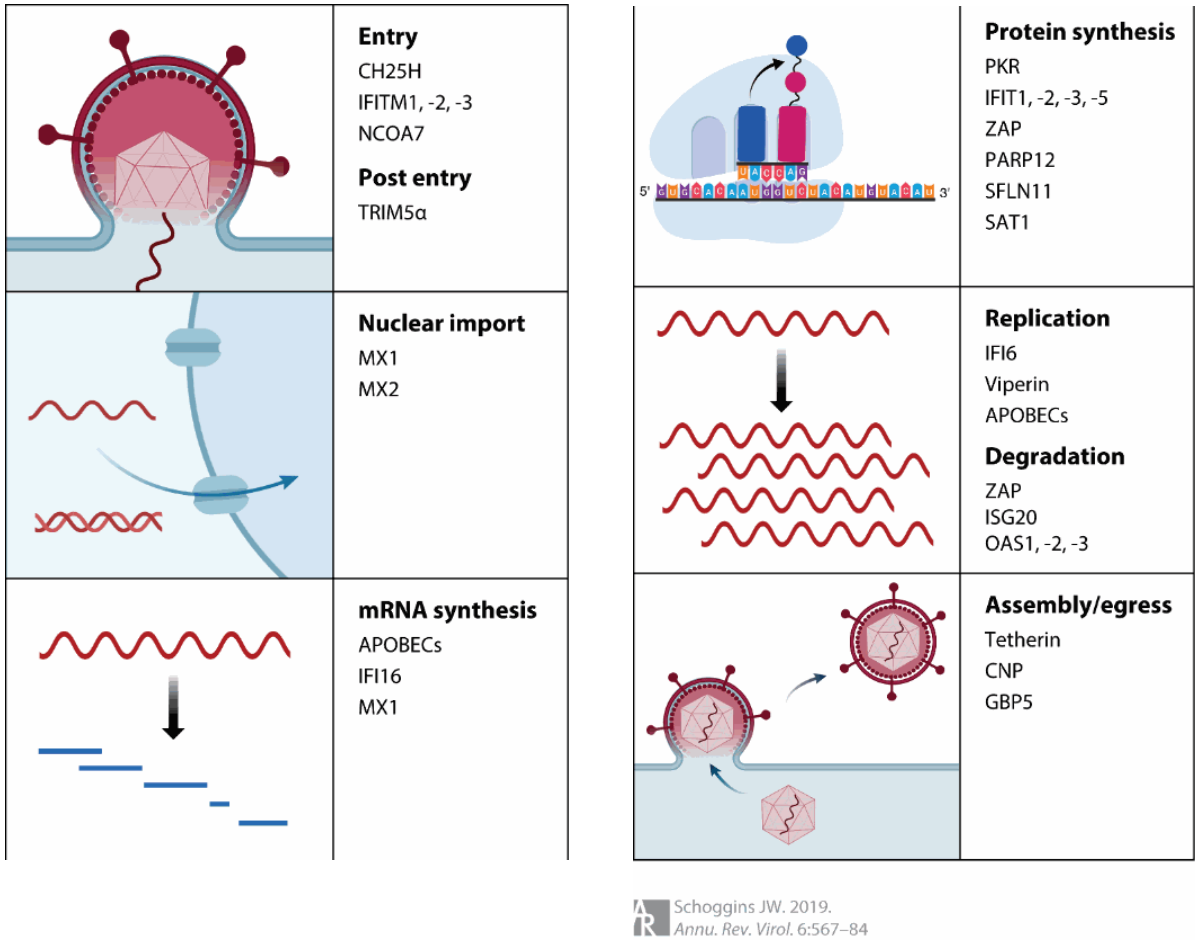
ISGs

Overview

- 67 genes in total were identified as antiviral ISGs
- The following are highlighted due to the ability of information and mainly the relevance to experiments
- Different methods of interference by ISGs →

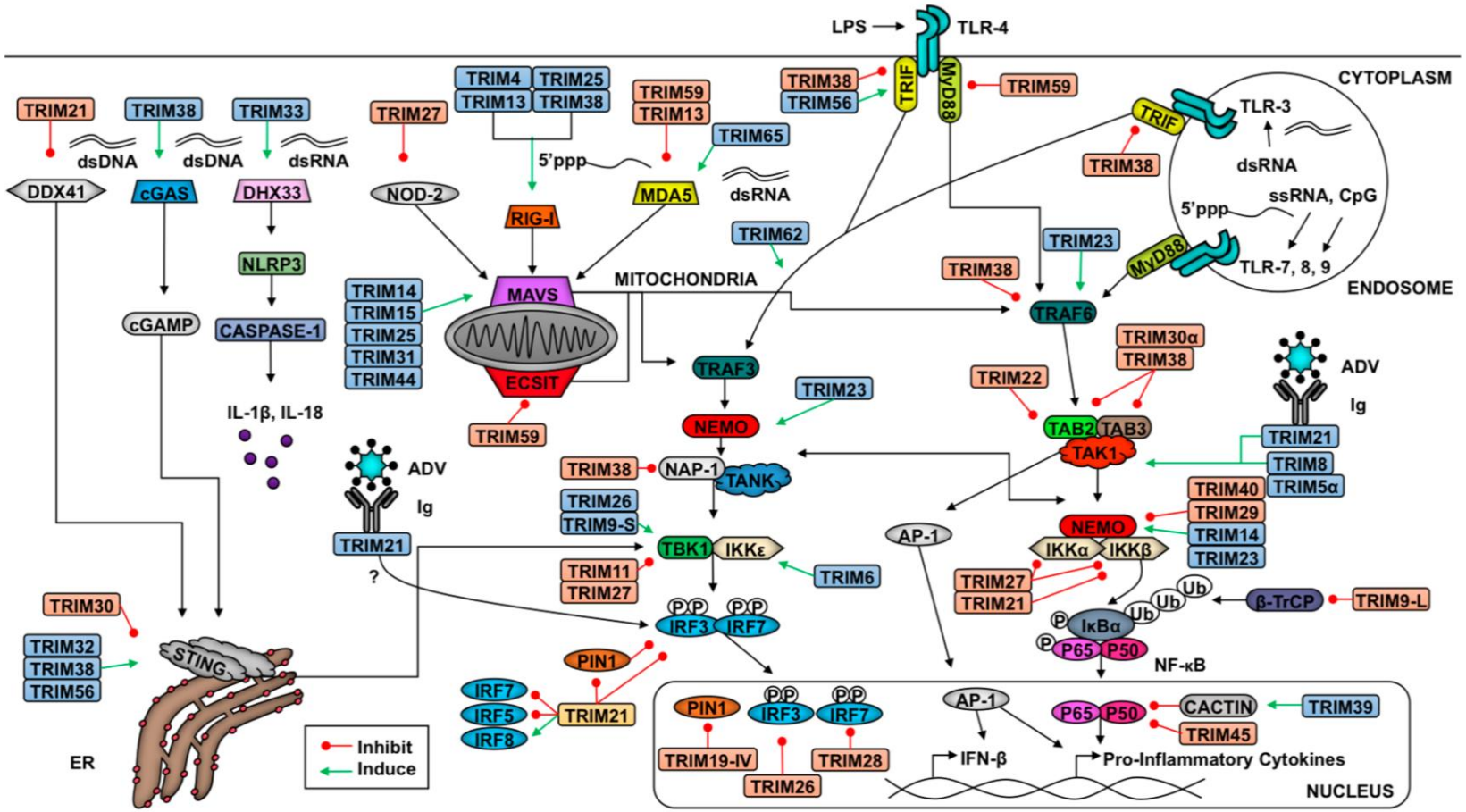
- Schoggins, J. W. (2019, September 29). *Interferon-stimulated genes: What do they all do?*. Annual Review of Virology. https://www.annualreviews.org/content/journals/10.1146/annurev-virology-092818-015756#cited



Tripartite Motif-Containing Proteins

- Ubiquitin System
- Involved in Apoptosis, Cell Cycle Regulation, Muscular Physiology, Innate Immune Response
- Structure; RING domain, B-Box, Coiled-Coil Region
- Functions; Antiviral Defense, Immune Response, Cell Proliferation, Cell Differentiation
- Biological Roles; Protein Degradation, Gene Regulation, Autophagy

Overview



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TRIM	Target molecule	Function	Refs
TLR-mediated innate immune response			
TRIM38	TRIF	Promoting proteasomal degradation of TRIF	(26, 27)
TRIM56	TRIF	Interacting with TRIF physically to promote TLR3 signaling activation	(28)
TRIM23	NEMO	Mediating K27-linked ubiquitination of NEMO	(29)
TRIM23	TRAF6	Promoting TRAF6 autoubiquitination	(30)
TRIM29	NEMO	Inducing proteasomal degradation of NEMO	(31)
TRIM27	IKKs	Interacting with the noncanonical and canonical IKK family members	(32)
TRIM28 (KAP1)	IRF7	Mediating SUMOylation of IRF7 to suppress transactivation	(33)
TRIM21 (Ro52/SS-A)	IRF7	Inducing proteasomal degradation of IRF7	(34)
TRIM21	IRF3	Inducing proteasomal degradation of IRF3	(35)
TRIM21	IRF3	Mediating autophagic degradation of IRF3	(36, 37)
TRIM19IV	Pin1	Regulating the cellular distribution of Pin1	(38, 39)

TRIM38	TRAF6	Inducing proteasomal degradation of TRAF6	(40)
TRIM12c	TRAF6	Interacting with TRAF6 and inducing TRAF6 ubiquitination	(41)
TRIM13	TRAF6	Inducing TRAF6 ubiquitination	(42)
TRIM5α	TAK1	Generating free ubiquitin chains, which activate the TAK1 kinase	(43, 44)
TRIM30α	TAB2 and TAB3	Interacting with TAK1 complex and promoting TAB2 and TAB3 degradation	(45)
TRIM22	TAB2	Targeting TAB2 for degradation	(46)
TRIM21	TAK1	Generating free ubiquitin chains, which activate the TAK1 kinase	(47, 48)
TRIM40	NEMO	Mediating neddylation of NEMO	(49)
TRIM21	IKKβ	Catalyzing monoubiquitin of IKKβ, which leads to IKKβ degradation by autophagolysosome	(50, 51)
TRIM25	RIG-I	Mediating K63-ubiquitination of RIG-I	(55, 56)
TRIM25	MAVS	Promoting MAVS ubiquitination to release the signaling complex into cytosol	(57)

TRIM14	MAVS	Interacting with MAVS and promoting the recruitment of NEMO	(62)
TRIM44	MAVS	Interacting with MAVS and stabilizing MAVS	(63)
TRIM31	MAVS	Promoting K63-polyubiquitination and aggregation of MAVS	(64)
TRIM9s	TBK1	Promoting phosphorylation of TBK1	(65)
TRIM38	NAP1	Inducing proteasomal degradation of NAP1	(66)
TRIM26	NEMO	linking TBK1 to NEMO for TBK1 activation	(67)
TRIM26	IRF3	Inducing proteasomal degradation of IRF3	(68)

TRIM26

- Viral Restriction; Inhibits viral entry and replication in host cells.
- Transcriptional Regulation; Modulates transcription factors, influencing gene expression related to immune responses.
- Function; Negatively regulates viral entry, positively regulates transcription factor activity, restricts virus infection in epithelial cells
- Pathways; Transferase, Organelle Envelope

TRIM25

- Antiviral Defense; Mediates ubiquitination of RIG-I, enhancing the detection of viral RNA and promoting an antiviral state.
- Immune Modulation; Influences interferon signaling.
- Function; Inhibits influenza A virus infection, destabilizes viral mRNA, mediates ubiquitination of RIG-I, IFIH1
- Protein Encoding; E3 Ubiquitin Ligase
- Expressed in Macrophages, Dendritic Cells

TRIM21

- Intracellular Immunity; Binds antibody-coated pathogens and targets them for degradation, acting as a defense mechanism inside cells.
- Autoimmunity Regulation; Interacts with autoantigens, potentially impacting autoimmune diseases.
- Function; Represses antiviral response, promotes cell pyropoptosis
- Expressed in T-Cells, Macrophages, Dendritic Cells

TRIM14

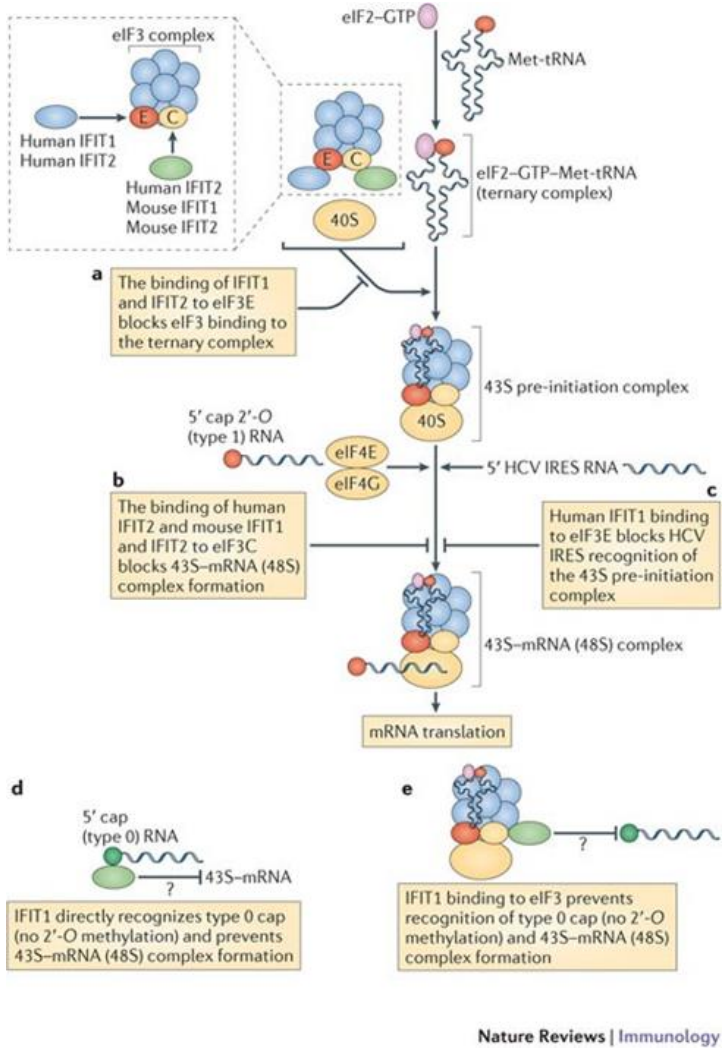
- Signal Transduction; Enhances transcription of immune related genes, plays role in early immune response.
- Cell Differentiation; Involved in embryonic stem cells differentiation, impacting development and cellular function
- Differentiation of embryonic stem cells

TRIM12C

- Cytokine Production; Stimulates pathways (Type I IFN and NK) crucial for antiviral and innate immune responses.
- Pathogen Recognition; Responds to interferons, aiding in the detection and response to pathogens.
- Function; Defense response as transcription co-activator, responds to IFN-gamma
- Expressed in Macrophage, Dendritic Cells

Ifit1/2/3

- This family of genes codes for proteins that interfere with viral replication and translation
- “both IFIT1 and IFIT2 are antiviral factors against influenza virus infection and inhibit viral RNA synthesis and polymerase activities.” 1
- “over-expression or knock down of IFIT3 resulted in the increase or decrease of anti-viral gene expression, respectively” 2

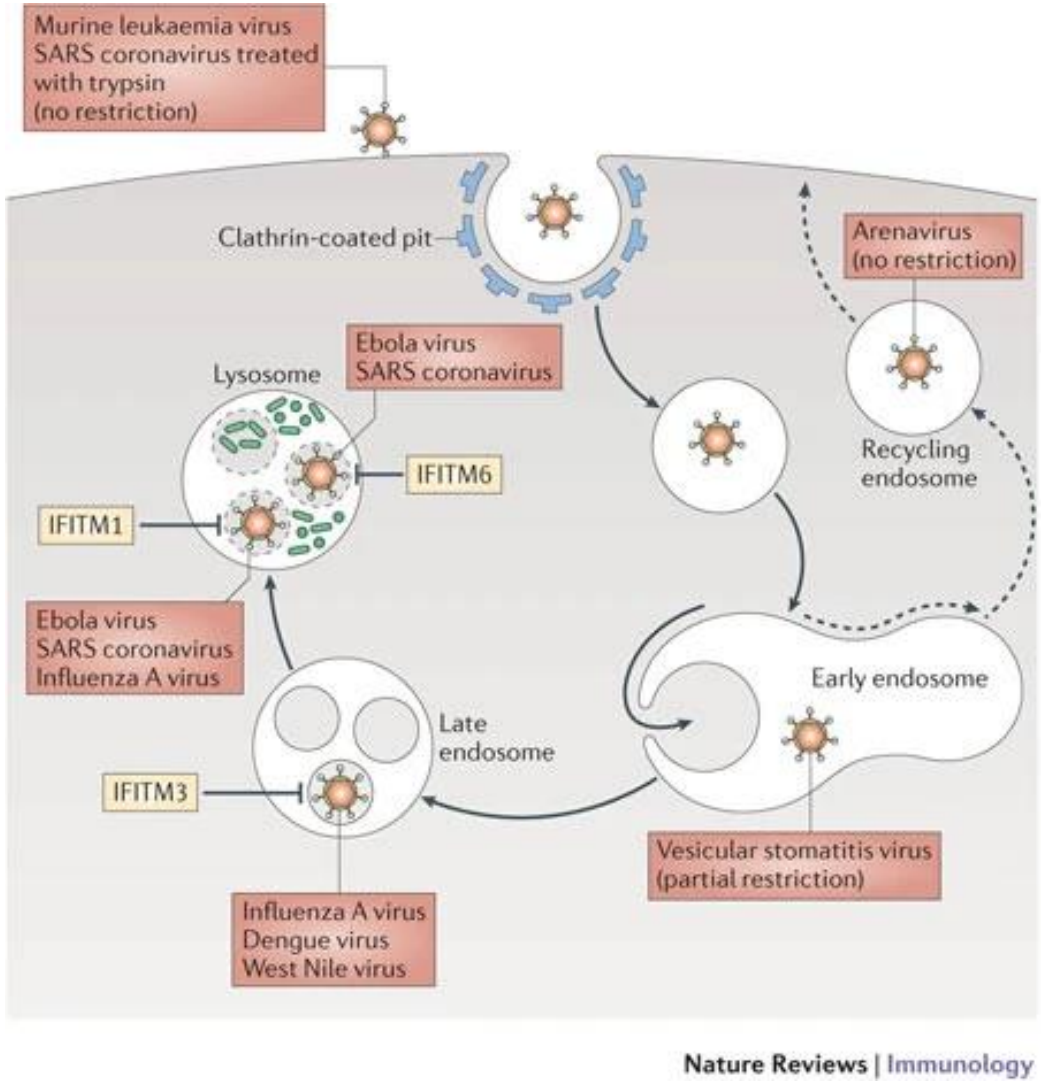


- Zhu, Z.; Yang, X.; Huang, C.; Liu, L. The Interferon-Induced Protein with Tetratricopeptide Repeats Repress Influenza Virus Infection by Inhibiting Viral RNA Synthesis. *Viruses* **2023**, *15*, 1412. https://doi.org/10.3390/v15071412
- Vladimer G.I. Gorna M.W. Superti-Furga G. IFITs: emerging roles as key anti-viral proteins Front. Immunol. 2014 5 94

Ifitm1/2/3

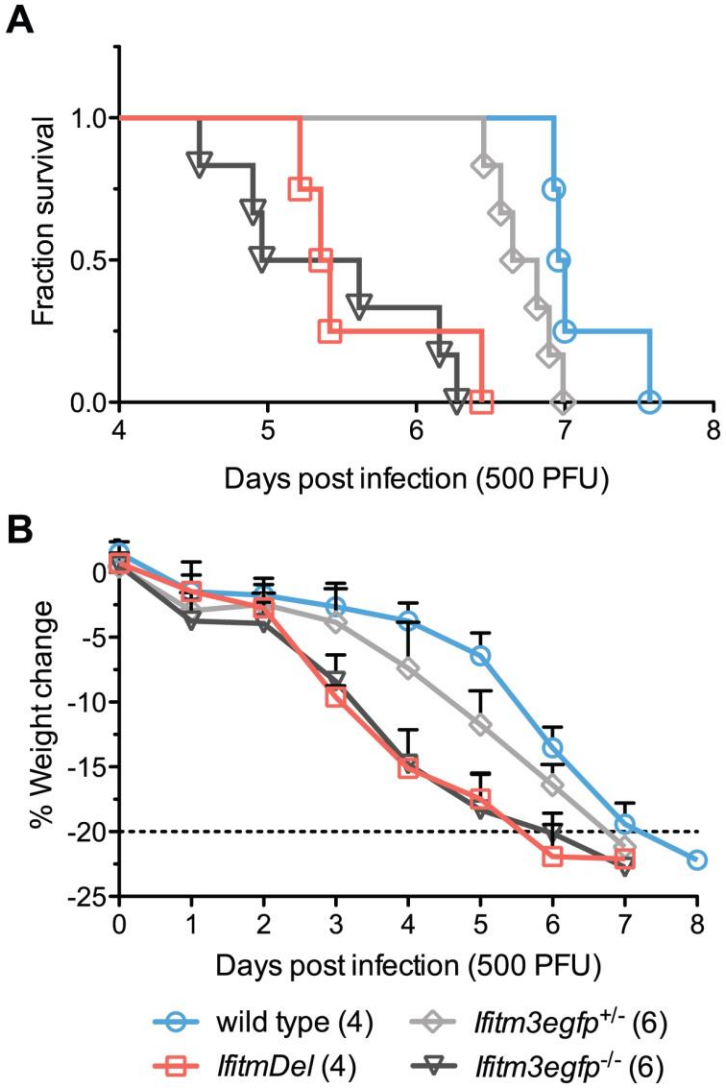
- The proteins encoded by this family of genes restrict viral entry into cells
- “IFITM-mediated restriction precedes the induction of type I IFNs in infected cells, which might explain the high basal level of expression of IFITM proteins in many tissues. IFN induction, however, can amplify IFITM expression and protect uninfected cells in a paracrine manner”

- Diamond, M., Farzan, M. The broad-spectrum antiviral functions of IFIT and IFITM proteins. *Nat Rev Immunol* **13**, 46–57 (2013). https://doi.org/10.1038/nri3344



Ifitm3 and Influenza

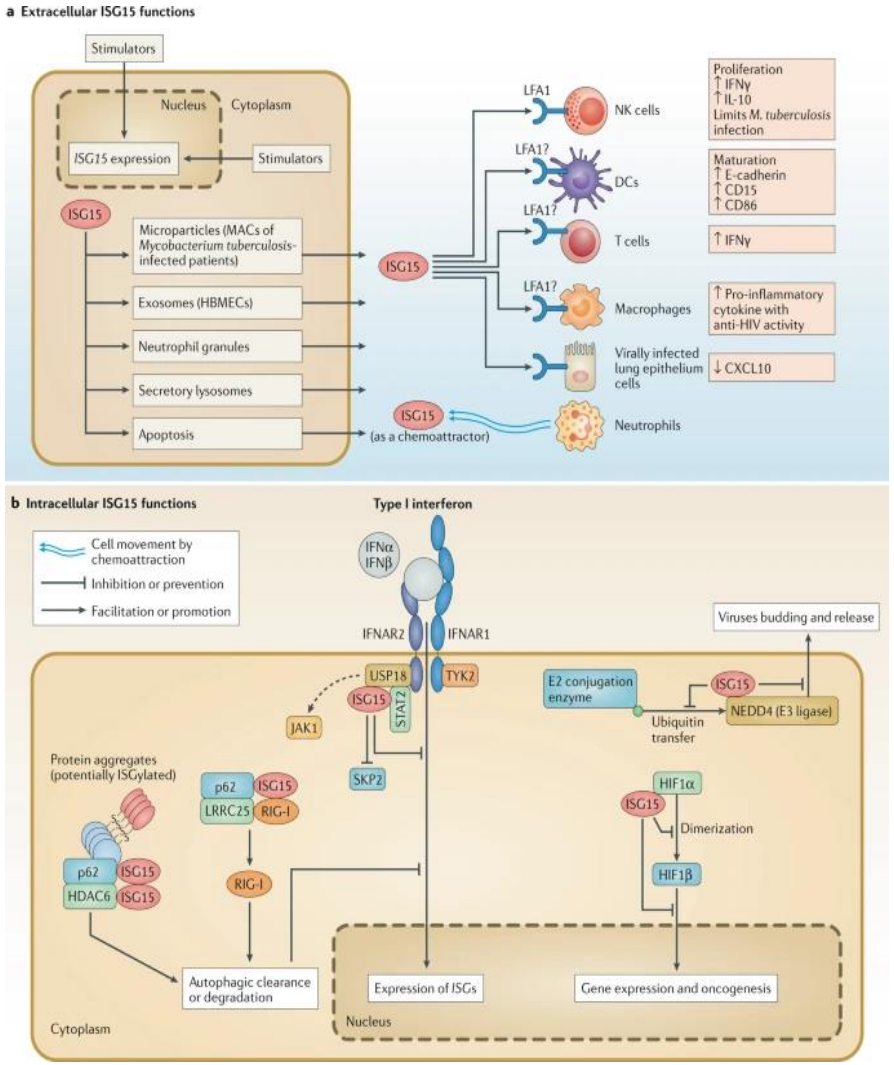
- IFITM3 expression acts as an essential barrier to influenza A virus infection *in vivo* and *in vitro*
- "IFITM3 is especially effective in controlling influenza A virus, as *Ifitm3*$^{-/-}$ mice challenged with an H1N1 influenza virus strain sustained higher viral loads and succumbed more rapidly to disease[78]. *Ifitm3*$^{-/-}$ mice had a viral infection phenotype indistinguishable from that of *IfitmDel* mice… which suggests that the other mouse IFITM proteins do not have a significant role in controlling influenza A virus infection"



- Bailey CC, Huang I-C, Kam C, Farzan M (2012) Ifitm3 Limits the Severity of Acute Influenza in Mice. PLoS Pathog 8(9): e1002909. https://doi.org/10.1371/journal.ppat.1002909

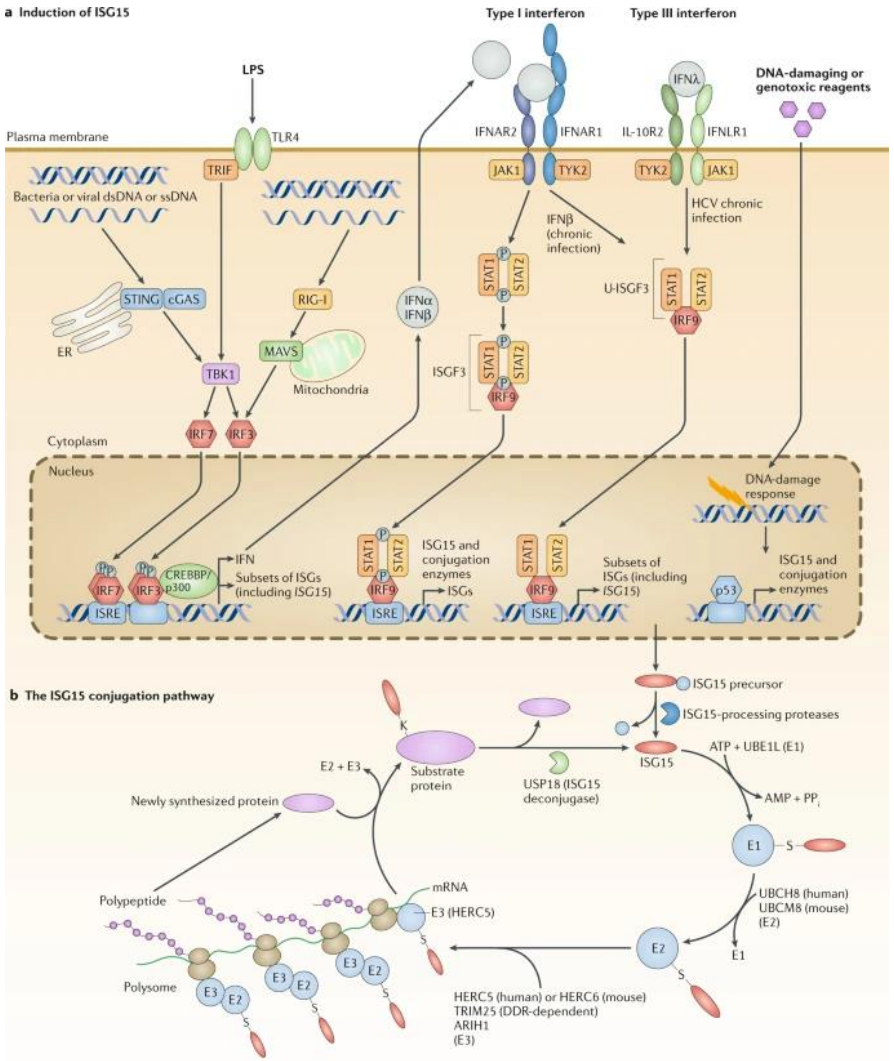
ISG15 and associates

- ISG15 inhibits viral translocation and restores host antiviral response
- Also involved in positive regulation of IFN beta production and cell to cell signaling
- ISG15 exerts antiviral effects by covalently binding to target proteins, inhibiting the release and replication of viral particles, and regulating the incubation period of viruses. In addition to the ISG15 covalent conjugate, the ISG15 monomer can promote the proliferation of NK cells and dendritic cells and enhance the chemotactic activity of neutrophils.



ISG15 and associates

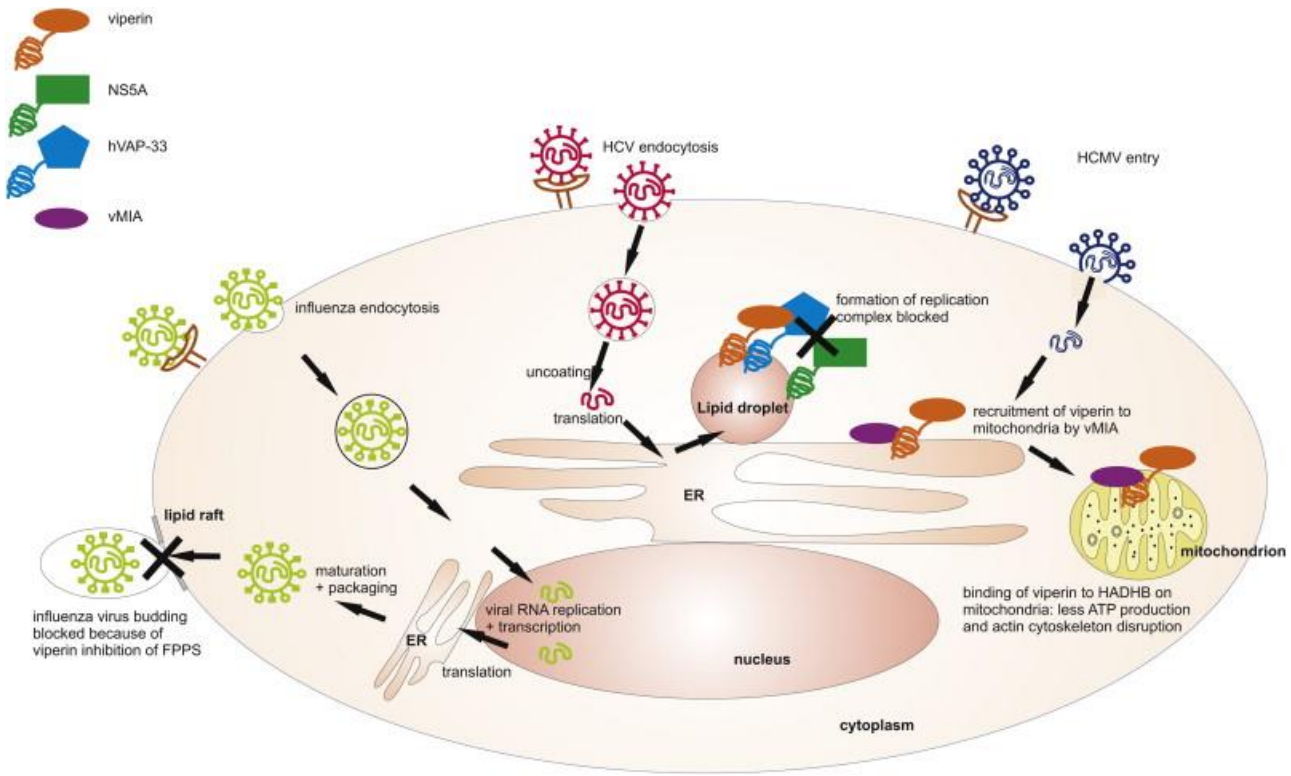
- ISG15 inhibits viral translocation and restores host antiviral response
- Also involved in positive regulation of IFN beta production and cell to cell signaling
- ISG15 works with several other protein coding genes such as Usp18, Uba7, Herc6, and Ube216 to restrict viral replication



- Zhang, M., Li, J., Yan, H., Huang, J., Wang, F., Liu, T., Zeng, L., & Zhou, F. (2021). ISGylation in Innate Antiviral Immunity and Pathogen Defense Responses: A Review. *Frontiers in cell and developmental biology*, *9*, 788410. https://doi.org/10.3389/fcell.2021.788410
- https://www.genecards.org/cgi-bin/carddisp.pl?gene=ISG15&keywords=isg15

Rsad2/Viperin

- “Normal expression levels of viperin are low. Its expression is, however, strongly induced by type I IFNs, a broad range of viruses [Rhinovirus being one of them], lipopolysaccharide (LPS) and poly(I:C), and to a lesser extent by type II IFN”
- “Viperin displays antiviral activity against influenza A virus by inhibiting influenza A virus release from infected cells, whereas other aspects of the virus replication cycle, for example receptor binding and protein synthesis, were unaffected by viperin overexpression”



- Iwasaki, A., Pillai, P. Innate immunity to influenza virus infection. *Nat Rev Immunol* **14**, 315–328 (2014). https://doi.org/10.1038/nri3665
- Sandy Mattijssen, Ger J.M. Pruijn, Viperin, a key player in the antiviral response, Microbes and Infection, Volume 14, Issue 5, 2012, ISSN 1286-4579, https://doi.org/10.1016/j.micinf.2011.11.015. (https://www.sciencedirect.com/science/article/pii/S1286457911002930)

Application

- Researching how the different methods of interference work as well as their effectiveness. (i.e interference of translation, translocation, and other viral mechanisms).
- Using up/down regulation data to infer antiviral effectiveness and duration during influenza pathogenesis.
- ISG15’s ability to positively regulate IFN production, restore innate immune response, and activate later pathways warrants further investigation and focus.
- Trim, Ifitm (ifitm3 specifically), and Rsad2 will likely also be relevant

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