

Viral Evasion Mechanisms of Host Interferon Signaling Pathways

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Abstract

Interferons (IFNs) are one of the core pillars of innate antiviral immunity that together forms a cascade in signaling network by intra- and inter-cellular responses, detecting viral infection, activating Janus kinase-signal transducer and activator of transcription (JAK–STAT), and ultimately inducing hundreds of interferon-stimulated genes (ISGs) which inhibit viral propagation. Nonetheless, viruses have developed intricate immune evasion strategies that target virtually all facets of the interferon response thus promoting viral survival, persistence, and pathogenesis. This review summarizes the basic molecular mechanisms of host interferon signaling and the various viruses that have evolved to counteract these pathways. Most notably with respect to viral interference with pattern recognition receptor signaling, type I interferon induction, JAK STAT signal transduction and ISGF3 complex formation and host restriction factors. Soon afterward, the review introduces how viruses manipulate post-translational modifications (PTMs), such as ubiquitination, ISGylation, SUMOylation and proteasomal degradation to potentiate their effects on innate immune responses. The coevolution between virus and host is emphasized as a key mechanism promoting viral immune antagonists in one hand and host antiviral restriction factors on the other, contributing to rapid diversification of both sectors. Finally, novel therapeutic approaches targeting the restoration of interferon signaling via host-directed therapies, inhibition of viral antagonists, modulation of pathways responsible for



post-translational modifications (PTMs) and personalized immunotherapies are thoroughly discussed. Targeting host–virus interaction networks rather than viral replication alone provide new avenues for broad-spectrum antiviral therapies, which are less susceptible to resistance due to the dynamic nature of host and virus evolution. Such integration of structural biology, systems immunology, multi-omics technologies with clinical investigation will be necessary for translating mechanistic insights into therapeutics against viral pathogens and enhancing preparedness to future viral threats.

Keywords: Interferon signaling; Type I interferon; JAK–STAT pathway; Viral immune evasion; Interferon-stimulated genes (ISGs); Pattern recognition receptors (PRRs); ISGylation; Innate antiviral immunity; Host-directed antiviral therapy.

Interferon Signaling Pathways

Pattern recognition receptors sense viral nucleic acids and induce induction of the type I interferon response through downstream signaling cascades that ultimately lead to transcription of IFN genes [1]. The secreted interferons, in turn, will act in an autocrine or paracrine manner to activate the JAK-STAT pathway causing the production of ISGF3 and hundreds of interferon-stimulated genes systemically upregulated [2,3]. Such amplification step would depend on the activation of transcription factors IRF3, IRF7 and NF- κ B, which would potentiate cytokine production following pathogen-associated molecular pattern detection [4,5]. In this regard, TANK-binding kinase 1-mediated phosphorylation of both IRF3 and IRF7 represents the key checkpoint for production of the first wave of IFN- β and IFN- α [6]. In addition, the induction of an antiviral state is amplified in a positive-feedback manner because ISGF3-induced expression of relevant signaling factors and transcriptional regulators sustains the cellular response to viral infection [7,8]. This process of amplification guarantees that even if levels of initial detection are low, the end result is a strong expression of effector proteins (e.g. IFIT and IFITM) that prevent viral replication actively [9]. In addition to this first line of induction, synthesis of IFN-stimulated genes mediates pan-drug antiviral activity that can inhibit progeny production at multiple steps



during the viral replicative cycle [10]. This gradually escalating signaling cascade depicts the most efficient approach for titrating a multi-layered defense, with autocrine and paracrine induction of nearby cells assuring that an anti-viral program is globally disseminated in the ample tissue [11,12]. However, this defense strategy is frequently countered by viral proteins that selectively target components of the sensing and transduction pathways required for the induction of the first step of cytokine production [13]. These viral antagonists typically block the phosphorylation of IRF3 and IRF7, or inhibit MAVS recruitment to suppress assembly of primary signaling complexes [14,15]. The host additionally employs redundant recognition systems that engage pathogen-associated molecular patterns by activating TLR-mediated signaling pathways via TRIF and MyD88, which ultimately promote increased transcription of pro-inflammatory cytokines [16]. These media act as a sensing mechanism based on the mitochondrial-mutant MAVS protein and endoparticle-like Toll receptors that recruit a scaffold protein complex that initiates soluble adaptive immunity [17,18].

Introduction:

Interferon (IFN) signaling pathway is a key component of the innate antiviral immune response. It is a complex molecular network that detects viral invasion within hours and sets up an antiviral state. A weak signal, such as viral recognition, can be transformed into a powerful antiviral program through a series of steps, including the sequential recruitment of pattern recognition receptors (PRRs), IRF3/IRF7 phosphorylation, interferon production, JAK-STAT signaling, and ISGF3-dependent transcription of thousands of genes that encode hundreds of interferon-stimulating genes (ISGs). This multi-step cascade ensures that all infected cells, as well as neighboring uninfected cells, become resistant to viral replication in a self- and neighbor-specific manner. It is also worth noting that innate immune sensing pathways are redundant. In addition, the presence of other pattern recognition receptors (such as RIG-I-like receptors and MAVS), TLR receptors that utilize TRIF-dependent pathways, and MyD88 transducers creates a surplus of immune evasion against viral pathogens. By purposefully exploiting this surplus, it reduces the likelihood that the virus can counteract type I interferon stimulation by targeting a specific signaling



molecule. This finding supports the prevailing view that host immunity has evolved to utilize multipurpose signaling pathways under evolutionary pressures, thereby enhancing the robustness of antiviral defenses. However, it also demonstrates that viruses have evolved as well, developing complex mechanisms to evade these protective host responses. Nevertheless, several viral proteins exhibit the ability to inhibit early stages of interferon production by blocking the phosphorylation of IRF3/IRF7 or MAVS-dependent signaling complexes (thus weakening/delaying host antiviral responses) [30]. This accounts for the rapid activation of interferon signaling, which is also an optimal time point of viral regulation to rival CDK1 in its innate immune evasion functionality; a process facilitated by molecular competition between both. Indeed, further investigation of these early regulatory events will have critical implications for strategies to design antiviral agents that would restore or boost interferon-mediated immunity. Interferon signaling pathway is among key components of innate antiviral immunity linking detection and propagation of a viral signal into the transcriptional control of interferon-stimulated genes (ISGs) through receptor-mediated cytoplasmic signaling events that galvanize an integrated host response to virus infection.

Cooperation of pattern recognition receptors (PRRs), IFN regulatory factor 3 (IRF3)/IRF7, Janus kinase–signal transducer and activator of transcription (JAK–STAT) signaling cascade and interferon-stimulated gene factor 3 (ISGF3) provides rapid and effective antiviral immunity while in combination redundant sensing mechanisms enhance robustness of host defense. Introduction to viral targeting of signaling molecules: the MAVS and IRF arms race Viruses are also rapidly evolving pathogens that can overcome host immune responses, evidenced by their ability to specifically target important signaling components such as mitochondria-associated membrane (MAM) protein VoN1660 and interferon regulatory factor (IRF) proteins. Thus, therapeutic preservation or restoration of interferon signaling therefore remains a hope for the enhancement of antiviral immunity and thus may represent an anti-viral disease target.



Type I IFN Induction

Induction is initiated when viral components like double-stranded DNA (dsDNA) or double stranded RNA (dsRNA) bind to their cytosolic sensors such as cGAS and RIG-I-like receptors [19]. And these sensors activate signaling cascades that cause phosphorylation and homodimerization of IRF3 after which it translocates to the nucleus to begin transcription of type I IFN [20]. At the same time, TNF receptor-associated factor 3 (TRAF3)-and TANK-binding kinase 1 (TBK1)-recruited phosphorylation of IRF7 that together with IRF3 promotes persistent expression of pro-inflammatory cytokines and type I IFNs [21]. This strong type I IFN production is mainly mediated by plasmacytoid dendritic cells, while other immune cells provide the more ubiquitous source of IFN- β to help systemic antiviral defenses [22]. Pattern recognition receptors such as TLRs, RIG-I and MDA5 recruit an adaptor molecule [MyD88, TRIF or MAVS] to execute kinase-mediated activation of IRFs [23].

MAVS is simultaneously nuclearization via RIG-I and MDA5 multimerization to provide a link between MAMP detection and the initiation of downstream IKK-related kinases [24]. These, in turn, instruct the phosphorylation and transfer of IRF3 and IRF7 into the nucleus that is critical for immediate expression of IFN- β and IFN- α genes [25,26]. In the context of this induction, secreted type I and III interferons bind to their corresponding cell-surface receptors—IFNAR1/IFNAR2 and IFNLR/IL10RB, respectively—and activate the JAK1 and TYK2 kinases [27,28]. These kinases phosphorylate STAT1 and STAT2, enabling their binding to IRF9 to form the ISGF3 complex, which regulates a large number of interferon-stimulated genes to establish a broad antiviral response [29, 30]. In addition to these cytoplasmic and endosomeal pathways, any mitochondrial damage during viral replication can enhance cGAS-STING signaling, thus providing a backup mechanism for increased IRF3/7-mediated IFN- α/β production [31]. Furthermore, IRF1 activation is a crucial compensatory mechanism, as rapid NF- κ B-mediated transcription of IRF1 mRNA, followed by proteolytic translation, leads to an immediate increase in the overall interferon response [32]. The presence of these specialized signaling pathways highlights functional redundancy within the innate



immune system, ensuring viral detection even when primary sensors are successfully bypassed [33, 34].

The presence of these specialized signaling pathways highlights functional redundancy within the innate immune system, ensuring viral detection even when primary sensors have been successfully bypassed [33, 34]. Stimulation of type I interferon production is one of the earliest and most crucial events in the innate immune response to viral infection. This is a highly regulated process requiring the parallel coupling of intracellular and extracellular signaling pathways, enabling timely recognition of viral nucleic acids and the activation of antiviral defense systems to protect the host from invasive infection. Cooperation between cytosolic sensors (cGAS, RIG-I and MDA5) and adaptor proteins (MAVS, MyD88 and TRIF) exhibits the robust nature of host immune surveillance system. This offers a rapid means to engage IRF3 and IRF7, the master transcription factors that serve as the primary regulators of type I IFN expression and pathway-mediated inflammatory responses. One of the most notable features emerges among all these pathways: a sufficient number of amplification and redundancy mechanisms that enhance antiviral immunity. The JAK1–TYK2/STAT1–STAT2 pathway is activated following the secretion of interferon and promotes ISGF3 complex formation to induce transcription hundreds of interferon-stimulated genes (ISGs), therefore establishing a far-reaching antiviral state. Concurrently, both cGAS–STING signaling and IRF1 activation function via distinct activated pathways to amplify the composite antiviral response, ultimately ensuring that antiviral signaling is intact in conditions of primary viral sensor suppression. This form of redundancy may serve as an evolutionary mechanism to minimize the chances for full viral immune escape.

On the cellular level, such diversity in the signaling pathways used for type I IFN induction reflects an evolutionary battle at work between viruses and their hosts. Additionally, host immune system pathways overlap in a way that individual defects in signaling could be compensated for by other pathways while viruses have escaped early recognition receptors or components of signaling intermediates. Consequently, effective viral infection is often dependent on the use of multivalent targeting of immune signaling



nodes rather than the targeting of individual molecular factors. These findings further support the notion that therapeutic strategies aimed at enhancing innate immune signaling — particularly those directed against sensors and pathways upstream or ISGF3 activation downstream of viral infection — could have broad-spectrum antiviral applications. Type I IFN induction is highly structured and begins with viral nucleic acids sensing that leads to downstream activation of ISG expression via JAK–STAT signaling. Together, the integrated actions of PRRs, adaptor proteins, IRF transcription factors and ISGF3 confer a highly potent antiviral state while multiple redundant signaling pathways conspire to mediate successful viral immune escape. Collectively, these properties indicate that the strength of some immune responses is intertwined with their overall robustness to complex system perturbations in the same way as functional redundancy maintains homeostasis, suggesting that strong kind I IFN induction pathway is an attractive target for anti-viral drug discovery and immunomodulation processes.

JAK-STAT Signal Transduction

The activation of Janus kinases ends up to the phosphorylation of these factors, it dissolves from the receptor and collects IRF9 in its e7[35]. The heterotrimeric ISGF3 then translocates to the nucleus, binds to interferon-stimulated response elements in promoter regions and activates transcription of hundreds of ISGs [36,37]. In parallel, the dimerization of two STAT1 proteins within homodimers upon type II IFN- γ signaling also binds to another class of sequences called the IFN- γ -activated sequence element that controls a different set of genes [38]. Such ISG products function at different steps in the viral replication cycle and thus contribute to a combinatorial antiviral response which blocks viral entry, genome transcription, and protein production [39]. In addition, the regulatory timeframe is highly important and many viruses may adopt strategies to inhibit JAK-STAT signaling or trap transcriptional complexes to turn down the downstream expression of antiviral effectors [40,41]. To limit homeostasis and avoid deleterious over-activation this signaling cascade is regulated through negative feedback with proteins including SOCS1 and SOCS3, which function to inhibit Janus kinase activity [42]. Aside from the canonical JAK-STAT pathway, emerging numbers of non-canonical signaling



mechanisms bonafide regulate ISGs transcription independent of known JAK-STAT intracellular signal transduction pathways, this extended list of players contributes to regulation of the antiviral landscape. Members of the IRF family (IRF1, IRF7 and IRF8) can bind ISRE sequences independently in response to all three interferon types (IFN α , IFN β and IFN γ) [43] giving cells a second chance at controlling their antiviral state. These atypical pathways are often accompanied by independent transcription factors; or activate other kinases usually to compensate for the viral proteins "winning" in a classic fight over your needed antiviral immunity utilizing JAK-STAT axis [44].

Most importantly, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway has been proposed to serve as the ubiquitous intracellular molecular channel through which interferons mediate extracellular antiviral signals to specific gene expression programs in a coherent fashion. After JAK1 and TYK2 were activated, phospho-STAT1 and phospho-STAT2 bound to IRF9 to form ISGF3 that induced transcription of hundreds of interferon-stimulated genes (ISGs), which act at distinct steps during the viral replicative cycle including entry, genome replication, transcription and protein translation to globally inhibit various steps in order to exert its function. Underpinning this dynamic signaling hub is the critical place of the JAK–STAT pathway in establishing a strong and broad-spectrum antiviral state. A critical element of this signaling cascade is that it serves both a host defense and an immune homeostasis function. While rapid ISG activation is essential to restricting viral replication, prolonged or excessive signaling can result in tissue injury and immunopathology. Therefore, pathways containing all known endogenous negative regulators such as SOCS1 and SOCS3 are an important feedback loop to inhibit the activation of Janus kinase and prevent excessive inflammatory response. Appropriate balance is revealed to rely on the type (de novo or systemic) and intensity of lot signals.

Moreover, non-canonical interferon signaling pathways provide additional evidence that the innate immune system retains considerable plasticity. Gene expression of antiviral proteins can continue since transcription factors IRF1, IRF7 and IRF8 can be activated in an independent manner from the canonical virus-suppressed JAK–STAT pathway. This



frivolous and seemingly redundant character is an evolutionarily significant there that confers robustness to the host's defense against viral immune evasion. At the same time, in particular through its intrinsic capacity of many viruses to inhibit JAK-STAT signaling our results emphasize how much this pathway can be considered as a principal virus immune evasion target and also presses it again as a superb therapeutic target for host-based antiviral treatment. The Janus kinase-signal transducer and activator of transcription (JAK–STAT) signaling pathway is the principal mediator of interferon-induced antiviral immunity, linking extracellular interferon signaling to the transcriptional induction of hundreds of diverse interferon-stimulated genes that inhibit viral replication. It is tightly regulated by feedback inhibitors to maintain immune homeostasis, while complementary non-canonical signaling pathways provide further safeguard against improper responses when canonical signaling fails. The preponderance of viral pathogens targeting JAK–STAT components highlight the intrinsic importance of this pathway in host defense and strengthens the rationale for therapeutically augmenting, preserving, restoring or possibly even replacing JAK–STAT signaling to improve antiviral immunity.

Viral Evasion Mechanisms

Viruses that infect vertebrates have evolved a variety of ingenious strategies to evade the action of host immunity categorized mostly by their targeted inhibition of certain signaling nodes within the interferon cascade [45,46]. These evasion strategies encompass the sequestration of pattern recognition receptors to block their initial sensing, enzymatic cleavage of host signaling adaptors, and direct inhibition of JAK-STAT components to limit the provocation of interferon-stimulated genes [47,48]. For instance, human herpesviruses have been known to use viral interferon regulatory factors (vIRFs) that physically block activation by JAK-STAT signaling or sequester essential components of the transcriptional machinery [49] in order to neutralize the innate antiviral potential of their hosts. Moreover, viruses can induce the expression of negative regulator proteins, such as SOCS, that inhibit signal transduction through JAK-STAT cascade—highly conserved pathways [50], or deploy viral proteins that block IFNAR-mediated signaling by forming nonfunctional inhibitory complexes. Moreover, certain viruses do so by



antagonizing the activation of STAT proteins or promoting their dephosphorylation to inhibit downstream transcriptional response [51,52]. In addition to these direct interferences, many viral pathogens also hijack endogenous negative regulators such as the ubiquitin-specific protease 18 (USP18), which outcompetes JAK1 in the receptor complex and subsequently decreases signaling intensity of type I interferons [53,54]. In addition, certain viruses actively target the proteasomal degradation of either STAT1 or STAT2 molecules so as to disconnect the IFN receptor signaling pathway from the formation of ISGF3 [55,56]. On the other hand, some viruses trap these phosphorylated STAT heterodimers in cytoplasm or nucleus to interfere with their compulsory binding with IRF9 and block the formation of functional ISGF3 [57, 58].

One of the most progressive of host–pathogen co-evolution Viral mechanisms employed to rescue immune apparatus are selective pressures sustained over time and space by natural selection and adaptive selection which interactively influence antiviral resistance through interferons-mediated immune defenses. Viruses exploit many molecular mechanisms to overcome this immune response, targeting multiple steps in the interferon signaling cascade rather than only one. Viruses can efficiently suppress the initiation and amplification of innate immunity by targeting pattern recognition receptors (PRRs), degrading signaling adaptors, inhibiting JAK–STAT signaling and blocking ISG expression³⁰. These examples all demonstrate an inherent specificity in antagonistic mechanisms, largely driven by the need to inhibit or delay host interferon signaling to ensure productive viral replication. Two virus immune evasion strategies are mechanistically the most prominent in targeting high-order signaling hubs (e.g., JAK1, STAT1, STAT2, IRF9 and IFNAR-associated components). Depletion or functional inactivation of the weaves of these proteins at hubs of communication essential for the signaling relay counteracts ISGF3 complex assembly, and ultimately further represses downstream antiviral gene spin. While viruses act to directly antagonize hos immunity, they also subvert host regulation to create a permissive pericellular environment that preserves virus persistence via the use of endogenous negative regulators like SOCS proteins and USP18. Especially since these mimics the in vivo immune control that is also there and it also counteracts antiviral defenses as well.



The ability of viruses to sequester phosphorylated STAT proteins, or to promote their dephosphorylation underscores the importance for a potent antiviral immunity of maintaining intact JAK–STAT signaling. Together, these results suggest that viral immune evasion is an evolving process with multiple points interacting with almost every level of interferon signaling. Therefore, strategies to prevent viral antagonism of interferon pathways or to restore disrupted JAK–STAT signaling offer the potential for broad-spectrum antiviral effects and reversion of viral pathogenicity across multiple virus families. Viruses have developed highly diverse and coordinated immune evasion strategies that target multiple components of the interferon signaling pathway including viral sensing mechanisms, signaling adaptors, JAK–STAT proteins, and ISGF3 complex formation. Viruses have evolved mechanisms to inhibit interferon-mediated antiviral responses, and thus they replicate more efficiently in host cells as the actions of direct inhibitors affect the antiviral response on one hand while manipulation of endogenous host regulatory pathways such as SOCS proteins (3, 4) and USP18(5) act at another level. These data reveal molecular mechanisms underlying host–virus interactions and inform the design of new antiviral reagents aimed at maintaining or restoring interferon signaling and bolstering innate immune defenses.

Direct IFN Antagonism

Many viral pathogens utilize exquisitely targeted proteins to physically sequester signaling intermediates out of active transcriptional complexes. Such as UL36USP from HSV-1, which can specifically interact with IFNAR2 to sterically block JAK1 recruitment by the receptor and thus impede the canonical signaling cascade without dependence on its deubiquitinase activity [59]. Counterintuitively, JAK kinases are also targeted by naturally occurring viral proteins; for example, filoviruses use matrix proteins such as VP40 which inhibit the autophosphorylation events associated with JAK1 thereby preventing downstream STATS signaling as part of immune evasion mechanisms [60]. In addition to sequestration, other viral proteins also induce the proteasomal degradation of important signal transducers — for example, nsp11 from some porcine reproductive and respiratory syndrome virus strains triggers STAT2 degradation and thereby disconnects signaling



downstream of the receptor from transcription of target genes [61]. In the same vein, JAKs are also targeted by a wide arrange of pathogens such as the pseudorabies virus and Zika virus that selectively trigger proteasomal degradation of JAK1 to eliminate the phosphorylation of downstream signaling effectors, neutralizing interferon-mediated antiviral response [62,63]. Moreover, many viruses, including ones from the Flavivirus family express unique proteins that trigger the loss on phosphorylation of STAT factors preventing ISGF3 transcription complex [64,65]. In addition, some viruses subvert the USP18-mediated feedback loop of host defense to activate or repress it: stabilizing protease acts to establish a continuously nonresponsive state, while mimicking its structural domain displacing JAK1 from IFNAR2 subunit [66–68]. Conversely, the blockade of IFNAR1 and IFNAR2 at the cell surface prevents JAKs recruitment preventing signal transduction to be initiated [69,70]. This strategy aims to block these receptors, but most of these blockade ends at inhibiting the heterotrimeric ISGF3 (IFN stimulated gene factor 3) complex forming which is an essential terminal step needed for coordinately regulating the expression of hundreds of antiviral genes [71,72]. Direct interferon (IFN) antagonism is among the most potent viral immune evasion mechanisms because it hits the core signaling components that initiate and maintain antiviral immunity. Instead, many viruses have developed highly specialized proteins that target specific IFN-induced molecular interactions along the pathway. These viral countermeasures target the IFNs in a variety of ways and their respective signaling pathways by preventing Janus kinase activation, degradation of essential signaling molecules (e.g. JAK1/STAT2) or blocking assembly of the ISGF3 transcriptional complex. This exact targeting demonstrates the role of the interferon pathway as a significant evolutionary barrier to effective viral replication.

Viruses have multiple complementary mechanisms to ensure the complete suppression of IFN signaling. In addition to receptor blockade and kinase inhibition, many viral proteins enhance the proteasomal degradation or dephosphorylation of STAT proteins. Importantly, now virus utilization of USP18-mediated negative feedback reinstatement indicates that viruses hijacking endogenous regulatory pathways establish persistent inhibition of interferon sensitivity with reduced extraneous cellular stress. Thus, these complex mechanisms illustrate a high level of molecular adaptation enabling viruses



to maintain persistent infection in the presence of an otherwise highly effective innate immune response. The democratic coalescence on common signal transducers including IFNAR, JAK1, STAT2 and ISGF3 reflects that these molecules are the pivotal bottlenecks of antiviral immunity. Therapeutic strategies that target viral proteins to shield crucial signaling components from antagonism or blockade of virus-host protein interactions may eventually restore sensitivity to interferons quite generally following diverse viral infections. Because they target conserved host signaling pathways rather than rapidly mutating viral genomes, such host-directed interventions may also reduce the likelihood of antiviral drug resistance [4]. Selective Viral Strategies to Antagonize Intrinsic Innate Immunity Direct IFN antagonism via receptor blockade, inhibition of JAK kinase activity, degradation or dephosphorylation of STAT proteins involved in ISGF3 complex formation and other negative regulatory pathways like USP18 are highly specialized viral strategies for suppressing innate antiviral immunity. These synergistic mechanisms converge on distinct steps in interferon signaling pathways that facilitate viral replication, and promote viral persistence. Knowledge of the molecular basis of direct IFN antagonism not only sheds light on host-virus interactions but also provides a rationale for future antiviral treatments that are intended to preserve some element of interferon signaling in order to restore the innate immune defense system in the host.

Inhibition of Signaling

A common mechanism is targeting the catalytic domains of JAK proteins by viral proteases to block the phosphorylation of STAT1 and STAT2, thus halting signal transduction at a receptor-proximal step [73]. For example, Sandfly fever viruses target NSs proteins to block the phosphorylation of these STAT proteins after receptor activation by Janus kinase 1 and Tyrosine kinase 2 [74]. Likewise, the influenza A virus subverts PB2 to bind directly with JAK1 and impede the kinase-mediated phosphorylation of downstream signal transducers [75]. In addition, many viruses take advantage of the innate expression of SOCS1 in the host to mediate selective ubiquitination and subsequent proteasomal degradation of JAK1 which guarantees complete inhibition of cytokine signaling [76]. In addition to blocking downstream enzymatic activity, pathogens such as



SARS-CoV-2 also cripple this pathway by promoting the depletion of IFNAR1 (and its associated Tyk2 kinase), leading to the disassembly of the proximal signaling scaffold [77]. In contrast, other viral proteins inhibit the JAK–STAT pathway by specifically binding to and targeting the STAT proteins for proteasomal degradation mediated by polyubiquitination [78]. An illustration is the flavivirus NS protein, such as NS5 in DENV and ZIKV, which recruits E3 ubiquitin ligase UBR4 to drive proteasomal degradation of STAT2 so that transcriptional complexes cannot form [79]. In addition, this pathway can be subverted by viruses in the nuclear compartment where viral effectors block the translocation of phosphorylated STAT heterodimers and their interaction with IRF9 [80,81]. Other viruses with this strategy are known to interfere with the assembly of the heterotrimeric ISGF3, a complex that is required for moving into the nucleus where transcription at IFN-responsive regulatory elements can happen [82,83]. Interferon signaling inhibition is a perfected viral method that abuses the host to prevent it from mounting an appropriate antiviral response.

Many viruses clearly do not just interfere with interferon production but rather play a much more sophisticated role in specifically targeting the host cell intracellular machinery responsible for signaling downstream of those signals derived from interferons. In summary, viruses suppress gene transcription using multiple mechanisms that act to inhibit JAK1 and TYK2 catalytic activity, block STAT1 and STAT2 phosphorylation, lead to the degradation of signaling proteins or disrupt ISGF3 assembly resulting in termination of signal propagation before the transcription of antiviral genes can take place. This underlines the point that intact JAK–STAT signaling is essential for an effective innate immune response, and its loss gives viruses a significant replication benefit.

Unlike other sections that have been described in this document where viruses can target multiple signaling types with a more organized action, an important trait discussed in this section is the diversity of molecular mechanisms by which many antiviral viruses prevent signaling at various sequential steps. In addition to inhibition of kinase activation, some viral proteins also hijack host repressor pathways that favor ubiquitination and subsequent rapid proteasomal degradation of JAK1 and other downstream signaling



proteins (e.g., SOCS1 mediated ubiquitination). Additionally, viruses such as SARS-CoV-2 degrade receptor-associated signaling complexes by downregulating IFNAR1 and TYK2 levels; *flaviviruses* use ubiquitin ligases such as UBR4 to specifically target STAT2 for destruction. Combined, these strategies provide robust antagonism of interferon response pathways and exemplify the impressive molecular plasticity of viral pathogens in evading host immune responses. In addition, the propagation of viral inhibition into the nuclear compartment demonstrates that immune evasion mechanisms are not limited to cytoplasmic signaling events. Viruses are able to circumvent this last step in signaling pathway activation through the prevention of nuclear translocation of phosphorylated STAT complexes or by preventing ISGF3 formation, thus inhibiting transcriptional activation of interferon-stimulated genes even when upstream receptor signaling has taken place. This multi-level inhibition highlights the selective evolutionary pressure experienced by viruses to evade any essential component of interferon signaling. Thus, therapeutic approaches that stabilize the components of JAK–STAT signaling pathway, inhibit mechanisms through which viruses inactivate essential immune functions or preserve ISGF3 complex integrity may offer effective and universal anti-viral protection by increasing Mφ capacity to limit viral pathogenicity.

Viruses block interferon signaling by a variety of coordinated mechanisms directed against JAK kinases, STAT proteins, interferon receptors and the ISGF3 transcriptional complex. These mechanisms include kinase inhibition, ubiquitin-mediated proteasomal degradation, receptor depletion, inhibition of STAT nuclear translocation and disruption of transcriptional complex assembly—all leading to significant abrogation of interferon-stimulated antiviral gene expression. These inhibitory mechanisms underline the pivotal role of JAK-STAT signaling in controlling antiviral immunity and further are supportive for devising host-directed therapeutic strategies aimed to maintain signal transduction whilst promoting effective IFN-mediated immune responses.



Coevolutionary Arms Race

All genotypes are subject to positive selective pressure from viral antagonism and, thus, undergo evolution in an ever-forward spiraled arms race—through this process, selective pressures acting on the host genome fine-tune a diversity of distinct interferon receptor motifs that preserve signal integrity against evolving viral antagonists [84]. In contrast, host organisms are constantly under selective pressure to develop effective innate immune components capable of resisting this type of hostility (as evidenced by the universal emergence of STAT2 resistance during mammalian evolution [85]). Thus, this dynamic conflict of evolutionary interests acts as an all-encompassing selective pressure from the virus to the host, often forcing viruses to reduce the likelihood of stimulating effective immune responses by employing redundant strategies exposed as an evolutionary protective mechanism, such as overstimulating multiple signaling nodes through both direct protein-protein interactions and hijacking of cellular evasion pathways that normally target these same signaling translocation chains [86,87]. This coevolutionary tension is evident, for instance, from the lineage-specific strategies of flavivirus NS5 proteins that evolved to inhibit STAT2 as a means to escape lineage-specific immune architectures [88]. Repeated selective pressures induced by viral infection emphasize the significance of viral replication fitness inducing structural alteration in these antagonistic proteins across a wide range of vertebrate hosts [89].

Furthermore, the emergence of different catabolic pathways that allow for autophagy-dependent degradation underlines how viruses may escape from conventional proteasomal innate immunity such as antiviral [1]. Viruses also induce various post-translational modifications against host factors or express a small protein capable of acquiring crucial factors [81,82], for example IL-6 by inducing JAK2 degradation inhibits assembly ISGF3 complex therefore developing a antiviral state [90,91]. This arms race has also resulted in the selection of viral proteins that actively select for key viral factors that directly act to influence either active or inactive conformations of host signaling factors [89,91], which prevents ISGF3 complex formation by keeping STAT2 bound as an inactive protein in the cytoplasm [92]. The reliance on these molecular interactions highlights the extraordinarily



strong selective pressure host and virus exerted on one another over evolutionary time, with within-host diversifying selection driving the evolution of immune components at the genome level that prevent viral hijacking [93]. This iterative process tends to produce an "evolutionary peak," where viruses occupy a narrow fitness range, preserving protein functions while acquiring mutations that enable them to overcome host-specific immune barriers [85]. This adaptation is often limited only by protein pluripotency; as shown in mammalian studies, mutations leading to immune evasion are frequently associated with significant fitness costs for the underlying viral replication [94,95]. These findings highlight relatively recently evolved viral strategies [96,97] of selectively degrading signaling components (such as STAT1 and STAT2) or depleting kinase scaffolds [98], where a signaling component is degraded via a specific mechanism that relies on resistance to the rapid changes necessary to achieve an evolutionary equilibrium that allows the virus to persist long-term without losing its basic reproducing fitness. The shared evolutionary dynamics between hosts and viruses can be illustrated by the functional diversity of host defense proteins, such as PKR, which have undergone duplication or positive selection in certain strains to respond to viral immune evasion [99].

Interestingly, the ongoing coevolution between viruses and their hosts is a double-edged sword. It shows that selective pressures from both pathogens and immune mechanisms have altered the evolutionary trajectory of viral immunity, leading to the loss of acquired functions, such as innate immunity in hosts. Thus, the apparent diversity of interferon receptors, STAT proteins, and other antiviral signaling molecules appears to be the product of substantial evolutionary selection by antivirals long ago (with data suggesting dates that coincide with gene-interaction-determined classifications). However, viruses continue to develop increasingly sophisticated mechanisms to evade host responses. This reciprocal evolutionary process may explain the considerable complexity and redundancy in the interferon signaling pathway, enabling the host immune system to withstand the virus's persistent attempts to disable it. A key criterion in this evolutionary arms race is the trade-off between viral fitness and immune evasion. Successful immune evasion, on either side, is likely to result in a reduced ability to replicate easily. Viruses acquire mutations that enhance their ability to inhibit signaling pathways in the host cell,



but most of this viral adaptation tends to preserve the essential functions of structural proteins critical for efficient replication. Consequently, the NS5 protein of flaviviruses, and other viral proteins, have evolved highly specialized strategies to target STAT2 signaling, reflecting the molecular optimization of immune evasion against the host's innate immune architecture. Similarly, a variety of other immune evasion strategies (such as autophagy-dependent lysis,[9] post-translational modifications,10 and even the disruption of specific STAT protein structures [10]) indicate that viral escape is remarkably adaptive as long as the virus remains capable of replication. Alongside this, the host cell's response is equally important. Gene expansion facilitated by actions remains positive under viral pressure on the host genome, which has become more responsive to Dat and other antigens. This ongoing evolutionary race has led to increasingly complex networks of antiviral signaling, even as it simultaneously pushes toward hyperspecificity in viral antigens.

The accelerated exploration of these shared evolutionary dynamics not only reveals the complexities of host-virus interactions but also highlights evolutionarily conserved molecular targets that could be exploited for broad-spectrum antiviral therapy with limited viral resistance. The ongoing co-evolutionary arms race between viruses and their hosts is shaped by reciprocal selective forces that continuously enhance both antiviral immunity and viral immune evasion mechanisms. Host adaptations, including the diversification of interferon signaling components and antiviral restriction factors, continue to compete with enhanced antiviral measures targeting a few key hosts signaling molecules (STAT1 [1,2], STAT2 [3], and JAK-associated proteins 4 [6]). While these viral adaptations enhance the virus's ability to evade the immune system, a delicate balance exists between sufficient viral replication and immune evasion. This evolutionary balance provides important clues about conserved interactions between the virus and the host, which may constitute potential molecular targets for the development of a long-lasting, broad-spectrum antiviral therapy capable of overcoming viral immune evasion.

Host Restriction Factors

Interferon-stimulated genes (ISGs) are potent host restriction factors that activate broad antiviral programs, including preventing viral entry and subsequent viral RNA lysis



[100]. When these factors bind to interferon-stimulated response elements, they induce the expression of genes that inhibit viral protein replication and translation [101, 102]. These ISGs belong to diverse pathways and exert their antiviral effect by trapping viral replication mediators or destroying viral transcripts [97, 103]. Notably, members of the IFITM family inhibit viral fusion to plasma membranes or endosomes, and OAS enzymes induce RNase L to mediate broader viral and host RNA lysis. Additionally, GTPases proteins from the MX family provide a second line of defense by assembling around viral nucleocapsids to trap them and prevent efficient replication. To overcome the strong impact of these robust host immune defenses, most viral assemblages exert strong selective pressure on each intracellular restriction factor through rapid diversification of viral binding sites, enabling them to quickly regain their replication capacity [104].

In addition to these basic effectors, the host cell also employs post-translational modifications (PTMs), including, but not limited to, the addition of the SUMO molecule, to maintain the stability of important signaling proteins and protect them from viral damage [105]. Beyond their direct effector functions, interferon-stimulating genes (ISGs), such as ISG15, act both directly and indirectly as multi-effect regulators that alter innate immune signaling through ubiquitin-like conjugation, promoting immune tolerance while inhibiting viral replication [106]. In addition to individual effects, these genes also confer regulatory behavior for cell reprogramming at the immune system level, going beyond direct viral restriction and inducing profound repercussions in host metabolism, chromatin regulation, and protein structure [107]. These shifts reflect a deeper biological transformation, where these genes are becoming increasingly context-dependent regulators of tumor immunity and tissue repair, rather than simply antiviral agents [108]. Moreover, the mechanisms of action of these genes are relatively subtle; CH25H reduces viral-cell membrane fusion by modifying the host cell membrane structure [17], while ZAP and the IFIT family sequester viral mRNA away from translation by the infection initiation complex—a restriction mechanism known as RNA silencing [109, 110]. These genes offer a therapeutic opportunity to exploit the exceptional diversity of mechanisms targeting RNA, such as exit points like viral media lysis or translation inhibition [111], which helps to eliminate infection, but must maintain the delicate balance necessary for cellular homeostasis.



Specifically, the unique prenyl status of the OAS1 protein is a key regulatory factor in this context, as its membrane-associated variants provide more efficient local sensing of viral RNA substrates [112].

Host restriction factors, encoded primarily by interferon-stimulating genes (ISGs), represent the main effector arm of innate antiviral immunity, directly inhibiting various steps in the viral replication cycle. The remarkable diversity of antiviral proteins—such as IFITM, OAS/RNase L, MX GTPases, ZAP, CH25H, and members of the IFIT family, to name just a few—demonstrates that host defense is not limited to a single antiviral mechanism. Rather, host defense relies on a coordinated network of complementary effectors working together to ward off viral infection. Collectively, these proteins are responsible for preventing viral entry, blocking viral transcription and translation, degrading viral nucleic acids, and interfering with replication complexes, thus producing an unfavorable internal environment across most pathways and enabling high levels of viral resistance. Notably, many of these host restriction factors are biologically multifunctional, extending beyond their direct antiviral activity. Post-translational modifications, such as the addition of SUMO and ISG molecules, contribute to the stabilization of signaling proteins and modulation of the innate immune response, as well as other broader cellular processes mediated by ISG genes, including metabolism, chromatin regulation, protein remodeling, tumor immunomodulation, and tissue repair. Our combined results indicate that interferon-stimulated genes have evolved into multifunctional regulators of this process, balancing viral virulence with antiviral defense and maintaining cellular homeostasis. This adaptive capacity enables the host to mount effective immune responses while minimizing tissue damage during infection control.

Constant viral selective pressure on these restriction factors has also facilitated their extremely rapid evolutionary diversification, particularly at points of interaction with the virus. This ongoing molecular adaptation exemplifies the co-evolutionary arms race between viral pathogens and host immune systems, where every improvement in antiviral restriction is met with viral mutations that restore the reproducing capacity of new viral variants. Therefore, studying the structure and regulation of host restriction factors will



provide valuable insights into novel strategies for enhancing one or more of these innate immune pathways, with the aim of developing new classes of antiviral drugs that are likely to be less prone to inducing resistance than conventional virus-targeted therapies by boosting the host's own defenses. Interferon-stimulated genes encode important host restriction factors that act as key active agents of innate antiviral immunity. These factors exert their functions through diverse mechanisms targeting the viral replicative cycle, such as viral entry, replication, transcription, translation, and genome stabilization. In addition to their direct antiviral effects, these molecules are also involved in immune regulation, cellular homeostasis, and other biological processes through specialized post-translational modifications and signaling networks. This ongoing co-evolution between viral pathogens and host restriction factors supports their prominent role in antiviral defense and suggests that human-encoded restriction factors could be a target for the development of novel, broad-spectrum antiviral and immunomodulatory therapeutic approaches.

Viral Counteradaptation

To avoid this potent restriction, viruses have evolved complex escape mechanisms from immune recognition via mutation-induced viral epitope diversification that can serve to reduce the efficiency at which the host immune sensors detect the presence of a virus [110]. As a specific example, viruses encode unique proteases or antagonists that block ISGylation in multiple ways by preventing ISG15 conjugation to viral substrates or expressing particular deconjugates to reverse the antiviral effects of these modifications [113]. Moreover, such pathogens often use point mutations in viral protein motifs to interfere with direct interactions of essential host effectors, for example MX proteins that sequester incoming nucleocapsids or RNase L-mediated degradation of viral RNA [109,114]. Most of these viral strategies eventually targeted the ISG15-mediated protein modification cascade to undermine this critical host barrier in fat against viral infection [115,116]. Certain viruses interfere with this cascade by lysing important enzymes like UBE1 [117,118], which may stop or reduce the ability to make ISG15–conjugated proteins associated with shutting down the intracellular lifecycle of pathogens. Moreover, the escalating mechanism of resistance immunomodulatory pathway tends to promote a few



viruses to evolve strategies for recruiting our innate derived DUB including USP18 into cells and thereby did circumvent consent partners on persistent gathering ISG15-conjugates in these organisms and achieve destabilization from a host defensive system [119]. This evolutionary stratagem includes deconstructions of host-species genomes, where immune gene signatures of selection exemplify pathways, like the bat niche that has evolved to use these instead promoting virus tolerance as opposed to malignant inflammation [120]. This class of interferon antagonists generally consists of the synthesis of specific proteases including those with OTU-domains which have wide substrate specificity to cleave ISG15 and ubiquitin conjugated to host proteins to inhibit immune pathways [121].

In addition, viral pathogens aggressively subdue RLRs sensing through sabotaging K63-linked polyubiquitination of RIG-I, a key step that leads to enhanced induction of downstream interferon production [2,122]. For example, the influenza A virus NS1 protein selectively inhibits the activation of essential signaling by targeting E3 ligases such as TRIM25 and RNF135 [123]. In the same view, SARS-CoV-2 used its papain-like protease (PLpro) to hijack this mechanism by removing ISG15 and ubiquitin from host proteins to facilitate viral replication and immune evasion [124]. This evasion strategy is reinforced in some cases through the exploitation of host E3 ubiquitin ligases to direct the proteasomal degradation of key innate immune signaling molecules [5].

Viruses evolve in response to host restriction factors and interferon-stimulated genes (ISGs), which leads to viral counteradaptation. Instead of just relying on structural mutations to avoid immune recognition, viruses have developed a wide range of molecular strategies that functionally neutralize the antiviral functions of host effector proteins. This involves interference with the ISGylation pathway, disruption of ubiquitination-dependent signaling, inhibition of RIG-I activation and recruitment of host deubiquitinating enzymes (such as USP18). Together, these strategies empower viruses to overcome numerous tiers of innate immune restriction and sustain Lallirieple replication in the face of a strong interferon response. The most incredible feature of viral counteradaptation is the large-scale exploitation of host post-translational modification pathways. To escape the antiviral



responses of their hosts, viruses pragmatically disassemble host signaling networks crucial for a successful antiviral response by encoding viral proteases that are either capable of cleaving all or a portion of ISG15 and ubiquitin from host proteins (as shown in panel B), or contending with enzymes such as UBE1 [6]. Similarly, blocking E3 ligases such as TRIM25 and RNF135 to prevent RIG-I ubiquitination hinders the earliest steps of interferon production [80]. These mechanisms show that instead of simply avoiding host immune responses, viruses have evolved to actively reprogram host cellular regulatory pathways to facilitate the development and maintenance of a viral-latency-inducing milieu. This emphasizes that viral counteradaptation is not a molecular-level problem, but one tied to the evolution of host species. The conserved trait that reservoir hosts like bats have adaptive changes that promote virus tolerance over toxic immunity highlights how prolonged host–virus coevolution shapes both viral pathology and regulatory pathways of the host immune response.

Therefore, elucidating the molecular mechanisms of viral counteradaptation allows us not only to understand key aspects of the evolutionary ecology of rapidly evolving viral diseases but also enables the identification of highly conserved host–virus interaction pathways that may serve as attractive targets for development of pan-viral therapies. Viral counteradaptation is encompassed by variable types of evolutionary events to evade host restriction factors targeting ISGylation, ubiquitination, innate immune sensing and interferon signaling⁹. Using distinct strategies, like specialized viral proteases, regulation of host regulatory enzymes, interference with RIG-I activation and exploitation of ubiquitin-dependent degradation systems viruses successfully inhibit innate antiviral defenses to facilitate replication and persistence. These advanced adaptations emphasize the ongoing host–virus coevolution and reveal that host posttranslational modification pathways are promising targets for development of novel antiviral agents.

Therapeutic Implications

Acceptance of the molecular details of viral IFN evasion as opportunities for developing new therapeutic targets is a novel approach for future antiviral targeting of these host-pathogen interfaces [125,126]. In these scenarios, small-molecule inhibitors that



permissively stabilize essential E3 ligase–substrate interactions or prevent viral proteases from shedding ISG15 moieties from signaling proteins may be able to counteract innate immune sensitivity [121,127]. In addition, therapeutic targeting of these pathways could also encompass small molecules that mimic the stabilizing effect of ISGylation on host sensors (eg. MDA5) to enhance cell-intrinsic innate immunity against diverse families of viruses [128]. These open possibilities for therapeutic strategies that target hubs critical for such host-pathogen protein crosstalk as HERC5 and the viral protease PLpro [124,129], which restore RIG-I-like receptor signaling integrity. These pharmacological strategies may be a viable approach to stabilize the virus in an already highly labile host-state via titrating the ubiquitination landscape thus enabling effective viral clearance even in cases of chronic infection [122, 123]. Furthermore, targeting viral deISGylating enzymes (vDEs)—like SARS-CoV-2 PLpro — offers a specific method by which to impede host-imposed antiviral protein modifications un-masking that reactivate cell-mediated immune surveillance function [130,131]. When administered in the same clinic, this directed protease inhibitors has a Synergy Potential with Existing Therapy—in that capacity they are capable both antiviral replication suppression as well as reestablishment of a robust interferon-mediated host immunity.

The historical success of protease inhibitors as therapeutic agents for chronic viral infections suggests that identifying these and other virally encoded cysteine proteases as clinical targets paves the way for dual-action drugs, which could, in turn, be key components of short- and long-term antiviral strategies against current or emerging pandemic threats [132-134]. Furthermore, the identification of host E3 ligases, such as RNF5, responsible for targeting viral proteins for proteasome degradation supports a broad-spectrum antiviral approach that specifically utilizes components of the host ubiquitin-proteasome system to eliminate pathogens [135]. Pharmacological modulation of the Met1-associated ubiquitin mechanism is another strategic avenue for controlling pathogen-induced inflammation by stabilizing key components of innate immune signaling [136]. In addition to the direct antiviral action described above, these pharmacological approaches may also be used in different clinical contexts so as to modify the "goldilocks" zone of immune activation resulting in attenuated systemic inflammation and improved



clinical outcomes for patients with a severe respiratory infection [137]. The reappropriation of pre-existing degrader technologies, e.g., the deprivation of GSPT1 proteins to target the RNA translation machinery repeat thus provide a basis for developing low-risk pan-viral therapeutic strategies that can condition an already affected tissue to stop virus propagation in vivo [138]. Understanding these altered functional consequences of post-translational modifications is essential to uncovering drug targets in terms of the druggable proteome and opportunistic for immune-related diseases [139]. Systematic mapping of these intricate PTM networks to inform the drug development is expected to require integration between systems biology, high-throughput proteomics—including affinity purification-mass spectrometry, and proximity-dependent labelling [140]. Gaining more insight into the molecular mechanisms through which viruses hijack host post-translational modification machinery, to the benefit of their replication cycle is essential for devising pathogen-agnostic strategies (141,142). In particular, elucidating the intricate molecular mechanisms of action for deubiquitinating enzymes and their regulators will likely make possible discovery of novel pharmacological targets that may be significant in alleviating numerous human diseases [48].

These research implications are particularly significant for antiviral therapy as they shift focus from solely anti-replicative mechanisms to the replacement of host immune system pathways that have been subverted by viral pathogenesis. For example, viral strategies for utilising ubiquitination, ISGylation and deubiquitination at the host–pathogen interface develop multiple therapeutic windows. Inhibiting viral enzymes including PLpro, maintaining ISG15 conjugation or stabilizing signaling proteins needed for antiviral function may inhibit virus replication and restore responsiveness to interferon. Such a dual mechanism may be particularly relevant in infections that critically demonstrate the role of immune suppression in viral persistence and severity. Another attractive area for development of broad-spectrum antivirals is in post-translational modification networks. Unlike most direct acting antivirals that are limited in their coverage to closely related viruses because they target a specific viral enzyme, host-directed strategies may inhibit cellular pathways utilized by multiple families of viruses. Accordingly, the tuning of ubiquitin ligases like HERC5 and RNF5, deISGylating enzymes or RIG-I-like receptor



signaling might induce pathogen-independent therapeutic effects. Furthermore, reducing viral proteases that act in concert with other factors could be explored together with existing antiviral compounds, once the liver's normal anti-viral defences are reconstituted. However, these HDM-hopes may potentially be hazardous to health and thus will require careful supervision because ubiquitination, ISGylation and interferon signaling also regulate normal cellular homeostasis, inflammation/GS-protein turnover as well as immune tolerance. If there is over-stimulation, systemic inflammation or tissue damage may occur and if host regulatory enzymes are overly inhibited, it would most likely lead to deleterious effects on important physiologic process. In a clinical translation, as noted above, treatment has to be effective by strengthening antiviral immunity sufficiently so as to assist clearance without causing detrimental immunopathology; the relevance of this is that it holds for an immune activation goldilocks zone [33].

The elucidation of viral–host interactions that are biologically relevant to pathogenesis will require systems biology and high-throughput approaches, complemented with proteomics, as well as additional pharmacological investigations using affinity purification–mass spectrometry methods and proximity-labeling technologies. They can resolve the transient and cell-type specific action of post-translational modifications, determine whether they serve as predictive biomarkers and distinguish therapeutic targets from proteins that would be unacceptably toxic to manipulate. In conclusion, greater optimism the future direction of which they will go is more likely to be selective-, time-locked and combination therapy, than over-generous stimulation of interferon signaling. This insight into how viruses hijack ubiquitination, ISGylation, deubiquitination and `interferon-regulatory networks provide large opportunities for new targets for antiviral drug development. Compounds that inhibit viral proteases such as PLpro, modulators of host E3 ligases, and drugs capable of preserving antiviral protein hapten modifications may augment direct limitation of viral replication while restoring innate immune sensitivity. These strategies may aid the development broad-spectrum pathogen-agnostic antivirals, particularly in combination with known therapies. However, successful clinical implementation will rely on target specificity, temporal analog of immune activation,



biomarker-guided patient selection and restrictive modulation to prevent inflammation-mediated toxicity and homeostatic cellular disruption.

IFN-Based Interventions

Although direct delivery of interferon-alpha/beta has been a clinical mainstay [60], therapeutic response is often suboptimal due to associated pleiotropic side effects, such as the induction of suppressors of cytokine signaling (SOCS) and negative feedback regulators such as USP18 that inhibit downstream signaling [143]. Therefore, novel therapeutic strategies are favoring host-targeted therapies including the design of small molecule antagonists that inhibit viral proteins engineered to regulate these feedback loops [134]. Moreover, pharmacological prevention of key viral effectors such as SARS-CoV-2 ORF3a or ORF7a might prevent these proteins' contribution to persistence of infected cells and promote better efficacy against viral clearance. Concurrently, the generation of inhibitors that specifically target host factors involved in critical viral replication steps, such as those mediating membrane trafficking or chromatin-remodeling processes is a powerful strategy to circumvent limitations originating from direct stimulation of the interferon cascade [2]. Nonetheless, their clinical utility is limited in part by the difficulty of achieving and maintaining the goldilocks zone whereby an optimal level of stimulation promotes viral clearance without instigating overwhelming local or systemic inflammation that can lead to tissue injury [137].

Conversely, combinatorial regimens combining STING agonists with autophagy-modulating agents are being investigated to align induction of secondary interferon waves and regulated viral degradation [144] in order to mitigate these risks. Future modifications to IFN-based regimens must overcome challenges such as limiting the production of IFN autoantibodies, and improving gene-editing approaches that provide specificity in enhancing cellular sensitivity to type I interferons [145]. Finally, it is necessary to integrate personalized approaches based on the host modifications in innate and adaptive immunity due to genetic predispositions, age and comorbidities which are determinants of response to exogenous IFN administration that can improve clinical success. [146]. Current data, however, gleaned from pre-clinical modelling and clinical evaluation also emphasize that



administration timing is an important predictor of outcome in all experimental models: At advance stages IFN interventions cause exacerbation of inflammatory pathology rather than limit viral replication [7,147,148]. Taking advantage of the unique kinetic profiles of type-I and type-III interferons may represent a more targeted approach, since the latter maintains an antiviral activity for much longer without interference from the USP18-mediated negative feed-back loops that commonly terminate type-I responses [149].

Due to their broad-spectrum immunomodulatory effects, Interferon (IFN)–based interventions remain an integral part of antivirals. Nevertheless, mounting data shows that direct delivery of type I interferons is limited by important limitations including systemic side effects, induction of negative regulators such as USP18, and heterogeneous clinical responses among patients. These discoveries have redirected current drug discovery efforts towards host-directed antivirals that would moderate the pathology whilst preserving or restoring natural interferon signaling, rather than using exogenous IFN alone. The targeting of viral antagonists like SARS-CoV-2 ORF3a and ORF7a, in combination with inhibition of critical host factors for viral replication provides a more specific strategy that could circumvent many of the limitations associated with conventional interferon therapy. The idea of the need for optimal immune activation, often called the 'goldilocks' zone, is an important concept in this section. However, inadequate host interferon responses allow unrestrained viral replication, but excessive or protracted activation can cause deleterious inflammatory pathology and tissue injury. As such, combining STING agonists with one or more agents that target autophagy-inducing proteins released by the pathogen or proteins in the virus-mediated immune evasion pathway makes integration an important option for the development of immunotherapies to improve antiviral immunity with reduced immunopathology. Also, complementary strategies that curtail the formation of IFN autoantibodies and enhance the cellular response capacity to IFN by gene-editing technologies may contribute to better clinical efficacy for IFN therapeutic applications.

Perhaps most important from a clinical perspective is that timely and tailored application of interferon therapy are key determinants of treatment outcome. Administration of interferons early in infection typically support effective viral clearance



while administration after the infection has progressed to a critical stage may augment inflammatory responses without significantly enhancing antiviral activity. Patient-specific factors, such as genetics, age, immune status, and comorbidities, significantly influence treatment efficacy. The renewed focus on type III interferons, which exhibit prolonged antiviral activity and reduced sensitivity to USP18-mediated negative feedback, is driving the trend toward more targeted and personalized immunotherapies. While type I interferons remain effective antiviral treatments, their clinical application is hampered by systemic toxicity, negative feedback regulation, and variability in patient responses. Interferon-based interventions are evolving rapidly, focusing on host-targeted therapies, immunosuppression, carefully planned combination therapies, and patient-specific approaches to maximize antiviral effects while minimizing immunopathology. Furthermore, the study of type III interferons offers new hope for improved clinical efficacy when administered at specific times and may contribute to the emergence of a new generation of interferon-based antiviral therapies.

Targeting Viral Antagonists

For example, small molecules can be developed to block the interaction between a viral-encoded protein, such as the SARS-CoV-2 3CL or ORF3a protease, and an immune sensor, thereby disrupting host cell pathways, including cGAS-STING receptor signaling [150]. These prophylactic RIG-I inducers and small-molecule inhibitors provide a strategy to counter the arsenal of viral evasion strategies, potentially offering an opportunity to restore acute interferon signaling [151]. However, given the broad expression of this pathway in almost all cell types, the clinical application of therapeutic targeting of STING remains complex and requires precise spatial and temporal control to avoid inducing maladaptive interferon disorders [152].

In addition to these focused strategies, additional studies will be needed to define the delicate balance of delayed vs strong early IFN responses since clinical data suggests that the therapeutic window for modifying these pathways is very narrow [23,153]. To fine-tune these interventions, viral RNA titers must be monitored using high-resolution longitudinal sampling in conjunction with proteomic profiles to precisely determine the



time point at which exogenous IFN therapies switch from protective to pro-inflammatory [154,155]. Furthermore, the incorporation of systems biology with a focus on patient-specific and clinically revisable molecular and cellular signatures can help guide IFN-based therapies only to cohorts likely to benefit from such interventions [156]. In addition to direct clinical applications, the future development of predictive biomarkers (e.g., those relating to gene signatures from specific interferon-stimulated genes) would be critical for identifying patients with a high intrinsic capacity to respond upon exogenous supplementation prior to severe late-stage pathological disease stages [27]. In addition to vaccination, the clinical application of chemoprophylaxis with nasal type I or III interferons remains an attractive therapeutic option for at-risk cohorts in settings in which vaccine efficacy may be limited due to endemic strains predominant in geographical regions [157]. These mechanisms of action behind novel therapeutics target natural pathogen sensing, exemplified by the selective protection of STING against viral-mediated proteolytic cleavage by 3CL protease inhibitors [158,159]. Additionally, small-molecule STING agonists have potential application as adjuvants to improve the strength of vaccine-mediated immune responses and perhaps overcome strong suppression of NF- κ B signaling by viral accessory proteins in some contexts [160].

Because targeting viral antagonists focuses instead on the molecular mechanism's viruses use to block innate immune responses, and not just inhibiting viral replication, it has emerged as one of the more rationally promising areas of modern antiviral therapy. 6 Viral proteins like SARS-CoV-2 3CL protease and ORF3a are therefore appealing antiviral targets since they functionally inhibit cGAS–STING and RIG-I signaling pathways in host cells. The pharmacological inhibition of those viral antagonists could restore endogenous interferon signaling and also help host-immune system to provide effective antiviral response, decreasing the virus persistence. An important take in this context is that it is not sufficient to select just the right molecular targets for successful immunomodulatory therapy, but more importantly one must also regulate treatment time as well as treatment intensity in a precise manner. While activation of the STING pathway and administration of RIG-I agonists give rise to potent antiviral immunity, their pharmacological applications can be limited since overactivation or chronic stimulation can cause pathological interferon



responses and inflammatory diseases. Therefore, accurately defining the therapeutic scope through longitudinal monitoring of viral RNA and proteomics, along with immunobiological biomarker studies, is crucial for determining when interferon-responsive interventions offer protection against disease progression. This underscores the need to integrate molecular diagnostics into treatment decision-making.

One of the most important implications of this is that it will enhance the ability to deliver antiviral immunotherapy using precision medicine. Systemic immunology, predictive interferon-stimulating gene (ISG) fingerprinting, and patient-specific molecular analysis are expected to be critical tools in identifying individuals most likely to benefit from interferon-based therapies. Furthermore, prophylactic approaches, such as intranasal administration of type I or III interferon and/or the use of STING inducers as vaccine adjuvants, could provide additional protection for certain high-risk populations, particularly with the emergence of viral strains that partially evade vaccine-acquired immunity. Taken together, these developments suggest that future antiviral therapies will most often combine specific antiviral immunomodulatory techniques with individualized immunomodulatory strategies aimed at optimizing the benefit-risk ratio.

Conclusion:

Interferon signaling is the cornerstone of innate antiviral immunity, mediating a highly coordinated response that recognizes viral invasion and amplifies immune signals to induce the expression of numerous interferon-stimulated genes (ISGs) with broad capacity to suppress virtually all steps in the viral replication cycle. This review details this complex molecular network associated with the interferon response from pathogen detection via pattern recognition receptors (PRRs), through JAK–STAT-mediated signaling and finally to robust antiviral state establishment by ISGF3-controlled gene modulation. While the defense mechanisms are highly effective, such viruses have evolved equally elaborate immune evasion strategies that aim to prevent interferons from operating effectively at several different stages of their signaling cascade. They involve inhibition of viral sensing, impairment of adaptor protein functionality and degradation or dephosphorylation of factors in the JAK–STAT pathway; tampering with host ubiquitin pathways and



ISGylation; and blocking transcriptional complexes necessary for expression of antiviral genes (Fig. 3). Such mechanisms provide a glimpse into the evolving arms race between viruses and their hosts, a reciprocal adaptation of viral antagonists and host immune restriction factors.

New, high-throughput technologies in molecular virology, structural biology, systems immunology and proteomics have greatly expanded the mapping of host–virus interactions and have uncovered numerous promising therapeutic targets. The rational design of emerging antiviral strategies based on inhibiting viral replication alone has begun to shift toward restoring endogenous interferon signaling as an area of active investigation through the targeting of viral immune antagonists, modulation of host post-translational modification pathways, and preservation of innate immunity signaling networks. Such strategies afford avenues towards broad-spectrum antiviral therapies that can prevent viral escape and dampen the development of resistance to anti-viral agents. In the end, only a complete understanding of how interferon signaling operates and how viruses evolve strategies to evade it will be required in order to rationally design next-generation antiviral therapeutics, tailor interventions via immunomodulation, selective vaccination, or other means for both human personal care and pandemic preparedness against older pathogens and emerging viral pathogens alike.

Research Gaps:

1. Despite tremendous progress in elucidating viral immune evasion, gaps in our knowledge remain.
2. However, the molecular mechanisms through which different viruses coordinately manipulate multiple interferons signaling pathways simultaneously are poorly understood.
3. Because the temporal dynamics of protective and pathological interferon responses we discovered here will guide optimal therapeutic timing, a deeper understanding of this transition is needed.
4. But the virus-antagonist interactions with host immune proteins, particularly STAT2, IFN receptors and ISGs are poorly characterized.



5. Due to their potential roles in viral immune escape, the biological relevance of non-canonical interferon signaling pathways and their effector contributions to antiviral immunity await elucidation.
6. However, the functions of post-translational modifications such as ISGylation, ubiquitination, SUMOylation and phosphorylation in regulating antiviral signaling are less well understood for different viruses.
7. Only minimal clinical evidence is available about the long-term safety and efficacy of host-directed antiviral therapies acting on components of interferon signaling pathways.
8. Although, predictive biomarkers that precisely identify patients who are most likely to benefit from interferon-based therapies is poorly validated.
9. Despite intact interferon signaling in chronic viral diseases, the molecular foundation of viral persistence remains poorly defined.
10. Further comparative analyses are required to reveal whether convergent interferon-evasion strategies operate in disparate viral families as universal therapeutic targets.
11. The Because these projects are such a large challenge that no one team can do it alone, these –omics technologies must be more integrated in order to build full host–virus interaction networks to help shape precision antiviral medicine.

Recommendations:

The following recommendations considering the existing evidence:

1. Focus research efforts on developing novel host-directed antiviral therapies that restore defects in interferon signaling, rather than only inhibiting viral replication.
2. Explore inhibitors of viral immune antagonists, including the use of specific viral proteases, deISGylating enzymes, and proteins disrupting JAK–STAT signaling
3. It explores broad-spectrum antiviral targeting of vaccine-escape by expanding on the known research on post-translational modification pathways through which viruses can evade immune system recognition in these cells as further potential targets for therapeutic intervention.



4. To ascertain individualized interferon-based therapy, develop precision medicine approaches using genomic, transcriptomic, proteomic and immunological biomarkers.
5. Balance the timing, dosage, and combination of interferons against each other to maximize antiviral activity while minimizing inflammatory complications.
6. Facilitate collaborative research across virology, immunology, structural biology, bioinformatics and clinical studies to speed translational research.
7. Champion standardized experimental models that allow for direct comparison of interferon-evasion mechanisms between unrelated viral species.
8. Promote the identification of antivirals that spare host immune signaling and thus reduce the risk of emergence of antiviral resistant hosts.
9. Enhance monitoring of new strains of the virus with unique immune-evasion mechanisms that could potentially render health care interventions unusable.

Future Studies:

1. There are a number of priority areas identified for future investigation that have the potential to change antiviral research.
2. First, high-resolution structural studies characterizing the interactions between viral and host proteins can reveal common molecular interfaces that are viable targets for broad-spectrum therapeutics.
3. Second, multi-omics datasets should be combined with systems biology and artificial intelligence to build models of interferon signaling in antemortem during viral infection.
4. Third, longitudinal clinical studies are needed to establish the best therapeutic window for delivering interferon in various viral diseases.
5. Finally, more studies should determine whether type III interferons, STING agonists, RIG-I agonists and any host-directed immunomodulator could be combined with the already available antiviral agents.
6. Fifth, we should use CRISPR-based genome editing and functional genomics to discover new host restriction factors and viral antagonists in immune evasion.



7. Sixth, future studies should determine the effects of host genetics, aging, sex differences, concurrent comorbidities and immune status on the responsiveness to various interferons respectively so as to design personalized antiviral therapy.
8. Finally, relevant multicenter clinical trials are warranted to translate emergent therapies targeting interferons and predictive biomarkers supporting treatment decisions into practice with standardized protocols for current virus outbreaks and future epidemics.

References

1. Rojas JM, Alejo A, Martín V, Sevilla N. Viral pathogen-induced mechanisms to antagonize mammalian interferon (IFN) signaling pathway. *Cellular and Molecular Life Sciences*. 2020 Oct 21;78(4):1423–44. <https://doi.org/10.1007/s00018-020-03671-z>
2. Minkoff JM, tenOever BR. Innate immune evasion strategies of SARS-CoV-2. *Nature Reviews Microbiology*. 2023 Jan 11 [cited 2026 Jan];21(3):178–94. Available from: <https://doi.org/10.1038/s41579-022-00839-1>
3. Raj K, Shrestha P, Yang B, Chen Y, Liu S, Maarouf M, et al. Acute Infection of Viral Pathogens and Their Innate Immune Escape. *Frontiers in Microbiology*. 2021 June 22;12:672026–672026. <https://doi.org/10.3389/fmicb.2021.672026>
4. Muhammad I, Contes KM, Bility MT, Tang Q. Chasing Virus Replication and Infection: PAMP-PRR Interaction Drives Type I Interferon Production, Which in Turn Activates ISG Expression and ISGylation. *Viruses*. 2025 Apr 4;17(4):528–528. Available from: <https://doi.org/10.3390/v17040528>
5. Chathuranga K, Weerawardhana A, Dodantenna N, Lee J. Regulation of antiviral innate immune signaling and viral evasion following viral genome sensing. *Experimental & Molecular Medicine*. 2021 Nov 1;53(11):1647–68. Available from: <https://doi.org/10.1038/s12276-021-00691-y>
6. Hurtado-Tamayo J, Requena-Platek R, Enjuanes L, Belló-Pérez M, Sola I. Contribution to pathogenesis of accessory proteins of deadly human coronaviruses.



- Frontiers in Cellular and Infection Microbiology. 2023 May 1;13:1166839–1166839. <https://doi.org/10.3389/fcimb.2023.1166839>
7. Ribeiro MS, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathogens. 2020 July 29;16(7). Available from: <https://doi.org/10.1371/journal.ppat.1008737>
 8. Rashid F, Xie Z, Suleman M, Shah A, Khan S, Luo S. Roles and functions of SARS-CoV-2 proteins in host immune evasion. Frontiers in Immunology. 2022 Aug 8;13:940756–940756. <https://doi.org/10.3389/fimmu.2022.940756>
 9. Lu Y, Michel HA, Wang P, Smith GL. Manipulation of innate immune signaling pathways by SARS-CoV-2 non-structural proteins. Frontiers in Microbiology. 2022 Nov 21;13:1027015–1027015. <https://doi.org/10.3389/fmicb.2022.1027015>
 10. Hu H, Feng Y, He M. Targeting Type I Interferon Induction and Signaling: How Zika Virus Escapes from Host Innate Immunity. International Journal of Biological Sciences. 2023 Jan 1;19(10):3015–28. <https://doi.org/10.7150/ijbs.83056>
 11. Villamayor L, López-García D, Rivero V, Martínez-Sobrido L, Nogales A, DeDiego ML. The IFN-stimulated gene IFI27 counteracts innate immune responses after viral infections by interfering with RIG-I signaling. Frontiers in Microbiology. 2023 Apr 28;14:1176177–1176177. <https://doi.org/10.3389/fmicb.2023.1176177>
 12. Bayat M, Nahid-Samiei R, Nahand JS, Naghili B. Interferon and immunity: the role of microRNA in viral evasion strategies. Frontiers in Immunology. 2025 May 9;16:1567459–1567459. <https://doi.org/10.3389/fimmu.2025.1567459>
 13. Acchioni M, Acchioni C, Hiscott J, Sgarbanti M. Origin and function of anti-interferon type I viral proteins. Virology. 2025 Feb 20;605:110456–110456. Available from: <https://doi.org/10.1016/j.virol.2025.110456>
 14. Yin Y, Ma J, Waesberghe CV, Devriendt B, Favoreel HW. Pseudorabies virus-induced expression and antiviral activity of type I or type III interferon depend on the type of infected epithelial cell. Frontiers in Immunology. 2022 Nov 2;13:1016982–1016982. <https://doi.org/10.3389/fimmu.2022.1016982>



15. Kembou-Ringert JE, Steinhagen D, Thompson KD, Daly JM, Adamek M. Immune responses to Tilapia lake virus infection: what we know and what we don't know. *Frontiers in Immunology*. 2023 Aug 9;14:1240094–1240094. Available from: <https://doi.org/10.3389/fimmu.2023.1240094>
16. Yasamineh S, Kalajahi HG, Yasamineh P, Yazdani Y, Gholizadeh O, Tabatabaie R, et al. An overview on nanoparticle-based strategies to fight viral infections with a focus on COVID-19. *Journal of Nanobiotechnology*. 2022 Oct 8;20(1):440–440. Available from: <https://doi.org/10.1186/s12951-022-01625-0>
17. Tian Z, Cao Q, Ma Z, Jiang CQ. Metabolic regulation of interferon-mediated innate antiviral immunity. *Frontiers in Immunology*. 2025 Oct 8;16:1680688–1680688. Available from: <https://doi.org/10.3389/fimmu.2025.1680688>
18. Stunnenberg M, Sprokholt JK, Hamme JL van, Kaptein TM, Zijlstra-Willems EM, Gringhuis SI, et al. Synthetic Abortive HIV-1 RNAs Induce Potent Antiviral Immunity. *Pure Amsterdam UMC*. 2020 Jan 23;11:8–8. <https://pure.amsterdamumc.nl/en/publications/b6a0a7e5-fa24-403c-a178-abd7781c17ad>
19. Zheng Y, Zhuang MW, Han L, Zhang J, Nan ML, Zhan P, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal Transduction and Targeted Therapy*. 2020 Dec 28;5(1):299–299. Available from: <https://doi.org/10.1038/s41392-020-00438-7>
20. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. *Frontiers in Immunology*. 2020 Aug 7;11:1949–1949. <https://doi.org/10.3389/fimmu.2020.01949>
21. Hoang H, Naeli P, Alain T, Jafarnejad SM. Mechanisms of impairment of interferon production by SARS-CoV-2. *Biochemical Society Transactions*. 2023 May 18;51(3):1047–56. <https://doi.org/10.1042/bst20221037>



22. Mazewski C, Perez RE, Fish EN, Platanias LC. Type I Interferon (IFN)-Regulated Activation of Canonical and Non-Canonical Signaling Pathways. *Frontiers in Immunology*. 2020 Nov 23;11:606456–606456. Available from: <https://doi.org/10.3389/fimmu.2020.606456>
23. Ji L, Li T, Chen H, Yang Y, Lu E, Liu J, et al. The crucial regulatory role of type I interferon in inflammatory diseases. *Cell & Bioscience*. 2023 Dec 20;13(1):230–230. <https://doi.org/10.1186/s13578-023-01188-z>
24. Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. *Nature Communications*. 2020 July 30;11(1):3810–3810. <https://doi.org/10.1038/s41467-020-17665-9>
25. Sugrue J, Bourke NM, O'Farrelly C. Type I Interferon and the Spectrum of Susceptibility to Viral Infection and Autoimmune Disease: A Shared Genomic Signature. *Frontiers in Immunology*. 2021 Nov 30;12:757249–757249. Available from: <https://doi.org/10.3389/fimmu.2021.757249>
26. Zhao L, Xia M, Wang K, Lai C, Fan H, Gu H, et al. A Long Non-coding RNA IVRPIE Promotes Host Antiviral Immune Responses Through Regulating Interferon β 1 and ISG Expression. *Frontiers in Microbiology*. 2020 Feb 19;11:260–260. Available from: <https://doi.org/10.3389/fmicb.2020.00260>
27. Kim Y, Shin E. Type I and III interferon responses in SARS-CoV-2 infection. *Experimental & Molecular Medicine*. 2021 May 1;53(5):750–60. Available from: <https://doi.org/10.1038/s12276-021-00592-0>
28. Lopez J, Mommert M, Mouton W, Pizzorno A, Brengel-Pesce K, Mezidi M, et al. Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. *The Journal of Experimental Medicine*. 2021 Aug 6;218(10). <https://doi.org/10.1084/jem.20211211>
29. Sharifi E, Yousefiasl S, Trovato M, Sartorius R, Esmaili Y, Goodarzi H, et al. Nanostructures for prevention, diagnosis, and treatment of viral respiratory infections: from influenza virus to SARS-CoV-2 variants. *Journal of*



- Nanobiotechnology. 2023 June 21;21(1):199–199. Available from: <https://doi.org/10.1186/s12951-023-01938-8>
30. Zhao K, Zhang S, Liu X, Guo X, Guo Z, Zhang X, et al. The game between host antiviral innate immunity and immune evasion strategies of senecavirus A - A cell biological perspective. *Frontiers in Immunology*. 2022 Dec 22;13:1107173–1107173. <https://doi.org/10.3389/fimmu.2022.1107173>
31. Islamuddin M, Mustfa SA, Ullah SNMN, Omer U, Kato K, Parveen S. Innate Immune Response and Inflammasome Activation During SARS-CoV-2 Infection. *Inflammation*. 2022 Aug 11;45(5):1849–63. <https://doi.org/10.1007/s10753-022-01651-y>
32. Feng H, Zhang YB, Gui J, Lemon SM, Yamane D. Interferon regulatory factor 1 (IRF1) and anti-pathogen innate immune responses. *PLoS Pathogens*. 2021 Jan 21;17(1). Available from: <https://doi.org/10.1371/journal.ppat.1009220>
33. Li D, Wu M. Pattern recognition receptors in health and diseases. *Signal Transduction and Targeted Therapy*. 2021 Aug 4;6(1):291–291. Available from: <https://doi.org/10.1038/s41392-021-00687-0>
34. Chen ZC, Behrendt R, Wild L, Schlee M, Bode C. Cytosolic nucleic acid sensing as driver of critical illness: mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*. 2025 Mar 19;10(1):90–90. Available from: <https://doi.org/10.1038/s41392-025-02174-2>
35. Piret J, Boivin G. Viral Interference between Respiratory Viruses. *Emerging infectious diseases*. 2022 Jan 20;28(2):273–81. Available from: <https://doi.org/10.3201/eid2802.211727>
36. Cornish EF, Filipovic I, Åsenius F, Williams D, McDonnell T. Innate Immune Responses to Acute Viral Infection During Pregnancy. *Frontiers in Immunology*. 2020 Sept 30;11:572567–572567. <https://doi.org/10.3389/fimmu.2020.572567>



37. Verburg SG, Lelievre RM, Westerveld MJ, Inkol JM, Sun Y, Workenhe ST. Viral-mediated activation and inhibition of programmed cell death. PLoS Pathogens. 2022 Aug 11;18(8). <https://doi.org/10.1371/journal.ppat.1010718>
38. Burkart SS, Schweinoch D, Frankish J, Sparn C, Wüst S, Urban C, et al. High-resolution kinetic characterization of the RIG-I-signaling pathway and the antiviral response. Life Science Alliance. 2023 Aug 9;6(10). Available from: <https://doi.org/10.26508/lsa.202302059>
39. Su CM, Du Y, Rowland RRR, Wang Q, Yoo D. Reprogramming viral immune evasion for a rational design of next-generation vaccines for RNA viruses. Frontiers in Immunology. 2023 Apr 17;14:1172000–1172000. Available from: <https://doi.org/10.3389/fimmu.2023.1172000>
40. Khalil AM, Nogales A, Martínez-Sobrido L, Mostafa A. Antiviral responses versus virus-induced cellular shutoff: a game of thrones between influenza A virus NS1 and SARS-CoV-2 Nsp1. Frontiers in Cellular and Infection Microbiology. 2024 Feb 5;14:1357866–1357866. <https://doi.org/10.3389/fcimb.2024.1357866>
41. Chen M, Ma Y, Chang W. SARS-CoV-2 and the Nucleus. International Journal of Biological Sciences. 2022 Jan 1;18(12):4731–4739. <https://doi.org/10.7150/ijbs.72482>
42. Saxena SK, Prakash H. Innate Immunity in Health and Disease. IntechOpen eBooks. IntechOpen; 2020. <http://doi.org/10.5772/intechopen.82921>
43. Boroujeni ME, Sekrecka A, Antonczyk A, Hassani S, Sekrecki M, Nowicka H, et al. Dysregulated Interferon Response and Immune Hyperactivation in Severe COVID-19: Targeting STATs as a Novel Therapeutic Strategy. Frontiers in Immunology. 2022 May 17;13:888897–888897. Available from: <https://doi.org/10.3389/fimmu.2022.888897>
44. Yang E, Li MMH. All About the RNA: Interferon-Stimulated Genes That Interfere With Viral RNA Processes. Frontiers in Immunology. 2020 Dec 9;11:605024–605024. <https://doi.org/10.3389/fimmu.2020.605024>



45. Yang H, Dong Y, Bian Y, Xu N, Wu Y, Yang F, et al. The influenza virus PB2 protein evades antiviral innate immunity by inhibiting JAK1/STAT signalling. *Nature Communications*. 2022 Oct 21;13(1):6288–6288. Available from: <https://doi.org/10.1038/s41467-022-33909-2>
46. Gracias S, Chazal M, Decombe A, Unterfinger Y, Sogues A, Pruvost L, et al. Tick-borne flavivirus NS5 antagonizes interferon signaling by inhibiting the catalytic activity of TYK2. *EMBO Reports*. 2023 Oct 20;24(12). Available from: <https://doi.org/10.15252/embr.202357424>
47. Zhang R, Tang J. Evasion of I Interferon-Mediated Innate Immunity by Pseudorabies Virus. *Frontiers in Microbiology*. 2021 Dec 14;12:801257–801257. Available from: <https://doi.org/10.3389/fmicb.2021.801257>
48. Qian G, Zhu L, Li G, Liu Y, Zhang Z, Pan J, et al. An Integrated View of Deubiquitinating Enzymes Involved in Type I Interferon Signaling, Host Defense and Antiviral Activities. *Frontiers in Immunology*. 2021 Oct 11;12:742542–742542. <https://doi.org/10.3389/fimmu.2021.742542>
49. Xiang Q, Yang Z, Nicholas J. STAT and Janus kinase targeting by human herpesvirus 8 interferon regulatory factor in the suppression of type-I interferon signaling. *PLoS Pathogens*. 2022 July 1;18(7). Available from: <https://doi.org/10.1371/journal.ppat.1010676>
50. Efstathiou C, Zhang Y, Kandwal S, Fayne D, Molloy EJ, Stevenson NJ. Respiratory syncytial virus NS1 inhibits anti-viral Interferon- α -induced JAK/STAT signaling, by limiting the nuclear translocation of STAT1. *Frontiers in Immunology*. 2024 June 13;15:1395809–1395809. <https://doi.org/10.3389/fimmu.2024.1395809>
51. Mahjoor M, Mahmoudvand G, Farokhi S, Shadab A, Kashfi M, Afkhami H. Double-edged sword of JAK/STAT signaling pathway in viral infections: novel insights into virotherapy. *Cell Communication and Signaling*. 2023 Oct 2;21(1):272–272. Available from: <https://doi.org/10.1186/s12964-023-01240-y>



52. Huang S, Liu K, Cheng A, Wang M, Cui M, Huang J, et al. SOCS Proteins Participate in the Regulation of Innate Immune Response Caused by Viruses. *Frontiers in Immunology*. 2020 Sept 25;11:558341–558341. Available from: <https://doi.org/10.3389/fimmu.2020.558341>
53. Agarwal S, Vierbuchen T, Ghosh S, Chan J, Jiang Z, Kandasamy RK, et al. The long non-coding RNA LUCAT1 is a negative feedback regulator of interferon responses in humans. *Nature Communications*. 2020 Dec 11;11(1):6348–6348. Available from: <https://doi.org/10.1038/s41467-020-20165-5>
54. Schiefer S, Hale BG. Proximal protein landscapes of the type I interferon signaling cascade reveal negative regulation by PJA2. *Nature Communications*. 2024 May 27;15(1):4484–4484. <https://doi.org/10.1038/s41467-024-48800-5>
55. Sun F, Ma W, Xu Y, He L, Xiao Y, Li X, et al. Sec10 suppresses antiviral innate immune response by facilitating STUB1-mediated STAT1 degradation. *PLoS Pathogens*. 2025 Sept 8;21(9). <https://doi.org/10.1371/journal.ppat.1013472>
56. Wittling MC, Cahalan SR, Levenson EA, Rabin RL. Shared and Unique Features of Human Interferon-Beta and Interferon-Alpha Subtypes. *Frontiers in Immunology*. 2021 Jan 19;11. <https://doi.org/10.3389/fimmu.2020.605673>
57. Muñoz-Moreno R, Martínez-Romero C, García-Sastre A. Induction and Evasion of Type-I Interferon Responses during Influenza A Virus Infection. *Cold Spring Harbor Perspectives in Medicine*. 2020 July 6;11(10). Available from: <https://doi.org/10.1101/cshperspect.a038414>
58. Wang F, Song H, Xu F, Xu J, Wang L, Yang F, et al. Role of hepatitis B virus non-structural protein HBx on HBV replication, interferon signaling, and hepatocarcinogenesis. *Frontiers in Microbiology*. 2023 Dec 21;14:1322892–1322892. Available from: <https://doi.org/10.3389/fmicb.2023.1322892>
59. Zhu H, Zheng C. The Race between Host Antiviral Innate Immunity and the Immune Evasion Strategies of Herpes Simplex Virus 1. *Microbiology and*



Molecular Biology Reviews. 2020 Sept 29;84(4).

<https://doi.org/10.1128/mmbr.00099-20>

60. Streicher F, Chantharath A, Jouvenet N. Viral interferon antagonism shapes host tropism. Europe PMC (PubMed Central). 2025 Oct 7;21(10). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/12503246>
61. Chen X, Qiao S, Li R, Wang J, Li X, Zhang G. Evasion strategies of porcine reproductive and respiratory syndrome virus. Frontiers in Microbiology. 2023 Mar 17;14:1140449–1140449. <https://doi.org/10.3389/fmicb.2023.1140449>
62. Du Y, Yang F, Wang Q, Xu N, Xie Y, Chen S, et al. Influenza A virus antagonizes type I and type II interferon responses via SOCS1-dependent ubiquitination and degradation of JAK1. Virology Journal. 2020 June 12;17(1):74–74. Available from: <https://doi.org/10.1186/s12985-020-01348-4>
63. Yin Y, Romero N, Favoreel HW. Pseudorabies Virus Inhibits Type I and Type III Interferon-Induced Signaling via Proteasomal Degradation of Janus Kinases. Journal of Virology. 2021 Aug 11;95(20). <https://doi.org/10.1128/jvi.00793-21>
64. Heuschkel MJ. Caractérisation de la Janus kinase JAK1 comme facteur d'hôte du virus de l'hépatite D et cible antivirale. theses.fr (ABES). 2023. Available from: <http://www.theses.fr/2023STRAJ073/document>
65. Badía R, García-Vidal E, Ballana E. Viral-Host Dependency Factors as Therapeutic Targets to Overcome Antiviral Drug-Resistance: A Focus on Innate Immune Modulation. Frontiers in Virology. 2022 July 5;2. Available from: <https://doi.org/10.3389/fviro.2022.935933>
66. Stanifer ML, Guo C, Doldan P, Boulant S. Importance of Type I and III Interferons at Respiratory and Intestinal Barrier Surfaces. Frontiers in Immunology. 2020 Dec 11;11:608645–608645. <https://doi.org/10.3389/fimmu.2020.608645>
67. Duncan CJ, Hambleton S. Human Disease Phenotypes Associated with Loss and Gain of Function Mutations in STAT2: Viral Susceptibility and Type I



- Interferonopathy. *Journal of Clinical Immunology*. 2021 Aug 26;41(7):1446–56. Available from: <https://doi.org/10.1007/s10875-021-01118-z>
68. Ott N, Faletti L, Heeg M, Andreani V, Grimbacher B. JAKs and STATs from a Clinical Perspective: Loss-of-Function Mutations, Gain-of-Function Mutations, and Their Multidimensional Consequences. *Journal of Clinical Immunology*. 2023 May 4;43(6):1326–59. <https://doi.org/10.1007/s10875-023-01483-x>
69. Feng L, Li W, Wu X, Li X, Yang X, Ran Y, et al. Human Cytomegalovirus UL23 Attenuates Signal Transducer and Activator of Transcription 1 Phosphorylation and Type I Interferon Response. *Frontiers in Microbiology*. 2021 July 9;12:692515–692515. <https://doi.org/10.3389/fmicb.2021.692515>
70. Chen Q, Li L, Guo S, Liu Z, Liu L, Tan C, et al. African swine fever virus pA104R protein acts as a suppressor of type I interferon signaling. *Frontiers in Microbiology*. 2023 Apr 6;14:1169699–1169699. Available from: <https://doi.org/10.3389/fmicb.2023.1169699>
71. Zoellner N, Coesfeld N, Vos FHD, Denter J, Xu HC, Zimmer E, et al. Synthetic mimetics assigned a major role to IFNAR2 in type I interferon signaling. *Frontiers in Microbiology*. 2022 Sept 2;13:947169–947169. Available from: <https://doi.org/10.3389/fmicb.2022.947169>
72. Sun M, Lin Q, Wang C, Xing J, Yan K long, Liu Z, et al. Enterovirus A71 2B Inhibits Interferon-Activated JAK/STAT Signaling by Inducing Caspase-3-Dependent Karyopherin- α 1 Degradation. *Frontiers in Microbiology*. 2021 Dec 21;12:762869–762869. <https://doi.org/10.3389/fmicb.2021.762869>
73. Schreiber G. The Role of Type I Interferons in the Pathogenesis and Treatment of COVID-19. *Frontiers in Immunology*. 2020 Sept 30;11:595739–595739. Available from: <https://doi.org/10.3389/fimmu.2020.595739>
74. Moalem Y, Malis Y, Voloshin K, Dukhovny A, Hirschberg K, Sklan EH. Sandfly Fever Viruses Attenuate the Type I Interferon Response by Targeting the



- Phosphorylation of JAK-STAT Components. *Frontiers in Immunology*. 2022 June 1;13:865797–865797. <https://doi.org/10.3389/fimmu.2022.865797>
75. Yang H, Dong Y, Bian Y, Huo C, Chuncheng Z, Qin T, et al. The synergistic effect of residues 32T and 550L in the PA protein of H5 subtype avian influenza virus contributes to viral pathogenicity in mice. *PLoS Pathogens*. 2023 July 3;19(7). Available from: <https://doi.org/10.1371/journal.ppat.1011489>
76. Du Y, Yang F, Wang Q, Xu N, Xie Y, Chen S, et al. Influenza A virus antagonizes type I and type II interferon responses via SOCS1-dependent ubiquitination and degradation of JAK1. *Research Square*. 2020. Available from: <https://doi.org/10.21203/rs.2.22023/v2>
77. Chen D, Khan N, Close BJ, Goel RK, Blum BC, Tavares AH, et al. SARS-CoV-2 Disrupts Proximal Elements in the JAK-STAT Pathway. *Journal of Virology*. 2021 July 14;95(19). Available from: <https://doi.org/10.1128/jvi.00862-21>
78. Barik S. Mechanisms of Viral Degradation of Cellular Signal Transducer and Activator of Transcription 2. *International Journal of Molecular Sciences*. 2022 Jan 1;23(1):489–489. Available from: <https://doi.org/10.3390/ijms23010489>
79. Zoladek J, Nisole S. Mosquito-borne flaviviruses and type I interferon: catch me if you can! *Frontiers in Microbiology*. 2023 Oct 30;14:1257024–1257024. Available from: <https://doi.org/10.3389/fmicb.2023.1257024>
80. Rashid F, Xie Z, Xie Z, Li M, Xie Z, Xie Z, et al. Roles and functions of IAV proteins in host immune evasion. *Frontiers in Immunology*. 2023 Dec 13;14:1323560–1323560. <https://doi.org/10.3389/fimmu.2023.1323560>
81. Zhang Q, Chen Z, Huang C, Sun J, Xue M, Feng T, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Membrane (M) and Spike (S) Proteins Antagonize Host Type I Interferon Response. *Frontiers in Cellular and Infection Microbiology*. 2021 Dec 7;11:766922–766922. Available from: <https://doi.org/10.3389/fcimb.2021.766922>



82. Gruber C, Martín-Fernández M, Ailal F, Qiu X, Taft J, Altman J, et al. Homozygous STAT2 gain-of-function mutation by loss of USP18 activity in a patient with type I interferonopathy. *The Journal of Experimental Medicine*. 2020 Feb 8;217(5). Available from: <https://doi.org/10.1084/jem.20192319>
83. Théry F, Eggermont D, Impens F. Proteomics Mapping of the ISGylation Landscape in Innate Immunity. *Frontiers in Immunology*. 2021 Aug 10;12:720765–720765. <https://doi.org/10.3389/fimmu.2021.720765>
84. Ezeonwumelu IJ, García-Vidal E, Ballana E. JAK-STAT Pathway: A Novel Target to Tackle Viral Infections. *Viruses*. 2021 Nov 27;13(12):2379–2379. Available from: <https://doi.org/10.3390/v13122379>
85. Veit EC, Salim MS, Jung M, Richardson RB, Boys IN, Quinlan M, et al. Evolution of STAT2 resistance to flavivirus NS5 occurred multiple times despite genetic constraints. *Nature Communications*. 2024 June 26;15(1):5426–5426. Available from: <https://doi.org/10.1038/s41467-024-49758-0>
86. Du Y, Yang F, Wang Q, Xu N, Xie Y, Chen S, et al. Influenza A virus antagonizes type I and type II interferon responses via SOCS1-dependent ubiquitination and degradation of JAK1. *Research Square*. 2020. Available from: <https://doi.org/10.21203/rs.2.22023/v1>
87. Wang TY, Sun M, Zhang H, Wang G, Zhan G, Tian Z, et al. Evasion of Antiviral Innate Immunity by Porcine Reproductive and Respiratory Syndrome Virus. *Frontiers in Microbiology*. 2021 June 23;12:693799–693799. Available from: <https://doi.org/10.3389/fmicb.2021.693799>
88. Biswal M, Yao W, Lu J, Chen J, Morrison J, Hai R, et al. A conformational selection mechanism of flavivirus NS5 for species-specific STAT2 inhibition. *Communications Biology*. 2024 Jan 10;7(1):76–76. Available from: <https://doi.org/10.1038/s42003-024-05768-8>



89. Parisien JP, Lenoir JJ, Alvarado G, Horvath CM. The Human STAT2 Coiled-Coil Domain Contains a Degron for Zika Virus Interferon Evasion. *Journal of Virology*. 2021 Oct 13;96(1). <https://doi.org/10.1128/jvi.01301-21>
90. Riera E, García-Belmonte R, Madrid R, Pérez-Núñez D, Revilla Y. African swine fever virus ubiquitin-conjugating enzyme pI215L inhibits IFN-I signaling pathway through STAT2 degradation. *Frontiers in Microbiology*. 2023 Jan 13;13:1081035–1081035. <https://doi.org/10.3389/fmicb.2022.1081035>
91. Riera E, Pérez-Núñez D, García-Belmonte R, Miorin L, García-Sastre A, Revilla Y. African Swine Fever Virus Induces STAT1 and STAT2 Degradation to Counteract IFN-I Signaling. *Frontiers in Microbiology*. 2021 Aug 26;12:722952–722952. <https://doi.org/10.3389/fmicb.2021.722952>
92. Wang Y, Song Q, Huang W, Lin Y, Wang X, Wang C, et al. A virus-induced conformational switch of STAT1-STAT2 dimers boosts antiviral defenses. *Cell Research*. 2020 Aug 5;31(2):206–18. <https://doi.org/10.1038/s41422-020-0386-6>
93. Tsu BV, Fay EJ, Nguyen KT, Corley MR, Hosuru B, Domínguez V, et al. Running With Scissors: Evolutionary Conflicts Between Viral Proteases and the Host Immune System. *Frontiers in Immunology*. 2021 Nov 1;12:769543–769543. Available from: <https://doi.org/10.3389/fimmu.2021.769543>
94. Richardson RB, Kikawa C, Garg A, Bednarski E, Salim MS, Bacsik DJ, et al. Coevolutionary constraints of Zika virus nonstructural protein 5 replication and interferon antagonism activities. *bioRxiv* (Cold Spring Harbor Laboratory). 2025 Dec 24; Available from: <https://doi.org/10.64898/2025.12.23.696258>
95. Tenthorey JL, Emerman M, Malik HS. Evolutionary Landscapes of Host-Virus Arms Races. *Annual Review of Immunology*. 2022 Jan 26;40(1):271–94. Available from: <https://doi.org/10.1146/annurev-immunol-072621-084422>
96. Fanunza E, Carletti F, Quartu M, Grandi N, Ermellino L, Milia J, et al. Zika virus NS2A inhibits interferon signaling by degradation of STAT1 and STAT2.



- Virulence. 2021 Aug 2;12(1):1580–96.
<https://doi.org/10.1080/21505594.2021.1935613>
97. Parisien J, Lenoir JJ, Alvarado G, Horvath CM. The Human STAT2 Coiled-Coil Domain Contains a Degron for Zika Virus Interferon Evasion. bioRxiv (Cold Spring Harbor Laboratory). Cold Spring Harbor Laboratory; 2021. Available from: <https://doi.org/10.1101/2021.10.01.462781>
98. Kumar A, Ishida R, Strilets T, Cole J, López-Orozco J, Fayad N, et al. SARS-CoV-2 Nonstructural Protein 1 Inhibits the Interferon Response by Causing Depletion of Key Host Signaling Factors. Journal of Virology. 2021 Apr 20 ;95(13). Available from: <https://doi.org/10.1128/jvi.00266-21>
99. Jacquet S, Culbertson M, Zhang C, Filali AE, Mory C de la M, Pons J, et al. Adaptive duplication and genetic diversification of protein kinase R contribute to the specificity of bat-virus interactions. Science Advances. 2022 Nov 23;8(47). Available from: <https://doi.org/10.1126/sciadv.add7540>
100. Grabowski F, Kochańczyk M, Korwek Z, Czerkies M, Prus W, Lipniacki T. Antagonism between viral infection and innate immunity at the single-cell level. PubMed Central. 2023 Sept 5;19(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/10503725>
101. Li X, Liu S, Liu S, Raj K, Zhou W, Wang S, et al. Initial activation of STAT2 induced by IAV infection is critical for innate antiviral immunity. Frontiers in Immunology. 2022 Sept 5;13:960544–960544. Available from: <https://doi.org/10.3389/fimmu.2022.960544>
102. Wu Y, Li M, Tian J, Yan H, Pan Y, Shi H, et al. Broad antagonism of coronaviruses nsp5 to evade the host antiviral responses by cleaving POLDIP3. PLoS Pathogens. 2023 Oct 6;19(10). <https://doi.org/10.1371/journal.ppat.1011702>
103. Zhang Y, Zhang Y, LIU C, Ren W, Li C, Guo Y, et al. A tunable immune-evasion function of Zika virus NS5 governs viral fitness and pathogenesis. bioRxiv (Cold



- Spring Harbor Laboratory). 2025 Dec 29; Available from: <https://doi.org/10.64898/2025.12.28.696729>
- 104.** Geiger R, Khera D, Tenthorey JL, Kochs G, Graf L, Emerman M, et al. Heterozygous and generalist MxA super-restrictors overcome breadth-specificity trade-offs in antiviral restriction. *Science Advances*. 2025 May 2;11(18). Available from: <https://doi.org/10.1126/sciadv.adu0062>
- 105.** Chelbi-Alix MK, Thibault P. Crosstalk Between SUMO and Ubiquitin-Like Proteins: Implication for Antiviral Defense. *Frontiers in Cell and Developmental Biology*. 2021 Apr 21;9:671067–671067. Available from: <https://doi.org/10.3389/fcell.2021.671067>
- 106.** Wen S, Song Y, Li C, Jin N, Zhai J, Lu H. Positive Regulation of the Antiviral Activity of Interferon-Induced Transmembrane Protein 3 by S-Palmitoylation. *Frontiers in Immunology*. 2022 June 13;13:919477–919477. Available from: <https://doi.org/10.3389/fimmu.2022.919477>
- 107.** Wallace IR, Baek K, Prabu JR, Vollrath R, Gronau S von, Schulman BA, et al. Insights into the ISG15 transfer cascade by the UBE1L activating enzyme. *Nature Communications*. 2023 Dec 2;14(1):7970–7970. Available from: <https://doi.org/10.1038/s41467-023-43711-3>
- 108.** Gao X, Sun Y. Unraveling the Biology of Interferon-Stimulated Genes: Mechanisms, Functions, and Clinical Implications. *Infection and Drug Resistance*. 2026 Jan 1;1–12. <https://doi.org/10.2147/idr.s565301>
- 109.** Potamias G, Gkoublia P, Kanterakis A. The two-stage molecular scenery of SARS-CoV-2 infection with implications to disease severity: An in-silico quest. *Frontiers in Immunology*. 2023 Nov 21;14:1251067–1251067. Available from: <https://doi.org/10.3389/fimmu.2023.1251067>
- 110.** Harioudh MK, Sarkar SN. Context-Specific Diversity of Antimicrobial Functions of Interferon-Stimulated Genes. *Viruses*. 2025 Dec 17;17(12):1635–1635. Available from: <https://doi.org/10.3390/v17121635>



111. Young HA. Faculty Opinions recommendation of All About the RNA: Interferon-Stimulated Genes That Interfere With Viral RNA Processes.. Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature. 2021. Available from: <https://doi.org/10.3410/f.739272461.793581617>
112. Wickenhagen A, Sugrue E, Lytras S, Kuchi S, Noerenberg M, Turnbull ML, et al. A prenylated dsRNA sensor protects against severe COVID-19. Science. 2021 Sept 28;374(6567). <https://doi.org/10.1126/science.abj3624>
113. Théry F, Martina L, Asselman C, Zhang Y, Vessely M, Repo H, et al. Ring finger protein 213 assembles into a sensor for ISGylated proteins with antimicrobial activity. Nature Communications. 2021 Oct 1;12(1):5772–5772. Available from: <https://doi.org/10.1038/s41467-021-26061-w>
114. Rathnasinghe R, Salvatore M, Zheng H, Jangra S, Kehrer T, Mena I, et al. Interferon mediated prophylactic protection against respiratory viruses conferred by a prototype live attenuated influenza virus vaccine lacking non-structural protein 1. Scientific Reports. 2021 Nov 12;11(1):22164–22164. Available from: <https://doi.org/10.1038/s41598-021-01780-8>
115. Zhang M, Li J, Yan H, Huang J, Wang F, Liu T, et al. ISGylation in Innate Antiviral Immunity and Pathogen Defense Responses: A Review. Frontiers in Cell and Developmental Biology. 2021 Nov 25;9:788410–788410. Available from: <https://doi.org/10.3389/fcell.2021.788410>
116. Kang JA, Kim YJ, Jeon YJ. The diverse repertoire of ISG15: more intricate than initially thought. Experimental & Molecular Medicine. 2022 Nov 1;54(11):1779–92. <https://doi.org/10.1038/s12276-022-00872-3>
117. Wang Y, Feng H, Li X, Ruan Y, Guo Y, Cui X, et al. Dampening of ISGylation of RIG-I by ADAP regulates type I interferon response of macrophages to RNA virus infection. PLoS Pathogens. 2024 May 22;20(5). Available from: <https://doi.org/10.1371/journal.ppat.1012230>



118. Liu H, Li C, He W, Chen J, Yang G, Chen L, et al. Free ISG15 inhibits Pseudorabies virus infection by positively regulating type I IFN signaling. *PLoS Pathogens*. 2022 Oct 31;18(10). <https://doi.org/10.1371/journal.ppat.1010921>
119. Xiong TC, Wei M, Li F, Shi M, Gan H, Tang Z, et al. The E3 ubiquitin ligase ARIH1 promotes antiviral immunity and autoimmunity by inducing mono-ISGylation and oligomerization of cGAS. *Nature Communications*. 2022 Oct 10;13(1):5973–5973. <https://doi.org/10.1038/s41467-022-33671-5>
120. Morales AE, Dong Y, Brown T, Baid K, Kontopoulos D- G, Gonzalez V, et al. Bat genomes illuminate adaptations to viral tolerance and disease resistance. *University Library (University of Saskatchewan)*. 2025 Jan 29;638(8050):449–58. Available from: <https://hdl.handle.net/10388/16908>
121. Munnur D, Banducci-Karp A, Sanyal S. ISG15 driven cellular responses to virus infection. *Biochemical Society Transactions*. 2022 Nov 23;50(6):1837–46. Available from: <https://doi.org/10.1042/bst20220839>
122. Chiang C, Liu G, Gack MU. Viral Evasion of RIG-I-Like Receptor-Mediated Immunity through Dysregulation of Ubiquitination and ISGylation. *Viruses*. 2021 Jan 26 [cited 2025 Nov];13(2):182–182. Available from: <https://doi.org/10.3390/v13020182>
123. Xu G, Wu Y, Xiao T, Qi F, Fan L, Zhang S, et al. Multiomics approach reveals the ubiquitination-specific processes hijacked by SARS-CoV-2. *Signal Transduction and Targeted Therapy*. 2022 Sept 7 [cited 2026 Jan];7(1):312–312. Available from: <https://doi.org/10.1038/s41392-022-01156-y>
124. Vere G, Alam MR, Farrar S, Kealy R, Kessler BM, O'Brien DP, et al. Targeting the Ubiquitylation and ISGylation Machinery for the Treatment of COVID-19. *Biomolecules*. 2022 Feb 12;12(2):300–300. Available from: <https://doi.org/10.3390/biom12020300>



125. Fernandez DJ, Hess S, Knobloch K. Strategies to Target ISG15 and USP18 Toward Therapeutic Applications. *Frontiers in Chemistry*. 2020 Jan 21;7:923–923. Available from: <https://doi.org/10.3389/fchem.2019.00923>
126. X G, Y S. Unraveling the Biology of Interferon-Stimulated Genes: Mechanisms, Functions, and Clinical Implications. *SHILAP Revista de lepidopterología*. 2026 Jan 1; <https://doaj.org/article/73fdb66900f543f5b44c4c4e140d6332>
127. Cai C, Tang Y, Zhai J, Zheng C. The RING finger protein family in health and disease. *Signal Transduction and Targeted Therapy*. 2022 Aug 30;7(1):300–300. Available from: <https://doi.org/10.1038/s41392-022-01152-2>
128. Afsar M, Liu G, Jia L, Ruben EA, Nayak D, Sayyad Z, et al. Cryo-EM structures of Uba7 reveal the molecular basis for ISG15 activation and E1-E2 thioester transfer. *Nature Communications*. 2023 Aug 8;14(1):4786–4786. Available from: <https://doi.org/10.1038/s41467-023-39780-z>
129. Mathieu NA, Paparisto E, Barr SD, Spratt DE. HERC5 and the ISGylation Pathway: Critical Modulators of the Antiviral Immune Response. *Viruses*. 2021 June 9;13(6):1102–1102. Available from: <https://doi.org/10.3390/v13061102>
130. Cruz ACT. Free ISG15 and Protein ISGylation Emerging in SARS-CoV-2 Infection. *Current Drug Targets*. 2022 Mar 17;23(7):686–91. Available from: <https://doi.org/10.2174/1389450123666220316094720>
131. Bonacci T, Emanuele MJ. DIG-DUBs: mechanisms and functions of ISG15 deconjugation by human and viral cross-reactive ubiquitin proteases. *Biochemical Society Transactions*. 2025 July 9;53(4):787–800. Available from: <https://doi.org/10.1042/bst20240859>
132. Vliet VJE van, Huynh N, Palà J, Patel A, Singer AU, Slater C, et al. Ubiquitin variants potently inhibit SARS-CoV-2 PLpro and viral replication via a novel site distal to the protease active site. *PLoS Pathogens*. 2022 Dec 22;18(12). Available from: <https://doi.org/10.1371/journal.ppat.1011065>



133. Shin DH, Mukherjee R, Grewe D, Bojková D, Baek K, Bhattacharya A, et al. Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature*. 2020 July 29;587(7835):657–62. Available from: <https://doi.org/10.1038/s41586-020-2601-5>
134. Cockram PE, Kist M, Prakash S, Chen S, Wertz IE, Vucic D. Ubiquitination in the regulation of inflammatory cell death and cancer. *Cell Death and Differentiation*. 2021 Jan 11;28(2):591–605. <https://doi.org/10.1038/s41418-020-00708-5>
135. Li Z, Hao P, Zhao Z, Gao W, Chen H, Li L, et al. The E3 ligase RNF5 restricts SARS-CoV-2 replication by targeting its envelope protein for degradation. *Signal Transduction and Targeted Therapy*. 2023 Feb 3;8(1):53–53. Available from: <https://doi.org/10.1038/s41392-023-01335-5>
136. Fiil BK, Gyrd-Hansen M. The Met1-linked ubiquitin machinery in inflammation and infection. *Cell Death and Differentiation*. 2021 Jan 20;28(2):557–69. Available from: <https://doi.org/10.1038/s41418-020-00702-x>
137. Sievers BL, Cheng MTK, Csiba K, Meng B, Gupta RK. SARS-CoV-2 and innate immunity: the good, the bad, and the “goldilocks.” *Cellular and Molecular Immunology*. 2023 Nov 20;21(2):171–83. Available from: <https://doi.org/10.1038/s41423-023-01104-y>
138. Zhong G, Chang X, Xie W, Zhou X. Targeted protein degradation: advances in drug discovery and clinical practice. *Signal Transduction and Targeted Therapy*. 2024 Nov 6;9(1):308–308. <https://doi.org/10.1038/s41392-024-02004-x>
139. Chen J, Qi D, Hu H, Wang X, Lin W. Unconventional posttranslational modification in innate immunity. *Cellular and Molecular Life Sciences*. 2024 July 6;81(1):290–290. Available from: <https://doi.org/10.1007/s00018-024-05319-8>
140. Çakır M, Obernier K, Forget A, Krogan NJ. Target Discovery for Host-Directed Antiviral Therapies: Application of Proteomics Approaches. *mSystems*. 2021 Sept 14;6(5). Available from: <https://doi.org/10.1128/msystems.00388-21>



141. Li X, Kabza AM, Ives AN, Thiel J, Waters KM, Qian W, et al. Proteome-wide characterization of PTMs reveals host cell responses to viral infection and identifies putative antiviral drug targets. *Frontiers in Immunology*. 2025 May 30;16:1587106–1587106 <https://doi.org/10.3389/fimmu.2025.1587106>
142. Hu J, Zhang L, Liu X. Role of Post-translational Modifications in Influenza A Virus Life Cycle and Host Innate Immune Response. *Frontiers in Microbiology*. 2020 Sept 4;11:517461–517461. <https://doi.org/10.3389/fmicb.2020.517461>
143. Stewart RW, Guitián XS, Gervais O, Jin Y, Salisbury SJ, Ballantyne M, et al. Characterisation of post-translational and transcriptional reprogramming of the immune response to ISAV and IPNV infections in salmon head kidney cells. *Frontiers in Immunology*. 2025 Oct 17;16:1532917–1532917. Available from: <https://doi.org/10.3389/fimmu.2025.1532917>
144. Cao G xiang, Liu F, Meng C, Ding C, Dai J, Qiu X. Virus infection and vesicle trafficking. *Frontiers in Immunology*. 2025 Oct 9;16:1682139–1682139. Available from: <https://doi.org/10.3389/fimmu.2025.1682139>
145. Xue J, Wang XY, Wang P, Qiao B, Gao P, Ren B, et al. Unraveled role of TLR7-mediated interferon signaling activation in COVID-19. *Frontiers in Cellular and Infection Microbiology*. 2025 Oct 8;15:1658249–1658249. Available from: <https://doi.org/10.3389/fcimb.2025.1658249>
146. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. *Nature reviews Immunology*. 2020 May 26;20(7):397–8. Available from: <https://doi.org/10.1038/s41577-020-0346-x>
147. Li G, Hilgenfeld R, Whitley RJ, Clercq ED. Therapeutic strategies for COVID-19: progress and lessons learned. *Nature Reviews Drug Discovery*. 2023 Apr 19 [cited 2026 Mar];22(6):449–75. <https://doi.org/10.1038/s41573-023-00672-y>
148. Lee JS, Shin E. The type I interferon response in COVID-19: implications for treatment. *Nature reviews Immunology* [Internet]. 2020 Aug 12;20(10):585–6. Available from: <https://doi.org/10.1038/s41577-020-00429-3>



149. Walter MR. The Role of Structure in the Biology of Interferon Signaling. *Frontiers in Immunology*. 2020 Nov 12;11:606489–606489. Available from: <https://doi.org/10.3389/fimmu.2020.606489>
150. Du Y, Hu Z, Luo Y, Wang HY, Yu X, Wang R. Function and regulation of cGAS-STING signaling in infectious diseases. *Frontiers in Immunology*. 2023 Feb 6;14:1130423–1130423. <https://doi.org/10.3389/fimmu.2023.1130423>
151. Maison DP, Deng Y, Gerschenson M. SARS-CoV-2 and the host-immune response. *Frontiers in Immunology*. 2023 June 19;14:1195871–1195871. Available from: <https://doi.org/10.3389/fimmu.2023.1195871>
152. Amurri L, Horvat B, Iampietro M. Interplay between RNA viruses and cGAS/STING axis in innate immunity. *Frontiers in Cellular and Infection Microbiology*. 2023 Apr 3;13:1172739–1172739. Available from: <https://doi.org/10.3389/fcimb.2023.1172739>
153. Carvalho T de A, Krammer F, Iwasaki A. The first 12 months of COVID-19: a timeline of immunological insights. *Nature reviews Immunology*. 2021 Mar 15;21(4):245–56. Available from: <https://doi.org/10.1038/s41577-021-00522-1>
154. Wang G, Gu Y, Wang C, Wang F, Hsu A. A Game of Infection – Song of Respiratory Viruses and Interferons. *Frontiers in Cellular and Infection Microbiology*. 2022 June 29;12:937460–937460. <https://doi.org/10.3389/fcimb.2022.937460>
155. Cuypers L, Keyaerts E, Hong SL, Gorissen S, Menezes SM, Starick MR, et al. Immunovirological and environmental screening reveals actionable risk factors for fatal COVID-19 during post-vaccination nursing home outbreaks. *Nature Aging*. 2023 May 22;3(6):722–33. <https://doi.org/10.1038/s43587-023-00421-1>
156. Diamond M, Lambris JD, Ting JP -Y., Tsang JS. Considering innate immune responses in SARS-CoV-2 infection and COVID-19. *Nature reviews Immunology*. 2022 July 4;22(8):465–70. <https://doi.org/10.1038/s41577-022-00744-x>



157. Hatton CF, Botting RA, Dueñas ME, Haq I, Verdon B, Thompson B, et al. Delayed induction of type I and III interferons mediates nasal epithelial cell permissiveness to SARS-CoV-2. *Nature Communications*. 2021 Dec 7;12(1):7092–7092. <https://doi.org/10.1038/s41467-021-27318-0>
158. Rui Y, Su J, Shen S, Hu Y, Huang D, Zheng W, et al. Unique and complementary suppression of cGAS-STING and RNA sensing- triggered innate immune responses by SARS-CoV-2 proteins. *Signal Transduction and Targeted Therapy*. 2021 Mar 15;6(1):123–123. <https://doi.org/10.1038/s41392-021-00515-5>
159. Xie F, Zhu Q. The regulation of cGAS-STING signaling by RNA virus-derived components. *Virology Journal*. 2024 May 1;21(1):101–101. Available from: <https://doi.org/10.1186/s12985-024-02359-1>
160. Deng L, Xu Z, Li F, Zhao J, Jian Z, Deng H, et al. Insights on the cGAS-STING Signaling Pathway During Herpesvirus Infections. *Frontiers in Immunology*. 2022 July 1;13:931885–931885. <https://doi.org/10.3389/fimmu.2022.931885>