

Systems biology unravels interferon responses to respiratory virus infections

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Abstract

Interferon production is an important defence against viral replication and its activation is an attractive therapeutic target. However, it has long been known that viruses perpetually evolve a multitude of strategies to evade these host immune responses. In recent years there has been an explosion of information on virus-induced alterations of the host immune response that have resulted from data-rich omics technologies. Unravelling how these systems interact and determining the overall outcome of the host response to viral infection will play an important role in future treatment and vaccine development. In this review we focus primarily on the interferon pathway and its regulation as well as mechanisms by which respiratory RNA viruses interfere with its signalling capacity.

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Key words: Respiratory virus; Interferon; Systems biology; Proteomics; Genomics; Innate immunity

Core tip: Many novel regulators of innate immune signalling pathways, such as the interferon signalling path-

way, have been discovered recently. These advances may be in part attributed to high-throughput systems biology techniques including genomic, proteomic, miRNA and siRNA screens, as well as through various confirmatory methods using quantitative polymerase chain reaction, microscopy, and animal models. Collectively, these studies have provided insights into novel drug targets that could boost host innate immunity or could potentially serve as broad-spectrum anti-virals against RNA respiratory viruses.

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INTRODUCTION TO SYSTEMS BIOLOGY AND INTERFERONS

Virus-host studies of a wide range of viruses have identified many host changes that occur upon infection, including the induction of a variety of anti-viral pathways. For example, these include autophagy, apoptosis, endoplasmic-reticular stress, nuclear-factor kappa B (NF- κ B) and proteasomal degradation pathways as well as the topic of this review, interferon signalling. Some of these studies have utilized global genomic, transcriptomics and proteomic technologies and have led to the characterizations of “infectomes”, “interactomes” and “interferomes”. One of the great advantages to systems biology tools is that they can provide a relatively unbiased “bottom-up” discovery approach such as with global transcriptome and siRNA screens. These have proven useful in the characterization of innate immune responses. Biological tools for detection of specific subsets of the cell are also continually being developed, including probes for specific

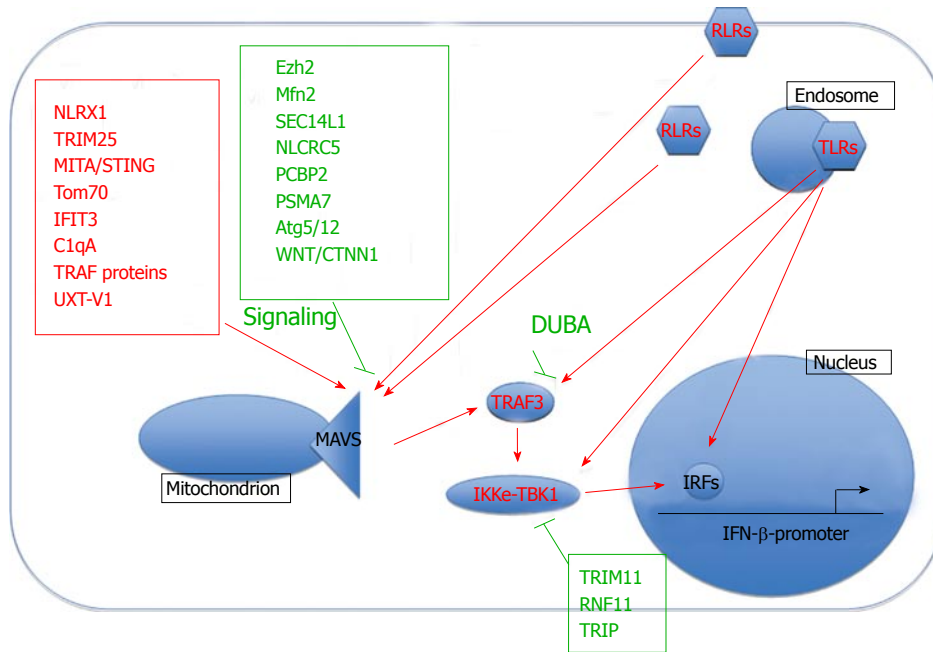


Figure 1 Interferon activation. NLRX1: Nucleotide-binding oligomerization domain, leucine rich repeat containing X1; TRIM25: Tripartite motif-containing 25; MITA/STING: Mediator of IRF3 activation/stimulator of interferon genes protein; TRIM11: Tripartite motif containing 11; RNF11: Ring finger protein 11; TRIP: Thyroid receptor-interacting protein; DUBA: Deubiquitinating enzyme A; RLRs: RIG-like receptors; TLRs: Toll-like receptors; IFIT3: Interferon-inducible transmembrane protein 3; MAVS: Mitochondrial antiviral signaling protein; NLCRC5: Nod-like receptor C5; PCBP2: Poly(rC)-binding protein 2; PSMA7: Proteasome subunit alpha type-7; TBK1: Tank binding kinase; IKKe: Inhibitor of nuclear factor kappa-B kinase; IRFs: Interferon regulatory factors; WNT/CTNNB1: Wnt/beta-catenin.

classes of enzymes, methods to detect different protein post-translational and epigenetic modifications, and sub-cellular fractionation techniques. As will be discussed below, many studies have begun to characterize gene transcription programs in response to viruses, have identified novel anti-viral proteins and regulators of interferon production and have experimented with novel approaches to treatment of viral infection.

The study of interferons (IFN) is one of the oldest known family of proteins with anti-viral properties. They are produced and released in response to pathogens, such as viruses and bacteria, and function in establishing an anti-viral state in host cells and activating immune cells (for review see^[1]). Type I interferons in humans include IFN- α , IFN- β , IFN- ϵ , IFN- κ and IFN- ω and are classified as such by their ability to bind the IFNAR1-IFNAR2 interferon receptor complex^[2]. IFN- γ is a type II interferon and signals through the IFNGR1-IFNGR2 receptor complex. A third class of interferons, type III, has been proposed and would likely contain IFN- λ 1, - λ 2 and - λ 3, which are also known as interleukin-29 (IL-29), IL-28A and IL-28B, respectively, and bind IFNLR1 (also known as IL-28 receptor- α , IL-28R α) and IL-10R β ^[3]. Effects of interferons are numerous and depend on downstream signaling pathways. The canonical activation of Janus-Kinase-Signal Transduction Activator (JAK-STAT) signalling^[4], for example, induces a variety of interferon-stimulated genes (ISGs) of which some have known anti-viral activities. Activation of mitogen-activated protein kinases^[5] has also been shown to have anti-viral as well as anti-proliferative effects. In contrast, phosphatidylinositol 3-kinase activation^[6] induces cell proliferation and increased protein synthesis (for review see^[7]). Autophagy has also been described as an inducer of interferon^[8,9] as well as being induced by interferons^[10,11]. The interactions and cross-regulation of these pathways are complex and are not well defined but overall, the ability of the host to

mount an effective interferon response typically plays a significant protective role against viral pathogenicity.

Regulation of the interferon signalling pathway is influenced by multiple cellular regulatory systems including phosphorylation, ubiquitination and miRNA silencing. In addition, viral components such as viral proteins and viral RNA can also significantly impact interferon production by the infected host cell. Systems biology approaches have substantially contributed to understanding the interactions of these various regulatory networks, the overall outcome of their actions, and their impact on respiratory virus replication. For example, it is becoming increasingly popular to combine various omics technologies such as transcriptome and proteomic screens with functional validation using techniques such as siRNA screens, pPCR and microscopy imaging.

REGULATION OF INTERFERON INDUCTION

Activation of viral pattern recognition receptors

Innate immune responses are initially triggered in response to viral infection through the recognition of highly conserved pathogen association molecular patterns (PAMPs). In terms of RNA viruses this typically involves activation of RIG-like (RLR), Toll-like (TLR) and Nod-like receptors (NLR) in the cytoplasm and at membranous surfaces such as the plasma membrane, endosomes and endoplasmic reticulum. A major outcome of RLR and TLR activation is the production of interferons. This induction, and its regulation, will be the focus of this review (summarized in Figure 1).

Coordination of antiviral responses at the mitochondrial outer membrane

An important event following RLR activation consists

of the formation of mitochondrion-centric anti-viral signalling complexes that regulate interferon and NF- κ B signalling cascades and subsequent immune responses. The mitochondrial anti-viral signaling protein (MAVS)/virus-induced signaling adaptor/interferon-beta promoter stimulator protein 1/Cardif protein is central to this process. Located at the outer mitochondrial membrane, it acts as a scaffolding protein that interacts with a variety of different host proteins that regulate downstream signalling pathways. There are many activators and facilitators of MAVS-mediated signalling and some of the most recently discovered ones include retinoic acid inducible gene I (RIG-I), nucleotide-binding oligomerization domain, leucine rich repeat containing X1 (NLRX1), MITA/Stimulator of interferon genes protein^[12], Tom70^[13], interferon-induced protein with tetratricopeptide repeats 3 (IFIT3)^[14], C1qA^[15], tumor necrosis factor receptor associated factor (TRAF) proteins^[16] and UXT-V1^[17]. The formation of MAVS-mediated complexes can subsequently lead to the recruitment of tank binding kinase (TBK1) and inhibitor of nuclear factor kappa-B kinase (IKK ϵ). However, this process is also carefully controlled through recruitment of negative regulators such as Ezh2^[18], Mfn2^[19], SEC14L1^[20] and Wnt/beta-catenin (WNT/CTNNB1) signalling^[21]. MAVS has also been described to associate with the endoplasmic reticulum^[12, 22-24], peroxisomes^[22], and autophagosomes^[25], although the outcome of these events are beyond the scope of this review. For further details we direct readers to a review by Belgnaoui^[26]. Overall, MAVS-interacting partners influence the extent of activation or inhibition of downstream interferon and NF- κ B anti-viral pathways.

Activation of interferon regulatory factors

RLR and TLR activation culminate in the phosphorylation, activation and nuclear translocation of various IRF transcription factors. Two well-known factors are IRF3 and IRF7, which can be activated by kinases TBK1, IKK ϵ , TAK1, and interleukin-1 receptor-associated kinase. This activation is carefully controlled through ubiquitin-mediated degradation of TBK1, which can be negatively regulated by tripartite motif containing 11 (TRIM11)^[27], ring finger protein 11 (RNF11)^[28] and thyroid receptor-interacting protein^[29]. Interaction with other molecules such as TRAF3, DDX3 [(DEAD (Asp-Glu-Ala-Asp) box polypeptide 3)]^[30] and nef-associated protein 1^[31] can also modulate downstream signalling. Interestingly, a recent study using triple IRF3/IRF5/IRF7 knockout mice^[32] demonstrated a formerly unappreciated role of IRF5 in interferon induction in myeloid dendritic cells. Genome-wide IRF1 binding sites have also been characterized in primary monocytes^[33]. Overall, the IRF family members are essential mediators of interferon signalling in response to RNA viral infection.

Other regulators of interferon production

Numerous other proteins have been described in regulating interferon production including activators Gab1^[34]

and suppressors protein tyrosine phosphatase 1^[35], forkhead box protein O3^[36], and toll/interleukin-1 receptor domain containing adaptor molecule 2 (TRIF) degradation^[37]. Several E3 ligases promote interferon signalling such as Pellino1^[38], TRIM25^[39], TRIM32^[40] and Riplet^[41]. Other E3 ligases have been characterized with a negative regulatory role in interferon production, such as Smurf1^[42], RNF125^[43], disintegrin and metalloproteinase domain-containing protein 15^[44], TRIM38^[37], TRIM11^[27] and TRIM21^[45]. Finally, several deubiquitinases appear to negatively regulate interferon responses, for example OTUB1^[46] and UCHL1^[47]. In addition, miRNAs are emerging as important regulators of interferon-mediated anti-viral responses such as miR-155^[48], miR-21^[49,50], miR-146^[51] and miR-4661^[52].

JAK-STAT signalling

Secreted type I interferons bind to interferon receptors at the cell-membrane and induce the janus activated kinase-signal transducer and activator (JAK-STAT) pathway. The bound receptor activates self-catalyzed kinase activity and causes phosphorylation, dimerization and nuclear translocation of STAT proteins. Ubiquitination has also been demonstrated to negatively regulate this pathway, for example, by ubiquitinating JAK1^[53] and STAT1^[54,55] as well as through binding of suppressor of cytokine signaling and protein inhibitor of activated STAT proteins, which recruit E3 ligases^[56]. In addition, mir-19a has been identified as a JAK-STAT regulator^[57].

ISG-induced gene transcription

There are many different interferon transcriptional programs that depend on factors such as the receptor and JAK isoforms, as well as the type of STAT dimer^[58] that are induced. These in turn are dependent on the stimulus, species, cell type, and co-stimuli. Because of this complexity, the study of interferon-stimulated gene (ISG) transcription patterns has benefited greatly from omics studies and has begun to provide powerful insights into the effects of interferons on host transcription. The response to interferon-gamma, for example, has been a source of recent interest and has been demonstrated to regulate ISGs at both the mRNA^[59] and miRNA level^[59,60]. A few specific miRNAs that have been identified as interferon regulators include miR-203^[61] and miR-9^[62]. Genome-wide DNA-binding sites for STAT1 have also been characterized using ChIP-Seq^[63]. Many quantitative proteomic studies have also identified altered expression patterns of interferon-induced proteins upon various stimuli, especially after viral infection; some of these genes have also been found to be dependent upon NF- κ B signalling^[64].

Microarrays and quantitative proteomics: Identifying global viral-induced alterations to the host response

A variety of models have been used to study the induction of innate immune pathways following virus infection, including epithelial cells, productive and abortive

Table 1 For example references

	Cell type	Proteomics	Genomics
Respiratory syncytial virus	Epithelial cells	[95-98]	[99]
	Macrophages	-	[65,100]
	Cord blood	-	[101]
Coronavirus	Epithelial cells	[79,80,102-104]	[76-78]
	Pro-monocytes	-	-
Influenza	Macrophages	[70,73,105,106]	[110]
	Epithelial cells	[71, 72, 107]	[111]
	Mice	[108]	[112,113]
	Ferrets	-	[114,115]
	Macaques	[109]	[112,116]
Reovirus	Epithelial cells	[117-120]	[64]
	Myocytes	[119]	-
	Mice	-	[121]
Rhinovirus	Epithelial cells	-	[74,122,123]
	Dendritic cells	[66]	-
	Human nasal cells	-	[75]

infections in macrophages^[65], dendritic cells^[66] and animal models (see Table 1). Microarrays have been particularly popular for these studies due to its ability to provide a comprehensive analysis of the entire cellular genome with relatively sensitive quantification of gene expression (see^[67] for review of microarray technologies). Quantitative proteomic studies have also been important in validating these findings at the protein level and have been useful, for example, in the search for biomarkers. Many respiratory viruses, such as influenza^[68-73], reovirus, and rhinovirus^[74,75], demonstrate a robust activation of antiviral pathways and pro-inflammatory cytokines. Both genomic and proteomic analyses have demonstrated hubs of gene and protein induction that are induced by key transcriptional factors such as IRFs, STAT proteins, NF- κ B and JNK. On the other hand, genomic profiling of respiratory syncytial virus^[65] and pathogenic coronaviruses such as severe acute respiratory syndrome (SARS) and EMC strains have been reported to elicit weaker innate immune responses^[76-78]. The absence of interferon signaling has also been recapitulated in several proteomic viral-host studies^[79-81].

Analyses of microRNA expression during influenza have recently begun to emerge in a variety of models including respiratory epithelial cells^[82-85], human blood^[86], immune cells^[87-89] and lung tissue in animal models^[90,91]. Collectively these have identified roles for miR-18a^[86,92] and miR-223^[86,93] in negative regulation of STAT3, mir-29 in IFN- γ 1 production^[89], and miR-449b as a positive regulator of IFN- β production^[85]. miR-23b has also been identified as a novel anti-viral molecule that is induced through RLR signaling during rhinovirus infection^[94].

Strain differences: One of the fundamental questions of virology revolves around deciphering factors of pathogenesis. Hence, some studies have attempted to identify pathways that are differentially altered by pathogenic viral strains compared to less pathogenic strains. Influenza has been particularly well studied in this respect and several host factors have been identified that are unique to the replication of strains such as the patho-

genic avian H5N1, the p2009 swine flu and the 1918 strain^[69,70,108,124]. However, rather than inducing radically different cell responses, many different influenza strains have been found to activate surprisingly similar immune signatures (reviewed in^[125]). It was, instead, the degree and timing of activation and resolution^[125] of these pathways that was found to significantly impact the severity of disease^[126]. Dysregulation of the host inflammatory response in particular is a major determinant of influenza pathogenicity and is influenced by both viral and host factors^[127]. Different rhinovirus strains, for example type 14 and 1B^[128,129], have also been demonstrated to have different abilities to attenuate interferon production and secretion from epithelial cells. This effect has been attributed to the inhibition of IRF3 dimerization^[74,129] but the viral mechanism leading to this is unknown.

Cell type differences: Cell types have also been demonstrated to express different basal levels of interferon and hence, have different innate susceptibilities to viral infection^[130,131]. For example, a direct comparison of interferon signaling between primary bronchial lung epithelial cells and the A549 continuous alveolar epithelial cell line suggested differences between either primary and cancer cell lines and/or epithelial cells of different origins in the lung^[72]. Additionally, different cell types have been shown to influence the degree of interferon activation after reovirus infection^[132].

Correlation of interferon signaling with pathogenesis: Generally interferon production is considered protective against viral infections. It has been shown numerous times that cells that produce less interferon, such as Vero cells, are more susceptible to viral infection and produce high titers of the virus^[133]. The extent of interferon inhibition by the influenza non-structural (NS)-1 protein^[134] and RSV NS1 and NS2 proteins^[135,136] has also been extensively studied and correlates negatively with pathogenicity^[137,138]. Similarly, models in which interferon signaling has been disrupted, such as by deleting IFNR, can produce high viral titers^[139] and display increased lung tissue pathology^[140]. Conversely, type I interferon signaling has also been shown to contribute to secondary bacterial infections^[141,142]. In some studies the degree of interferon induction correlated positively with the degree of pathogenicity. For example, the reovirus T3D strain is considered more pathogenic than the T1L strain, but the T3D strain was found to induce higher levels of innate immunity proteins^[64,117,118]. The role of interferons in these situations is not currently understood.

Altered innate immune responses in chronic lung diseases: Many studies with rhinovirus have investigated differences in the immune response between healthy and non-healthy donor cells. In one study, infection of chronic obstructive pulmonary disorder (COPD) epithelial cells induced higher transcription levels of cytokines, chemokines, RNA helicases, interferons and increased apoptosis compared to infection of healthy control cells. In addi-

tion, basal levels of several antiviral signalling pathways were altered in COPD patients^[128]. Similarly, asthma-derived epithelial cells also showed altered expression of several immunity genes both at basal levels and during rhinovirus infection^[122,143]. Modulation of rhinovirus-induced host responses has also been investigated in the presence of Echinacea extracts and cigarette smoke^[123].

Core innate immune responses shared by multiple respiratory viruses: While many studies that have been discussed in this review have focused on identifying global host responses towards a single virus, a few studies have directly compared viruses from multiple families. For example, Smith *et al.*^[144] identified common gene networks that were activated in response to seven respiratory viruses: influenza A virus, respiratory syncytial virus, rhinovirus, SARS-coronavirus, metapneumonia virus, coxsackievirus and cytomegalovirus^[144]. Among those responses were pathways associated with a general immune response including interferon signalling^[144]. A second study also identified core immune responses to four respiratory viruses including apoptosis induction, endoplasmic reticulum stress and interferon signalling^[98]. In addition several host interferon-induced proteins have been tested against multiple families and strains of viruses. For example, IFIT1^[145], Interferon-inducible transmembrane (IFITM) proteins^[146], ISG15^[147,148] and Viperin^[149-152] protect against multiple virus families.

Overall, microarrays and quantitative proteomics have allowed sensitive and comprehensive analyses of the host genome, and have contributed substantially to understanding the types and kinetics of signaling pathways that are activated upon viral infections.

Identification of host-virus interactions and novel restriction factors

Interactomes, viral-mediated antagonism of interferon signaling: As many viruses encode interferon-antagonizing proteins, there has been significant interest in defining their interacting partners in the host cell. Several studies have also been undertaken to identify host proteins that recognize dsRNA and 5'pppRNA. This has, for example, led to the discovery and characterization of the IFIT family^[145] and their role anti-viral innate immunity.

Influenza: The influenza NS1 protein is a well-known antagonist of interferon signalling and is able to interfere with multiple anti-viral pathways. Viral-host studies have identified additional host proteins that interact with the influenza NS1 protein, using either plasmid-based expression of NS1^[153-155] or during whole virus infection^[153,156]. Collectively, the integration of multiple interactome studies has allowed networks such as Flu-Pol to be established which provide the basis for comparing differences and commonalities between influenza strains and cell types and are useful for targeted drug design.

RSV: RSV proteins NS1 and NS2 strongly inhibit IFN α/β by preventing the phosphorylation of the IFN regulatory factor-3^[157,158] as well as activation of NLRX1 and RIG-I^[35]. Additionally, the RSV NS1 protein inter-

feres with interferon signaling through interaction with an elonginC-cullin2 E3 ligase complex that ubiquitinates and degrades STAT2^[97,159]. RSV NS1 and NS2 have also been shown to alter miRNA expression, which can contribute to antagonism of interferon and NF- κ B responses^[160].

Coronavirus: In studies with coronaviruses, it has been previously proposed that the viral deubiquitinase, PLpro, plays a major role in suppressing interferon-alpha induction. In support of this idea, Li *et al.*^[161] recently demonstrated that PLpro overexpression mediated the down-regulation of mitogen-activated protein kinase and up-regulation of the ubiquitinase Ubiquitin ligase (UBC E2-25k). The open reading frame 6 protein has also been shown to attenuate antiviral responses by sequestering host nuclear impact factors including STAT1^[162], vitamin D receptor, cyclic AMP-responsive element-binding protein 1, mothers against decapentaplegic homolog 4, p53, Epas I and Oct3/4^[163].

Rhinovirus: Despite induction of interferon gene transcription, rhinovirus (type 14) infection can strongly attenuate interferon secretion from epithelial cells. This effect has been attributed to the inhibition of IRF3 dimerization^[74,129] but the viral mechanism leading to this is unknown. In contrast, rhinovirus 1B readily stimulated interferon production in bronchial smooth muscle cells^[164], suggesting different interferon regulation between strains and/or cell types.

Reovirus: The degree of IFN- α/β induction after reovirus infection has been attributed to both host and viral factors but is not well understood. However, repression of interferon signaling has been mapped to the *M1*, *L2* and *S2*^[152,165] genes.

Knockdown/Knockout studies: siRNA technology has been important in testing functional effects of interferon-induced proteins. Both whole genome siRNA screens, and individual knockdown experiments have discovered and validated anti-viral effects of many including interferon-induced proteins such as the IFITM1-3 proteins^[166], IRF3 and IRF2 (Shapira), ISG15^[147] and Viperin^[167]. In contrast, several interferon pathway members have been assigned pro-viral functions such as MxB^[168] and IFIT2^[156,168].

Knock-out animals have also underscored the protective effects of interferon signaling during respiratory virus infections, for example, ISG15^{-/-}^[147,169], IFNAR^{-/-}^[170], and MxA^{-/-}^[171]. In addition to its role in innate immunity, interferons have also been demonstrated to have profound effects on the adaptive immune system, for example, by priming CD⁺ T-cells during influenza infection^[172] and inhibiting neurotropism of reovirus infection^[173,174]. Although discussion of the effects of interferon on whole host immunity is beyond the scope of this review, further discussion can be found in several comprehensive reviews^[175,176].

Collectively, these studies have provided fundamental insights into how cells respond to RNA virus infection and have highlighted the importance of interferon induction in restricting virus replication and activating an appropriate host immune response. Many new and unex-

pected regulators of interferon signalling have been discovered and have demonstrated how multiple anti-viral networks interact such as ubiquitin-mediated regulation of interferon signalling molecules. As large omics studies move forward, it will become possible to compare and draw connections between anti-viral networks that are induced by different viruses.

FUTURE DIRECTIONS: INTERFERON SIGNALING AS A BROAD-SPECTRUM ANTI-VIRAL PATHWAY?

Using interferons therapeutically has been most extensively studied in models of hepatitis. However, it has also shown some promise in protecting against a variety of other virus families, including the respiratory viruses discussed in this review. For example, exogenous IFN- α treatment has proven effective against influenza^[177-179], rhinovirus^[128,180] and coronavirus^[181-183]. Interferons are also important in protecting against reovirus infections^[184]. The role of type III interferons is generally not as well understood as type I but may also afford protection against respiratory viruses^[185].

Interferons can also be endogenously elicited through a variety of RLR and TLR agonists. 5'pppRNA, for example, is a well-known and potent RIG-I agonist and has been demonstrated to protect against both RNA and DNA viruses, including Dengue virus, influenza, hepatitis C and human immunodeficiency virus-1^[186]. Similarly, TLR agonists such as dsRNA^[187,188] or inosine-containing ssRNA^[189] have been shown to protect against coronavirus, influenza, and respiratory syncytial virus infections in mice. A commercial compound, Arbidol, has also had some success in neutralizing various respiratory viruses such as influenza, rhinovirus, adenovirus, coxsackie virus and RSV^[190]. Additional small molecules that induce type I interferons have recently been identified using high-throughput screens^[191,192]. Alternatively, inhibiting antagonists of interferon signaling can also boost the production of interferon. As discussed above, these antagonists can either be host molecules or viral proteins, and inhibitors to each have been described^[193]. Interestingly, ribavirin treatment of RSV-infected epithelial cells was shown to enhance interferon-stimulated gene expression^[194] and treating RSV-infected macrophages with lovastatin was shown to blunt pro-inflammatory cytokine gene expression^[100]. These therapies may have potential for broad-spectrum anti-viral properties.

Despite successfully treating some viral infection with interferon, it has also been noted that interferon stimulation can increase lung inflammation. Many gene array studies have also positively correlated pathogenicity or cytopathology with the induction of interferon and/or inflammatory genes. For example, the severe pathology of the 1918 influenza pandemic and of H5N1 (bird flu) viruses has been attributed to a "cytokine storm" (reviewed by^[125]). It is therefore important to identify the mecha-

nisms behind interferon-dependent protection against viruses. Numerous studies, for example, have suggested that MxA is a major effector of IFN- α pre-treatment against influenza^[195-197]; other newly identified interferon-induced anti-viral proteins include IFITM proteins^[146,198], ISG15^[147] and Viperin^[149-152]. It may also be useful to combine interferon treatment with anti-inflammatory compounds such as curcumin^[199-201], resveratrol^[202], S1P agonists^[203,204], COX-2 inhibitors^[205,206] and statins^[100,207].

CONCLUSION

The study of immune responses to viral infection has benefited greatly from viral proteomic studies. However, knowledge of proteomic subsets is still limited and future studies could provide more detailed insight into the dynamics of protein localization, activity and regulation through post-translational modifications during virus infection. Based on current technologies and identified networks, it may be beneficial to also investigate alterations of the phosphoproteome, ubiquitome, and the activity of proteasomes after viral infection. The development of broad-spectrum anti-virals has also shown some potential and could benefit from comparative analyses of multiple viruses.

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