IFITM2/IFITM3 HUVEC: IFITM1/IFITM3 > IFITM2 293T: IFITM3 > IFITM1/IFITM2	[3,18–20]
Rift Valley fever virus	No	IFITM2/IFITM3	[21,22]
La Crosse virus	No	IFITM1/IFITM2/IFITM3	[21,23,24]
Andes virus	No	IFITM1/IFITM2/IFITM3	[21,25]
Hantaan virus	No	IFITM1/IFITM2/IFITM3	[21,26,27]
Vesicular stomatitis Indiana virus	No	IFITM3 > IFITM1 > IFITM2	[2,5,21,22,28,29]
Scophthalmus maximus rhabdovirus	Unknown	IFITM1 (*Paralichthys olivaceus*)	[30,31]
HIV-1	No	SUPT1: IFITM1 > IFITM3/IFITM2, IFITM3 does not block HIV-1 from infecting TZM-bl HeLa cells	[13,32–35]
JSRV	No	HTX: IFITM1 > IFITM2 > IFITM3 293: IFITM1 > IFITM3 > IFITM2 Cos7: IFITM1 > IFITM3	[5,36,37]
Reovirus	No	IFITM3	[38,39]
Rana grylio virus	Unknown	IFITM1 (*Paralichthys olivaceus*)	[30,40]

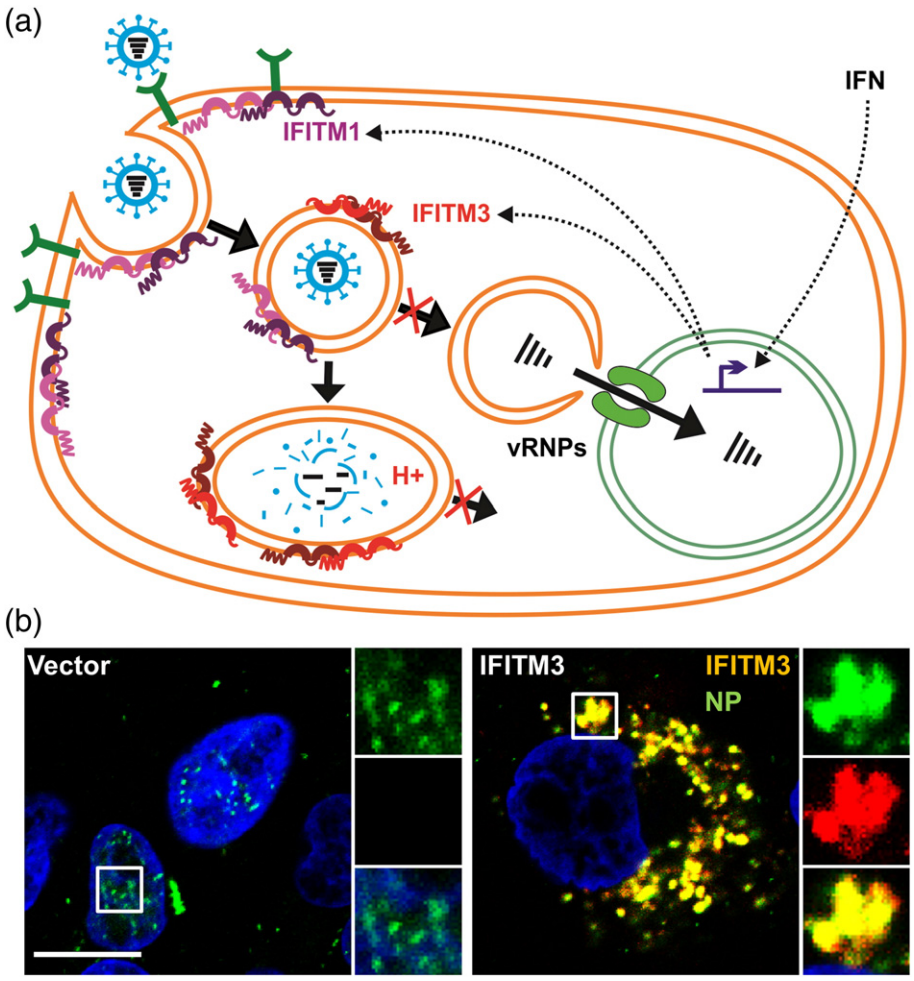

Fig. 1. (a) Model of IFITM3-mediated restriction of viral replication. IAVs (blue with genomes in black) first interact with a cell surface receptor (green) and then enter the cell through endocytosis. IFITM1 (purple, with light and dark hues representing two distinct IFITM1 molecules), located in the cytosolic leaflet of the plasma membrane and endosomal membrane, prevents the fusion of viruses that enter in the early endosomes (i.e., HCV) as well as viruses fusing later in the endosomal pathway (i.e., IAV). IFITM3 (red, with dark and light hues representing two distinct IFITM3 molecules) resides in the late endosomal membranes and lysosomal membranes, and prevents viral fusion of viruses that enter from those compartments. Because of the block to fusion, there is no release of viral RNPs (vRNPs) and therefore no viral replication. As a result of IFITM-mediated restriction, the trapped viral particles are destroyed in the lysosomes and/or autolysosomes. IFITM3 is present at baseline; however, IFN up-regulates its levels and induces the expression of IFITM1 (broken lines). (b) IFITM3 prevents IAV cytosolic entry and nuclear entry. Confocal images of Mardin Darby canine kidney cells stably transduced with the empty retroviral vector, pQCXIP (Vector, Clontech), or one expressing IFITM3, that were infected with IAV [A/Puerto Rico/8/1934 (H1N1) (PR8, Charles River Labs)] for 90 min. The cells were then washed, fixed, permeabilized, and immunostained for IAV nucleoprotein (NP, green), IFITM3 (red), or nuclear DNA (blue) [4]. In the vector cells, the IAV NP can be seen in the host cell nucleus (left panel). In contrast, in the IFITM3 cells, the virus is prevented from entering the cytosol and instead the NP is seen sequestered in the IFITM3-positive endosomal compartments. The scale bar represents 10 μm.

Consistent with an early role in intrinsic immunity, the IFITM1, 2, and 3 proteins are ubiquitously expressed, with IFITM2 and IFITM3 present at baseline in most primary and transformed cells (Tables 2 and 3). In contrast, IFITM1's basal expression is considerably less. The levels of these three IFITMs are increased by IFN-α or IFN-γ. Remarkably, the depletion of IFITM3 alone results in the loss of 50–80% of the *in vitro* anti-IAV actions of IFN [2,61]. Furthermore, mice null for only Ifitm3 are more susceptible to IAV infection, testifying to the importance of IFITM-mediated restriction *in vivo* [65,101]. In sum, these data suggest that the IFITMs may prevent or ameliorate multiple viral illnesses. Indeed, such is the case for influenza infection, where a human allele of IFITM3, rs12252-C, is associated with worse influenza

infections, suggesting that the IFITM3 status of a population may influence the course of seasonal influenza epidemics and pandemics [65,66].

Recent studies regarding the IFITMs have focused on their structure–function as well as their potential mechanism of action. In addition, several efforts have reported new families of IFITM-sensitive viruses. Herein, we discuss these results together with previous work and compare and contrast the various models proposed to explain how the IFITMs protect our cells.

The IFITM and CD225 Families

In addition to IFITM3, four more members of the IFITM family are present in both man (IFITM1, 2, 5, and 10; Fig. 2a and Table 3) and mouse (Ifitm1, 2, 5, and 6). The IFITMs each contain two hydrophobic membrane-associated domains separated by a conserved intracellular loop (CIL, Fig. 2a). The IFITM family belongs to a larger family of membrane-associated proteins, the CD225/pfam04505 protein superfamily, with greater than 300 members sharing homology across their first membrane-associated domains and CILs.[†] Interestingly, while IFITM5 has been shown to prevent infection by multiple viruses, it also is restricted in its expression to osteoblasts, where it plays a role in bone formation *in vitro* and *in vivo* [69,102]. Consistent with these data, a variant allele of IFITM5 is associated with a human brittle bone disease, osteogenesis imperfecta type V [61,87]. Remarkably, the protein encoded by this rare IFITM5 allele possesses an additional five amino acids at its N-terminus; this is in keeping with our unpublished data showing the IFITMs do not function in a wild-type manner when epitope tagged at their N-termini.

Additional human CD225 family members include PRRT1, PRRT2, TMEM91, TMEM233, TUSC5, SYNDIG1, and SYNDIG1L, with little if anything known about the functions of these proteins (Fig. 3a and Table 3). However, PRRT2, which is expressed in the nervous system, has received considerable attention for its genetic association with multiple movement disorder syndromes, many of which arise in the setting of its haploinsufficiency [87–89]. Therefore, among the 12 CD225 family members present in humans, there are currently three proteins with human disease associations: IFITM3, PRRT2, and IFITM5 (Table 3). Many additional CD225 proteins are found among prokaryotes, including several plant pathogens, suggesting that the CD225 domain confers a selective advantage across kingdoms. Interestingly, while both fish and amphibians express CD225 family members, none have been found in plants, fungi, insects, or worms, leading to the fascinating hypothesis that a gene encoding a prokaryotic CD225 family member may have been transferred to an ancestral metazoan [103].

Membrane Topology and Cellular Localization

Two hydrophobic domains are separated by a CIL in each of the IFITMs. Our appreciation of whether these hydrophobic domains are transmembrane or intramembrane continues to evolve over time [42,104]. Initial studies suggested that IFITM3 possessed two transmembrane domains predicated on the extracellular accessibility of epitopes located on either the N- or C-terminus [2]. However, mass spectrometry (MS) analyses by several groups (Table 4; Ref. [104]; PhosphoSite) have detected prevalent ubiquitinylation of IFITM3's lysine 24, which could occur only if the N-terminal domain (NTD) was cytosolic (Table 4; Ref. [104]). Similarly, a tyrosine in the NTD of IFITM3, Y20, was also shown to undergo phosphorylation a clathrin-mediated endocytosis motif (see below) [33]. In support of these latter results, large-scale MS studies have also reported detecting Y20-P, in addition to several other posttranslational modifications occurring in the respective NTDs of the other human CD225 proteins. For example, PRRT2's S239 has been reported to undergo phosphorylation by nine groups at PhosphoSite Plus. Furthermore, an engineered IFITM3 possessing both an N-terminal myristoylation site and a C-terminal prenylation site was modified by these cytosolic-resident enzymes and restricted IAV [104]. Collectively, these data argue for both N- and C-termini residing intracellularly, similar to the reticulon and caveolin proteins [104,110], with both hydrophobic regions being intramembranous (IM1 and IM2, Fig. 2b). However, the strongest data exists for the N-terminus' orientation. We note that IFITMs residing in the cytosolic leaflet of the membrane would shield it both from neutralization by invading viruses and from degradation by lysosomal enzymes. An intramembranous topology also has potential implications for altering the membrane's biophysical properties, a point discussed below. Of importance, this topology remains controversial, and to reflect that, we refer the reader to a recent review that also presents the alternatively proposed transmembrane topology in graphic form [42].

Endogenous IFITM1 is predominantly located in the plasma membrane and in early endosomes [3,4], where it resides in lipid rafts and interacts with the cell surface proteins CD19 and CD81, the latter being a co-receptor for HCV [111–113]. In contrast, the majority of endogenous IFITM2 and 3 are present in late endosomes, lysosomes, and autolysosomes, colocalizing with RAB7, CD63, and LAMP1 [3,4,109]. Overexpression of IFITM1, 2, or 3 results in the exogenous proteins localizing to a highly acidified and expanded late endosomal and lysosomal compartment [3,4]. However, even when overexpressed, a substantial amount of IFITM1 can still be detected near the cell surface [3,15,61]. We

Table 2. Viruses not inhibited by IFITM proteins

Virus	Family	Host receptor	Endocytic pathway	Where the virus enters the host cell	pH Requirement	Cathepsin processing	IFITM specificity	References
Lymphocytic choriomeningitis virus	Arenavirus	Dystroglycan (DG)	Clathrin independent, caveolin independent, dynamin independent, Potentially Rab5/Rab7 independent	Late Endosome Lysosome	pH 4.5	Unknown	Immune	[2,43–46,50,124]
Lassa virus	Arenavirus	Preferred: dystroglycan(DG); potential: DC-SIGN, LSECtin, Tyro3/Axl/Mer (TAM)	Clathrin independent, caveolin independent, dynamin independent, Potentially Rab5/Rab7 independent	Late Endosome Lysosome	pH 4.5	Unknown	Immune	[2,44–46,50,124]
Machupo virus	Arenavirus	Transferrin receptor 1 (TfR1)	Clathrin-mediated endocytosis	RAB7+ late endosomes after acidic pH induced dissociation of GP1 and GP2	pH 5.5	No	Immune	[2,43,45,47,124]
Junin virus	Arenavirus	Unknown	Clathrin-mediated endocytosis	RAB7+ late endosomes after acidic pH induced dissociation of GP1 and GP2	pH 5.5	No	Immune	[48–50,124]
MLV	Gammaretrovirus	Murine cationic amino acid transporter-1 (mCAT-1)	Clathrin independent	Cell surface	None	No	Immune	[2,51–53]
SeV	Paramyxovirus	Sialic acid-containing ganglioside receptors (SA-R); alternate: asialoglycoprotein receptor (ASGP-R)	Clathrin independent	Cell surface	None	No	Immune	[54–57]
CCHFV	Bunyavirus	Nucleolin	Clathrin-mediated endocytosis	RAB5+ early endosomes	pH 6.5	No	Immune	[21,58–60]

have observed that the overexpression of epitope-tagged IFITMs can produce partial mislocalization and diminution of their antiviral function. For example, epitope-tagged IFITM1 appears more in the late endosomes and lysosomes than the endogenous protein. As noted, in our experience, N-terminal epitope tags alter the intracellular localization of the IFITMs more than C-terminal tags. Moreover, the addition of green fluorescent protein or *discosoma* species red protein to either terminus of IFITM3 results in chimeric proteins that do not restrict viral replication and are retained in the cellular interior (our unpublished data). The molecular determinants underlying IFITM cellular localization are discussed in Structure and Function.

Specificity of Action

IFITMs inhibit the entry of a number of viruses, with enveloped RNA viruses reported most frequently (Table 1). Remarkably, the IFITMs block the entry of viruses from each of the three classes of viral fusion proteins. Furthermore, susceptible viruses are prevented from entering via the cell surface, the early and late endosomes, as well from the lysosome. While overlap exists among which IFITMs inhibit which viruses, some specificity is apparent, with IFITM1 better preventing infection by early endosomal-entering viruses and IFITM3 exerting more resistance to viruses that enter in the late endosomes or lysosomes, including IAV, DENV, and the *Bunyaviridae*, including Rift Valley fever virus (RVFV). These late-entering viruses share common features including their dependence on greater endosomal acidification ($pH < 6$) and the actions of RAB7, a host protein required for late endosomal trafficking and acidification [114]. IFITM2 behaves similarly to IFITM3 in terms of viral specificity, albeit with weaker effect, and so it will not be the focus of additional comment [2].

IFITM3 is less proficient than IFITM1 at inhibiting viruses that enter at the cell surface or in the early RAB5+ endosomes ($pH > 6$). For example, IFITM1 prevents human immunodeficiency virus type 1 (HIV-1) entry in both T cell lines and HeLa cells [13,32]. In contrast, we saw no effect on HIV-1 when IFITM3 was overexpressed in HeLa cells (TZM-bl cell line, National Institutes of Health AIDS Reagent Resource) and only a twofold effect with its overexpression in Jurkat T cells (our unpublished data; Ref. [2]), suggesting that it plays a minor role in regulating HIV-1 entry. An additional example is IFITM3's modest restriction of vesicular stomatitis virus-g protein-mediated entry, which is RAB5 dependent and requires a pH of 6.5 or less to fuse. IFITM1 also blocks HCV, a hepacivirus that enters in RAB5+ endosomes with a pH requirement of 6.5 [15]. Our previous work overexpressing IFITM3 in the HCV JFH1-permissive cell line, Huh7.5.1, showed no effect on HCV infection [2]. Similarly, IFITM1, but not IFITM3, halted infection by pseudoparticles bearing the Jaagsiekte sheep retrovirus (JSRV) envelope, which also fuses in the RAB5+ early endosomes at pH 6.3 [5]. Furthermore, although bunyaviruses express a similar glycoprotein (GP) that mediates fusion, they differed in their respective susceptibilities to IFITM3 [Lacrosse virus > RVFV > Andes virus > Hantaan virus > Crimean Congo hemorrhagic fever virus (CCHFV)] [21]. RVFV was only restricted by IFITM3, and CCHFV showed no inhibition by IFITM1, 2, or 3. Interestingly, IFITM3 was equally as effective in blocking the same virus from infecting different cell types, while IFITM1's efficacy varied more across cell lines; this suggests that IFITM1's actions were cell-type specific (Table 1). The difference in localization may provide one explanation as to why the viral specificities of IFITM1 and 3 differ, as they may preferentially inhibit viruses that enter where they are located. However, an exception to this rule is IFITM1s outperforming IFITM3 in inhibiting the very late-entering viruses, SARS CoV, EBOV, and MARV [3]. In addition, chimeric IFITM1 proteins containing the NTD of IFITM3 are located similarly to wild-type IFITM3 but do not curtail IAV as potently, suggesting that location alone may not fully explain these observations.

The list of IFITM-resistant viruses is short by comparison, although a bias against reporting negative data may be contributory (Table 2). Both the Moloney leukemia virus (MLV) and Sendai virus (SeV) envelopes fuse at the cell surface in a pH-independent manner and both are immune to the IFITMs [2,54]. Among the reported pH-independent viruses that fuse at the plasmalemma, only HIV-1 is blocked by IFITM1, making this perhaps the best site to avoid IFITM-mediated restriction. The largest enrichment of IFITM-resistant viral envelopes occurs among the arenaviruses, including both the old world (Lassa virus, lymphocytic choriomeningitis virus) and new world (Machupo, Junin) classes. Due to the pathogenicity of these viruses, this work has been done almost exclusively using pseudoparticles bearing the viral GP receptors [2,3,21]. To date, the arenaviruses and the bunyavirus CCHFV are the only late endosomal-entering viruses immune to IFITM3. Intriguingly, the only attribute shared between the two classes of arenavirus pseudoparticles is the GP spike because the old world arena viruses enter in a clathrin-independent manner after binding to the α-dystroglycan receptor, while the new world viruses bind to the transferrin receptor and enter the host cell via clathrin-mediated endocytosis [115].

Structure and Function

Efforts to elucidate the structure and function of the IFITMs have focused on IFITM3. For brevity, we now highlight a few of these insights (Fig. 2).

Table 3. Human CD225 protein superfamily members

Gene name	Entrez gene ID	Function	Cellular expression pattern
IFITM1	8519	Viral restriction; cell adhesion; tumor suppression	Cell surface, early endosomes > late endosomes
IFITM2	10581	Viral restriction; cell adhesion; tumor suppression	Late endosomes and lysosomes
IFITM3	10410	Viral restriction; cell adhesion; tumor suppression	Late endosomes and lysosomes
IFITM5	387733	Bone mineralization; regulates association of CD9 with FK506 binding protein (FKBP11)–CD81–prostaglandin F2 receptor negative regulator (FPRP) complex	Cell surface, most intense membrane localization at cell-to-cell junctions (HEK293 cells overexpressing the mouse homolog)
IFITM10	402778	Unknown	Unknown
PRRT1	80863	Interacts with AMPA receptors; oncogenesis	Unknown
PRRT2	112476	Unknown; truncating mutations cause of paroxysmal kinesigenic dystonia (PKD) and infantile convulsions with choreoathetosis (ICCA) syndrome	Unknown
TUSC5	286753	Responsive to insulin, glucose, glucocorticoids and/r PPARγ agonists; potential role in fat cell physiology; down-regulated in breast adenocarcinoma	Unknown
TMEM91	641649	Unknown	Unknown
TMEM233	387890	Unknown	Unknown
SYNDIG1	79953	Regulates synaptic AMPAR content; regulates AMPAR- and NMDAR-mediated transmission; may play a role in regulating synaptogenesis	Unknown
SYNDIG1L	646658	Unknown; possible role in the pathogenesis of Huntington disease; suggested role in striatal function	*cis*-Golgi (mouse protein fused to yellow fluorescence protein in Chinese ovary cells and HeLa cells)

IFITM3's NTD and Y20: The N-termini of IFITM2 and 3 share strong homology across their first 21 amino acids, a region absent in IFITM1 (Fig. 2). Mutation of a single tyrosine, Y20, within this region produces a 50% or greater loss in restriction, coincident with the mutant isoform's mislocalization to the cell periphery [33,61]. This work demonstrates that Y20 is required for the proper trafficking of IFITM3 to the late endosomes and lysosomes and thus is a major functional determinant within this IFITM2/3-specific portion of the NTD. Moreover, Y20 appears to be a key component of the amino acid cluster, YXXϕ, which is similar to many bona fide clathrin-mediated endocytosis motifs (CMEMs) [6,33]. It follows that the lack of this CMEM within IFITM1 contributes to its differential localization, given that both IFITM1 and 3 are comparably palmitoylated on either C72 (IFITM3) or C50 (IFITM1, see section below) [109]. The localization of IFITM1/3 chimeras is also strongly influenced by their respective NTDs [61].

IFITM3's IM1 and IFITM complexes: While searching for proteins that interact with IFITM3 using affinity purification coupled with MS, it was noted that the IFITMs formed homo- and heteromeric complexes [61]. These associations persisted after high-speed ultracentrifugation, suggesting that they were direct in nature. Alanine scanning (AS) mutagenesis identified two redundant phenylalanine residues in IFITM3's IM1, F75 and F78, which were needed for both complex formation and restriction. The existence of IFITM multimers whose disruption coincides with decreased restriction and whose formation is dependent on residues within IM1 suggests that such interactions may alter the properties of the host cell membrane.

Cysteine palmitoylation: To prevent viral fusion, the IFITMs must traffic to vulnerable regions. As

Table 3 (*continued*)

Tissue expression pattern	Human genetic determinants	References
Ubiquitous	Unknown	[2,61–63]
Ubiquitous	Unknown	[61,63,64]
Ubiquitous	rs12252-C; rs3888188 Increase in IAV disease severity	[2,33,61, 63,65–68]
Bone; localized to mineralizing nodules (WT protein expressed in rat osteoblast cultures)	c.-14C > T, 5-amino-acid N-terminal addition. Associated with a brittle bone disease, osteogenesis imperfecta type 5	[3,69–84]
Adrenal gland, blood, bone, brain, connective tissue, eye, intestine, kidney, larynx, liver, lung, mammary gland, mouth, pancreas, placenta, prostate, salivary gland, skin, testis, trachea	Unknown	
Brain, cervix, esophagus, intestine, kidney	Unknown	[85,86]
Embryonic tissue, Nervous system (globus pallidus, cerebellum, subthalamic nucleus, cerebellar peduncles, caudate nucleus, spinal cord, cerebral cortex, hippocampus). Low levels in heart, lung, kidney, skin	rs199662641; rs200926711; rs76335820; c.649–650insC; c.776dupG; c.649dupC. Associated with paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile seizure/epilepsy (BFIS)/(BFIE), infantile convulsions with choreoathetosis syndrome (ICCA)	[87–96]
White/Brown Adipose Tissue, Peripheral nervous system somatosensory neurons, mammary gland	Unknown	[97,98]
Blood, bone, brain, cervix, connective tissue, eye, heart, intestine, kidney, lung, placenta, prostate, skin, spleen, testis, thyroid, uterus	Unknown	
Bone, brain, eye, lung, muscle, pancreas, thyroid		
Brain, embryonic tissue, esophagus, eye, heart, intestine, kidney, lung, ovary, pancreas, prostate, stomach, testis, thymus, umbilical cord	Unknown	[99]
Brain, connective tissue, eye, kidney, lung, nerve, pancreas	Unknown	[100]

discussed, IFITM1 is primarily located in the plasma membrane and in early endosomes, and IFITM3 resides in the late endosomes and lysosomes. Palmitoylation of proteins on cysteines directs them to cellular membranes and in some instances into the endosomal pathway [116]. Preventing the addition of a palmitate to C72 diminished IFITM3's antiviral actions and resulted in the mutant's more central cellular location [61,109]. Similar results were also reported for murine Ifitm1 [54]. Thus, palmitoylation of a single conserved residue in the CD225 domain plays an important part in preventing viral entry and correctly positioning IFITM1 and 3 [61,109].

The CD225 domain: While this domain defines one of the largest families of membrane-associated proteins, little data exist regarding its function. The structural and functional data for the CD225 domain of IFITM3, presented below, reveal a strong link between proper intracellular location and restriction, thus lending support for a location-restriction rule. This simply predicts that any perturbation or mutation that alters the location of the IFITMs in respect to the cytosolic membrane or endosomal pathway will decrease restriction [2,4,61,104,109]. AS mutagenesis in six residue increments identified the CD225 domain as being the most important region of IFITM3 in terms of its cellular localization and expression level [61]. The importance of F75 and F78 for IFITM complex formation, together with the role of C72's palmitoylation for localization, provides the earliest structural and functional associations for the CD225 domain and demonstrates this domain's importance for intrinsic immunity [2,4,61,109]. Additional CD225 domain molecular determinants required for IFITM3's restriction of IAV and DENV were found within IM1, with IFITM3 AS mutants 67AS (amino acids 67–72)

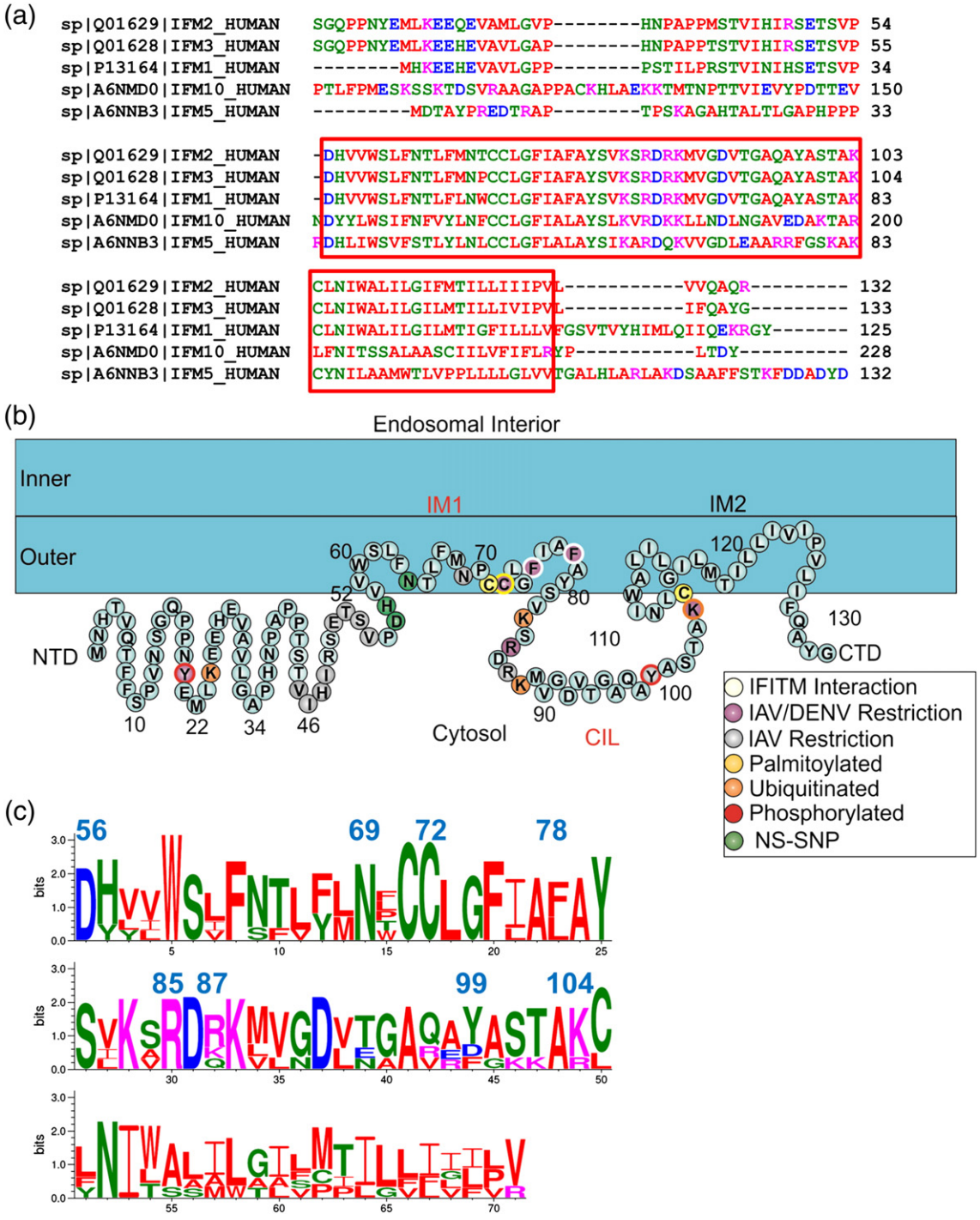

Fig. 2. (a) Alignment of the human IFITM1, IFITM2, IFITM3, IFITM5, and IFITM10 protein sequences (ClustalW2). The amino acids are color coded as follows: red, hydrophobic amino acids; green, polar amino acids; pink, basic amino acids; blue, acidic amino acids. The CD225 domain and the adjacent IM2s of the aligned proteins are outlined in red. Gaps introduced to maximize alignment are indicated by dashes. (b) Cartoon of IFITM3 in the endosomal membrane. The molecular determinants required for the IFITM3-mediated restriction, sites of posttranslational modifications, and nonsynonymous single-nucleotide polymorphisms (NS-SNP) are indicated in the key (bottom right). The NTD, intramembrane domain 1 (IM1), CIL, and intramembrane domain 2 (IM2) are indicated. IM1 and the CIL are in red font to convey that they comprise the canonical CD225 domain. The outer and inner leaflets of the endosomal membrane are noted. (c) Sequence logo for the CD225 domains and IM2s of the human IFITMs in (a). The respective amino acid properties color coded as above. Blue numbers indicate residues in IFITM3 found to be required for restriction, localization, or expression. These and similar figures were generated using Weblogo and the CLUSTALW freeware programs.

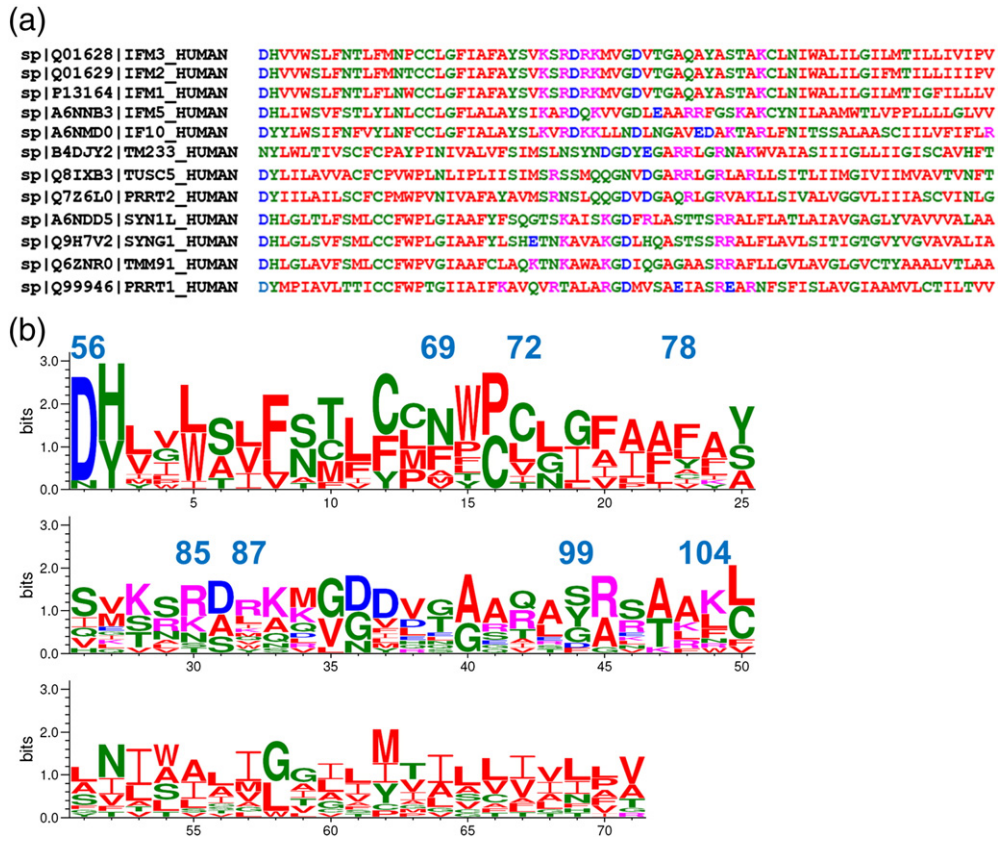

Fig. 3. (a) Alignment of the CD225 domains and IM2s of the human CD225 proteins (ClustalW2). The amino acids are color coded as above. (b) Sequence logo for the human CD225 proteins. Blue numbers indicate residues in IFITM3 found to be required for restriction, localization, or expression. This figure was generated using Weblogo.

and 73AS (amino acids 73–78) being defective in intracellular localization and antiviral activity; subsequent work has revealed that N69 is likely the most critical residue in this region for both functions (our unpublished data; Ref. [61]; Fig. 3). Again, several mutations revealed a strong link between proper intracellular location and restriction. Within IFITM3's CIL, R85, R87, Y99, and K104 were all needed for viral restriction. Y99 has been reported to be phosphorylated on PhosphoSitePlus; however, similar to Y20, both the functional significance and the possible regulation of this PTM remain to be determined. Y99's mutation decreased restriction of IAV more so than DENV, demonstrating that differing structural requirements may be necessary for controlling various infections [61]. Interestingly, Y99A, along with R87A, were mutations that lowered restriction but had intracellular distributions indistinguishable from wild-type IFITM3, thus separating these phenotypes and demonstrating that the CD225 domain functions in both proper positioning and restriction.

To compare the prevalence of these functionally important residues, the CLUSTAL and Weblogo programs were used to construct probability diagrams for amino acids in the IM1, CIL, and IM2 regions of the human IFITMs (IFITM1, 2, 3, 5, and 10; Fig. 2c) with or without an additional seven human CD225 proteins (Fig. 3b) [117]. These analyses revealed that across the IFITMs, N69, C72, F75, R85, and K104 were among the residues with the highest conservation, consistent with their functional importance to IFITM3-mediated restriction. D56, D86, and D92 are conserved across the CD225 proteins and were found to be required for IFITM3 expression, suggesting important roles in stability [61]. D56 is situated immediately prior to IM1 and thus may maintain membrane topology. Though the IM1s of the IFITMs contain a higher percentage of conserved polar residues than found in the IM2s, only N69 was found to be required for restriction by IFITM3, suggesting an alternative functional role and/or redundancy (Fig. 2c). IM2 is not a designated portion of the CD225 domain since its sequence conservation is low; however, in all the human CD225 proteins, the segment following the CIL is hydrophobic, and in many instances, a leucine/isoleucine zipper is demonstrable. Consideration should be given to extending the CD225 domain to include a distal hydrophobic segment predicted to be

Table 4. IFITM protein family posttranslational modifications

Protein	Posttranslational modification (PTM)	Functional role	References[a]
IFITM1	Mouse: S-palmitoylation cysteines 49, 50, 83, 103	Localization to membrane	[54]
	Phosphorylation lysine 67	Unknown	[105–107]
IFITM2	Phosphorylation serine 9	Unknown	[108]
	Ubiquitination lysine 87	Unknown	[105–107]
IFITM3	Phosphorylation tyrosine 20	Required for proper trafficking from the cell surface and localization to late endosomes and lysosomes; required for restriction of IAV and DENV, not present in IFITM1.	[33,61], PhosphoSitePlus
	Ubiquitination lysine 24	Most robustly ubiquitinated of the four lysines found in IFITM3. The combined mutation of K24, K83, K88, and K104 to alanine increased protein stability, augmented the formation of autolysosomes, and promoted restriction of IAV	[54,104], PhosphoSitePlus
	S-palmitoylation cysteines 71,72,105	Mutation of C72 to alanine disrupts proper cellular localization and decreases restriction for IAV and DENV. Mutation of either C71 or C105 to alanine has no effect on these attributes	[61,109]
	Ubiquitination lysine 83	Mutation to alanine had no effect on restriction	[61,104]
	Ubiquitination lysine 88	Mutation to alanine had no effect on restriction	[61,104], PhosphoSitePlus
	Phosphorylation tyrosine 99	Mutation to alanine decreased restriction of DENV more than IAV but did not alter localization	[61], PhosphoSitePlus
	Ubiquitination lysine 104	Mutation to alanine decreased restriction (IAV > DENV) without altering localization	[61,104], PhosphoSitePlus

[a] For PTMs with greater than three citations on PhosphoSitePlus, the reader is referred to the website using the following link where those citations are visible upon clicking the specific PTM (http://www.phosphosite.org/homeAction.do).

membrane associated. AS mutagenesis of IFITM3's IM2 revealed that the amino acid side chains within this region were not required for either restriction or localization [61]. However, because a hydrophobic-based mutagenesis strategy was employed, the resulting alterations may have been too conservative. Therefore, IM2 may indeed serve a role in decreasing membrane fluidity based on its hydrophobic properties and potential leucine zipper motif (discussed below).

IFITM3's Role *In Vivo*

IFITM3's potent restriction of IAV *in vitro* suggested that it might also play an important role in *vivo*; such is the case, as mice deficient in Ifitm3 succumb more readily to IAV infection when compared to wild-type littermates [65,101]. While these experiments involved the animals' first exposure to IAV, an additional *in vivo* role for Ifitm3 in protecting long-term memory CD8+ T cells during re-infection has also been reported [118].

Fig. 4. Model of IFITM antiviral action. We postulate that one or more of the following IFITM-mediated events "toughen" the host cell membrane and prevent viral fusion. (a) Inhibition of sequential host co-receptor interactions. After binding of the viral receptor-binding protein (blue, downward facing) to a host receptor (orange, upward facing, left panel), the pair then moves through the membrane surface until one or more required co-receptors (green) are encountered (middle panel), ultimately triggering fusion peptide insertion (not shown). In contrast, we postulate that adjacent IFITMs interact via their IM1s to decrease membrane fluidity and restrict the lateral movement of the partially assembled receptor complex. Black arrows, movement through the membrane; white arrows, diminished movement; red arrows, resistance within the membrane generated by IFITMs. (b) Inhibition of viral envelope protein clustering. Two HA receptors (blue) are shown with their fusion peptides (red) inserted into the host membrane (left panel). The engaged receptors then move through the membrane and coalesce (middle panel). This juxtapositioning permits the HA receptors to coordinately generate a fusion pore (c) [120]. Similar to (a), the presence of intramembranous IFITMs decreases HA receptor movement and prevents their effective association. Arrows are as above. (c) HA-mediated fusion: Top row: As in (b), but in the absence of IFITMs, the HA receptors have now been able to coordinately generate a fusion pore (right panel). However, IFITMs residing in the membrane alter the properties of the host membrane due to intramolecular interactions and asymmetric membranous insertions. The association of IFITMs via their IM1s decreases membrane fluidity. Furthermore, the insertions of the IM domains of each IFITM into the outer leaflet of the membrane produces a curvature directed away from the HA receptors drawing force. We envision that this induced curvature would require that greater force be exerted by the viral fusion machinery, thus preventing the formation of a pore. Arrows are as above. (d) Superior view of IFITM–IFITM interactions occurring in the membrane. We speculate that IFITMs multiplex via their IM1s (assorted-color ovals binding to one another at a central IM1-generated hub, left panel). A pentamer is shown as one possible IFITM complex. Radiating from this common interaction point, the more distal IM2s form interactions with the transmembrane or intramembrane domains of additional proteins (blue), that is, the tetraspanins. When such IFITM units are symmetrically multiplied, they could possibly form an integrated matrix that alters the membrane's fluidity and bending modulus (right panel). This meshwork may also enhance the membrane-rigidifying properties of cholesterol (pink stars [119]) The CILs that connect IM1 and IM2 and lie in the cytosol are represented by dotted lines.

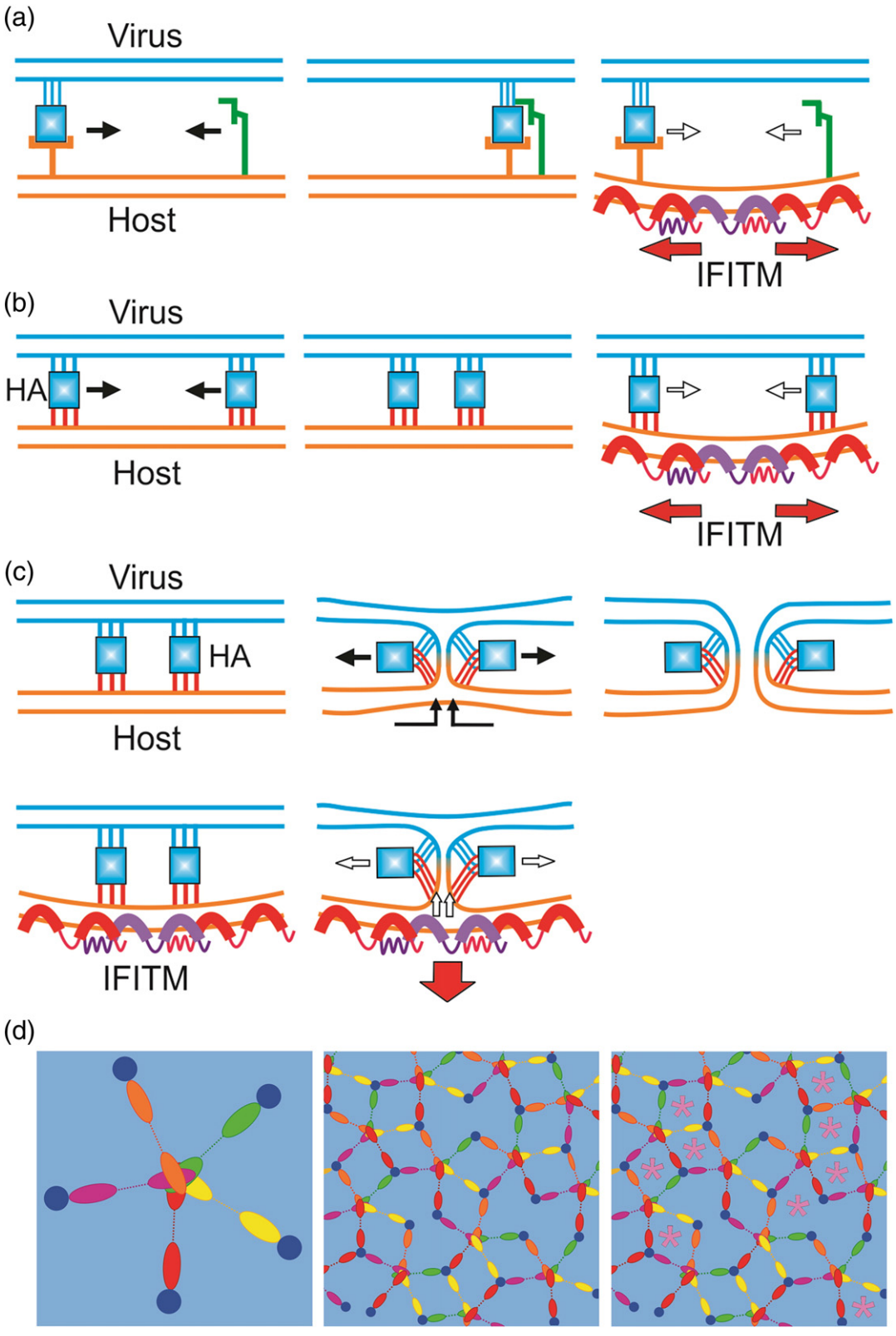

Fig. 4 (*legend on previous page*)

Notably, when Everitt *et al.* investigated how IFITM3 might influence the clinical course of humans infected with IAV, they found that a minor allele, SNP rs12252-C, was enriched in patients hospitalized due to pandemic H1N1/09 infection in England and Scotland [65]. While the mechanistic role of this allele remains under investigation, the rs12252 C/C SNP alters a predicted splice acceptor site suggesting several scenarios. While comparatively rare in Caucasian populations, the rs12252-C allele is considerably more prevalent in Han Chinese individuals. Therefore, it was noteworthy when in an independent study rs12252-C was subsequently found to be enriched for in patients with severe influenza (69% severe influenza *versus* 25% mild) [66]. Based on these results, the rs12252 allele is estimated to confer a sixfold higher risk for severe influenza. Therefore, populations expressing higher percentages of the rs12252 allele such as in regions of China and Japan may be more at risk for seasonal influenza epidemics and pandemics [66]. It follows that IFITM3 genotyping may be beneficial to clinicians serving these populations because it could help with risk stratification including decisions for closer observation and administration of therapy. Moreover, these results suggest that IFITM levels and/or actions may influence the clinical course of additional illnesses caused by IFITM-sensitive viruses.

Mechanism of Action

IFITMs block viral fusion and prevent the cytosolic entry of viral genomes. Instead of successfully fusing with the host membrane, IFITM-sensitive viruses are arrested at the cell surface and trapped in the endosomal pathway, resulting in their traveling to the lysosomes or autolysosomes, where they are destroyed (Fig. 1a and b). The end result, the sequential inhibition and destruction of the virion, serves to lower the inoculum and is an effective means of preventing invasion by an array of viruses that exploit the endocytic pathway.

How do the IFITMs prevent viral entry? In addressing this, several points must be considered: (i) the IFITM's inhibition of an array of viruses that enter at various cell locations using divergent fusion machinery; (ii) the ability of some viruses to resist one IFITM but not another; (iii) the IFITM immunity of SeV, MLV, and all of the arenaviruses envelopes thus tested; (iv) previous data showing that their overarching effect is the inhibition of viral fusion subsequent to viral binding and endocytosis; and (v) data concerning the molecular determinants required for restriction. Recently, we and others have postulated that the IFITMs alter the physical properties of the host cell's membrane, thus interfering with viral fusion [5,54,61,119]. In this “tough-membrane” model, we postulate that intramembranous interactions between the IMI domains of adjacent IFITMs alter both the fluidity and the bending modulus of the host cell membrane, making it resistant to the viral fusion machinery (Fig. 4) [61]. Additionally, the intramembranous insertions of the IMs may asymmetrically compress the outer leaflet, generating a curvature directed away from the viral fusion machinery's drawing force. Precedent for this last part comes from studies of the reticulons, which shape the endoplasmic reticulum into a tubular structure by inserting their two IM domains into the outer leaflet of the membrane [110]. The tough-membrane model predicts that IFITMs must be at the site of viral entry, which has been shown to be the case in mutagenesis studies. Moreover, it accounts for the specificity of IFITM actions, with IFITM1 primarily blocking early endosomal-entering viruses and IFITM3 acting on late endosomal-entering pathogens. In addition, this scenario would account for the rapid action of the IFITMs and their effective inhibition of diverse viruses.

Decreasing membrane fluidity may impede the lateral movements of membrane-associated proteins and thus inhibit both the sequential interaction of viral envelopes with multiple host receptors, as is required for HIV-1 and HCV, and the coalescence of multiple viral envelopes, as has been demonstrated for IAV entry (Fig. 4a–c) [120]. It is also possible that viral membranes that originate from the host and contain IFITMs will have decreased fluidity. Although speculative, this scenario could also explain why some viruses are immune to the IFITMs; perhaps the IFITM-resistant viral fusion machinery possesses intrinsic properties (strength, cooperativity) that permit them to overcome the increased rigidity of the host membrane. Alternatively, viruses that either depend on a single host receptor (MLV and SeV) or more readily achieve the clustering of the required envelopes to fuse may also overcome restriction. For viruses that are susceptible to the IFITMs but only rely on one host receptor, that is, JSRV, one possibility is that an additional co-receptor requirement may await detection. An obvious concern with this scenario is that while a more viral-resistant membrane would be advantageous, it could potentially interfere with normal cellular physiology, for example, endocytic trafficking, vesicular fusion, and cytokinesis, all of which are impacted by membrane fluidity.

How do a relatively few IFITM molecules alter the cell's membrane surfaces? One explanation may come from IFITM1 locating to lipid rafts, an area of the membrane where many viruses bind to host receptors and are endocytosed [112]. This suggests that IFITMs may have been selected to concentrate at, or rapidly move to, viral attachment and entry zones that are enriched for host receptors; one means of achieving this may be seen with IFITM1's association with the tetraspanins, including CD19 and CD81, which reside in lipid rafts [15]. Binding to proteins that are enriched in lipid rafts could efficiently home the IFITMs to a location

where they can block multiple viruses without needing to interact with each virus' host receptor; these associations could potentially involve a predicted leucine zipper in IM2. Together, the paired interactions of IM1 and 2 could foreseeably tether each end of the IFITMs to create a protective mesh stretching across viral entry zones (Fig. 4d). Indeed, a meshwork of tetraspanins, the tetraspanin web, has been previously proposed [121]; however, in contrast to earlier pro-viral models of tetraspanin interactions, this scenario would instead be antiviral. For IFITM3, located in late endosomes, this model predicts its association with viral entry zones as the pathogen-bearing endosomes sequentially mature along the endocytic pathway.

While such a direct model of IFITM-induced restriction addresses some issues, we note that the IFITMs cause changes in the endosomal environment, including its expansion and acidification, suggesting that modulation of endosomal conditions may also contribute to viral inhibition [3,4,21,104,122]. In light of this, it has recently been proposed that IFITMs antagonize the host cell's lipid homeostasis, resulting in the mislocalization of high levels of cholesterol to the late endosomes producing a block to viral fusion [119]. While cholesterol itself is required by many viruses for fusion, it also can inhibit infection. IFITM1, 2, and 3 are reported to strongly bind to the endocytic trafficking protein, vesicle-associated membrane protein-A (VAPA). The IFITM–VAPA interaction interferes with the binding of VAPA to oxysterol binding protein (OSBP) [123]. OSBP is a known regulator of cholesterol trafficking and has been shown to bind to numerous host proteins, including VAPA. Therefore, a competition may exist between OSBP and the IFITMs for VAPA, with higher IFITM levels sending more cholesterol to the late endosomes and blocking viral fusion. An attractive aspect of this model is that the general alteration of membrane cholesterol levels readily explains how a relatively small number of IFITMs can prevent different viruses from entering from the late endosomes and lysosomes. However, it is unclear how the mislocalization of cholesterol to the late endosomal compartment would inhibit early endosomal-entering viruses such as HIV-1, HCV, and JSRV. Similarly, this model cannot fully explain IFITM specificity because the interaction of either IFITM1 or 3 with VAPA does not appear to direct excess cholesterol to a particular compartment; that is, IFITM1 is not shown to relocate cholesterol to the early endosomes to block HCV and JSRV. While these early attempts to explain the antiviral effects of the IFITMs may prove useful, much additional experimentation is required, perhaps leading to the integration of several components of these models. For example, increased cholesterol in combination with IFITM complexes could further toughen the host membrane against viral entry (Fig. 4d, right panel). These unanswered mechanistic issues notwithstanding, the IFITMs represent a broadly acting and previously unappreciated class of restriction factor that traps and degrades invading pathogens, thereby protecting the host individually as well as at a population level.

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Abbreviations used:
IFITM, interferon-inducible transmembrane protein; IFN, interferon; IAV, influenza A virus; DENV, dengue virus; SARS CoV, severe acute respiratory syndrome coronavirus; HCV, hepatitis C virus; EBOV, Ebola virus; MARV, Marburg virus; CIL, conserved intracellular loop; MS, mass spectrometry; NTD, N-terminal domain; RVFV, Rift Valley fever virus; HIV-1, human immunodeficiency virus type 1; JSRV, Jaagsiekte sheep retrovirus; GP, glycoprotein; CCHFV, Crimean Congo hemorrhagic fever virus; MLV, Moloney leukemia virus; SeV, Sendai virus; CMEM, clathrin-mediated endocytosis motif; AS, alanine scanning; VAPA, vesicle-associated membrane protein-A; OSBP, oxysterol binding protein.

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