

Decoding type I and III interferon signalling during viral infection

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Interferon (IFN)-mediated antiviral responses are central to host defence against viral infection. Despite the existence of at least 20 IFNs, there are only three known cell surface receptors. IFN signalling and viral evasion mechanisms form an immensely complex network that differs across species. In this Review, we begin by highlighting some of the advances that have been made towards understanding the complexity of differential IFN signalling inputs and outputs that contribute to antiviral defences. Next, we explore some of the ways viruses can interfere with, or circumvent, these defences. Lastly, we address the largely under-reviewed impact of IFN signalling on host tropism, and we offer perspectives on the future of research into IFN signalling complexity and viral evasion across species.

Across species, the innate immune response serves as the first line of defence against viral infection. Pattern recognition receptors (PRRs) within the host cell sense pathogen-associated molecular patterns, triggering a range of signalling cascades and subsequent gene activation¹. For many viral infections, this results in the production and secretion of interferons (IFNs), which are critical for innate immunity and also have profound impacts on adaptive immune responses. IFN signalling in turn induces transcription of hundreds of IFN-stimulated genes (ISGs) that further the immune response against the viral infection.

Many viruses have evolved to avoid, subvert or directly interfere with the IFN signalling of their hosts. This is accomplished through numerous mechanisms extensively reviewed elsewhere^{2–7}; however, some new discoveries are highlighted later in this Review. A given virus' ability to antagonize and prevent the inputs and outputs of IFN signalling not only dictates the success of the infection, but is also a direct factor that contributes to the host and tissue range of a given virus.

Originally discovered in the 1950s and named for their ability to 'interfere' with viral replication, IFNs form a diverse family of cytokines⁸. Each class of IFN—type I, II and III—signals through a distinct heterodimeric receptor and induces gene expression through the Janus kinase–signal transducer and activator of transcription (JAK–STAT) signalling pathway (Fig. 1). In humans, type I IFNs are comprised of IFN- β , 13 subtypes of IFN- α , as well as IFN- ϵ and IFN- ω . A number of distantly related genes and pseudogenes have been identified in other species and are included in the type I classification. Three type III IFNs (IFN- λ 1, IFN- λ 2 and IFN- λ 3) were simultaneously discovered by two groups in 2003 and shown to be structurally related to interleukin-10 (IL-10) (refs. ^{9,10}). A fourth type III IFN, IFN- λ 4, was identified in 2013 and was associated with impaired clearance of hepatitis C virus (HCV) infection¹¹. The type II IFN class has only one member: IFN- γ . Given that type II fits the classic model of one ligand for one receptor, this Review will focus only on type I and III IFNs.

IFNs vary considerably with regards to structure, receptor distribution and tissue-specific biological activities¹², but are all capable of inducing an antiviral state. Type I IFN signalling within humans antagonizes innumerable viruses, such as influenza virus, West Nile

virus (WNV), yellow fever virus (YFV), vesicular stomatitis virus (VSV), dengue virus (DENV), herpes simplex virus (HSV) and several hepatitis viruses¹³. As such, evading type I IFN signalling is crucial for viruses to successfully replicate within their hosts, as is demonstrated by many flaviviruses; Zika virus (ZIKV), Japanese encephalitis virus (JEV), WNV and DENV are all able to antagonize type I IFN signalling in human cells to promote replication of their genomes¹⁴. Deleting individual type I IFNs *in vivo* has revealed some of their specific roles during viral infection: within its extensive repertoire of immune functions, IFN- β is required for the production of IFN- α during vaccinia virus infection¹⁵ and IFN- ϵ protects the female reproductive tract against HSV (ref. ¹⁶). Less is known about type III IFNs, although studies have shown they are critical for antagonism of many viruses, particularly at epithelial surfaces¹⁷. However, across type I and III IFNs, there are vast differences with respect to their regulation and signalling outputs, which can dictate viral evasion strategies and ultimately impact host and tissue tropism.

Much remains unknown about how antiviral defences are encoded by IFN receptors, how viruses navigate these defences, and how differences in both of these areas contribute to viral susceptibility and permissivity across species. While many aspects of IFNs have been reviewed extensively elsewhere^{12,13,18}, this Review will attempt to construct a holistic picture of the complicated relationship between IFN signalling and viral infection. To this end, we will progressively expand in scope with each section. We will begin at the level of individual IFN receptors, then broaden out to a discussion of IFN-mediated antiviral defences. We will then tackle some of the ways viruses can modulate or evade these defences. Lastly, we will consider how this intricate relationship between viruses and IFNs impacts host tropism.

Complex inputs

Despite the existence of approximately 20 IFNs, there are only three cell surface IFN receptors. The type I IFN receptor (IFNAR) is composed of subunits IFNAR1 and IFNAR2; the type II IFN receptor (IFNGR) is made up of subunits IFNGR1 and IFNGR2; and the type III IFN receptor (IFNLR) consists of subunits IFNLR1 and IL-10R β , the latter of which is shared by the IL-10 receptor. Of the three

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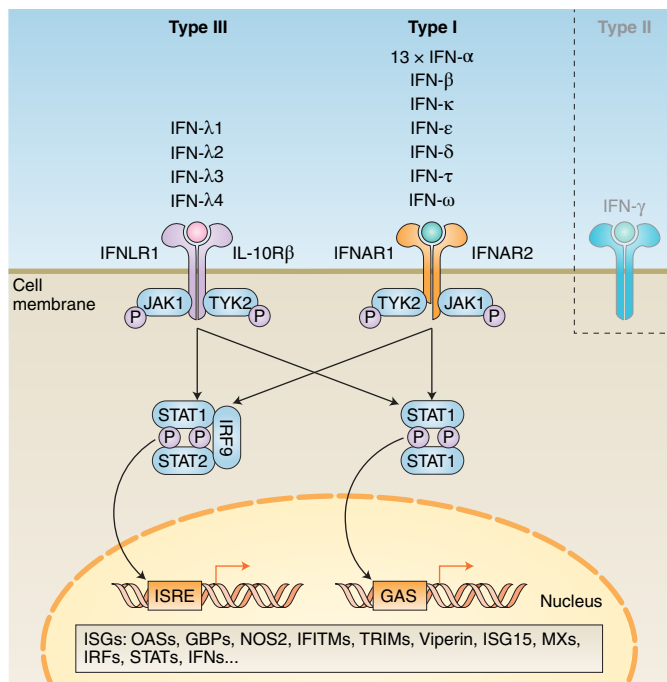


Fig. 1 | Simplified schematic of type I and III IFN signalling cascades.

Within type I and III, there are multiple IFNs; within type II, there is only a single IFN. Each type has a distinct heterodimeric cell surface receptor: type I IFNs bind to the IFNAR receptor complex (composed of IFNAR1 and IFNAR2); type III IFNs bind to the IFNLR receptor complex (composed of IFNLR1 and IL-10R β). Binding of an IFN to either receptor complex results in cross-phosphorylation of JAK1 and TYK2 on the cytoplasmic domains of the receptor subunits. This triggers phosphorylation of STAT1 and STAT2. Following phosphorylation, these STATs form various complexes that translocate into the nucleus, where they bind IFN-stimulated response elements (ISREs) or gamma-activated sequences (GASs) on the promoters of ISGs. Binding to these promoter elements results in the transcription of hundreds of genes involved in antiviral response, including ISGs, IFNs, IRFs and STATs. P, phosphate; OASs, oligoadenylate synthases; GBPs, guanylate-binding proteins; NOS2, nitric oxide synthase 2; IFITMs, IFN-induced transmembrane proteins; TRIMs, tripartate motif proteins.

receptors, only IFNGR has one ligand: IFN- γ (ref. 19). In contrast, the type I and III receptors are shared by many IFNs. While the type I receptor is present on all nucleated cell types, the type III receptor is restricted mainly to epithelial cells, although some studies have observed that other cell types—such as epithelial cells²⁰ and neutrophils²¹—are responsive to type III IFNs. Evidence suggests that type I and III IFNs can differentially engage their receptor to produce different signalling outcomes^{22,23}.

How shared IFN receptors decipher the complexity of IFN signalling inputs remains elusive, yet it could be influenced by a variety of factors, such as ligand binding affinities, negative regulation, positive regulation and signal amplification, receptor expression and assembly, and biomolecular condensation (Fig. 2). These will be explored in detail in this section. Other factors that could not be extensively addressed here include post-translational modifications, epigenetics and epitranscriptomic regulation of IFN signalling components^{24,25}. Among epigenetic modifications are STAT-mediated acetylation of histone H3 (ref. 26) and IFN-stimulated ubiquitination of histone 2B (ref. 27), both of which are associated with elevated expression of ISGs. Epitranscriptomic regulation includes RNA modifications by adenosine deaminases acting on RNA that inhibit IFN signalling²⁸. Combinations of all of these factors may allow the type I and type III IFN receptors to process a dynamic range of

signalling inputs during viral infection. Since many aspects of IFN signalling regulation have been reviewed elsewhere^{12,22,29–31}, we will mainly highlight some of the emerging themes and new insights from the past few years.

An overarching model that has gained favourability is that many signalling differences result from changes in the stability of the ternary receptor complexes. This stability can be influenced by numerous factors, among which is ligand binding strength. Across type I IFNs, ligand binding affinities for IFNAR vary significantly, with IFN- β displaying the strongest affinity³². Differences in binding affinities appear to arise from the specific interactions each IFN makes with its receptor in addition to conserved ligand anchor points³³. Type I IFNs that bind more strongly form a more stable ternary complex with the two receptor subunits, potentially resulting in increased binding duration^{34,35}. Binding of type III IFNs with IFNLR forms a similar ternary complex, the stability of which increases when ligands are engineered to bind more strongly³⁶. These studies suggest that stronger ligand binding affinities can stabilize the type I and type III receptors by increasing the duration of binding between the receptor subunits and ligand.

In contrast, negative regulatory mechanisms can obstruct the stability of the ternary receptor complexes and interfere with various stages of the IFN signalling cascade. For example, type I and type III IFN signalling induces expression of ubiquitin-specific protease 18 (USP18) (ref. 37), rendering the type I IFN receptor insensitive to IFN- α but not to IFN- β , thus implicating USP18 in the differential signalling activities of type I IFNs (ref. 38). Since overall IFN receptor expression remains unaltered, USP18 may participate in regulating receptor plasticity by preventing IFN- α (but not IFN- β) subtypes from recruiting IFNAR1 to the type I receptor complex³⁹. Other well-characterized negative feedback mechanisms involve suppressor of cytokine signalling (SOCS) proteins, namely SOCS1 and SOCS3, whose targets include JAK1 (ref. 40) and tyrosine kinase 2 (TYK2) (ref. 41), which otherwise cross-phosphorylate to propagate the IFN signal relay and stabilize the receptor subunits. STAT proteins 1–6 have complicated roles in either propagating IFN signals or fine-tuning the cascade. For example, IFN- α/β -induced expression of STAT3 negatively regulates type I IFN signalling by sequestering STAT1 monomers⁴² or targeting transcription of IFN signalling components⁴³. Strikingly, type III IFN signalling is negatively regulated by SOCS1, but not by SOCS3 or USP18 (ref. 44). These data indicate that negative regulatory mechanisms contribute to different signalling outcomes for type I IFNs, as well as the observed signalling differences between type I and III IFNs.

Conversely, positive regulatory mechanisms augment the IFN signalling cascade to maintain or amplify expression of ISGs or IFNs (refs. 30,45). Cascade components involved in amplifying IFN signals include STAT1 and IFN regulatory factor 9 (IRF9), which associate with STAT2 to form the ISGF3 transcription factor that binds to ISG promoter elements. Increased expression of these components in response to IFN- β prolongs expression of ISGs, resulting in enhanced viral resistance⁴⁶. In addition to promoting the secretion of cytokines, positive feedback mechanisms can lock cells into an autocrine signalling loop that sustains IFN signal transduction⁴⁷. Many positive regulatory mechanisms are cell type-specific, but certain factors such as IRF7 are thought to be common across many tissues⁴⁸. Many details of positive regulation and signal amplification still need to be uncovered, as do the nuances of negative and positive regulation that keep IFN-mediated inflammation in check.

Upstream of many of these mechanisms, IFN receptors can decode signalling inputs through adjustments to receptor expression levels or assembly. It has been proposed that receptor expression levels contribute to the differential signalling observed by certain type I IFNs. For example, the potency of IFN- α surpasses that of IFN- β when human cells are engineered to overexpress IFNAR subunits⁴⁹; however, the potency of IFN- β barely changes

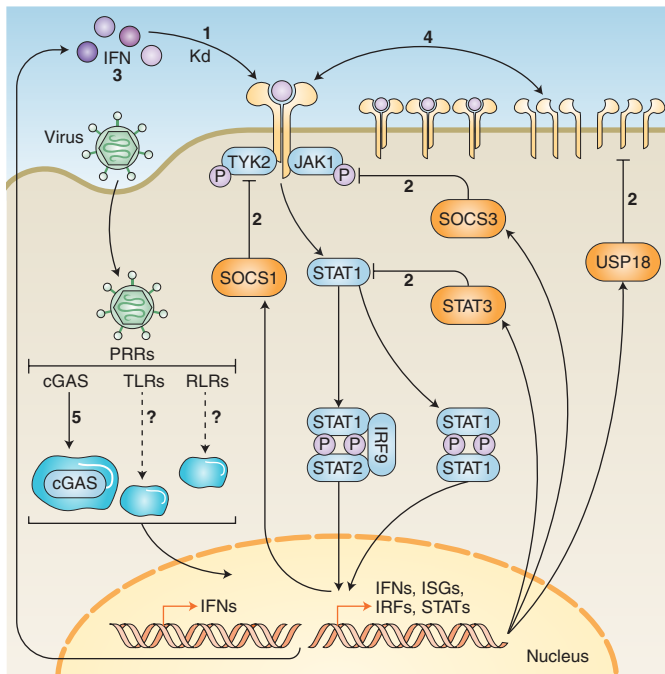


Fig. 2 | Factors that influence the decoding of IFN signalling inputs.

Various factors influence the decoding of IFN signalling inputs. (1) Receptor-binding affinities: each type I IFN binds to the IFNAR complex with varied affinities. These affinities correspond with differences in certain signalling outputs. As of yet, the binding affinities of type III IFNs have not been calculated. (2) Negative regulation: gene products induced by IFN signalling have the ability to negatively regulate the cascade at various stages; for example, SOCS1 and SOCS3, which interfere with TYK2 and JAK1, and STAT3, which can suppress STAT1 monomers, preventing homodimerization. (3) Positive regulation and signal amplification: factors such as STAT1, IRF9 and IRF7 can enhance IFN signal transduction. This leads to prolonged expression and secretion of antiviral cytokines and IFNs that can adjust the IFN cascade or lock the cell into an autocrine signalling loop. (4) Receptor expression and assembly: levels of receptor expression at the cell membrane contribute to differential signalling abilities of IFNs across cell types. Further, alterations to receptor assembly, such as the kinetics of subunit endocytosis, can influence signalling. (5) Biomolecular condensation: formation of cellular compartments caused by phase separation of biomolecules appears to influence various stages of IFN signalling; for example, phase separation of cGAS facilitates sensing of viral genetic material to induce expression of IFNs. Kd, dissociation constant.

in response to receptor expression levels⁵⁰. Beyond this, some models suggest that dynamic alterations to IFN receptor assembly may account for signalling differences. After formation of the ternary complex, receptor subunits are endocytosed. The kinetics of subunit endocytosis may factor into how signalling inputs are propagated²². Homodimerization of the IFNAR2 subunit may even be sufficient to induce certain signalling events⁵¹. However, to what extent receptor subunits can homodimerize and the role this plays in physiological conditions is still unknown. In all, it appears that adjusting the factors involved in receptor plasticity—expression, assembly and dimerization patterns—may fine-tune the signalling inputs of different IFNs.

Although somewhat distant from the other factors discussed, biomolecular condensates have been gaining attention as novel signalling structures that may guide the host response to viral infection. These are cellular compartments that lack a cell membrane and are typically formed by phase separation of polymeric biomolecules⁵². It was recently demonstrated that liquid phase separation of cyclic

guanosine monophosphate (GMP)–adenosine monophosphate synthase (AMP) synthase (cGAS) plays a role in sensing pathogenic DNA upstream of IFN production⁵³ (Fig. 2). Additionally, IFN- α signalling can prompt myxovirus resistance protein A (MxA) to form cytoplasmic, organelle-like structures adjacent to the cytoskeleton⁵⁴. Since oligomerization of MxA is necessary for its antiviral activity against influenza virus⁵⁵ and expression of MxA positively regulates IFN signalling in response to HCV infection⁵⁶, biomolecular condensation of this ISG may facilitate IFN signalling during viral infection. Further studies should address the extent to which biomolecular condensation of ISGs and immune proteins in general influences IFN signalling dynamics.

Complex outputs

Complex IFN signalling inputs correspond with distinct transcriptional outputs and cellular responses during viral infection. Activation of type I and type III receptors triggers the transcription of hundreds of different ISGs as well as genes encoding other proteins, such as STATs 1–6. Signalling through IFN receptors also leads to the production of multiple other IFNs, which may vary in response to different viral infections⁵⁷, although this phenomenon requires more study and characterization. Overall, the magnitude, kinetics and composition of IFN-stimulated transcriptional profiles appear to vary depending on which IFN initiated the signalling cascade⁵⁸ (Fig. 3). As a result of these varied transcriptional profiles, IFNs induce different cellular responses, such as those associated with antiviral immunity, proliferation, apoptosis and clinical outcomes¹². Often, differences in these transcriptional and biological outputs are both cell type- and IFN-specific. Understanding these outputs is imperative to relate differential IFN signalling to the antiviral responses of a cell.

As a group, ISGs can target most steps of viral replication, amplify IFN signalling cascades to strengthen the host response and exert combinatorial antiviral activities⁵⁹. Mice deficient in certain ISG pathways still mount antiviral responses via other ISGs; such redundancy highlights the crucial role for ISG transcription during host defence⁶⁰. The first ISGs discovered (now considered ‘classical ISGs’) were shown to induce potent antiviral responses by themselves (for example, Mx proteins⁶¹ or Protein kinase R (ref. 62)). Over time, however, the identification of less-potent ISGs indicates that weaker ISGs work together to temper the immune response depending on the type and magnitude of infection⁵⁹. While much remains unknown about the roles of ISGs during viral infection and pathogenesis, large-scale ISG screens have identified and characterized hundreds of ISGs present during viral infection^{63,64}, many with virus-, cell- and species-specific effects.

Unique ISG panels are induced in response to different viral infections⁵⁷, resulting in specific antiviral responses. Some viruses are targeted primarily at a specific point during infection; for example, many ISGs that target HCV do so during translation of the entering genome⁶³. Other viruses, such as DENV and WNV, are targeted by a number of ISGs at multiple stages of the viral replication cycle⁶⁵. ISGs can exert virus-specific activities; for example, IFN- α -inducible protein 6 was found to selectively inhibit replication of certain flaviviridae family viruses by interfering with the formation of endoplasmic reticulum (ER) microenvironments⁶⁶. Combinations of ISGs frequently increase defences against viruses. Additive effects were observed when pairs of ISGs were tested against viruses from different families, such as HCV, HIV-1 and YFV (ref. 63). ISG feedback loops also enhance or fine-tune antiviral effects by regulating expression of other ISGs or IFNs (ref. 45). In particularly striking cases, ISGs act in a manner that appears pro-viral on first glance. While some ISGs may indeed be co-opted by viruses to facilitate viral infection, others with curiously ‘pro-viral’ functions may in fact be working to fine-tune the IFN response against viral infection. For example, in humans (but not mice), ISG15 interacts with

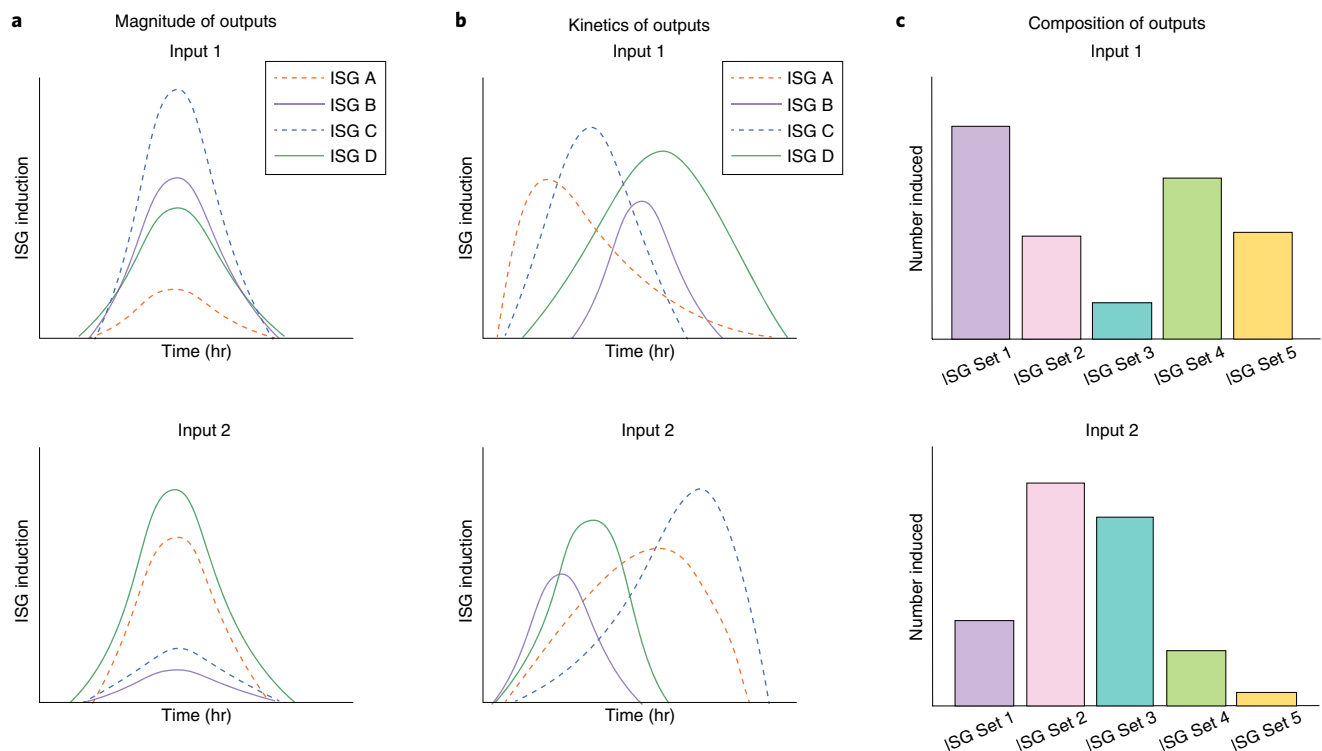


Fig. 3 | Hypothetical models of different transcriptional outputs in response to viral infection. During viral infection, differential IFN signalling inputs may manifest as differences in the magnitude of induced ISGs (a), kinetics of ISG transcription and degradation (b) or composition of ISGs expressed in the transcriptional profile (c). These variations, or a combination thereof, appear to play a significant role in cell-, virus- and species-specific antiviral responses.

and stabilizes USP18, allowing for appropriate downregulation of IFN signalling⁶⁷. Since ISG15 possesses well-documented antiviral properties⁶⁸, these findings point to a species-specific ability of ISG15 to adjust the IFN signalling cascade during the later stages of viral infection in humans. Such studies indicate that ISGs can modulate the host's antiviral response to fit the type of virus or stage of infection.

In early studies aiming to understand IFN signalling outputs, differential ISG outputs and cellular responses were linked with variations in the receptor-binding affinities of IFNs. Type I IFNs that bind more strongly to IFNAR, such as IFN- β , induce a subset of ISGs that are not expressed by the binding of weaker IFNs; furthermore, universally expressed ISGs are induced to a greater extent by IFN- β (refs. ^{64,69}). A linear correlation exists between the binding affinities of type I IFNs and their anti-proliferative potency; however, the relationship between receptor-binding affinity and antiviral activity is less straightforward³². Although the signalling outputs of type III IFNs have been less thoroughly explored, an engineered IFN- λ that binds IFNLR with increased affinity leads to a corresponding increase in antiviral activity³⁶. In contrast, increasing the binding affinity of a synthetic type I IFN does not increase antiviral activity compared with wild-type IFN, which may suggest that type I IFNs already exert their maximal antiviral potency³⁶. Future studies should continue to explore how other factors contribute to the complexity of IFN-mediated transcriptional and antiviral signalling outputs.

An increasing number of reports have revealed instances where type I and III IFNs function together to coordinate viral clearance. Genetic disruption of type I and III signalling in mice results in pronounced viral neuroinvasion and overall hyper-susceptibility to infection by attenuated YFV (ref. ⁷⁰). Hyper-susceptibility is also observed during influenza infection of mice deficient in type I and III IFN signalling; deficiency of either type alone does not abolish transcription of ISGs, which allows the type I and III IFN systems

to compensate for the loss of the other⁷¹. Further research suggests that type III IFN signalling acts as the first line of defence in the lung epithelium during early influenza virus infection, and subsequent signalling by type I IFNs may offer enhanced protection during the later stages of viral spread⁷². Additionally, a comprehensive analysis of the antiviral landscape in mice infected with influenza virus found diverse antiviral gene signatures, indicating that the magnitude or number of rounds of influenza infection dictates the nature of IFN protection⁷³. It thus appears that integration of the type I and III IFN systems, especially at barrier surfaces, can modulate or heighten a host's antiviral response during infection by certain viruses.

While the antiviral activities of type I IFNs have been thoroughly explored¹³, those of type III are still being elucidated. Type III IFNs may hold therapeutic potential against viruses that preferentially infect cells of epithelial origin. Research in mice has demonstrated that IFN- λ signalling at the blood-brain barrier prevents neuroinvasion by WNV, and treatment with pegylated IFN- λ 2 improves survival against viral challenge²⁰. Similarly, intestinal epithelial cells infected with rotavirus respond more strongly to treatment with IFN- λ than type I IFNs *in vivo*⁷⁴, and type III IFN signalling appears sufficient to restrict the spread of influenza virus in the respiratory tract⁷⁵. IFN- λ also displays potent antiviral action against hepatitis viruses⁷⁶, and promising clinical studies have tested pegylated IFN- λ against chronic HBV or HCV infection^{77,78}. Counterintuitively, IFN- λ 4 has been associated with lower viral clearance of HCV in humans⁷⁹, possibly due to its ability to accentuate negative feedback mechanisms such as SOCS1 (ref. ⁸⁰). However, certain IFN- λ 4 genotypes may influence the efficacy of IFN therapy, as shown for HCV (refs. ^{81,82}). Since IFNLR is expressed on fewer cell types than IFNAR, side effects from IFN- λ treatment may be more limited than those induced by treatment with type I IFNs (ref. ⁸³). These studies and others indicate that type III IFNs can launch significant

Table 1 | Examples of RNA viral antagonism upstream of IFN induction

Viral family	Virus	Proposed mechanism of evasion upstream of IFN signalling	References
Flaviviridae	DENV, WNV, ZIKV and JEV	Viral protease NS2B3 cleaves STING	14, 91,118
Flaviviridae	YFV	Viral protein NS4B interacts with STING	124
Flaviviridae	HCV	Viral protein NS4B interacts with and disrupts STING signalling complexes	125,126
Coronaviridae	HCoV-NL63	Viral protein PLP2-TM interacts with and disrupts STING signalling complexes	127,128
Coronaviridae	PEDV	Viral protein PLP2 interacts with and disrupts polyubiquitination of STING	129
Coronaviridae	SARS-CoV	Viral protein P1pro-TM interacts with and disrupts STING signalling complexes	127, 128,130
Flaviviridae	HCV	Viral protease NS34A cleaves MAVS	131,132
Picornaviridae	HAV	Viral protease precursor 3ABC cleaves MAVS	133
Flaviviridae	DENV	Viral protease NS2B3 cleaves MAVS	134
Flaviviridae	HCV	Viral protease NS34A cleaves TRIF	135
Picornaviridae	HAV	Viral protease intermediate cleaves TRIF	136
Arteriviridae and Bunyaviridae	Arterivirus and nairovirus	Viral protease deubiquitinates RIG-I	137
Arenaviridae	Arena virus synthetic molecules	Viral 5'ppp overhangs act as RIG-I decoy	138
Arenaviridae	GTOV, JUNV, MAVC and SABV	Viral Z protein binds to and inhibits RIG-I	139
Paramyxoviridae	hPIV5	Viral V protein binds LGP2, cooperatively inhibiting induction by RIG-I ligands	140
Reoviridae	Synthetic reovirus RNA mimics	Synthetic particles trigger RIG-I; virus trims 5'ppp for innate immune evasion	141
Orthomyxoviridae	IAV	Viral protein NS1 binds RIG-I and prevents activation; RIG-I selectively evolved to distinguish self from non-self	142,143
Bornaviridae	BDV	Viral P protein antagonizes TBK1	144
Bunyaviridae	SFTSV	Viral protein NSs sequesters TBK1/IKK- ϵ	145
Bunyaviridae	Hantavirus	Dephosphorylation of TBK1/IRF3	146-148
Filoviridae	Ebola virus	Viral protein VP35 sequesters viral RNA	149,150
Togaviridae	Sindbis virus	Viral protein nsP2 downregulates IFN and minimizes virus visibility	151
Bunyaviridae	ANDV	Viral NP and GPC proteins inhibit IFN- β induction	152
Bunyaviridae	SNV	Viral GPC protein inhibits IFN- β induction	152
Bornaviridae	BDV	Evades detection by genome trimming	153

GTOV, Guanarito virus; JUNV, Junin virus; MAVC, Machupo virus; SABV, Sabia virus; PLP2, papain-like protease 2; TM, transmembrane domain; VP35, virion protein 35; SFTSV, severe fever with thrombocytopenia syndrome virus; GPC, glycoprotein precursor; PEDV, porcine epidemic diarrhea virus; P1pro, papain-like protease; 3ABC, stable intermediate product of HAV polyprotein processing including viral proteins 3A, 3B and 3C; nsP2, non-structural protein 2; NP, nucleocapsid protein.

antiviral responses against a number of viruses and may be seriously considered as a clinical treatment; as such, type III IFNs will be an important area for future research.

Viral evasion of IFN-mediated defences

Viruses have evolved along with their hosts to evade these IFN systems, allowing them to propagate within their hosts and spread to neighbouring cells. Disruption of innate immune signalling both upstream (Table 1 and Fig. 4) and downstream (Table 2 and Fig. 5) of IFN induction is quite common among viruses. Many mechanisms behind such evasion have been extensively reviewed elsewhere²⁻⁷, but a few are briefly mentioned here: viruses can evade IFN-dependent innate immunity by hiding their genomes from detection, inhibit interactions with host inducers of the IFN response, regulate phosphorylation, ubiquitinylation related pathways of the host's cellular machinery, cleave/ mark for degradation proteins vital to stimulating the IFN response, regulate host gene transcription and translation, regulate RNA processing and trafficking, and employ protein decoys. Rather than reiterate these evasion strategies, this section aims to highlight more recent discoveries relating to novel roles for organelle stress responses during viral infection and viral antagonism, both up- and downstream of host IFN signalling. These new discoveries broaden our understanding of host antagonism and, specifically, host tropism of RNA viruses.

The ER and mitochondria are two organelles that play important roles in detecting and responding to viral infection upstream of IFN induction. The organelle-damaging effects of certain viral infections signal to the host cell that something is amiss, prompting the cell to trigger antiviral responses through IFN signalling. In a healthy cell, ER stress induced by the unfolded protein response leads to ER-associated protein degradation⁸⁴. Conversely, in a cell infected with influenza A virus (IAV), a potent antiviral response is triggered by the overproduction of viral haemagglutinin glycoproteins which stimulate the unfolded protein response⁸⁵, offering a new perspective on the role of the ER during viral infection. Further, the homo-cysteine-induced ER protein (HERP), induced by the unfolded protein response and by ER stress, is implicated in antiviral immunity against IAV and several other RNA viruses. Mitochondrial antiviral signalling protein (MAVS), a vital host protein involved in the retinoic acid-inducible gene I (RIG-I) like receptor (RLR)-IFN signalling cascade, was shown to enhance HERP expression following viral infection⁸⁶. HERP then binds TANK-binding kinase 1 (TBK1) to amplify the MAVS signalling cascade⁸⁶, which, in turn, represses the replication of several RNA viruses, including Sendai virus (SeV), IAV, VSV and enterovirus 71 (EV71) (ref. ⁸⁶) (Fig. 4). Similarly, viruses such as DENV and ZIKV can cause mitochondrial damage through elongation induced by viral non-structural proteins during infection⁸⁷, but, in the past few years, several studies have come to conflicting conclusions regarding cellular defences

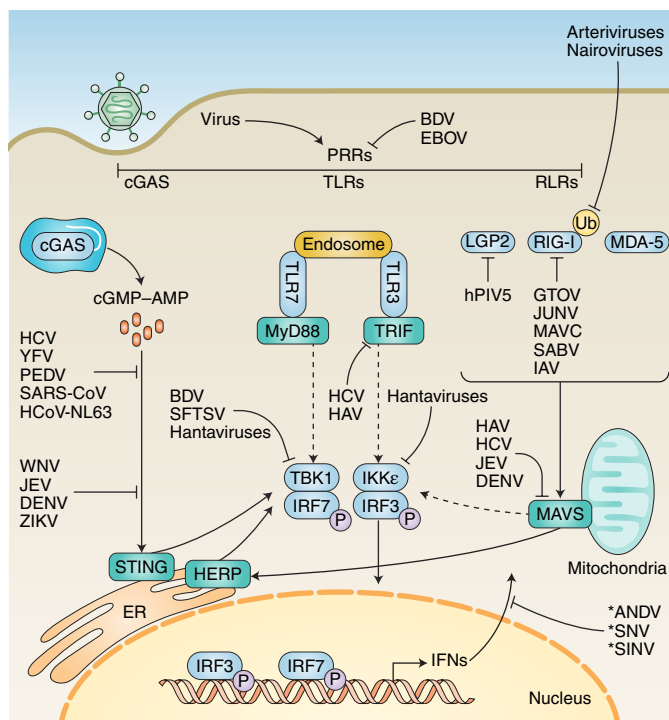


Fig. 4 | Examples of RNA viral antagonism upstream of IFN induction.

After entering a cell, viral genetic material may be recognized by one or more of the host's PRRs. These include RLRs, Toll-like receptors (TLRs) and cGAS. Recognition by one or more of these PRRs triggers a signalling cascade that culminates in the transcription and subsequent generation of IFNs. Different viruses have evolved to antagonize these pathways at virtually all stages, indicated by blunt end arrows. Solid arrows indicate direct pathway connections. Dashed arrows indicate signal cascade components present in vivo but not shown for space concerns. Asterisks indicate viral antagonism by an unknown mechanism. See Table 1 for specific mechanisms at each stage. LGP2, laboratory of genetics and physiology protein 2; MDA-5, melanoma differentiation-associated protein 5; TRIF, TIR domain-containing adapter-inducing IFN- β ; IKK- ϵ , I κ B kinase- ϵ ; HAV, hepatitis A virus; hCoV-NL63, human coronavirus NL63; PEDV, porcine epidemic diarrhea virus; GTOV, Guanarito virus; JUNV, Junin virus; MAVC, Machupo virus; SABV, Sabia virus; BDV, Borna disease virus; SFTSV, severe fever with thrombocytopenia syndrome virus; JEV, Japanese encephalitis virus; ANDV, Andes virus; SNV, Sin Nombre virus.

against RNA virus-induced damage to this vital organelle, as outlined below.

It has been shown that IFNs can be induced in healthy cells when mitochondrial DNA (mtDNA) stress is induced by a deficiency in mtDNA binding protein⁸⁸. This points to a role played by the fidelity and/or decompartmentalization of mtDNA in antiviral signalling. On the one hand, viruses from different viral families can prompt leakage of mtDNA into the cytosol, stimulating the DNA sensor cGAS, thereby elevating ISG expression through stimulator of IFN genes (STING)–IRF3 dependent signalling^{88,89}. DENV (an RNA virus) has evolved to disrupt this canonical DNA sensing pathway by virally encoded, protease-mediated cleavage of STING (refs. 89–91). Additionally, the DENV non-structural protein NS4B causes mitochondrial elongation, compromising the integrity of ER-mitochondrial interfaces that are critical for RIG-I-mediated innate immune signalling⁸⁷. Similarly, it was shown that other RNA viruses of diverse families, such as VSV, Sindbis virus, SeV, IAV and reovirus type 3 Dearing strain, all replicate at higher levels in cells expressing short-hairpin RNAs targeting STING (ref. 92). On the other hand, however, it is argued that STING exhibits an antiviral

response through translational inhibition in an RLR-dependent manner and is not required for the sensing of leaked mtDNA due to organelle damage. This conclusion was drawn from findings that cells depleted of mtDNA are able to retain their ability to diminish viral RNA replication in a STING-dependent manner, and that STING-dependent translational inhibition does not depend on MAVS (ref. 92). These findings argue that RLR responses to RNA viral infections mediate IFN induction through MAVS and restrict viral translation through STING. Regardless of mechanism, RNA viruses must bypass these innate IFN signalling pathways to successfully and robustly replicate. More research is needed to understand the exact, and likely multifaceted, functions of STING during viral infection.

Similarly, it was recently discovered that like DNA sensors affecting RNA viral replication, the opposite is also true; several groups are now studying the mechanisms by which RIG-I is able to bind host RNA as a means to stimulate the innate immune response during viral infection. HSV-1, a DNA alpha herpes virus, was shown to induce the relocalization of host-derived 5S ribosomal RNA pseudogene 141 (RNA5SP141) from the nucleus to the cytoplasm, where it binds RIG-I and induces the type I IFN response⁹³. This occurs due to viral induced shutoff of RNA5SP141-interacting proteins, thus freeing RNA5SP141 for interaction with RIG-I; silencing of RNA5SP141 was shown to dampen the antiviral response to not only HSV-1, but also to Epstein–Barr virus and IAV (ref. 93). Further, host RNAs were shown to facilitate the host immune response to Kaposi's sarcoma-associated herpesvirus (KSHV), a gammaherpesvirus, which is capable of establishing latent and lysogenic infections. It was discovered that KSHV lytic reactivation from latency is restricted by RLRs through recognition of host-derived RNAs (ref. 94); this is accomplished by an infection-induced reduction in a cellular triphosphatase, leading to the accumulation of misprocessed, noncoding RNAs that are detected by RIG-I. These results, taken together with the above findings regarding cGAS–STING, demonstrate our recent advances in understanding the surprising interplay between the virus and host prior to IFN induction.

How RNA viruses antagonize antiviral responses downstream of IFN signalling appears to be largely restricted to a small subset of host proteins, albeit through a variety of viral proteins and mechanisms (Table 2 and Fig. 5). For example, STAT proteins serve as a key point of convergence within host defences. STAT2 is antagonized by the non-structural viral protein NS5 of numerous viruses, including DENV (refs. 95–98), ZIKV (refs. 99,100), WNV (refs. 101,102), JEV (refs. 103–105) and tick-borne encephalitis virus¹⁰². Notably, YFV also uses its NS5 protein to antagonize STAT2 and the STAT-signalling pathway, but this requires events upstream of IFN signalling to take place (specifically, phosphorylation of STAT1 and polyubiquitination of YFV NS5) (ref. 106). Less closely related viruses, such as human parainfluenza virus types 1 and 3 (hPIV1 and hPIV3) and SeV, also antagonize the STAT-signalling pathway by inhibiting STAT protein phosphorylation and/or STAT nuclear translocation, thereby blunting ISG induction^{107–110}. Similarly, by mutating the critical residues of the STAT binding domain of rabies virus P protein, mice do not progress to a lethal neurological disease state, even following direct cranial inoculation by the mutant virus¹¹¹, demonstrating that STAT inhibition is required for the lethality of the virus. Discoveries such as these highlight how certain viruses have evolved to counter IFN-mediated host defences, and allow us to look at how host and tissue tropism is dictated by differential regulation and antagonism of these host innate immune pathways.

Impact of IFN signalling complexity on host tropism

Determining the impact of IFN signalling on host tropism is vital to the pursuit of clinical interventions. However, gaining these insights comes with its fair share of challenges. Research conducted using different methods and bioinformatics analyses can be difficult to

Table 2 | Examples of RNA viral antagonism downstream of IFN induction

Viral family	Virus	Proposed mechanism of evasion downstream of IFN signalling	References
Paramyxoviridae	Hendra virus and Nipah virus	Prevents STAT protein nucleocytoplasmic trafficking by preventing STAT complex formation via viral N protein	154
Paramyxoviridae	hPIV1	Viral C accessory protein prevents nuclear translocation of STAT proteins by an unknown mechanism	107
Paramyxoviridae	hPIV3	Viral C accessory protein prevents phosphorylation of STAT proteins	6
Paramyxoviridae	RSV	Viral NS1 and NS2 proteins induce proteosomal degradation of STAT complexes	155,156
Paramyxoviridae	SeV	Viral C accessory protein associates with STAT 1, blocking STAT 1 and STAT2 activation	109,110
Paramyxoviridae	hPIV5	Viral V protein induces STAT1 antagonism in a STAT2 dependent manner	157,158
Flaviviridae	JEV	Viral protein NS5 prevents tyrosine phosphorylation of TYK2 and STAT1	104
Flaviviridae	WNV	Viral protein NS5 prevents accumulation of phosphorylated STAT1	101
Paramyxoviridae	Hendra virus and Nipah virus	Viral V protein sequester STAT2 in the cytoplasm	159-162
Paramyxoviridae	hPIV2	Viral V protein induces STAT2 degradation	163
Paramyxoviridae	Measles virus	Viral V protein sequesters STAT2	164
Flaviviridae	DENV	Viral protein NS5 reduces STAT2 expression, mediates STAT2 binding and degradation, blocks STAT2 phosphorylation, and co-opts host UBR4 protein, mediating STAT2 degradation	95-98
Flaviviridae	ZIKV	Viral protein NS5 mediates STAT2 degradation in humans, but not in mice	99,100
Flaviviridae	JEV	Unknown viral protein blocks tyrosine phosphorylation, blunting JAK-STAT signalling	103
Flaviviridae	YFV	IFN-I activation of the JAK-STAT pathway allows viral protein NS5 to inhibit STAT signalling	106
Bunyaviridae	ANDV and SNV	Viral GPC protein inhibits JAK-STAT signal amplification	152
Flaviviridae	WNV and TBEV	Viral protein NS5 sequesters cellular prolidase, limiting expression of IFNAR1 cell surface expression	102
Paramyxoviridae	Measles virus	Viral V protein induces type I IFN in a STAT2-dependent and STAT1-independent manner, subverting antiviral IFN effects	165
Flaviviridae	JEV	Viral protein NS5 prevents IFN- β induced responses, such as ISG expression	105

compare holistically and are typically carried out on a single-species level. This usually results in studies without sufficient power to understand and identify key evolutionary features, leaving it hard to draw meaningful conclusions from expanding data sets. The first piece of the puzzle is to understand how other species respond, or are immune to, varying infections that plague humans. Genomic- or transcriptomic-based studies are useful to investigate these differences, but require a well-annotated reference genome for the species in question as well as an ample number of samples from different donors to ensure the data represents the larger population. Identifying gene orthologues between species can be fruitless without a complete or near-complete reference genome for each species of interest. However, these complications pale in comparison to what we can learn about host-pathogen interactions from analysing other species, and we can be continually surprised by how other hosts combat, or even tolerate, viral infections.

Studies that analyse viral infection in multiple species using a single method are able to avoid the challenge of comparing results gathered from differing methods and bioinformatics analysis pipelines. One such study compared the type I 'interferome' of 10 species (human, rat, cow, sheep, pig, horse, dog, microbat, fruit bat and chicken), revealing a conserved core of 62 genes, some of which were not previously associated with response to type I IFN stimulation¹¹². These conserved ISGs highlight the longstanding role of the innate immune system in responding to different pathogens. Additionally, ISG expression patterns were more similar in more closely related species than distant ones, while 14 conserved IFN repressing genes were upregulated in all species that target different points in the type I IFN pathway, demonstrating the importance of avoiding excess stimulation of these pathways¹¹². While studies of this kind are necessary to draw comparisons across multiple species simultaneously, studies restricted to fewer species also have the potential to illuminate

specific differences that confer resistance to, or tolerance of, different pathogens that already cross the species barrier.

Bats are a known reservoir for many pathogenic viruses that plague humans, such as Nipah virus, Hendra virus, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle Eastern respiratory syndrome coronavirus and Marburg virus^{113,114}. Originally, it was thought that certain species of bats become asymptotically infected with these viruses due to enhanced potency of their antiviral response. A new hypothesis has recently emerged that immune responses in bats are differentially regulated compared to other species, leading to tolerance rather than clearance of infection. This differential immune regulation may occur because the metabolic demands of flight cause DNA damage, which releases host mtDNA into the cytoplasm. This is exemplified by Egyptian Rousette bats (*Rousette aegyptiacus*), in which the type I IFN subfamily IFN- ω is expanded to almost two dozen subtypes, whereas humans only have one¹¹⁵. Some bat species constitutively express type I IFNs (namely IFN- α) (ref. ¹¹⁶), but IFN- ω subfamily genes are only highly induced in *R. aegyptiacus* following infection with VSV. Additionally, bats have a high occurrence of point mutations in the innate immune signalling protein, STING. The Ser 358 residue of STING is conserved across all non-bat mammals¹¹⁷ and is a critical phosphorylation site for downstream IFN activation in these species. In bats, however, this residue can be mutated to asparagine, histidine or aspartic acid, preventing activation of cGAS-STING and thus resulting in a dampened innate immune response¹¹⁷. Taken together, these studies shed light on how bats evolved to differentially regulate innate immune signalling pathways, leading to infection tolerance and allowing them to be a reservoir for zoonotic pathogens. Notably, in other species such as mice, mutations in STING don't impart a tolerance of viral infection, but rather prevent infection by some viruses altogether.

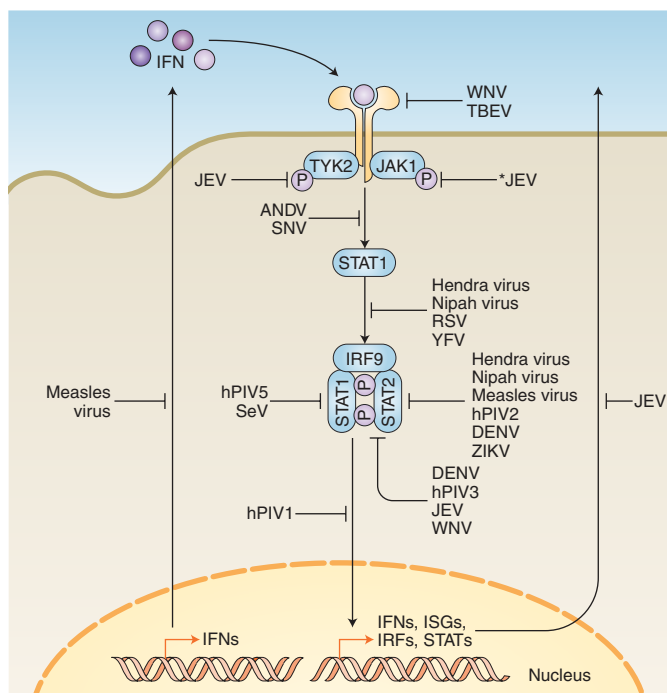


Fig. 5 | Examples of RNA viral antagonism downstream of IFN induction.

Following IFN binding to their receptor in an autocrine or paracrine manner, a signalling cascade takes place that results in the transcription and expression of ISGs. These ISGs are critical for establishing an antiviral state in the host and bystander cells. Different viruses have evolved to antagonize this pathway at virtually all stages, indicated by blunt end arrows. Solid arrows indicate direct pathway connections. The asterisk indicates viral antagonism by an unknown mechanism. See Table 2 for specific mechanisms at each stage.

Mice do not support productive infection of many flaviviruses that affect humans, and one key mechanism behind this was recently elucidated. The viral protease NS2B3 in ZIKV, WNV and JEV, but not YFV, was found to mediate cleavage of human STING, increasing the permissiveness of mouse cells expressing human STING to ZIKV infection (including higher production of infectious particles and greater ZIKV RNA copy numbers)¹⁴; strikingly, murine STING is not cleavable by viral proteases in DENV (ref.¹¹⁸) or ZIKV (ref.¹⁴), thereby restricting the ability of these viruses to infect mice. Notably, STING-deficient mice are not more susceptible to ZIKV infection, pointing to other redundant antiviral pathways controlling ZIKV infection *in vivo*¹⁴. However, cGAS- or STING-deficient mice are more likely to progress to lethal infection by several DNA viruses¹⁹, demonstrating the vital role of this IFN signalling pathway's ability to hinder viral replication following infection. Further, mouse STAT2, but not human STAT2, is known to restrict early DENV replication⁹⁶, conferring additional resistance against DENV to mice. Similarly, the NS5 protein of ZIKV is able to bind and degrade human STAT2, but not mouse STAT2, preventing ZIKV from evading the innate immune response in mice^{99,100,120}, and subsequently establishing a successful infection. Due to differing immune responses to differing infections, it can be hard to relevantly study these pathogens using mammalian model organisms. Recently, however, a large step forward for ZIKV was made by the generation of an immunocompetent mouse model for ZIKV infection. By garnering a key mutation in the NS4B gene of ZIKV to enhance replication in neuronal stem cells and the brain in mice, and replacing mouse STAT2 with human STAT2, an immunocompetent mouse model with which to study ZIKV was generated¹²¹, allowing for further research of this important human pathogen.

Future perspectives

Much remains to be learned about the complexity of IFN signalling during viral infection. Many factors have been proposed to explain how type I IFNs signal differently through their shared receptor. However, it is still unclear how many of these factors function individually as well as together. It is still relatively unknown as to what extent type III IFNs produce different signalling outputs and whether these outputs result from the same mechanisms that impact type I signalling. Further, given the complexity and vastness of ISG outputs uncovered by large-scale screening efforts, more work is needed to fully understand the transcriptional profiles associated with IFN signalling and their effect on viral antagonism. Future studies should continue to investigate the roles of upregulated ISGs and the antiviral consequences of downregulated genes in response to IFN signalling, which have been understudied so far.

As for viral evasion of host signalling pathways, new concepts and convergence points are starting to emerge. Fully elucidating the role of cGAS and STING in the detection of, and antagonism by, RNA viruses is a currently unfolding story. Likewise, the involvement of RNA sensors for fighting DNA viral infections is an intriguing new area of investigation. A better understanding of how certain species resist infection by pathogens that affect humans will further our efforts to develop interventions and treatments.

There is still much work to be done to understand viral species and tissue tropism. Ongoing difficulties associated with comparing genomic and transcriptomic studies across different species still pose a barrier to the field. Additional difficulties arise when developing appropriate models to study viral infections. Working with certain species may not be possible due to ethical or practical reasons, and cell models may not give us a biologically relevant picture of virus–host interactions. The use of induced pluripotent stem cells generated from naturally susceptible and permissive species may shed light on questions that cannot be answered using other models.

Efforts to understand host tropism, tissue tropism and viral pathogenicity may be aided by considering the evolution of host and viral factors. For example, in non-human primates, a conserved mutation in MAVS imparts an escape from hepaciviral protease antagonism, severely enhancing IFN response in the presence of HCV and other flaviviruses that infect primates, as demonstrated in cells expressing primate MAVS (ref.¹²²). Additionally, for duck Tembusu virus, a single point mutation in the envelope protein confers airborne transmissibility to the virus in the absence of its natural vector, the mosquito; this expands its tropism and ability to replicate in the lung tissue of its host¹²³. Altogether, studies such as these demonstrate how small evolutionary changes can have drastic impacts on the viability of both the virus and host, and illustrate an important knowledge gap in the field that has yet to be filled.

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E.V.M., R.A.L. and A.P. conceived and wrote this Review.

Competing interests

The authors declare no competing interests.

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