Interferon-Stimulated Genes as Influenza Virus Host Restriction Factors

Subjects: Virology

Contributor: Matloob Husain

Influenza virus exploits host factors to promote each step of its lifecycle. In turn, the host deploys antiviral or restriction factors that inhibit or restrict the influenza virus lifecycle at each of those steps. Two broad categories of host restriction factors can exist in virus-infected cells: (1) encoded by the interferon-stimulated genes (ISGs) and (2) encoded by the constitutively expressed genes that are not stimulated by interferons (non-ISGs). There are hundreds of ISGs known, and many, e.g., Mx, IFITMs, and TRIMs, have been characterized to restrict influenza virus infection at different stages of its lifecycle, by (1) blocking viral entry or progeny release, (2) sequestering or degrading viral components and interfering with viral synthesis and assembly, or (3) bolstering host innate defenses.

Keywords: interferon-stimulated genes (ISGs) ; Influenza virus ; Mx ; IFITM3 ; TRIM ; Host Restriction ; Restriction Factors ; Antiviral Factors

1. Introduction

A variety of host factors facilitate and restrict the influenza virus lifecycle at each stage [1]. The host factors that restrict the infection are called host restriction factors or antiviral factors and, broadly, can be of two types: (1) encoded by the interferon-stimulated genes (ISGs) and (2) encoded by the genes that are constitutively expressed or are not stimulated by interferons (non-ISGs). Many host restriction factors in both categories have been identified, some through the latest genetic techniques, such as RNA interference and CRISPR-Cas9 and characterized to restrict influenza virus infection.

2. Interferon-Stimulated Genes

The expression of ISGs, as the name suggests, is induced by interferons. Interferons are the first line of defense molecules produced by host cells after sensing the virus infection through pattern recognition receptors. The existence of ISGs was first detected in the later part of the 20th century [2][3]. Since then, several hundreds of ISGs have been identified [4] and characterized to inhibit the infection of many viruses [5]. Likewise, many ISGs, encoding both proteins and non-coding RNAs (ncRNAs), have been identified to express in response to the influenza virus infection and restrict its infection at different stages of the viral lifecycle.

2.1. Mx Proteins

The Mx (myxovirus) gene encoding an ~75 kDa protein was the first ISG to be discovered to confer resistance to influenza virus infection [6][7][8][9][10]. Except for chickens [11][12][13][14], Mx proteins in the majority of influenza virus hosts, e.g., humans [15], pigs [16][17], and horses [18], exhibit antiviral activity. Mx proteins are dynamin-like GTPases [19][20][21], which oligomerize into ring-like structures [22][23][24][25][26] and target influenza virus vRNPs to exert their antiviral function [27][28]. Human Mx protein interacts with viral NP and PB2 to sense and sequester the incoming vRNPs in the cytoplasm and inhibit their nuclear import and subsequent viral RNA transcription and replication [18][27][28][29][30][31]. Human Mx protein is a barrier to the zoonotic transmission of avian influenza viruses and recently discovered bat influenza viruses to humans [32][33][34][35][36][37]. To escape this barrier, avian influenza viruses acquire human-adaptive mutations in their NPs or increase their RNA polymerase activity or vRNP nuclear export [33][36][37][38][39][40][41]. Some influenza viruses can also escape this barrier in humans and animals carrying naturally occurring Mx allele variants, which either lack or exhibit reduced antiviral activity [16][42][43][44][45][46].

2.2. IFITM Proteins

The IFITM (interferon-inducible transmembrane) genes encoding 14–16 kDa proteins were identified as ISGs around the same time as the Mx gene [47][48][49][50]. However, the antiviral function of IFITM proteins 1, 2, and 3 during influenza virus

infection was discovered much later in a genomic screen [51]. IFITM proteins are broad host restriction factors of the influenza virus, as IFITMs from multiple host tissues and species (including bacteria [52]) are capable of inhibiting influenza virus infection [53][54][55][56][57][58][59][60][61][62][63][64][65][66][67]. IFITMs 1, 2, and 3 are closely related proteins and share 70–90% homology, and all three inhibit influenza virus infection by inhibiting its entry to the host cells [51]. IFITM3 is a type II transmembrane protein and localizes to the endosomes and lysosomes, where it interacts with influenza virus HA and prevents the fusion of viral envelope with the endosomal membrane by interfering with lipid homeostasis, consequently preventing vRNP release into the cytoplasm [68][69][70][71][72][73][74][75][76][77][78][79].

The antiviral activity of IFITM3 is regulated by posttranslational modifications like palmitoylation, ubiquitination, and methylation [59][80][81][82][83][84][85][86]. Specifically, the palmitoylation of IFITM3 promotes its antiviral activity by enhancing its membrane affinity and endosomal localization [59][80][81][82][87]. In contrast, the ubiquitination of IFITM3 reduces its antiviral activity by decreasing its stability and localization to the endosomes [81][85]. Also, the methylation of IFITM3 reduces its antiviral activity and influenza disease severity [83][86]. The phosphorylation of IFITM3 reduces its ubiquitination and may indirectly promote its antiviral activity [84]. These findings indicate that the influenza virus potentially employs the ubiquitin ligases, e.g., NEDD4 [85], and methyltransferases, e.g., SET7 [86], to antagonize the antiviral function of IFITM3 and escape IFITM3 restriction. Furthermore, avian influenza A virus subtypes H5N1 and H7N9 may escape IFITM3 restriction in cells with inefficient endosomal acidification [88].

Influenza virus may also escape IFITM3 restriction and cause severe disease in humans carrying single nucleotide polymorphisms (SNPs) in the IFITM3 gene [54][89][90]. The IFITM3 allele carrying SNP rs12252-C encodes an N-terminally truncated IFITM3 variant, which is incapable of localizing to the endosomes and allows the influenza virus to escape IFITM3 restriction [54][71][91][92]. Consequently, rs12252-C has been associated with severe influenza disease [54]. However, the evidence of this association has been found in studies involving the cohorts mainly from Asian ethnicity [90][93][94][95][96][97][98][99][100] and not from other ethnicities [101][102][103][104][105][106][107]. Further, the SNPs in IFITM1 are not associated with influenza disease severity [108].

2.3. TRIM Proteins

TRIM (tripartite motif) proteins are a large family of proteins that comprise a conserved architecture known as RBCC (a RING finger domain, one to two B-box domains, a coiled coil domain, and a variable C-terminus) [109][110]. Among TRIMs, TRIM19, also known as promyelocytic leukemia (PML) protein, was the first to be identified as an ISG [111]. Soon after, it was discovered to inhibit influenza virus infection [112]. Now, over 80 TRIMs are known [110], of which at least 27 TRIMs have been identified as ISGs [113]. In addition to TRIM19, TRIMs 14, 21, 22, 25, 35, and 56 have been shown to inhibit influenza virus infection [114][115][116][117][118][119][120][121]. TRIMs are E3 ubiquitin ligases and are part of the ubiquitin–proteasome system, which degrades proteins. Hence, most TRIMs exert their antiviral function by targeting the viral proteins for degradation. Specifically, TRIM14 [117] and TRIM22 [114] target viral NP, TRIM21 targets viral M1 [122], and TRIM35 targets viral PB2 [118] for ubiquitin ligase-dependent degradation. However, the NP of some influenza A virus H1N1 subtypes is resistant to TRIM22-mediated restriction [123]. The TRIM25 [116][120] and TRIM56 [115] interfere with viral RNA synthesis or stability though in an E3 ligase-independent manner. Also, TRIM25 has been reported to inhibit influenza virus infection by facilitating its RIG-I-mediated host sensing in a ubiquitin ligase-dependent manner [124][125][126][127]. However, influenza virus antagonizes the latter function of TRIM25 via NS1 protein, which is the main influenza virus virulence factor that antagonizes host defenses. NS1 binds TRIM25 and interferes with its ubiquitin ligase activity [124][125][126][127][128].

2.4. OAS Proteins

OAS (2′,5′-oligoadenylate synthetase) proteins 1, 2, and 3, and OAS-like (OASL) protein were among the first ISGs to be discovered [129][130]. OAS 1, 2, and 3 are activated by sensing the viral RNA and then convert the ATP to 2′,5′-oligoadenylate [130], which, in turn, activates the ribonuclease (RNase) L [131]. Subsequently, RNase L restricts influenza virus infection by degrading the viral RNA [132][133][134]. However, OASL restricts influenza virus infection in an RNase L-independent manner [135]. In turn, influenza virus escapes the OAS-mediated restriction via NS1, which competes with OAS proteins for viral RNA binding [132]. Furthermore, the influenza virus may escape this restriction in humans carrying the SNP rs10774671 in OAS1 gene [136].

2.5. IFIT Proteins

The IFIT (interferon-induced proteins with tetratricopeptide repeats) family has four proteins, IFITs 1, 2, 3, and 5 (or ISGs 56, 54, 60, and 58, respectively), which have been characterized in humans [137]. IFIT1 is the prototypic member of the family and was the first to be identified as an ISG in the IFIT family [138][139], followed by the rest [137]. The indication of an

antiviral function of human IFITs 1, 2, and 3 during influenza virus infection was first discovered in a proteomic screen [140]. Later, it was demonstrated that human IFITs 1, 2, and 3 and avian IFIT5 exhibit antiviral properties during influenza virus infection [141][142][143][144][145]. The human and chicken IFITs exert their antiviral function by sequestering the viral RNA by binding its 5′-triphosphate group, called PPP-RNA [140][143][146], whereas the duck IFIT sequesters viral NPs [142]. However, Pinto et al. found no antiviral activity of human IFIT1 during influenza virus function [147], while Tran et al. found influenza virus rather exploiting the RNA binding property of IFIT2 to promote viral mRNA translation [148].

2.6. hGBP Proteins

The hGBPs (human guanylate-binding proteins), like Mx proteins, belong to GTPase family [149][150], and hGBPs -1, -2, -3, and -5 have been shown to inhibit influenza virus infection [151][152][153][154]. The hGBP-3 exerts its antiviral function by targeting viral RNA polymerase activity [151], whereas hGBP-2 and hGBP-5 target the host furin protease, which primes the HA of the highly pathogenic influenza A viruses, like H5N1 subtype, for infection [153]. Nevertheless, influenza virus NS1 antagonizes the hGBP-1 by inhibiting its GTPase activity [154].

2.7. Tetherin

Tetherin, also known as BST-2/CD317/HN1.24, is a GPI-anchored transmembrane protein [155] and restricts virus infection by tethering the viral progeny to the cell surface. The antiviral role of tetherin during influenza virus infection is inconclusive and has been controversial. However, tetherin expression is induced in influenza virus-infected cells in an interferon-dependent manner [156]. Human tetherin was observed to effectively tether the budding influenza virus-like particles to the plasma membrane [157][158][159][160]; however, the same was not observed with live influenza virus particles [156][157][161] or tetherin from other host species [162][163]. In other studies, tetherin was observed to inhibit the influenza virus release [159][160][164][165], but this restriction was either viral NA-dependent [159][165] or countered by viral M2 protein, which facilitated the downregulation of tetherin on the cell surface [160].

2.8. ISG15

ISG15 gene [166] encodes a 15-kDa protein [167], which inhibits the influenza virus infection [168] by targeting critical viral [169][170] and host [171] proteins. ISG15 is a ubiquitin-like protein [167] and is conjugated to target proteins by sequential action of several conjugation enzymes, some of which are also ISGs [172][173][174][175][176][177]. This process is also called ‘ISGylation’. ISG15 ISGylates influenza virus NS1 protein and cripples its ability to perform various antagonistic functions [169][170]. Further, the ISGylation of host protein Tsg101 inhibits the trafficking of viral HA to the plasma membrane, the site of influenza virus assembly [171].

2.9. PKR

PKR (protein kinase R) is a dsRNA-activated serine/threonine protein kinase and phosphorylates the eukaryotic translation initiation factor 2 (eIF-2α); this leads to the inhibition of the initiation of global protein synthesis [178]. This leads to the inhibition of viral protein synthesis too, and consequently, the influenza virus infection [179][180]. Influenza virus counteracts this restriction through NS1, which binds to dsRNA and blocks PKR activation [180][181][182]. Influenza virus NP also can block PKR activation by activating the cellular PKR inhibitor, P58 [183].

2.10. Other Proteins

CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) expression was first shown to be induced by interferon-gamma [184]. CEACAM1 inhibits influenza virus infection by suppressing the mTOR (mammalian target of rapamycin) activity, consequently inhibiting the global protein synthesis in infected cells [185].

IFI16 (interferon γ-inducible 16) is a ~80-kDa nucleic acid-binding protein [186][187]. IFI16 is a PYHIN (pyrin and hematopoietic interferon-inducible nuclear (HIN) domain) family protein and was initially identified as an intracellular DNA sensor [188]. Recently, IFI16 has been discovered to inhibit influenza virus infection by sensing the viral RNA and promoting the RIG-I-mediated innate antiviral response [189][190].

ISG20 (interferon-stimulated gene 20), as the name suggests, is a 20-kDa protein with 3′ to 5′ exonuclease activity that is specific for single-stranded RNA [191][192]. ISG20 inhibits influenza virus infection by interfering with viral RNA transcription and replication [193][194].

MOV10 (Moloney leukemia virus 10) is a member of the RNA helicase superfamily [195], and its expression can be stimulated by interferons [5]. MOV10 inhibits influenza virus infection by binding to NP and sequestering the incoming

vRNPs in the cytoplasm, consequently inhibiting their nuclear import [196][197][198]. However, the antiviral function of MOV10 is independent of its RNA helicase activity [197][198].

MUC1 (mucin 1) is a member of mucins, a family of highly glycosylated proteins that are expressed on the surface of respiratory epithelial cells, which are the target of influenza virus infection. MUC1 potentially acts as a receptor decoy and inhibits influenza virus infection by binding to virus particles and blocking their attachment to target cells [199][200][201].

NCOA7 (nuclear receptor coactivator 7) expression is induced by the interferon-beta [202]. NCOA7 inhibits influenza virus infection by inhibiting the fusion of viral envelope with the endosomal membrane during entry [203].

The p21 is a cyclin-dependent kinase inhibitor and inhibits influenza virus infection by interfering with viral RNA polymerase activity [204].

Serpin 1 or plasminogen activator inhibitor 1 (PAI-1) inhibits influenza virus infection by neutralizing host proteases, like trypsin, and preventing the cleavage of HA, which is required for influenza virus entry [205]. However, influenza virus may escape this restriction in humans carrying the naturally occurring SNP rs6092 in serpin 1 gene [205].

SERTAD3 (SERTA domain containing 3), also called RBT1 (replication protein A binding transactivator 1), is one of the SERTA family transcription factors, and its expression is induced by the interferons [206]. SERTAD3 inhibits influenza virus infection by disrupting the formation of viral RNA polymerase complex [206].

SLFN11 and SLFN14 are Schlafen family proteins and possess an RNA helicase domain [207]. SLFN11 and SLFN14 expression is induced by the interferons, and both inhibit influenza virus infection by contributing to host innate defenses [208][209].

SPOCK2 (SPARC/osteonectin CWCV and Kazal-like domains 2) or testican 2 is a secreted proteoglycan, and it inhibits influenza virus infection by blocking the attachment of virus particles to cell surface [210].

RABGAP1L (RAB GTPase-activating protein 1-like) or TBC1D18 (Tre2/Bub2/Cdc16 (TBC)-domain-containing 18) protein restricts influenza virus infection by disrupting the endosome function hence virus entry [211].

Viperin (virus inhibitory protein, endoplasmic reticulum-associated, interferon-inducible) protein [212], also called RSAD2, inhibits influenza virus infection by disrupting the lipid rafts on the plasma membrane and inhibiting viral progeny release [213][214].

ZAP (zinc finger antiviral) or ZC3HAV1 (Zinc finger CCCH-type antiviral 1) protein exists in two forms, short (ZAPS) and long (ZAPL), and both forms exhibit anti-influenza virus properties [215][216][217]. The ZAPS exerts its antiviral function by promoting the degradation of viral mRNA but is antagonized by NS1, which competes with ZAPS for viral mRNA binding [216]. Whereas ZAPL promotes the degradation of viral PA and PB2 and is antagonized by viral PB1, which binds ZAPL and displaces PA and PB2 [215].

2.11. ncRNAs

Much of the human genome is transcribed into non-coding RNAs (ncRNAs), which do not translate into a protein. Based on their length, these ncRNAs are called microRNAs or miRNAs (~22 nucleotides), small-interfering RNAs or siRNAs (21–25 nucleotides), piwi-related RNAs or piRNAs (24–33 nucleotides), vault RNAs or vtRNAs (80–150 nucleotides), or long non-coding RNAs or lncRNAs (>200 nucleotides). Further, some lncRNAs exist as covalently-closed circular RNAs or circRNAs. Many ncRNAs are upregulated in response to the influenza virus infection and inhibit infection by targeting the viral proteins and critical host proteins [218].

The lncRNAs are the prominent form of ncRNAs that have been identified to be upregulated in response to the influenza virus infection or interferon treatment [219][220][221][222][223][224][225][226]. Those lncRNAs inhibit influenza virus infection primarily by strengthening the antiviral state in infected cells through various mechanisms, e.g., stabilization of RIG-I–TRIM25 complex for host sensing of influenza virus [220], epigenetic modifications of regulatory regions of innate response genes [223][225], and manipulation of regulators (including miRNAs) of interferon signaling [219][221][224][226].

Also, circRNAs, circVAMP3, and AIVRs are upregulated in response to influenza virus infection and restrict the infection by different mechanisms [227][228]. The circVAMP3 acts as a decoy to viral NP and NS1 and interferes with their function [228], while the AIVR sequesters a microRNA, which degrades an enhancer of the interferon production [227].

In addition, the miRNAs, miR-101, miR-485, ssc-miR-221-3p, and ssc-miR-222, have been identified to be upregulated in response to influenza virus infection and inhibit infection by distinct mechanisms [229][230][231]. The miR-101, like ISG CEACAM1 [185], inhibits influenza virus infection by targeting the mTOR pathway [230], whereas miR-485 targets host RIG-I and viral PB1 and reduces their mRNA levels [229]. Further, swine ssc-miR-221-3p and ssc-miR-222 may restrict the interspecies transmission of avian influenza viruses to pigs by targeting their viral RNA [231].

3. Summary

A plethora of ISGs has been identified that restrict the influenza virus infection by inhibiting viral attachment, entry, synthesis, assembly and release, and strengthening the host innate antiviral response. However, influenza virus seems to have the upper hand and effectively antagonizes the restriction imposed by ISGs. Furthermore, the genetic diversity of some ISGs (IFITM3, Mx, OAS-1, Serpin-1) in various hosts and human populations also helps influenza virus to escape host restriction. Nevertheless, an exhaustive list of influenza virus host restriction factors and their restriction mechanisms is yet to be compiled.

References

1. Husain, M. Host factors involved in influenza virus infection. Emerg. Top. Life Sci. 2020, 4, 389–398.
2. Knight, E., Jr.; Korant, B.D. Fibroblast interferon induces synthesis of four proteins in human fibroblast cells. Proc. Natl. Acad. Sci. USA 1979, 76, 1824–1827.
3. Larner, A.C.; Jonak, G.; Cheng, Y.S.; Korant, B.; Knight, E.; Darnell, J.E., Jr. Transcriptional induction of two genes in human cells by beta interferon. Proc. Natl. Acad. Sci. USA 1984, 81, 6733–6737.
4. de Veer, M.J.; Holko, M.; Frevel, M.; Walker, E.; Der, S.; Paranjape, J.M.; Silverman, R.H.; Williams, B.R. Functional classification of interferon-stimulated genes identified using microarrays. J. Leukoc. Biol. 2001, 69, 912–920.
5. Schoggins, J.W.; Wilson, S.J.; Panis, M.; Murphy, M.Y.; Jones, C.T.; Bieniasz, P.; Rice, C.M. A diverse range of gene products are effectors of the type I interferon antiviral response. Nature 2011, 472, 481–485.
6. Haller, O.; Arnheiter, H.; Gresser, I.; Lindenmann, J. Virus-specific interferon action. Protection of newborn Mx carriers against lethal infection with influenza virus. J. Exp. Med. 1981, 154, 199–203.
7. Haller, O.; Arnheiter, H.; Lindenmann, J.; Gresser, I. Host gene influences sensitivity to interferon action selectively for influenza virus. Nature 1980, 283, 660–662.
8. Horisberger, M.A.; Staeheli, P.; Haller, O. Interferon induces a unique protein in mouse cells bearing a gene for resistance to influenza virus. Proc. Natl. Acad. Sci. USA 1983, 80, 1910–1914.
9. von Wussow, P.; Jakschies, D.; Hochkeppel, H.K.; Fibich, C.; Penner, L.; Deicher, H. The human intracellular Mx-homologous protein is specifically induced by type I interferons. Eur. J. Immunol. 1990, 20, 2015–2019.
10. Chang, K.C.; Hansen, E.; Foroni, L.; Lida, J.; Goldspink, G. Molecular and functional analysis of the virus- and interferon-inducible human MxA promoter. Arch. Virol. 1991, 117, 1–15.
11. Bernasconi, D.; Schultz, U.; Staeheli, P. The interferon-induced Mx protein of chickens lacks antiviral activity. J. Interf. Cytokine Res. 1995, 15, 47–53.
12. Schusser, B.; Reuter, A.; von der Malsburg, A.; Penski, N.; Weigend, S.; Kaspers, B.; Staeheli, P.; Hartle, S. Mx is dispensable for interferon-mediated resistance of chicken cells against influenza A virus. J. Virol. 2011, 85, 8307–8315.
13. Daviet, S.; Van Borm, S.; Habyarimana, A.; Ahanda, M.L.; Morin, V.; Oudin, A.; Van Den Berg, T.; Zoorob, R. Induction of Mx and PKR failed to protect chickens from H5N1 infection. Viral. Immunol. 2009, 22, 467–472.
14. Benfield, C.T.; Lyall, J.W.; Tiley, L.S. The cytoplasmic location of chicken mx is not the determining factor for its lack of antiviral activity. PLoS ONE 2010, 5, e12151.
15. Pavlovic, J.; Zurcher, T.; Haller, O.; Staeheli, P. Resistance to influenza virus and vesicular stomatitis virus conferred by expression of human MxA protein. J. Virol. 1990, 64, 3370–3375.
16. Nakajima, E.; Morozumi, T.; Tsukamoto, K.; Watanabe, T.; Plastow, G.; Mitsuhashi, T. A naturally occurring variant of porcine Mx1 associated with increased susceptibility to influenza virus in vitro. Biochem. Genet. 2007, 45, 11–24.
17. Palm, M.; Garigliany, M.M.; Cornet, F.; Desmecht, D. Interferon-induced Sus scrofa Mx1 blocks endocytic traffic of incoming influenza A virus particles. Vet. Res. 2010, 41, 29.

18. Fatima, U.; Zhang, Z.; Zhang, H.; Wang, X.F.; Xu, L.; Chu, X.; Ji, S.; Wang, X. Equine Mx1 Restricts Influenza A Virus Replication by Targeting at Distinct Site of its Nucleoprotein. Viruses 2019, 11, 1114.
19. Nakayama, M.; Nagata, K.; Kato, A.; Ishihama, A. Interferon-Inducible Mouse Mx1 Protein That Confers Resistance to Influenza-Virus Is Gtpase. J. Biol. Chem. 1991, 266, 21404–21408.
20. Staeheli, P.; Pitossi, F.; Pavlovic, J. Mx proteins: GTPases with antiviral activity. Trends Cell Biol. 1993, 3, 268–272.
21. Pitossi, F.; Blank, A.; Schroder, A.; Schwarz, A.; Hussi, P.; Schwemmle, M.; Pavlovic, J.; Staeheli, P. A functional GTP-binding motif is necessary for antiviral activity of Mx proteins. J. Virol. 1993, 67, 6726–6732.
22. Kochs, G.; Haener, M.; Aebi, U.; Haller, O. Self-assembly of human MxA GTPase into highly ordered dynamin-like oligomers. J. Biol. Chem. 2002, 277, 14172–14176.
23. Gao, S.; von der Malsburg, A.; Paeschke, S.; Behlke, J.; Haller, O.; Kochs, G.; Daumke, O. Structural basis of oligomerization in the stalk region of dynamin-like MxA. Nature 2010, 465, 502–506.
24. Gao, S.; von der Malsburg, A.; Dick, A.; Faelber, K.; Schroder, G.F.; Haller, O.; Kochs, G.; Daumke, O. Structure of myxovirus resistance protein a reveals intra- and intermolecular domain interactions required for the antiviral function. Immunity 2011, 35, 514–525.
25. Melen, K.; Ronni, T.; Broni, B.; Krug, R.M.; von Bonsdorff, C.H.; Julkunen, I. Interferon-induced Mx proteins form oligomers and contain a putative leucine zipper. J. Biol. Chem. 1992, 267, 25898–25907.
26. Nigg, P.E.; Pavlovic, J. Oligomerization and GTP-binding Requirements of MxA for Viral Target Recognition and Antiviral Activity against Influenza A Virus. J. Biol. Chem. 2015, 290, 29893–29906.
27. Verhelst, J.; Parthoens, E.; Schepens, B.; Fiers, W.; Saelens, X. Interferon-inducible protein Mx1 inhibits influenza virus by interfering with functional viral ribonucleoprotein complex assembly. J. Virol. 2012, 86, 13445–13455.
28. Xiao, H.; Killip, M.J.; Staeheli, P.; Randall, R.E.; Jackson, D. The human interferon-induced MxA protein inhibits early stages of influenza A virus infection by retaining the incoming viral genome in the cytoplasm. J. Virol. 2013, 87, 13053–13058.
29. Lee, S.; Ishitsuka, A.; Noguchi, M.; Hirohama, M.; Fujiyasu, Y.; Petric, P.P.; Schwemmle, M.; Staeheli, P.; Nagata, K.; Kawaguchi, A. Influenza restriction factor MxA functions as inflammasome sensor in the respiratory epithelium. Sci. Immunol. 2019, 4, eaau4643.
30. Ashenberg, O.; Padmakumar, J.; Doud, M.B.; Bloom, J.D. Deep mutational scanning identifies sites in influenza nucleoprotein that affect viral inhibition by MxA. PLoS Pathog. 2017, 13, e1006288.
31. Pavlovic, J.; Haller, O.; Staeheli, P. Human and mouse Mx proteins inhibit different steps of the influenza virus multiplication cycle. J. Virol. 1992, 66, 2564–2569.
32. Dittmann, J.; Stertz, S.; Grimm, D.; Steel, J.; Garcia-Sastre, A.; Haller, O.; Kochs, G. Influenza A virus strains differ in sensitivity to the antiviral action of Mx-GTPase. J. Virol. 2008, 82, 3624–3631.
33. Zimmermann, P.; Manz, B.; Haller, O.; Schwemmle, M.; Kochs, G. The viral nucleoprotein determines Mx sensitivity of influenza A viruses. J. Virol. 2011, 85, 8133–8140.
34. Ciminski, K.; Pulvermuller, J.; Adam, J.; Schwemmle, M. Human MxA is a potent interspecies barrier for the novel bat-derived influenza A-like virus H18N11. Emerg. Microbes Infect. 2019, 8, 556–563.
35. Haller, O.; Kochs, G. Mx genes: Host determinants controlling influenza virus infection and trans-species transmission. Hum. Genet. 2020, 139, 695–705.
36. Petric, P.P.; King, J.; Graf, L.; Pohlmann, A.; Beer, M.; Schwemmle, M. Increased Polymerase Activity of Zoonotic H7N9 Allows Partial Escape from MxA. Viruses 2022, 14, 2331.
37. Gotz, V.; Magar, L.; Dornfeld, D.; Giese, S.; Pohlmann, A.; Hoper, D.; Kong, B.W.; Jans, D.A.; Beer, M.; Haller, O.; et al. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Sci. Rep. 2016, 6, 23138.
38. Mänz, B.; Dornfeld, D.; Götz, V.; Zell, R.; Zimmermann, P.; Haller, O.; Kochs, G.; Schwemmle, M. Pandemic influenza A viruses escape from restriction by human MxA through adaptive mutations in the nucleoprotein. PLoS Pathog. 2013, 9, e1003279.
39. Riegger, D.; Hai, R.; Dornfeld, D.; Manz, B.; Leyva-Grado, V.; Sanchez-Aparicio, M.T.; Albrecht, R.A.; Palese, P.; Haller, O.; Schwemmle, M.; et al. The nucleoprotein of newly emerged H7N9 influenza A virus harbors a unique motif conferring resistance to antiviral human MxA. J. Virol. 2015, 89, 2241–2252.
40. Deeg, C.M.; Hassan, E.; Mutz, P.; Rheinemann, L.; Gotz, V.; Magar, L.; Schilling, M.; Kallfass, C.; Nurnberger, C.; Soubies, S.; et al. In vivo evasion of MxA by avian influenza viruses requires human signature in the viral nucleoprotein. J. Exp. Med. 2017, 214, 1239–1248.

41. Dornfeld, D.; Petric, P.P.; Hassan, E.; Zell, R.; Schwemmle, M. Eurasian Avian-Like Swine Influenza A Viruses Escape Human MxA Restriction through Distinct Mutations in Their Nucleoprotein. J. Virol. 2019, 93, 00997-18.

42. Shin, D.L.; Hatesuer, B.; Bergmann, S.; Nedelko, T.; Schughart, K. Protection from Severe Influenza Virus Infections in Mice Carrying the Mx1 Influenza Virus Resistance Gene Strongly Depends on Genetic Background. J. Virol. 2015, 89, 9998–10009.

43. Nurnberger, C.; Zimmermann, V.; Gerhardt, M.; Staeheli, P. Influenza Virus Susceptibility of Wild-Derived CAST/EiJ Mice Results from Two Amino Acid Changes in the MX1 Restriction Factor. J. Virol. 2016, 90, 10682–10692.

44. Chen, Y.; Graf, L.; Chen, T.; Liao, Q.; Bai, T.; Petric, P.P.; Zhu, W.; Yang, L.; Dong, J.; Lu, J.; et al. Rare variant MX1 alleles increase human susceptibility to zoonotic H7N9 influenza virus. Science 2021, 373, 918–922.

45. Graf, L.; Dick, A.; Sendker, F.; Barth, E.; Marz, M.; Daumke, O.; Kochs, G. Effects of allelic variations in the human myxovirus resistance protein A on its antiviral activity. J. Biol. Chem. 2018, 293, 3056–3072.

46. Mitchell, P.S.; Patzina, C.; Emerman, M.; Haller, O.; Malik, H.S.; Kochs, G. Evolution-guided identification of antiviral specificity determinants in the broadly acting interferon-induced innate immunity factor MxA. Cell Host Microbe 2012, 12, 598–604.

47. Friedman, R.L.; Manly, S.P.; McMahon, M.; Kerr, I.M.; Stark, G.R. Transcriptional and posttranscriptional regulation of interferon-induced gene expression in human cells. Cell 1984, 38, 745–755.

48. Chen, Y.X.; Welte, K.; Gebhard, D.H.; Evans, R.L. Induction of T cell aggregation by antibody to a 16kd human leukocyte surface antigen. J. Immunol. 1984, 133, 2496–2501.

49. Jaffe, E.A.; Armellino, D.; Lam, G.; Cordon-Cardo, C.; Murray, H.W.; Evans, R.L. IFN-gamma and IFN-alpha induce the expression and synthesis of Leu 13 antigen by cultured human endothelial cells. J. Immunol. 1989, 143, 3961–3966.

50. Lewin, A.R.; Reid, L.E.; McMahon, M.; Stark, G.R.; Kerr, I.M. Molecular analysis of a human interferon-inducible gene family. Eur. J. Biochem. 1991, 199, 417–423.

51. Brass, A.L.; Huang, I.C.; Benita, Y.; John, S.P.; Krishnan, M.N.; Feeley, E.M.; Ryan, B.J.; Weyer, J.L.; van der Weyden, L.; Fikrig, E.; et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. Cell 2009, 139, 1243–1254.

52. Melvin, W.J.; McMichael, T.M.; Chesarino, N.M.; Hach, J.C.; Yount, J.S. IFITMs from Mycobacteria Confer Resistance to Influenza Virus When Expressed in Human Cells. Viruses 2015, 7, 3035–3052.

53. Bailey, C.C.; Huang, I.C.; Kam, C.; Farzan, M. Ifitm3 limits the severity of acute influenza in mice. PLoS Pathog. 2012, 8, e1002909.

54. Everitt, A.R.; Clare, S.; Pertel, T.; John, S.P.; Wash, R.S.; Smith, S.E.; Chin, C.R.; Feeley, E.M.; Sims, J.S.; Adams, D.J.; et al. IFITM3 restricts the morbidity and mortality associated with influenza. Nature 2012, 484, 519–523.

55. Sun, X.; Zeng, H.; Kumar, A.; Belser, J.A.; Maines, T.R.; Tumpey, T.M. Constitutively Expressed IFITM3 Protein in Human Endothelial Cells Poses an Early Infection Block to Human Influenza Viruses. J. Virol. 2016, 90, 11157–11167.

56. Kenney, A.D.; McMichael, T.M.; Imas, A.; Chesarino, N.M.; Zhang, L.; Dorn, L.E.; Wu, Q.; Alfaour, O.; Amari, F.; Chen, M.; et al. IFITM3 protects the heart during influenza virus infection. Proc. Natl. Acad. Sci. USA 2019, 116, 18607–18612.

57. Smith, S.E.; Gibson, M.S.; Wash, R.S.; Ferrara, F.; Wright, E.; Temperton, N.; Kellam, P.; Fife, M. Chicken interferon-inducible transmembrane protein 3 restricts influenza viruses and lyssaviruses in vitro. J. Virol. 2013, 87, 12957–12966.

58. Lanz, C.; Yángüez, E.; Andenmatten, D.; Stertz, S. Swine interferon-inducible transmembrane proteins potently inhibit influenza A virus replication. J. Virol. 2015, 89, 863–869.

59. Benfield, C.T.; MacKenzie, F.; Ritzefeld, M.; Mazzon, M.; Weston, S.; Tate, E.W.; Teo, B.H.; Smith, S.E.; Kellam, P.; Holmes, E.C.; et al. Bat IFITM3 restriction depends on S-palmitoylation and a polymorphic site within the CD225 domain. Life Sci. Alliance 2020, 3, e201900542.

60. Horman, W.S.J.; Kedzierska, K.; Rootes, C.L.; Bean, A.G.D.; Nguyen, T.H.O.; Layton, D.S. Ferret Interferon (IFN)-Inducible Transmembrane Proteins Are Upregulated by both IFN-alpha and Influenza Virus Infection. J. Virol. 2021, 95, e0011121.

61. Lu, G.; Ou, J.; Cai, S.; Lai, Z.; Zhong, L.; Yin, X.; Li, S. Canine Interferon-Inducible Transmembrane Protein Is a Host Restriction Factor That Potently Inhibits Replication of Emerging Canine Influenza Virus. Front. Immunol. 2021, 12, 710705.

62. Rohaim, M.A.; Al-Natour, M.Q.; Abdelsabour, M.A.; El Naggar, R.F.; Madbouly, Y.M.; Ahmed, K.A.; Munir, M. Transgenic Chicks Expressing Interferon-Inducible Transmembrane Protein 1 (IFITM1) Restrict Highly Pathogenic H5N1 Influenza

Viruses. Int. J. Mol. Sci. 2021, 22, 8456.

63. Benfield, C.T.O.; Smith, S.E.; Wright, E.; Wash, R.S.; Ferrara, F.; Temperton, N.J.; Kellam, P. Bat and pig IFN-induced transmembrane protein 3 restrict cell entry by influenza virus and lyssaviruses. J. Gen. Virol. 2015, 96, 991–1005.
64. Blyth, G.A.; Chan, W.F.; Webster, R.G.; Magor, K.E. Duck Interferon-Inducible Transmembrane Protein 3 Mediates Restriction of Influenza Viruses. J. Virol. 2016, 90, 103–116.
65. Infusini, G.; Smith, J.M.; Yuan, H.; Pizzolla, A.; Ng, W.C.; Londrigan, S.L.; Haque, A.; Reading, P.C.; Villadangos, J.A.; Wakim, L.M. Respiratory DC Use IFITM3 to Avoid Direct Viral Infection and Safeguard Virus-Specific CD8+ T Cell Priming. PLoS ONE 2015, 10, e0143539.
66. Wakim, L.M.; Gupta, N.; Mintern, J.D.; Villadangos, J.A. Enhanced survival of lung tissue-resident memory CD8(+) T cells during infection with influenza virus due to selective expression of IFITM3. Nat. Immunol. 2013, 14, 238–245.
67. Smith, J.; Smith, N.; Yu, L.; Paton, I.R.; Gutowska, M.W.; Forrest, H.L.; Danner, A.F.; Seiler, J.P.; Digard, P.; Webster, R.G.; et al. A comparative analysis of host responses to avian influenza infection in ducks and chickens highlights a role for the interferon-induced transmembrane proteins in viral resistance. BMC Genom. 2015, 16, 574.
68. Feeley, E.M.; Sims, J.S.; John, S.P.; Chin, C.R.; Pertel, T.; Chen, L.M.; Gaiha, G.D.; Ryan, B.J.; Donis, R.O.; Elledge, S.J.; et al. IFITM3 inhibits influenza A virus infection by preventing cytosolic entry. PLoS Pathog. 2011, 7, e1002337.
69. Amini-Bavil-Olyaee, S.; Choi, Y.J.; Lee, J.H.; Shi, M.; Huang, I.C.; Farzan, M.; Jung, J.U. The antiviral effector IFITM3 disrupts intracellular cholesterol homeostasis to block viral entry. Cell Host Microbe 2013, 13, 452–464.
70. Desai, T.M.; Marin, M.; Chin, C.R.; Savidis, G.; Brass, A.L.; Melikyan, G.B. IFITM3 restricts influenza A virus entry by blocking the formation of fusion pores following virus-endosome hemifusion. PLoS Pathog. 2014, 10, e1004048.
71. Jia, R.; Xu, F.; Qian, J.; Yao, Y.; Miao, C.; Zheng, Y.M.; Liu, S.L.; Guo, F.; Geng, Y.; Qiao, W.; et al. Identification of an endocytic signal essential for the antiviral action of IFITM3. Cell Microbiol. 2014, 16, 1080–1093.
72. Chesarino, N.M.; Compton, A.A.; McMichael, T.M.; Kenney, A.D.; Zhang, L.; Soewarna, V.; Davis, M.; Schwartz, O.; Yount, J.S. IFITM 3 requires an amphipathic helix for antiviral activity. EMBO Rep. 2017, 18, 1740–1751.
73. Kummer, S.; Avinoam, O.; Krausslich, H.G. IFITM3 Clusters on Virus Containing Endosomes and Lysosomes Early in the Influenza A Infection of Human Airway Epithelial Cells. Viruses 2019, 11, 548.
74. Rahman, K.; Datta, S.A.K.; Beaven, A.H.; Jolley, A.A.; Sodt, A.J.; Compton, A.A. Cholesterol Binds the Amphipathic Helix of IFITM3 and Regulates Antiviral Activity. J. Mol. Biol. 2022, 434, 167759.
75. Klein, S.; Golani, G.; Lolicato, F.; Lahr, C.; Beyer, D.; Herrmann, A.; Wachsmuth-Melm, M.; Reddmann, N.; Brecht, R.; Hosseinzadeh, M.; et al. IFITM3 blocks influenza virus entry by sorting lipids and stabilizing hemifusion. Cell Host Microbe 2023, 31, 616–633.e20.
76. Xu, W.; Wang, Y.; Li, L.; Qu, X.; Liu, Q.; Li, T.; Wu, S.; Liao, M.; Jin, N.; Du, S.; et al. Transmembrane domain of IFITM3 is responsible for its interaction with influenza virus HA(2) subunit. Virol. Sin. 2022, 37, 664–675.
77. Bailey, C.C.; Kondur, H.R.; Huang, I.C.; Farzan, M. Interferon-induced transmembrane protein 3 is a type II transmembrane protein. J. Biol. Chem. 2013, 288, 32184–32193.
78. Spence, J.S.; He, R.; Hoffmann, H.H.; Das, T.; Thinon, E.; Rice, C.M.; Peng, T.; Chandran, K.; Hang, H.C. IFITM3 directly engages and shuttles incoming virus particles to lysosomes. Nat. Chem. Biol. 2019, 15, 259–268.
79. Li, K.; Markosyan, R.M.; Zheng, Y.M.; Golfetto, O.; Bungart, B.; Li, M.; Ding, S.; He, Y.; Liang, C.; Lee, J.C.; et al. IFITM proteins restrict viral membrane hemifusion. PLoS Pathog. 2013, 9, e1003124.
80. Yount, J.S.; Moltedo, B.; Yang, Y.Y.; Charron, G.; Moran, T.M.; Lopez, C.B.; Hang, H.C. Palmitoylome profiling reveals S-palmitoylation-dependent antiviral activity of IFITM3. Nat. Chem. Biol. 2010, 6, 610–614.
81. Yount, J.S.; Karssemeijer, R.A.; Hang, H.C. S-palmitoylation and ubiquitination differentially regulate interferon-induced transmembrane protein 3 (IFITM3)-mediated resistance to influenza virus. J. Biol. Chem. 2012, 287, 19631–19641.
82. Hach, J.C.; McMichael, T.; Chesarino, N.M.; Yount, J.S. Palmitoylation on conserved and nonconserved cysteines of murine IFITM1 regulates its stability and anti-influenza A virus activity. J. Virol. 2013, 87, 9923–9927.
83. Shan, Z.; Han, Q.; Nie, J.; Cao, X.; Chen, Z.; Yin, S.; Gao, Y.; Lin, F.; Zhou, X.; Xu, K.; et al. Negative regulation of interferon-induced transmembrane protein 3 by SET7-mediated lysine monomethylation. J. Biol. Chem. 2013, 288, 35093–35103.
84. Chesarino, N.M.; McMichael, T.M.; Hach, J.C.; Yount, J.S. Phosphorylation of the antiviral protein interferon-inducible transmembrane protein 3 (IFITM3) dually regulates its endocytosis and ubiquitination. J. Biol. Chem. 2014, 289, 11986–11992.

85. Chesarino, N.M.; McMichael, T.M.; Yount, J.S. E3 Ubiquitin Ligase NEDD4 Promotes Influenza Virus Infection by Decreasing Levels of the Antiviral Protein IFITM3. PLoS Pathog. 2015, 11, e1005095.

86. Shan, J.; Zhao, B.; Shan, Z.; Nie, J.; Deng, R.; Xiong, R.; Tsun, A.; Pan, W.; Zhao, H.; Chen, L.; et al. Histone demethylase LSD1 restricts influenza A virus infection by erasing IFITM3-K88 monomethylation. PLoS Pathog. 2017, 13, e1006773.

87. McMichael, T.M.; Zhang, L.; Chemudupati, M.; Hach, J.C.; Kenney, A.D.; Hang, H.C.; Yount, J.S. The palmitoyltransferase ZDHHC20 enhances interferon-induced transmembrane protein 3 (IFITM3) palmitoylation and antiviral activity. J. Biol. Chem. 2017, 292, 21517–21526.

88. Hensen, L.; Matrosovich, T.; Roth, K.; Klenk, H.D.; Matrosovich, M. HA-Dependent Tropism of H5N1 and H7N9 Influenza Viruses to Human Endothelial Cells Is Determined by Reduced Stability of the HA, Which Allows the Virus To Cope with Inefficient Endosomal Acidification and Constitutively Expressed IFITM3. J. Virol. 2019, 94, e01223-19.

89. Allen, E.K.; Randolph, A.G.; Bhangale, T.; Dogra, P.; Ohlson, M.; Oshansky, C.M.; Zamora, A.E.; Shannon, J.P.; Finkelstein, D.; Dressen, A.; et al. SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. Nat. Med. 2017, 23, 975–983.

90. Kim, Y.C.; Jeong, M.J.; Jeong, B.H. Strong association of regulatory single nucleotide polymorphisms (SNPs) of the IFITM3 gene with influenza H1N1 2009 pandemic virus infection. Cell Mol. Immunol. 2020, 17, 662–664.

91. Jia, R.; Pan, Q.; Ding, S.; Rong, L.; Liu, S.L.; Geng, Y.; Qiao, W.; Liang, C. The N-terminal region of IFITM3 modulates its antiviral activity by regulating IFITM3 cellular localization. J. Virol. 2012, 86, 13697–13707.

92. John, S.P.; Chin, C.R.; Perreira, J.M.; Feeley, E.M.; Aker, A.M.; Savidis, G.; Smith, S.E.; Elia, A.E.; Everitt, A.R.; Vora, M.; et al. The CD225 domain of IFITM3 is required for both IFITM protein association and inhibition of influenza A virus and dengue virus replication. J. Virol. 2013, 87, 7837–7852.

93. Zhang, Y.H.; Zhao, Y.; Li, N.; Peng, Y.C.; Giannoulatou, E.; Jin, R.H.; Yan, H.P.; Wu, H.; Liu, J.H.; Liu, N.; et al. Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. Nat. Commun. 2013, 4, 1418.

94. Pan, Y.; Yang, P.; Dong, T.; Zhang, Y.; Shi, W.; Peng, X.; Cui, S.; Zhang, D.; Lu, G.; Liu, Y.; et al. IFITM3 Rs12252-C Variant Increases Potential Risk for Severe Influenza Virus Infection in Chinese Population. Front. Cell Infect. Microbiol. 2017, 7, 294.

95. Wang, Z.; Zhang, A.; Wan, Y.; Liu, X.; Qiu, C.; Xi, X.; Ren, Y.; Wang, J.; Dong, Y.; Bao, M.; et al. Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection. Proc. Natl. Acad. Sci. USA 2014, 111, 769–774.

96. Xuan, Y.; Wang, L.N.; Li, W.; Zi, H.R.; Guo, Y.; Yan, W.J.; Chen, X.B.; Wei, P.M. IFITM3 rs12252 T>C polymorphism is associated with the risk of severe influenza: A meta-analysis. Epidemiol. Infect. 2015, 143, 2975–2984.

97. Lee, N.; Cao, B.; Ke, C.; Lu, H.; Hu, Y.; Tam, C.H.T.; Ma, R.C.W.; Guan, D.; Zhu, Z.; Li, H.; et al. IFITM3, TLR3, and CD55 Gene SNPs and Cumulative Genetic Risks for Severe Outcomes in Chinese Patients With H7N9/H1N1pdm09 Influenza. J. Infect. Dis. 2017, 216, 97–104.

98. Kim, Y.C.; Jeong, B.H. Ethnic variation in risk genotypes based on single nucleotide polymorphisms (SNPs) of the interferon-inducible transmembrane 3 (IFITM3) gene, a susceptibility factor for pandemic 2009 H1N1 influenza A virus. Immunogenetics 2020, 72, 447–453.

99. Yang, X.; Tan, B.; Zhou, X.; Xue, J.; Zhang, X.; Wang, P.; Shao, C.; Li, Y.; Li, C.; Xia, H.; et al. Interferon-Inducible Transmembrane Protein 3 Genetic Variant rs12252 and Influenza Susceptibility and Severity: A Meta-Analysis. PLoS ONE 2015, 10, e0124985.

100. Mehrbod, P.; Eybpoosh, S.; Fotouhi, F.; Shokouhi Targhi, H.; Mazaheri, V.; Farahmand, B. Association of IFITM3 rs12252 polymorphisms, BMI, diabetes, and hypercholesterolemia with mild flu in an Iranian population. Virol. J. 2017, 14, 218.

101. Mills, T.C.; Rautanen, A.; Elliott, K.S.; Parks, T.; Naranbhai, V.; Ieven, M.M.; Butler, C.C.; Little, P.; Verheij, T.; Garrard, C.S.; et al. IFITM3 and susceptibility to respiratory viral infections in the community. J. Infect. Dis. 2014, 209, 1028–1031.

102. Gaio, V.; Nunes, B.; Pechirra, P.; Conde, P.; Guiomar, R.; Dias, C.M.; Barreto, M. Hospitalization Risk Due to Respiratory Illness Associated with Genetic Variation at IFITM3 in Patients with Influenza A(H1N1)pdm09 Infection: A Case-Control Study. PLoS ONE 2016, 11, e0158181.

103. Lopez-Rodriguez, M.; Herrera-Ramos, E.; Sole-Violan, J.; Ruiz-Hernandez, J.J.; Borderias, L.; Horcajada, J.P.; Lerma-Chippirraz, E.; Rajas, O.; Briones, M.; Perez-Gonzalez, M.C.; et al. IFITM3 and severe influenza virus infection. No evidence of genetic association. Eur. J. Clin. Microbiol. Infect. Dis. 2016, 35, 1811–1817.

104. Randolph, A.G.; Yip, W.K.; Allen, E.K.; Rosenberger, C.M.; Agan, A.A.; Ash, S.A.; Zhang, Y.; Bhangale, T.R.; Finkelstein, D.; Cvijanovich, N.Z.; et al. Evaluation of IFITM3 rs12252 Association With Severe Pediatric Influenza Infection. J. Infect. Dis. 2017, 216, 14–21.

105. Martins, J.S.C.; Oliveira, M.L.A.; Garcia, C.C.; Siqueira, M.M.; Matos, A.R. Investigation of Human IFITM3 Polymorphisms rs34481144A and rs12252C and Risk for Influenza A(H1N1)pdm09 Severity in a Brazilian Cohort. Front. Cell Infect. Microbiol. 2020, 10, 352.

106. David, S.; Correia, V.; Antunes, L.; Faria, R.; Ferrao, J.; Faustino, P.; Nunes, B.; Maltez, F.; Lavinha, J.; Rebelo de Andrade, H. Population genetics of IFITM3 in Portugal and Central Africa reveals a potential modifier of influenza severity. Immunogenetics 2018, 70, 169–177.

107. Makvandi-Nejad, S.; Laurenson-Schafer, H.; Wang, L.; Wellington, D.; Zhao, Y.; Jin, B.; Qin, L.; Kite, K.; Moghadam, H.K.; Song, C.; et al. Lack of Truncated IFITM3 Transcripts in Cells Homozygous for the rs12252-C Variant That is Associated With Severe Influenza Infection. J. Infect. Dis. 2018, 217, 257–262.

108. Kim, Y.C.; Won, S.Y.; Jeong, B.H. The first association study of single-nucleotide polymorphisms (SNPs) of the IFITM1 gene with influenza H1N1 2009 pandemic virus infection. Mol. Cell Toxicol. 2021, 17, 179–186.

109. Reddy, B.A.; Etkin, L.D.; Freemont, P.S. A novel zinc finger coiled-coil domain in a family of nuclear proteins. Trends Biochem. Sci. 1992, 17, 344–345.

110. Reymond, A.; Meroni, G.; Fantozzi, A.; Merla, G.; Cairo, S.; Luzi, L.; Riganelli, D.; Zanaria, E.; Messali, S.; Cainarca, S.; et al. The tripartite motif family identifies cell compartments. EMBO J. 2001, 20, 2140–2151.

111. Lavau, C.; Marchio, A.; Fagioli, M.; Jansen, J.; Falini, B.; Lebon, P.; Grosveld, F.; Pandolfi, P.P.; Pelicci, P.G.; Dejean, A. The acute promyelocytic leukaemia-associated PML gene is induced by interferon. Oncogene 1995, 11, 871–876.

112. Chelbi-Alix, M.K.; Quignon, F.; Pelicano, L.; Koken, M.H.; de The, H. Resistance to virus infection conferred by the interferon-induced promyelocytic leukemia protein. J. Virol. 1998, 72, 1043–1051.

113. Carthagena, L.; Bergamaschi, A.; Luna, J.M.; David, A.; Uchil, P.D.; Margottin-Goguet, F.; Mothes, W.; Hazan, U.; Transy, C.; Pancino, G.; et al. Human TRIM gene expression in response to interferons. PLoS ONE 2009, 4, e4894.

114. Di Pietro, A.; Kajaste-Rudnitski, A.; Oteiza, A.; Nicora, L.; Towers, G.J.; Mechti, N.; Vicenzi, E. TRIM22 inhibits influenza A virus infection by targeting the viral nucleoprotein for degradation. J. Virol. 2013, 87, 4523–4533.

115. Liu, B.; Li, N.L.; Shen, Y.; Bao, X.; Fabrizio, T.; Elbahesh, H.; Webby, R.J.; Li, K. The C-Terminal Tail of TRIM56 Dictates Antiviral Restriction of Influenza A and B Viruses by Impeding Viral RNA Synthesis. J. Virol. 2016, 90, 4369–4382.

116. Meyerson, N.R.; Zhou, L.; Guo, Y.R.; Zhao, C.; Tao, Y.J.; Krug, R.M.; Sawyer, S.L. Nuclear TRIM25 Specifically Targets Influenza Virus Ribonucleoproteins to Block the Onset of RNA Chain Elongation. Cell Host Microbe 2017, 22, 627–638 e627.

117. Wu, X.; Wang, J.; Wang, S.; Wu, F.; Chen, Z.; Li, C.; Cheng, G.; Qin, F.X. Inhibition of Influenza A Virus Replication by TRIM14 via Its Multifaceted Protein-Protein Interaction With NP. Front. Microbiol. 2019, 10, 344.

118. Sun, N.; Jiang, L.; Ye, M.; Wang, Y.; Wang, G.; Wan, X.; Zhao, Y.; Wen, X.; Liang, L.; Ma, S.; et al. TRIM35 mediates protection against influenza infection by activating TRAF3 and degrading viral PB2. Protein Cell 2020, 11, 894–914.

119. Charman, M.; McFarlane, S.; Wojtus, J.K.; Sloan, E.; Dewar, R.; Leeming, G.; Al-Saadi, M.; Hunter, L.; Carroll, M.W.; Stewart, J.P.; et al. Constitutive TRIM22 Expression in the Respiratory Tract Confers a Pre-Existing Defence Against Influenza A Virus Infection. Front. Cell Infect. Microbiol. 2021, 11, 689707.

120. Choudhury, N.R.; Trus, I.; Heikel, G.; Wolczyk, M.; Szymanski, J.; Bolembach, A.; Dos Santos Pinto, R.M.; Smith, N.; Trubitsyna, M.; Gaunt, E.; et al. TRIM25 inhibits influenza A virus infection, destabilizes viral mRNA, but is redundant for activating the RIG-I pathway. Nucleic Acids Res. 2022, 50, 7097–7114.

121. Wang, X.; Xiong, J.; Zhou, D.; Zhang, S.; Wang, L.; Tian, Q.; Li, C.; Liu, J.; Wu, Y.; Li, J.; et al. TRIM34 modulates influenza virus-activated programmed cell death by targeting Z-DNA-binding protein 1 for K63-linked polyubiquitination. J. Biol. Chem. 2022, 298, 101611.

122. Lin, L.; Wang, X.; Chen, Z.; Deng, T.; Yan, Y.; Dong, W.; Huang, Y.; Zhou, J. TRIM21 restricts influenza A virus replication by ubiquitination-dependent degradation of M1. PLoS Pathog. 2023, 19, e1011472.

123. Pagani, I.; Di Pietro, A.; Oteiza, A.; Ghitti, M.; Mechti, N.; Naffakh, N.; Vicenzi, E. Mutations Conferring Increased Sensitivity to Tripartite Motif 22 Restriction Accumulated Progressively in the Nucleoprotein of Seasonal Influenza A (H1N1) Viruses between 1918 and 2009. mSphere 2018, 3, 00110–00118.

124. Gack, M.U.; Albrecht, R.A.; Urano, T.; Inn, K.S.; Huang, I.C.; Carnero, E.; Farzan, M.; Inoue, S.; Jung, J.U.; Garcia-Sastre, A. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor

RIG-I. Cell Host Microbe 2009, 5, 439–449.

125. Rajsbaum, R.; Albrecht, R.A.; Wang, M.K.; Maharaj, N.P.; Versteeg, G.A.; Nistal-Villan, E.; Garcia-Sastre, A.; Gack, M.U. Species-specific inhibition of RIG-I ubiquitination and IFN induction by the influenza A virus NS1 protein. PLoS Pathog. 2012, 8, e1003059.

126. Koliopoulos, M.G.; Lethier, M.; van der Veen, A.G.; Haubrich, K.; Hennig, J.; Kowalinski, E.; Stevens, R.V.; Martin, S.R.; Reis e Sousa, C.; Cusack, S.; et al. Molecular mechanism of influenza A NS1-mediated TRIM25 recognition and inhibition. Nat. Commun. 2018, 9, 1820.

127. Evseev, D.; Miranzo-Navarro, D.; Fleming-Canepa, X.; Webster, R.G.; Magor, K.E. Avian Influenza NS1 Proteins Inhibit Human, but Not Duck, RIG-I Ubiquitination and Interferon Signaling. J. Virol. 2022, 96, e0077622.

128. Zhu, Q.; Yang, H.; Chen, W.; Cao, W.; Zhong, G.; Jiao, P.; Deng, G.; Yu, K.; Yang, C.; Bu, Z.; et al. A naturally occurring deletion in its NS gene contributes to the attenuation of an H5N1 swine influenza virus in chickens. J. Virol. 2008, 82, 220–228.

129. Knight, M.; Cayley, P.J.; Silverman, R.H.; Wreschner, D.H.; Gilbert, C.S.; Brown, R.E.; Kerr, I.M. Radioimmune, radiobinding and HPLC analysis of 2-5A and related oligonucleotides from intact cells. Nature 1980, 288, 189–192.

130. Kerr, I.M.; Brown, R.E. pppA2′p5′A2′p5′A: An inhibitor of protein synthesis synthesized with an enzyme fraction from interferon-treated cells. Proc. Natl. Acad. Sci. USA 1978, 75, 256–260.

131. Floyd-Smith, G.; Slattery, E.; Lengyel, P. Interferon action: RNA cleavage pattern of a (2’-5’)oligoadenylate--dependent endonuclease. Science 1981, 212, 1030–1032.

132. Min, J.Y.; Krug, R.M. The primary function of RNA binding by the influenza A virus NS1 protein in infected cells: Inhibiting the 2’-5’ oligo (A) synthetase/RNase L pathway. Proc. Natl. Acad. Sci. USA 2006, 103, 7100–7105.

133. Cooper, D.A.; Banerjee, S.; Chakrabarti, A.; Garcia-Sastre, A.; Hesselberth, J.R.; Silverman, R.H.; Barton, D.J. RNase L targets distinct sites in influenza A virus RNAs. J. Virol. 2015, 89, 2764–2776.

134. Li, Y.; Banerjee, S.; Wang, Y.; Goldstein, S.A.; Dong, B.; Gaughan, C.; Silverman, R.H.; Weiss, S.R. Activation of RNase L is dependent on OAS3 expression during infection with diverse human viruses. Proc. Natl. Acad. Sci. USA 2016, 113, 2241–2246.

135. Zhao, Z.; Li, J.; Feng, Y.; Kang, X.; Li, Y.; Chen, Y.; Li, W.; Yang, W.; Zhao, L.; Huang, S.; et al. Host DNA Demethylation Induced by DNMT1 Inhibition Up-Regulates Antiviral OASL Protein during Influenza a Virus Infection. Viruses 2023, 15, 1646.

136. Sanchez-Gonzalez, M.T.; Cienfuegos-Jimenez, O.; Alvarez-Cuevas, S.; Perez-Maya, A.A.; Borrego-Soto, G.; Marino-Martinez, I.A. Prevalence of the SNP rs10774671 of the OAS1 gene in Mexico as a possible predisposing factor for RNA virus disease. Int. J. Mol. Epidemiol. Genet. 2021, 12, 52–60.

137. Fensterl, V.; Sen, G.C. The ISG56/IFIT1 gene family. J. Interf. Cytokine Res. 2011, 31, 71–78.

138. Chebath, J.; Merlin, G.; Metz, R.; Benech, P.; Revel, M. Interferon-induced 56,000 Mr protein and its mRNA in human cells: Molecular cloning and partial sequence of the cDNA. Nucleic Acids Res. 1983, 11, 1213–1226.

139. Kusari, J.; Sen, G.C. Transcriptional analyses of interferon-inducible mRNAs. Mol. Cell Biol. 1987, 7, 528–531.

140. Pichlmair, A.; Lassnig, C.; Eberle, C.A.; Gorna, M.W.; Baumann, C.L.; Burkard, T.R.; Burckstummer, T.; Stefanovic, A.; Krieger, S.; Bennett, K.L.; et al. IFIT1 is an antiviral protein that recognizes 5’-triphosphate RNA. Nat. Immunol. 2011, 12, 624–630.

141. Rohaim, M.A.; Santhakumar, D.; Naggar, R.F.E.; Iqbal, M.; Hussein, H.A.; Munir, M. Chickens Expressing IFIT5 Ameliorate Clinical Outcome and Pathology of Highly Pathogenic Avian Influenza and Velogenic Newcastle Disease Viruses. Front. Immunol. 2018, 9, 2025.

142. Rong, E.; Hu, J.; Yang, C.; Chen, H.; Wang, Z.; Liu, X.; Liu, W.; Lu, C.; He, P.; Wang, X.; et al. Broad-spectrum antiviral functions of duck interferon-induced protein with tetratricopeptide repeats (AvIFIT). Dev. Comp. Immunol. 2018, 84, 71–81.

143. Santhakumar, D.; Rohaim, M.; Hussein, H.A.; Hawes, P.; Ferreira, H.L.; Behboudi, S.; Iqbal, M.; Nair, V.; Arns, C.W.; Munir, M. Chicken Interferon-induced Protein with Tetratricopeptide Repeats 5 Antagonizes Replication of RNA Viruses. Sci. Rep. 2018, 8, 6794.

144. Zhu, Z.; Yang, X.; Huang, C.; Liu, L. The Interferon-Induced Protein with Tetratricopeptide Repeats Repress Influenza Virus Infection by Inhibiting Viral RNA Synthesis. Viruses 2023, 15, 1412.

145. Hou, L.; Li, J.; Qu, H.; Yang, L.; Chen, Y.; Du, Q.; Liu, W. Inhibition of replication and transcription of WSN influenza A virus by IFIT family genes. Sheng Wu Gong Cheng Xue Bao 2015, 31, 123–134.

146. Abbas, Y.M.; Pichlmair, A.; Gorna, M.W.; Superti-Furga, G.; Nagar, B. Structural basis for viral 5’-PPP-RNA recognition by human IFIT proteins. Nature 2013, 494, 60–64.

147. Pinto, A.K.; Williams, G.D.; Szretter, K.J.; White, J.P.; Proenca-Modena, J.L.; Liu, G.; Olejnik, J.; Brien, J.D.; Ebihara, H.; Muhlberger, E.; et al. Human and Murine IFIT1 Proteins Do Not Restrict Infection of Negative-Sense RNA Viruses of the Orthomyxoviridae, Bunyaviridae, and Filoviridae Families. J. Virol. 2015, 89, 9465–9476.

148. Tran, V.; Ledwith, M.P.; Thamamongood, T.; Higgins, C.A.; Tripathi, S.; Chang, M.W.; Benner, C.; Garcia-Sastre, A.; Schwemmle, M.; Boon, A.C.M.; et al. Influenza virus repurposes the antiviral protein IFIT2 to promote translation of viral mRNAs. Nat. Microbiol. 2020, 5, 1490–1503.

149. Cheng, Y.S.; Colonno, R.J.; Yin, F.H. Interferon induction of fibroblast proteins with guanylate binding activity. J. Biol. Chem. 1983, 258, 7746–7750.

150. Schwemmle, M.; Staeheli, P. The Interferon-Induced 67-Kda Guanylate-Binding Protein (Hgbp1) Is a Gtpase That Converts Gtp to Gmp. J. Biol. Chem. 1994, 269, 11299–11305.

151. Nordmann, A.; Wixler, L.; Boergeling, Y.; Wixler, V.; Ludwig, S. A new splice variant of the human guanylate-binding protein 3 mediates anti-influenza activity through inhibition of viral transcription and replication. FASEB J. 2012, 26, 1290–1300.

152. Feng, J.; Cao, Z.; Wang, L.; Wan, Y.; Peng, N.; Wang, Q.; Chen, X.; Zhou, Y.; Zhu, Y. Inducible GBP5 Mediates the Antiviral Response via Interferon-Related Pathways during Influenza A Virus Infection. J. Innate Immun. 2017, 9, 419–435.

153. Braun, E.; Hotter, D.; Koepke, L.; Zech, F.; Gross, R.; Sparrer, K.M.J.; Muller, J.A.; Pfaller, C.K.; Heusinger, E.; Wombacher, R.; et al. Guanylate-Binding Proteins 2 and 5 Exert Broad Antiviral Activity by Inhibiting Furin-Mediated Processing of Viral Envelope Proteins. Cell Rep. 2019, 27, 2092–2104 e2010.

154. Zhu, Z.; Shi, Z.; Yan, W.; Wei, J.; Shao, D.; Deng, X.; Wang, S.; Li, B.; Tong, G.; Ma, Z. Nonstructural protein 1 of influenza A virus interacts with human guanylate-binding protein 1 to antagonize antiviral activity. PLoS ONE 2013, 8, e55920.

155. Kupzig, S.; Korolchuk, V.; Rollason, R.; Sugden, A.; Wilde, A.; Banting, G. Bst-2/HM1.24 is a raft-associated apical membrane protein with an unusual topology. Traffic 2003, 4, 694–709.

156. Winkler, M.; Bertram, S.; Gnirss, K.; Nehlmeier, I.; Gawanbacht, A.; Kirchhoff, F.; Ehrhardt, C.; Ludwig, S.; Kiene, M.; Moldenhauer, A.S.; et al. Influenza A virus does not encode a tetherin antagonist with Vpu-like activity and induces IFN-dependent tetherin expression in infected cells. PLoS ONE 2012, 7, e43337.

157. Watanabe, R.; Leser, G.P.; Lamb, R.A. Influenza virus is not restricted by tetherin whereas influenza VLP production is restricted by tetherin. Virology 2011, 417, 50–56.

158. Yondola, M.A.; Fernandes, F.; Belicha-Villanueva, A.; Uccelini, M.; Gao, Q.; Carter, C.; Palese, P. Budding capability of the influenza virus neuraminidase can be modulated by tetherin. J. Virol. 2011, 85, 2480–2491.

159. Gnirss, K.; Zmora, P.; Blazejewska, P.; Winkler, M.; Lins, A.; Nehlmeier, I.; Gartner, S.; Moldenhauer, A.S.; Hofmann-Winkler, H.; Wolff, T.; et al. Tetherin Sensitivity of Influenza A Viruses Is Strain Specific: Role of Hemagglutinin and Neuraminidase. J. Virol. 2015, 89, 9178–9188.

160. Hu, S.; Yin, L.; Mei, S.; Li, J.; Xu, F.; Sun, H.; Liu, X.; Cen, S.; Liang, C.; Li, A.; et al. BST-2 restricts IAV release and is countered by the viral M2 protein. Biochem. J. 2017, 474, 715–730.

161. Bruce, E.A.; Abbink, T.E.; Wise, H.M.; Rollason, R.; Galao, R.P.; Banting, G.; Neil, S.J.; Digard, P. Release of filamentous and spherical influenza A virus is not restricted by tetherin. J. Gen. Virol. 2012, 93, 963–969.

162. Londrigan, S.L.; Tate, M.D.; Job, E.R.; Moffat, J.M.; Wakim, L.M.; Gonelli, C.A.; Purcell, D.F.; Brooks, A.G.; Villadangos, J.A.; Reading, P.C. Endogenous murine BST-2/tetherin is not a major restriction factor of influenza A virus infection. PLoS ONE 2015, 10, e0142925.

163. Zheng, Y.; Hao, X.; Zheng, Q.; Lin, X.; Zhang, X.; Zeng, W.; Ding, S.; Zhou, P.; Li, S. Canine Influenza Virus is Mildly Restricted by Canine Tetherin Protein. Viruses 2018, 10, 565.

164. Mangeat, B.; Cavagliotti, L.; Lehmann, M.; Gers-Huber, G.; Kaur, I.; Thomas, Y.; Kaiser, L.; Piguet, V. Influenza virus partially counteracts restriction imposed by tetherin/BST-2. J. Biol. Chem. 2012, 287, 22015–22029.

165. Leyva-Grado, V.H.; Hai, R.; Fernandes, F.; Belicha-Villanueva, A.; Carter, C.; Yondola, M.A. Modulation of an ectodomain motif in the influenza A virus neuraminidase alters tetherin sensitivity and results in virus attenuation in vivo. J. Mol. Biol. 2014, 426, 1308–1321.

166. Farrell, P.J.; Broeze, R.J.; Lengyel, P. Accumulation of an mRNA and protein in interferon-treated Ehrlich ascites tumour cells. Nature 1979, 279, 523–525.

167. Haas, A.L.; Ahrens, P.; Bright, P.M.; Ankel, H. Interferon induces a 15-kilodalton protein exhibiting marked homology to ubiquitin. J. Biol. Chem. 1987, 262, 11315–11323.

168. Lenschow, D.J.; Lai, C.; Frias-Staheli, N.; Giannakopoulos, N.V.; Lutz, A.; Wolff, T.; Osiak, A.; Levine, B.; Schmidt, R.E.; Garcia-Sastre, A.; et al. IFN-stimulated gene 15 functions as a critical antiviral molecule against influenza, herpes, and Sindbis viruses. Proc. Natl. Acad. Sci. USA 2007, 104, 1371–1376.

169. Tang, Y.; Zhong, G.; Zhu, L.; Liu, X.; Shan, Y.; Feng, H.; Bu, Z.; Chen, H.; Wang, C. Herc5 attenuates influenza A virus by catalyzing ISGylation of viral NS1 protein. J. Immunol. 2010, 184, 5777–5790.

170. Zhao, C.; Hsiang, T.Y.; Kuo, R.L.; Krug, R.M. ISG15 conjugation system targets the viral NS1 protein in influenza A virus-infected cells. Proc. Natl. Acad. Sci. USA 2010, 107, 2253–2258.

171. Sanyal, S.; Ashour, J.; Maruyama, T.; Altenburg, A.F.; Cragnolini, J.J.; Bilate, A.; Avalos, A.M.; Kundrat, L.; Garcia-Sastre, A.; Ploegh, H.L. Type I interferon imposes a TSG101/ISG15 checkpoint at the Golgi for glycoprotein trafficking during influenza virus infection. Cell Host Microbe 2013, 14, 510–521.

172. Kim, K.I.; Giannakopoulos, N.V.; Virgin, H.W.; Zhang, D.E. Interferon-inducible ubiquitin E2, Ubc8, is a conjugating enzyme for protein ISGylation. Mol. Cell Biol. 2004, 24, 9592–9600.

173. Zhao, C.; Beaudenon, S.L.; Kelley, M.L.; Waddell, M.B.; Yuan, W.; Schulman, B.A.; Huibregtse, J.M.; Krug, R.M. The UbcH8 ubiquitin E2 enzyme is also the E2 enzyme for ISG15, an IFN-alpha/beta-induced ubiquitin-like protein. Proc. Natl. Acad. Sci. USA 2004, 101, 7578–7582.

174. Dastur, A.; Beaudenon, S.; Kelley, M.; Krug, R.M.; Huibregtse, J.M. Herc5, an interferon-induced HECT E3 enzyme, is required for conjugation of ISG15 in human cells. J. Biol. Chem. 2006, 281, 4334–4338.

175. Wong, J.J.; Pung, Y.F.; Sze, N.S.; Chin, K.C. HERC5 is an IFN-induced HECT-type E3 protein ligase that mediates type I IFN-induced ISGylation of protein targets. Proc. Natl. Acad. Sci. USA 2006, 103, 10735–10740.

176. Zou, W.; Zhang, D.E. The interferon-inducible ubiquitin-protein isopeptide ligase (E3) EFP also functions as an ISG15 E3 ligase. J. Biol. Chem. 2006, 281, 3989–3994.

177. Yuan, W.; Krug, R.M. Influenza B virus NS1 protein inhibits conjugation of the interferon (IFN)-induced ubiquitin-like ISG15 protein. EMBO J. 2001, 20, 362–371.

178. Meurs, E.; Chong, K.; Galabru, J.; Thomas, N.S.; Kerr, I.M.; Williams, B.R.; Hovanessian, A.G. Molecular cloning and characterization of the human double-stranded RNA-activated protein kinase induced by interferon. Cell 1990, 62, 379–390.

179. Balachandran, S.; Roberts, P.C.; Brown, L.E.; Truong, H.; Pattnaik, A.K.; Archer, D.R.; Barber, G.N. Essential role for the dsRNA-dependent protein kinase PKR in innate immunity to viral infection. Immunity 2000, 13, 129–141.

180. Bergmann, M.; Garcia-Sastre, A.; Carnero, E.; Pehamberger, H.; Wolff, K.; Palese, P.; Muster, T. Influenza virus NS1 protein counteracts PKR-mediated inhibition of replication. J. Virol. 2000, 74, 6203–6206.

181. Katze, M.G.; Tomita, J.; Black, T.; Krug, R.M.; Safer, B.; Hovanessian, A. Influenza virus regulates protein synthesis during infection by repressing autophosphorylation and activity of the cellular 68,000-Mr protein kinase. J. Virol. 1988, 62, 3710–3717.

182. Lu, Y.; Wambach, M.; Katze, M.G.; Krug, R.M. Binding of the influenza virus NS1 protein to double-stranded RNA inhibits the activation of the protein kinase that phosphorylates the eIF-2 translation initiation factor. Virology 1995, 214, 222–228.

183. Sharma, K.; Tripathi, S.; Ranjan, P.; Kumar, P.; Garten, R.; Deyde, V.; Katz, J.M.; Cox, N.J.; Lal, R.B.; Sambhara, S.; et al. Influenza A virus nucleoprotein exploits Hsp40 to inhibit PKR activation. PLoS ONE 2011, 6, e20215.

184. Chen, C.J.; Lin, T.T.; Shively, J.E. Role of interferon regulatory factor-1 in the induction of biliary glycoprotein (cell CAM-1) by interferon-gamma. J. Biol. Chem. 1996, 271, 28181–28188.

185. Vitenshtein, A.; Weisblum, Y.; Hauka, S.; Halenius, A.; Oiknine-Djian, E.; Tsukerman, P.; Bauman, Y.; Bar-On, Y.; Stern-Ginossar, N.; Enk, J.; et al. CEACAM1-Mediated Inhibition of Virus Production. Cell Rep. 2016, 15, 2331–2339.

186. Dawson, M.J.; Trapani, J.A. The interferon-inducible autoantigen, IFI 16: Localization to the nucleolus and identification of a DNA-binding domain. Biochem. Biophys Res. Commun. 1995, 214, 152–162.

187. Trapani, J.A.; Browne, K.A.; Dawson, M.J.; Ramsay, R.G.; Eddy, R.L.; Show, T.B.; White, P.C.; Dupont, B. A novel gene constitutively expressed in human lymphoid cells is inducible with interferon-gamma in myeloid cells. Immunogenetics 1992, 36, 369–376.

188. Unterholzner, L.; Keating, S.E.; Baran, M.; Horan, K.A.; Jensen, S.B.; Sharma, S.; Sirois, C.M.; Jin, T.; Latz, E.; Xiao, T.S.; et al. IFI16 is an innate immune sensor for intracellular DNA. Nat. Immunol. 2010, 11, 997–1004.

189. Jiang, Z.; Wei, F.; Zhang, Y.; Wang, T.; Gao, W.; Yu, S.; Sun, H.; Pu, J.; Sun, Y.; Wang, M.; et al. IFI16 directly senses viral RNA and enhances RIG-I transcription and activation to restrict influenza virus infection. Nat. Microbiol. 2021, 6, 932–945.

190. Mishra, S.; Raj, A.S.; Kumar, A.; Rajeevan, A.; Kumari, P.; Kumar, H. Innate immune sensing of influenza A viral RNA through IFI16 promotes pyroptotic cell death. iScience 2022, 25, 103714.

191. Gongora, C.; David, G.; Pintard, L.; Tissot, C.; Hua, T.D.; Dejean, A.; Mechti, N. Molecular cloning of a new interferon-induced PML nuclear body-associated protein. J. Biol. Chem. 1997, 272, 19457–19463.

192. Nguyen, L.H.; Espert, L.; Mechti, N.; Wilson, D.M., 3rd. The human interferon- and estrogen-regulated ISG20/HEM45 gene product degrades single-stranded RNA and DNA in vitro. Biochemistry 2001, 40, 7174–7179.

193. Espert, L.; Degols, G.; Gongora, C.; Blondel, D.; Williams, B.R.; Silverman, R.H.; Mechti, N. ISG20, a new interferon-induced RNase specific for single-stranded RNA, defines an alternative antiviral pathway against RNA genomic viruses. J. Biol. Chem. 2003, 278, 16151–16158.

194. Qu, H.; Li, J.; Yang, L.; Sun, L.; Liu, W.; He, H. Influenza A Virus-induced expression of ISG20 inhibits viral replication by interacting with nucleoprotein. Virus Genes 2016, 52, 759–767.

195. Gregersen, L.H.; Schueler, M.; Munschauer, M.; Mastrobuoni, G.; Chen, W.; Kempa, S.; Dieterich, C.; Landthaler, M. MOV10 Is a 5' to 3' RNA helicase contributing to UPF1 mRNA target degradation by translocation along 3′ UTRs. Mol. Cell 2014, 54, 573–585.

196. Sun, N.; Sun, W.; Li, S.; Yang, J.; Yang, L.; Quan, G.; Gao, X.; Wang, Z.; Cheng, X.; Li, Z.; et al. Proteomics Analysis of Cellular Proteins Co-Immunoprecipitated with Nucleoprotein of Influenza A Virus (H7N9). Int. J. Mol. Sci. 2015, 16, 25982–25998.

197. Zhang, J.; Huang, F.; Tan, L.; Bai, C.; Chen, B.; Liu, J.; Liang, J.; Liu, C.; Zhang, S.; Lu, G.; et al. Host Protein Moloney Leukemia Virus 10 (MOV10) Acts as a Restriction Factor of Influenza A Virus by Inhibiting the Nuclear Import of the Viral Nucleoprotein. J. Virol. 2016, 90, 3966–3980.

198. Li, J.; Hu, S.; Xu, F.; Mei, S.; Liu, X.; Yin, L.; Zhao, F.; Zhao, X.; Sun, H.; Xiong, Z.; et al. MOV10 sequesters the RNP of influenza A virus in the cytoplasm and is antagonized by viral NS1 protein. Biochem. J. 2019, 476, 467–481.

199. McAuley, J.L.; Corcilius, L.; Tan, H.X.; Payne, R.J.; McGuckin, M.A.; Brown, L.E. The cell surface mucin MUC1 limits the severity of influenza A virus infection. Mucosal. Immunol. 2017, 10, 1581–1593.

200. Dabbagh, D.; He, S.; Hetrick, B.; Chilin, L.; Andalibi, A.; Wu, Y. Identification of the SHREK Family of Proteins as Broad-Spectrum Host Antiviral Factors. Viruses 2021, 13, 832.

201. Iverson, E.; Griswold, K.; Song, D.; Gagliardi, T.B.; Hamidzadeh, K.; Kesimer, M.; Sinha, S.; Perry, M.; Duncan, G.A.; Scull, M.A. Membrane-Tethered Mucin 1 Is Stimulated by Interferon and Virus Infection in Multiple Cell Types and Inhibits Influenza A Virus Infection in Human Airway Epithelium. mBio 2022, 13, e0105522.

202. Yu, L.; Croze, E.; Yamaguchi, K.D.; Tran, T.; Reder, A.T.; Litvak, V.; Volkert, M.R. Induction of a unique isoform of the NCOA7 oxidation resistance gene by interferon beta-1b. J. Interferon Cytokine Res. 2015, 35, 186–199.

203. Doyle, T.; Moncorge, O.; Bonaventure, B.; Pollpeter, D.; Lussignol, M.; Tauziet, M.; Apolonia, L.; Catanese, M.T.; Goujon, C.; Malim, M.H. The interferon-inducible isoform of NCOA7 inhibits endosome-mediated viral entry. Nat. Microbiol. 2018, 3, 1369–1376.

204. Ma, C.; Li, Y.; Zong, Y.; Velkov, T.; Wang, C.; Yang, X.; Zhang, M.; Jiang, Z.; Sun, H.; Tong, Q.; et al. p21 restricts influenza A virus by perturbing the viral polymerase complex and upregulating type I interferon signaling. PLoS Pathog. 2022, 18, e1010295.

205. Dittmann, M.; Hoffmann, H.H.; Scull, M.A.; Gilmore, R.H.; Bell, K.L.; Ciancanelli, M.; Wilson, S.J.; Crotta, S.; Yu, Y.; Flatley, B.; et al. A serpin shapes the extracellular environment to prevent influenza A virus maturation. Cell 2015, 160, 631–643.

206. Sun, N.; Li, C.; Li, X.F.; Deng, Y.Q.; Jiang, T.; Zhang, N.N.; Zu, S.; Zhang, R.R.; Li, L.; Chen, X.; et al. Type-IInterferon-Inducible SERTAD3 Inhibits Influenza A Virus Replication by Blocking the Assembly of Viral RNA Polymerase Complex. Cell Rep. 2020, 33, 108342.

207. De la Casa-Esperon, E. From mammals to viruses: The Schlafen genes in developmental, proliferative and immune processes. Biomol. Concepts 2011, 2, 159–169.

208. Seong, R.K.; Seo, S.W.; Kim, J.A.; Fletcher, S.J.; Morgan, N.V.; Kumar, M.; Choi, Y.K.; Shin, O.S. Schlafen 14 (SLFN14) is a novel antiviral factor involved in the control of viral replication. Immunobiology 2017, 222, 979–988.

209. Jitobaom, K.; Sirihongthong, T.; Boonarkart, C.; Phakaratsakul, S.; Suptawiwat, O.; Auewarakul, P. Human Schlafen 11 inhibits influenza A virus production. Virus Res. 2023, 334, 199162.

210. Ahn, N.; Kim, W.J.; Kim, N.; Park, H.W.; Lee, S.W.; Yoo, J.Y. The Interferon-Inducible Proteoglycan Testican-2/SPOCK2 Functions as a Protective Barrier against Virus Infection of Lung Epithelial Cells. J. Virol. 2019, 93, e00662-19.

211. Fernbach, S.; Spieler, E.E.; Busnadiego, I.; Karakus, U.; Lkharrazi, A.; Stertz, S.; Hale, B.G. Restriction factor screening identifies RABGAP1L-mediated disruption of endocytosis as a host antiviral defense. Cell Rep. 2022, 38, 110549.

212. Chin, K.C.; Cresswell, P. Viperin (cig5), an IFN-inducible antiviral protein directly induced by human cytomegalovirus. Proc. Natl. Acad. Sci. USA 2001, 98, 15125–15130.

213. Wang, X.; Hinson, E.R.; Cresswell, P. The interferon-inducible protein viperin inhibits influenza virus release by perturbing lipid rafts. Cell Host Microbe 2007, 2, 96–105.

214. Tan, K.S.; Olfat, F.; Phoon, M.C.; Hsu, J.P.; Howe, J.L.C.; Seet, J.E.; Chin, K.C.; Chow, V.T.K. In vivo and in vitro studies on the antiviral activities of viperin against influenza H1N1 virus infection. J. Gen. Virol. 2012, 93, 1269–1277.

215. Liu, C.H.; Zhou, L.; Chen, G.; Krug, R.M. Battle between influenza A virus and a newly identified antiviral activity of the PARP-containing ZAPL protein. Proc. Natl. Acad. Sci. USA 2015, 112, 14048–14053.

216. Tang, Q.; Wang, X.; Gao, G. The Short Form of the Zinc Finger Antiviral Protein Inhibits Influenza A Virus Protein Expression and Is Antagonized by the Virus-Encoded NS1. J. Virol. 2017, 91, 01909–01916.

217. Zhang, B.; Goraya, M.U.; Chen, N.; Xu, L.; Hong, Y.; Zhu, M.; Chen, J.L. Zinc Finger CCCH-Type Antiviral Protein 1 Restricts the Viral Replication by Positively Regulating Type I Interferon Response. Front. Microbiol. 2020, 11, 1912.

218. Ma, Y.; Ouyang, J.; Wei, J.; Maarouf, M.; Chen, J.L. Involvement of Host Non-Coding RNAs in the Pathogenesis of the Influenza Virus. Int. J. Mol. Sci. 2016, 18, 39.

219. Chai, W.; Li, J.; Shangguan, Q.; Liu, Q.; Li, X.; Qi, D.; Tong, X.; Liu, W.; Ye, X. Lnc-ISG20 Inhibits Influenza A Virus Replication by Enhancing ISG20 Expression. J. Virol. 2018, 92, e00539-18.

220. Lin, H.; Jiang, M.; Liu, L.; Yang, Z.; Ma, Z.; Liu, S.; Ma, Y.; Zhang, L.; Cao, X. The long noncoding RNA Lnczc3h7a promotes a TRIM25-mediated RIG-I antiviral innate immune response. Nat. Immunol. 2019, 20, 812–823.

221. Maarouf, M.; Chen, B.; Chen, Y.; Wang, X.; Rai, K.R.; Zhao, Z.; Liu, S.; Li, Y.; Xiao, M.; Chen, J.L. Identification of lncRNA-155 encoded by MIR155HG as a novel regulator of innate immunity against influenza A virus infection. Cell Microbiol. 2019, 21, e13036.

222. Pan, Q.; Zhao, Z.; Liao, Y.; Chiu, S.H.; Wang, S.; Chen, B.; Chen, N.; Chen, Y.; Chen, J.L. Identification of an Interferon-Stimulated Long Noncoding RNA (LncRNA ISR) Involved in Regulation of Influenza A Virus Replication. Int. J. Mol. Sci. 2019, 20, 5118.

223. Zhao, L.; Xia, M.; Wang, K.; Lai, C.; Fan, H.; Gu, H.; Yang, P.; Wang, X. A Long Non-coding RNA IVRPIE Promotes Host Antiviral Immune Responses Through Regulating Interferon beta1 and ISG Expression. Front. Microbiol. 2020, 11, 260.

224. Liu, Q.; Yang, H.; Zhao, L.; Huang, N.; Ping, J. A Novel lncRNA SAAL Suppresses IAV Replication by Promoting Innate Responses. Microorganisms 2022, 10, 2336.

225. van Solingen, C.; Cyr, Y.; Scacalossi, K.R.; de Vries, M.; Barrett, T.J.; de Jong, A.; Gourvest, M.; Zhang, T.; Peled, D.; Kher, R.; et al. Long noncoding RNA CHROMR regulates antiviral immunity in humans. Proc. Natl. Acad. Sci. USA 2022, 119, e2210321119.

226. Zhang, Y.; Chi, X.; Hu, J.; Wang, S.; Zhao, S.; Mao, Y.; Peng, B.; Chen, J.; Wang, S. LncRNA LINC02574 Inhibits Influenza A Virus Replication by Positively Regulating the Innate Immune Response. Int. J. Mol. Sci. 2023, 24, 7248.

227. Qu, Z.; Meng, F.; Shi, J.; Deng, G.; Zeng, X.; Ge, J.; Li, Y.; Liu, L.; Chen, P.; Jiang, Y.; et al. A Novel Intronic Circular RNA Antagonizes Influenza Virus by Absorbing a microRNA That Degrades CREBBP and Accelerating IFN-beta Production. mBio 2021, 12, e0101721.

228. Min, J.; Li, Y.; Li, X.; Wang, M.; Li, H.; Bi, Y.; Xu, P.; Liu, W.; Ye, X.; Li, J. The circRNA circVAMP3 restricts influenza A virus replication by interfering with NP and NS1 proteins. PLoS Pathog. 2023, 19, e1011577.

229. Ingle, H.; Kumar, S.; Raut, A.A.; Mishra, A.; Kulkarni, D.D.; Kameyama, T.; Takaoka, A.; Akira, S.; Kumar, H. The microRNA miR-485 targets host and influenza virus transcripts to regulate antiviral immunity and restrict viral replication. Sci. Signal 2015, 8, ra126.

230. Sharma, S.; Chatterjee, A.; Kumar, P.; Lal, S.; Kondabagil, K. Upregulation of miR-101 during Influenza A Virus Infection Abrogates Viral Life Cycle by Targeting mTOR Pathway. Viruses 2020, 12, 444.

231. Song, J.; Sun, H.; Sun, H.; Jiang, Z.; Zhu, J.; Wang, C.; Gao, W.; Wang, T.; Pu, J.; Sun, Y.; et al. Swine MicroRNAs ssc-miR-221-3p and ssc-miR-222 Restrict the Cross-Species Infection of Avian Influenza Virus. J. Virol. 2020, 94, e01700-20.