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Review

Transcriptional Regulation of Antiviral Interferon-Stimulated Genes

Wenshi Wang,[1] Lei Xu,[1] Junhong Su,[2]
Maikel P. Peppelenbosch,[1] and Qiuwei Pan[1,*]

Interferon-stimulated genes (ISGs) are a group of gene products that coordinately combat pathogen invasions, in particular viral infections. Transcription of ISGs occurs rapidly upon pathogen invasion, and this is classically provoked via activation of the Janus kinase/signal transducer and activator of transcription (JAK–STAT) pathway, mainly by interferons (IFNs). However, a plethora of recent studies have reported a variety of non-canonical mechanisms regulating ISG transcription. These new studies are extremely important for understanding the quantitative and temporal differences in ISG transcription under specific circumstances. Because these canonical and non-canonical regulatory mechanisms are essential for defining the nature of host defense and associated detrimental proinflammatory effects, we comprehensively review the state of this rapidly evolving field and the clinical implications of recently acquired knowledge in this respect.

Host Antiviral Defense

IFN-mediated innate immune response forms a forward line of cell-autonomous defense against pathogens. Virus invasion (e.g., the presence of single-stranded RNA in endosomes or cytosolic double-stranded RNA) triggers the host cells to recognize the infection through pattern recognition receptors (PRRs), that in turn mediate the production of IFNs [1]. The thus-released IFN molecules bind to cell-surface receptors and initiate signal transduction prominently involving the Janus kinase/signal transducer and activator of transcription (JAK–STAT) pathway. This activates the transcription of hundreds of so-called ISGs that are the effectors of cell-autonomous antiviral defense. Representative and well-studied ISG members with specific or broad antiviral activities include RIG-I, MDA5, MX2, IRF1, IRF3, IRF7, IRF9, IFITM3, ISG15, and OASL [2]. ISGs act at different stages of the viral life cycle, from entry, replication, assembly to release. This leads to a remarkable antiviral state that provides adequate cellular immunity against positive-, negative-, and double-stranded RNA viruses, DNA viruses, and even intracellular bacteria and parasites.

Although the JAK–STAT pathway plays key roles in regulating ISG transcription, a far more complex cell signaling network with both canonical and non-canonical mechanisms is involved [3]. The signaling strength, kinetics, and specificity of regulatory pathways on ISG transcription are modulated at various levels by distinct mechanisms operating in conjunction. Understanding the different mechanisms of ISG transcription and how their modes of action relate to clinically used antiviral medications will provide new insights into virus–host interactions and novel avenues for antiviral drug development. Therefore, we aim to comprehensively review the classical and non-classical mechanisms regulating ISG transcription with emphasis on their clinical implications.

Trends

Transcriptional regulation of ISGs defines the state of host anti-pathogen defense.

In light of the recently identified regulatory elements and mechanisms of the IFN–JAK–STAT pathway, new insights have been gained into this classical cascade in regulating ISG transcription.

A variety of non-canonical mechanisms have been recently revealed that coordinately regulate ISG transcription.

With regards to the adverse effects of IFNs in clinic, ISG-based antiviral strategy could be the next promising frontier in drug discovery.

[1]Department of Gastroenterology and Hepatology, Erasmus MC–University Medical Center and Postgraduate School Molecular Medicine, Rotterdam, The Netherlands
[2]Medical Faculty, Kunming University of Science and Technology, Kunming, PR China

*Correspondence:
q.pan@erasmusmc.nl (Q. Pan).

Classical Mechanisms of Regulating ISG Transcription: The IFN–JAK–STAT Pathway

Upon IFN binding to its cognate cell-surface receptors, a signal is transmitted through the membrane into the cell via the JAK–STAT pathway, leading to rapid transcriptional activation of ISGs [4]. Decades of dedicated efforts have elucidated this classical regulatory network, as outlined here (Figure 1).

IFNs and Their Receptor-Dependent Regulation

Genes encoding IFNs and their receptors have been duplicated extensively throughout vertebrate evolution, indicating substantial evolutionary pressure on this system in combating pathogens [5]. Until now >20 distinct IFN genes/proteins have been identified. Based on the type of receptor through which they signal, the multitude of different IFNs in mammalian

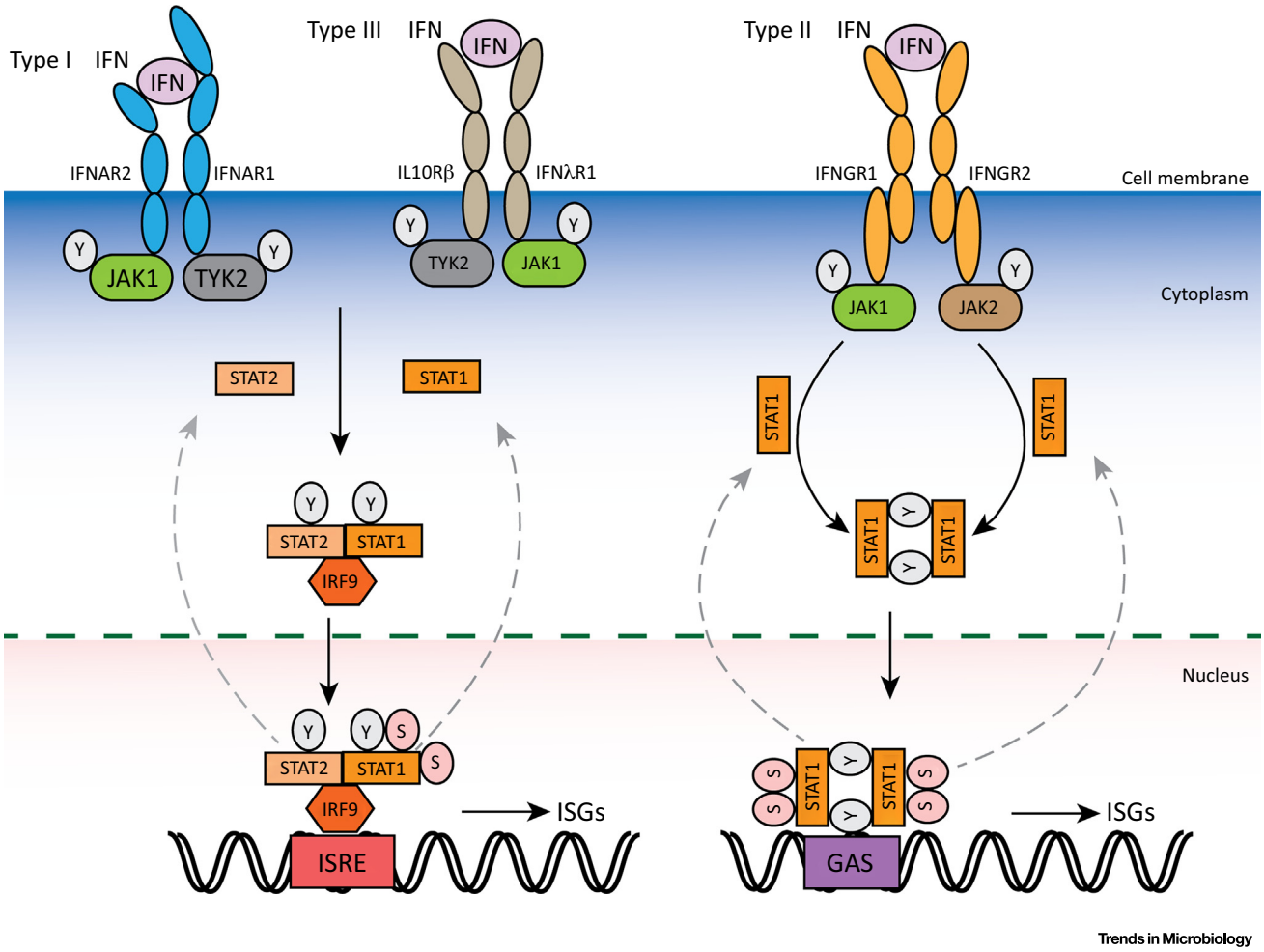

Figure 1. The Classical Interferon (IFN) Signaling Pathways in Regulating IFN-Stimulated Gene (ISG) Transcription. The three different classes of IFNs signal through their corresponding receptor complexes, leading to phosphorylation of preassociated Janus kinases. For type I and III IFNs, the phosphorylated Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) in turn phosphorylate the receptors at specific intracellular tyrosine residues. This leads to the recruitment and phosphorylation of signal transducers and activators of transcription 1 and 2 (STAT1 and STAT2) at specific tyrosine residues. STAT1 and 2 then recruit IRF9 to form the IFN-stimulated gene factor 3 (ISGF3). For type II IFNs, the phosphorylated JAK1 and JAK2 tyrosine kinases phosphorylate the receptors on tyrosines, leading to homodimerization of STAT1. Both ISGF3 and STAT1 homodimers translocate to the nucleus for further phosphorylation at specific serine residues of STAT1, thereby achieving full activation. Consequently, ISGs are transcriptionally activated by binding of ISGF3 and STAT1 homodimers to IFN-stimulated response elements (ISREs) and γ-activated sequence (GAS) promoter elements, respectively. Conversely, specific phosphatases in the nucleus dephosphorylate STAT1 and STAT2 to avoid excessive and detrimental responses.

genome are classified into three major types: I, II, and III. In humans, type I IFNs include IFN-α (which can be further subdivided into 13 different subtypes), IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-τ, and IFN-ω1–3. All type I IFNs bind to a common cell-surface receptor, the type I IFN heterodimeric receptor complexes comprising two subunits: IFN-α receptor 1 (IFNAR1) and IFN-α receptor 2 (IFNAR2). Unlike type I IFNs, there is only one type II IFN, IFN-γ. It has no marked structural homology with type I IFNs. IFN-γ binds to a different cell-surface receptor composed of two subunits: IFNGR1 and IFNGR2. The type III IFN family comprises four members: IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B), and IFN-λ4 (frameshift variant of IL-28B). They signal through the IFN-λ receptor (IFNλR) which is composed of two subunits: IFNλR1 (IL28Rα) and IL10Rβ.

Type II IFN signaling leads to STAT1 phosphorylation, followed by homodimerization, nuclear translocation, and DNA binding at γ-activated sequence (GAS) elements located within promoter regions of IFN-γ-induced genes. While both type I and III IFN signaling activate a similar intracellular JAK–STAT pathway to generate the transcription complex, ISGF3, that transcribes ISGs, they utilize distinct receptor complexes for signaling [6]. However, IFNAR is ubiquitously expressed in all nucleated cells, whereas IFNλR1 is only expressed on specific tissues/cells of epithelial origin [7], suggesting a selectivity of type III IFNs compared with type I IFNs.

For optimal activation, signaling through the IFN receptor complex depends on tyrosine phosphorylation, serine phosphorylation, and acetylation of IFN receptors (Table 1) [8–10]. Nevertheless, negative regulation is also essential for balancing its beneficial antiviral versus detrimental proinflammatory effects. Primarily, this is achieved by (i) phosphorylation-induced IFN receptor ubiquitination and degradation [11]; (ii) blocking the interaction between IFNAR and downstream signaling elements, such as the function of USP18, ISG15, and SOCS1 [12–16]; (iii) receptor-mediated ligand internalization/degradation [17]; and (iv) modulating cell-surface IFN receptor levels [18,19].

JAK Kinase-Dependent Regulation

The JAKs comprise four members, three of which (JAK1, JAK2, and TYK2) function in IFN signaling and are ubiquitously expressed [20]. They are preassociated with the corresponding IFN receptor. Upon IFN binding to the receptor, they become activated through close-proximity *trans*-phosphorylation (JAK1, $Tyr^{1022,1023}$; JAK2, $Tyr^{1007,1008}$; and TYK2, $Tyr^{1054,1055}$). Subsequently, activated JAKs phosphorylate the cytoplasmic regions of the receptor, generating docking sites for SH2 domain-containing proteins, in particular STAT1 and STAT2 [21]. Activation of JAK enzymatic activity also triggers negative feedback on antiviral immunity. Phosphatases, including T cell protein tyrosine phosphatase (TCPTP), and protein tyrosine phosphatases (PTP) 1B and CD45, are the most important negative regulators [22–25]. The SOCS-1 protein also negatively regulates this process through phosphorylation-mediated proteasomal degradation of JAK [26]. The key function of JAKs in cell signaling has made them ideal targets for controlling a range of autoimmune diseases. Several JAK inhibitors have been approved by the FDA or are in clinical trials for the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, and ankylosing spondylitis [27].

STAT-Dependent Regulation

There are seven STAT members in mammals, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. STAT1 and STAT2 are the most important STATs with respect to IFN signaling [2]. In response to IFNs, STAT1 is phosphorylated on Tyr^{701}, Ser^{708}, and Ser^{727}. These sites are all positively related to signaling transduction [28,29]. STAT2 acquires transcriptional activation upon tyrosine phosphorylation (Tyr^{690}). Conversely, serine phosphorylation (Ser^{287}) of STAT2 negatively regulates the IFN response [21,30]. Although JAKs play key

Table 1. Classical Polypeptide Modifications in the IFN–JAK–STAT Pathway.

	Modification site	Modification type[a]	Signal transduction	Refs
IFNAR1	Tyr^{466}	Phosphorylation	Activation	[125]
IFNAR1	Tyr^{512} and Tyr^{337}	Phosphorylation	Activation	[126]
IFNAR1	Ser^{535}, Ser^{539}	Phosphorylation	Inactivation	[11]
IFNAR1	Lys^{501}, Lys^{525}, and Lys^{526}	Ubiquitination	Inactivation	[11]
IFNAR2	Ser^{364}, Ser^{384}	Phosphorylation	Activation	[9]
IFNAR2	Lys^{399}	Acetylation	Activation	[9]
IFNGR1	Pro^{267}	ND	Activation	[127]
IFNGR1	Tyr^{440}	Phosphorylation	Activation	[128]
IFNGR1	^{270}LI^{271}	ND	Inactivation	[17]
IFNGR1	Tyr^{441}	Phosphorylation	Inactivation	[16,128]
IFNGR2	^{263}PPSIP^{267} and ^{270}IEEYL^{274}	ND	Activation	[10]
JAK1	$Tyr^{1022,1023}$	Phosphorylation	Activation	[21]
JAK2	$Tyr^{1007,1008}$	Phosphorylation	Activation	[21]
TYK2	$Tyr^{1054,1055}$	Phosphorylation	Activation	[21]
STAT1	Tyr^{701}	Phosphorylation	Activation	[129]
STAT1	Ser^{727}	Phosphorylation	Activation	[129]
STAT1	Ser^{708}	Phosphorylation	Activation	[28]
STAT1	Lys^{703}	SUMO-1 binding	Inactivation	[47]
STAT2	Tys^{690}	Phosphorylation	Activation	[30]
STAT2	Ser^{287}	Phosphorylation	Inactivation	[30]

[a]ND, not determined.

role in STAT1 phosphorylation and activation, other cellular factors are also required. Tyrosine kinase non-receptor 1 (TNK1) and retinoic acid-inducible gene I (RIG-I) potentiate dual phosphorylation of STAT1 at Tyr^{701} and Ser^{727} [31–33], whereas nuclear cyclin-dependent kinase 8 (CDK8) phosphorylates Ser^{727} of STAT1 [34,35]. Protein kinase C family members, PKC-δ or PKC-ε, mediate phosphorylation of STAT1 on Ser^{727} (no effect on STAT1 tyrosine phosphorylation) via the upstream phosphatidylinositol 3-kinase (PI3K)–Akt pathway [36–39]. Interestingly, stress signals can also induce phosphorylation of STAT1 (Ser^{727}) via the p38–MAPK pathway [40]. Because p38–MAP kinase inhibitors are well-tolerated and safe for humans, it is thus tempting to speculate that such inhibitors might be used to mitigate proinflammatory effects following IFN-γ therapy [41].

Evidently, phosphatase-dependent STAT1 dephosphorylation constitutes an important negative-regulatory event that is central in titrating the IFN response. The functional phosphatases include SHP-2 [42,43], the nuclear isoform of TCPTP, TC45 [44], and SHPTP1 [45]. Phosphatase dysregulation has been reported in cancers and autoimmune disorders, thus representing potential therapeutic targets [46]. A small ubiquitin-related modifier 1 (SUMO-1) was also reported to conjugate at Lys^{703} of STAT1 to inhibit signal transduction [47]. Thus, a plethora of molecular mechanisms can balance the IFN response through acting on STAT1.

IRF9 is a major DNA binding component of the ISGF3 complex. IRF9 alone binds to DNA and recognizes the specific promoter elements denoted as IFN-stimulated response elements (ISRE), but has no transcriptional activity. Upon DNA binding, IRF9 provides specific protein–DNA interaction sites for STAT1 and STAT2. Activated STAT1 and STAT2 bind to the ISRE region together with IRF9 to exert strong pro-transcriptional activity [48]. Theoretically, IRF9 (as

part of the ISGF3 complex) is only involved in regulating ISG transcription downstream of type I and III IFN signaling. However, IFN-γ-induced ISG activation and the antiviral state were severely impaired in the absence of IRF9, indicating that IRF9 may also be involved in type II IFN signaling [49,50]. More interestingly, IFN-γ pretreatment induces high levels of IRF9, which serves as an important subunit of the latent precursor to ISGF3. In this way, IFN-α and IFN-γ synergize to induce the formation of ISGF3 complex, leading to much stronger ISG transcription [51].

Regulation of ISGs at the Transcriptional Level

In the case of type I and III IFNs, ISGF3 is the predominant transcriptional factor binding to ISREs within the promoter region of ISGs; whereas for type II IFN homodimers or heterodimers of STATs are the determinant of binding to GAS elements. However, this is a simplified model and other regulatory elements are also involved (Figure 2).

Chromatin Modulators

Histone octamers bind to DNA and organize chromatin into higher-order nucleosomes, prohibiting transcription factor binding and gene expression [52]. As a consequence, the induction of ISGs by IFNs requires chromatin remodeling. The condensed chromatin needs to be transformed into a more relaxed structure. In humans, the nucleosome remodeling complexes BAF and PBAF prime ISG promoters by utilizing ATP-derived energy to maintain chromatin in a constitutively open conformation, allowing fast and potent induction of ISGs after IFN exposure [53–56]. Histone acetylation and deacetylation are also essential in chromatin modulation. These reactions are typically catalyzed by enzymes with histone acetyltransferase (HAT) or histone deacetylase (HDAC) activity. HAT activity transforms chromatin into a more relaxed structure, while HDAC activity organizes chromatin into higher-order nucleosomes. Therefore, the HAT family members, including p300/CBP and GCN5, are essential for

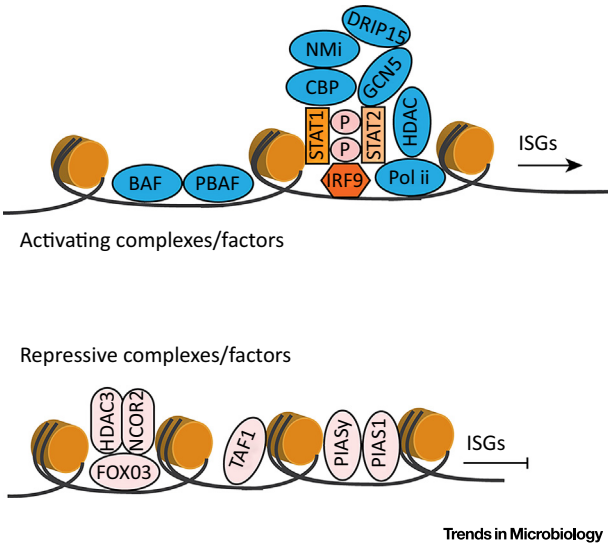

Figure 2. Transcriptional Regulation of IFN-Stimulated Genes (ISGs) Involves Chromatin Remodeling and Various Coactivators and Corepressors. Upon IFN stimulation, IFN-stimulated gene factor 3 (ISGF3) or STAT1 homodimers bind to ISG promoter regions, recruiting various chromatin remodeling factors and transcriptional coactivators. These factors include the nucleosome remodeling complexes BAF and PBAF, p300/CBP and GCN5 histone acetyltransferase (HAT), histone deacetylase (HDAC), minichromosome maintenance 3 and 5 (MCM3 and MCM5), N-Myc interactor (NMi), and DRIP150 (a subunit of the multimeric mediator coactivator complex). Consequently, the condensed chromatin transforms into a more relaxed structure to facilitate the transcription of ISGs. Conversely, corepressor factors can inhibit ISG transcription either via the facilitation of a closed chromatin configuration or by interfering with the recruitment of STAT1 or ISGF3 to ISG promoters. Abbreviation: Pol II, RNA polymerase II.

transcriptional activation of ISGs [57,58]. HATs are positive regulators of transcription in general. However, HDAC activity is also essential for transcriptional induction of ISGs [59–64]. HDAC activity has been reported to be required for recruiting RNA polymerase II to the promoters of ISGs [65], although how HDACs regulate the transcriptional activation of ISG remains unclear. In addition, the FOXO3 and PI3K/AKT pathways coordinately modulate chromatin structure. FOXO3, together with nuclear corepressor 2 (NCOR2) and HDAC3, forms a ternary complex to facilitate a closed chromatin structure, thereby limiting ISG transcription under basal conditions. However, type I IFN can activate the PI3 K/AKT pathway, which in turn leads to FOXO3 degradation and ISG transcription [66].

Coactivators and Corepressors

Particular coactivators or corepressors mediate the transcription of ISGs via the interaction with ISGF3 or STAT1 homodimers. The coactivators, such as MCM5 (minichromosome maintenance) and MCM3 protein complex [67,68], N-Myc interactor (NMi) [69], and DRIP150 [70], facilitate the transcriptional activation of ISGs. Conversely, corepressors, such as TAF-1 [71] and the protein inhibitor of activated STAT proteins (PIAS1 and PIASγ [72,73]), suppress the formation of transcription complexes on ISG promoters to limit transcription. Recently, four previously unrecognized regulatory factors (ETV6, ATF3, LYN, and TBK1) of ISG transcription have been identified [74]. These efforts have led to a more comprehensive understanding of ISG transcription.

Non-canonical Regulation of ISG Transcription

All three types of IFNs signal through the JAK–STAT pathway to elicit antiviral activity. Nevertheless, type II IFN is thought to do so only through STAT1 homodimers, whereas type I and III IFNs activate both STAT1 and STAT2 to form ISGF3 together with IRF9. However, accumulating evidence highlights a far more complex process of activation and function beyond this classical theory. The heterogeneity of the regulatory mechanisms of ISG transcription has been recently highlighted. A substantial fraction of these cascades have little or no link to STAT1/2 and ISGF3, paralleling the existence of non-canonical mechanisms outside the JAK–STAT axis [74]. We review here both JAK–STAT axis-dependent and -independent non-canonical mechanisms of ISG transcription (Figure 3).

Non-canonical ISGF3 Complex

To date, three different forms of non-canonical ISGF3 complexes have been identified, including $ISGF3^{II}$, the STAT2–IRF9 complex, and unphosphorylated ISGF3 (U-ISGF3). IFN-γ treatment has been reported to lead to the formation of a new ISGF3 complex ($ISGF3^{II}$) containing phosphorylated STAT1, unphosphorylated STAT2, and IRF9 [75]. In the absence of STAT1, STAT2 was found to interact with IRF9 to form an ISGF3-like complex to mediate specific ISG transcription [76]. Finally, following continuous exposure to low levels of exogenous IFNs, U-ISGF3 formed by IFN-induced IRF9 and unphosphorylated STAT1 and STAT2 can lead to increased expression of a subset of ISGs [77,78].

STAT5–CrkL Complex

Apart from STAT1 and STAT2, STAT5 is also involved in type I IFN-induced ISG transcription. STAT5 interacts constitutively with IFN receptor-associated TYK-2. Upon type I IFN stimulation, STAT5 is phosphorylated on both tyrosine and serine sites, thus acting as a docking site for the SH2 domain of CrkL. CrkL and STAT5 then form a complex that translocates to the nucleus and binds to GAS elements to activate type I IFN-dependent gene transcription [3,79].

IRFs

IRF1 has been shown to function as a transcription factor. The DNA sequences (IRF-E site) recognized by IRF1 overlap with the ISRE, and in this way IRF1 induces a subset of ISGs. IRF1

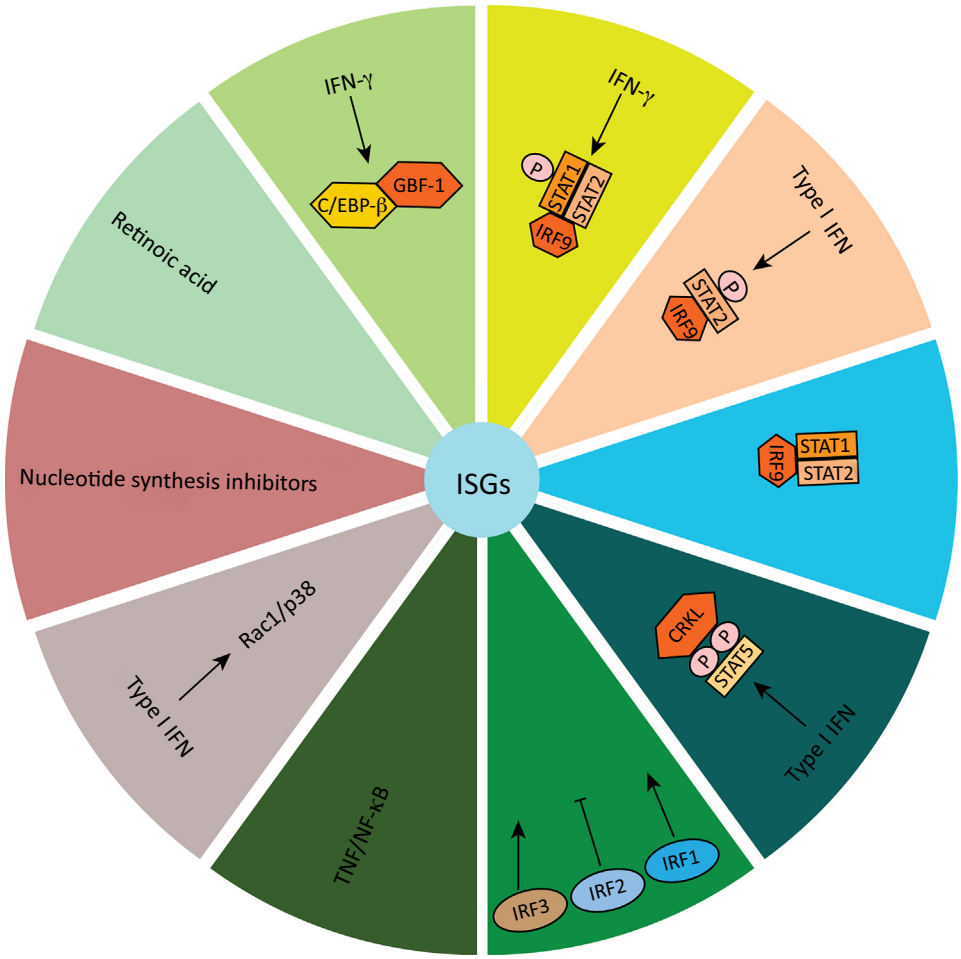

Figure 3. Non-canonical Mechanisms Regulating ISG Transcription. Non-canonical mechanisms both within and outside the IFN–JAK–STAT axis are summarized. Together with canonical mechanisms, they coordinately regulate ISG transcription, thus defining cellular defense status against pathogen invasion.

can also enhance the levels of both total and phosphorylated STAT1 to amplify ISG transcription via the JAK–STAT pathway [80]. Conversely, IRF2 binds to the same IRF-E site to repress IRF1-induced transcription [81,82]. Upon virus infection, IRF3 is activated and cooperates with NF-κB and ATF-2/c-Jun to form a transcriptionally active enhanceosome complex on the IFN-β promoter. Newly synthesized IFN binds to cognate receptors to activate ISG transcription via the JAK–STAT pathway. Importantly, IRF3 has also been reported to directly induce a subset of ISGs in an IFN-independent manner through ISREs in their promoters [83,84].

Crossregulation between TNF and IFN Signaling

It is well documented that, when combined with TNF-α, type I or II IFN operates cooperatively to induce antiviral ISG expression, and TNF-α and IFN exert synergistic antiviral effects [85–88]. TNF-α has been reported to inhibit hepatitis C virus (HCV) infection-caused degradation of IFNAR2, thus maintaining IFN signaling and ISG expression [88]. TNF-α alone can already moderately induce the transcription of a subset of ISGs [85,86]. This is mainly through the NF-κB protein complex, a key downstream element of TNF-α signaling. This may explain the documented antiviral activity of TNF-α on different viruses [87,89–91].

Rac1/p38 Pathway

Rac1/p38 MAP kinase signaling regulates IFN induced ISG transcription. Type I IFN treatment results in activation of Rac1 and its downstream effectors including MAP kinase kinase 3 (MKK3), MAP kinase kinase 6 (MKK6) [92,93], and cytosolic phospholipase A2 [94,95]. In turn, these events provoke phosphorylation and activation of the p38 MAP kinase, an important mediator of the inflammatory response [96]. p38 MAP kinase activation leads to downstream MapKapK-2 and MapKapK-3 activation, contributing to type I IFN-dependent transcriptional regulation of ISGs. However, Rac1/p38 MAP kinase signaling is not required for IFN-dependent phosphorylation of STAT1 at both sites (Ser^{727} and Tyr^{701}) and has no impact on the formation of the ISGF3 complex [97,98]. Histone phosphorylation and chromatin remodeling are possible mechanisms employed by this cascade [97]. Many immune-relevant gene products are subject to post-transcriptional regulation by this signaling [99], but ISGs have not been investigated in this respect.

IFN-γ-Activated Response Element (GATE)

In response to IFN-γ, two factors bind to a unique IFN-γ-activated response element known as GATE – these are the CCAAT/enhancer binding protein C/EBP-β and the GATE binding factor GBF-1. MEK1, ERK1, and ERK2 are the upstream kinases necessary to activate C/EBP-β in response to IFN-γ [100]. This novel IFN-γ-activated pathway promotes ISG expression in a STAT1- but not JAK1-dependent manner.

Nucleotide Synthesis Inhibitor

Purine and pyrimidine nucleotides are the major cellular energy carriers and are subunits of nucleic acids. Nucleotides can be synthesized *de novo* through a series of enzymatic reactions or are recycled through salvage pathways. Interestingly, purine and pyrimidine synthesis inhibitors (such as ribavirin, mycophenolic acid, and brequinar) can efficiently induce ISG expression and exert strong and broad antiviral responses [101–103]. However, this process is independent of the classical JAK–STAT cascade, suggesting a non-canonical mechanism that is independent of IFNs [104]. Ribavirin, an inhibitor of the IMPDH enzyme, was shown to reset a subset of ISG promoters to a 'ready to be activated' state, thus potentiating ISG activation [105]. However, crosstalk between nucleotide synthesis and the innate immune response remains to be further elucidated.

Retinoic Acid (RA)

RA is a metabolite of vitamin A that mediates the functions of vitamin A in growth and development. RA activates transcriptional via heterodimers of retinoic acid receptors (RAR) and retinoid X receptors (RXR), and these bind to regions in promoters known as retinoic acid response elements (RAREs). Numerous studies have reported antiviral activities of RA against a variety of pathogens [106,107]. Interestingly, intracellular RA increases ISG expression at basal levels and augments ISG induction in response to IFNs [108]. This is consistent with the clinical observation that RA enhances the response to IFN-based antiviral therapy [107,109]. Strikingly, a bioinformatics study showed that most ISG regulatory regions contain RARE sequences [108]. This indicates that RA can induce transcriptional activation of these ISGs containing RAREs, facilitating the binding of additional transcription factors to the promoters of these ISGs. Consequently, RA initiates and works synergistically with IFNs to induce ISG expression.

IFNs and ISGs: Clinical Implications and Future Perspective

IFNs have been used in various clinical settings to counteract pathogen-related diseases. Because of its robust and broad antiviral activity, IFN-α has represented the standard treatment for chronic hepatitis B virus (HBV) or HCV infections for decades. Its application also extends to other virus infections as an off-label treatment, for example hepatitis E virus [110] and severe acute respiratory syndrome [111]. IFN-λ has been shown to play a crucial role in cancer,

autoimmune disease, and viral infections [112]. The antitumor and anti-infection activities of IFN-γ have been comprehensively evaluated and used in a variety of clinical indications. It has been approved by FDA to treat chronic granulomatous disease and osteopetrosis, and is experimentally used for the treatment of idiopathic pulmonary fibrosis and Friedreich's ataxia [113]. However, IFN-γ has not been successful in treating viral infections [114,115]. IFN-λ has shown specific antiviral activity in both chronic HBV and HCV patients; although its efficacy was not superior compared to IFN-α therapy, IFN-λ had more limited side effects [116,117]. This is because IFNλR1 has a more restricted tissue-specific pattern of expression. IFN-λ has also been shown to determine the intestinal epithelial antiviral host defense against rotavirus infection. It acts synergistically with IL-22 for the induction of ISGs, and eventually controls rotavirus infection in animal models [118,119]. Thus, IFN-λ might be an attractive option for the treatment of many viral infections. Although the clinical application of IFNs, in particular for HCV, will be limited because of the recent launch of direct-acting antiviral agents, it may extend to other devastating viral diseases such as Ebola, Zika, or dengue virus infections.

Mechanistically, for all three types of IFNs, ISGs are the ultimate antiviral effectors. Recent studies on the function of individual ISGs indicate that different viruses are targeted by unique sets of ISGs. Some ISGs possess broad antiviral properties whereas others have specific antiviral effects [120]. Thus, characterization of individual ISGs with respect to their antiviral spectrum or specificity provides new avenues for improving current antiviral therapies. Interestingly, several ISGs have been reported to paradoxically enhance the replication of certain viruses, illustrating the complexity of the network of mutual interaction between ISGs and viruses [120]. In preclinical or clinical studies, the expression patterns of some specific ISGs have been identified as biomarkers to predict treatment responses, disease progression, or outcomes in both infectious (e.g., HCV and HIV infections) [121–123] and non-infectious human diseases (e.g., Aicardi-Goutières syndrome and systemic lupus erythematosus) [124,125]. Some ISGs (e.g., TLR3, TLR7, RIG-I, and MDA5) belong to the class of PRRs. Given their key roles in innate immune responses, there is growing interest in targeting PRRs for the prevention and treatment of cancer, autoimmune diseases, and infections. Specific activators are now undergoing preclinical and clinical evaluation for safety and efficacy [126]. With regards to the adverse effects of IFNs in the clinic, ISG-based antiviral strategies could be the next promising frontier in drug discovery.

Concluding Remarks

Decades of research have shaped a picture of the complex networks regulating ISG transcription. These includes both canonical and non-canonical mechanisms within and outside the IFN–JAK–STAT axis, coordinately defining the cellular defense status against pathogen invasion. We expect that the spectrum of new elements involved in both canonical and non-canonical regulation of ISG transcription will continue to grow, and their mechanism-of-actions will be further clarified (see Outstanding Questions). Because of their importance in clinical implication, this knowledge is highly relevant in guiding the development of new therapies that promote the eradication of severe pathogen infections while avoiding autoimmune diseases and toxic effects to the host.

Outstanding Questions

Although signaling through the same receptor, there are many type I IFNs in the genome. How do cells dynamically control the production of particular members of these type I IFNs?

Upon IFN-λ binding, what types of modification (e.g., phosphorylation, acetylation) take place to IFNλRs to allow them to trigger ISG transcription?

Generally, HAT activity transforms chromatin into a more relaxed structure, while HDAC activity organizes chromatin into higher-order nucleosomes. Counterintuitively, HDAC activity has been reported to be required for ISG transcription, but what is the underlying mechanism?

How exactly do nucleotide synthesis pathways mediate ISG transcription?

Will ISG-based antiviral strategy circumvent the issue of side effects caused by IFN treatment while retaining therapeutic potency in patients?

Acknowledgments

This research is supported by a Dutch Digestive Foundation (MLDS) career development grant (CDG 1304), a Daniel den Hoed Foundation for a Centennial Award fellowship, an Erasmus MC Mrace grant, and a Dutch Cancer Society Young Investigator Grant (10140) (to Q.P.), and by China Scholarship Council PhD fellowships to W.W. (201303250056) and L.X. (201306300027).

References

1. Wu, J. and Chen, Z.J. (2014) Innate immune sensing and signaling of cytosolic nucleic acids. *Annu. Rev. Immunol.* 32, 461–488
2. Schneider, W.M. *et al.* (2014) Interferon-stimulated genes: a complex web of host defenses. *Annu. Rev. Immunol.* 32, 513–545

3. Platanias, L.C. (2005) Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat. Rev. Immunol.* 5, 375–386
4. Stark, G.R. and Darnell, J.E., Jr (2012) The JAK–STAT pathway at twenty. *Immunity* 36, 503–514
5. Krause, C.D. and Pestka, S. (2015) Cut, copy, move, delete: the study of human interferon genes reveal multiple mechanisms underlying their evolution in amniotes. *Cytokine* 76, 480–495
6. Kotenko, S.V. (2011) IFN-lambdas. *Curr. Opin. Immunol.* 23, 583–590
7. Galani, I.E. *et al.* (2015) Type III interferons (IFNs): emerging master regulators of immunity. *Adv. Exp. Med. Biol.* 850, 1–15
8. Tang, X. *et al.* (2007) Acetylation-dependent signal transduction for type I interferon receptor. *Cell* 131, 93–105
9. New, M. *et al.* (2012) HDAC inhibitor-based therapies: can we interpret the code? *Mol. Oncol.* 6, 637–656
10. Schroder, K. *et al.* (2004) Interferon-gamma: an overview of signals, mechanisms and functions. *J. Leukoc. Biol.* 75, 163–189
11. Kumar, K.G. *et al.* (2004) Phosphorylation and specific ubiquitin acceptor sites are required for ubiquitination and degradation of the IFNAR1 subunit of type I interferon receptor. *J. Biol. Chem.* 279, 46614–46620
12. Malakhova, O.A. *et al.* (2006) UBP43 is a novel regulator of interferon signaling independent of its ISG15 isopeptidase activity. *EMBO J.* 25, 2358–2367
13. Zhang, X. *et al.* (2015) Human intracellular ISG15 prevents interferon-alpha/beta over-amplification and auto-inflammation. *Nature* 517, 89–93
14. Fenner, J.E. *et al.* (2006) Suppressor of cytokine signaling 1 regulates the immune response to infection by a unique inhibition of type I interferon activity. *Nat. Immunol.* 7, 33–39
15. Linossi, E.M. *et al.* (2013) Suppression of cytokine signaling: the SOCS perspective. *Cytokine Growth Factor Rev.* 24, 241–248
16. Starr, R. *et al.* (2009) SOCS-1 binding to tyrosine 441 of IFN-gamma receptor subunit 1 contributes to the attenuation of IFN-gamma signaling *in vivo*. *J. Immunol.* 183, 4537–4544
17. Farrar, M.A. and Schreiber, R.D. (1993) The molecular cell biology of interferon-gamma and its receptor. *Annu. Rev. Immunol.* 11, 571–611
18. Bernabei, P. *et al.* (2001) Interferon-gamma receptor 2 expression as the deciding factor in human T, B, and myeloid cell proliferation or death. *J. Leukoc. Biol.* 70, 950–960
19. Bach, E.A. *et al.* (1995) Ligand-induced autoregulation of IFN-gamma receptor beta chain expression in T helper cell subsets. *Science* 270, 1215–1218
20. Babon, J.J. *et al.* (2014) The molecular regulation of Janus kinase (JAK) activation. *Biochem. J.* 462, 1–13
21. Steen, H.C. and Gamero, A.M. (2013) STAT2 phosphorylation and signaling. *JAKSTAT* 2, e25790
22. Myers, M.P. *et al.* (2001) TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B. *J. Biol. Chem.* 276, 47771–47774
23. Irie-Sasaki, J. *et al.* (2001) CD45 is a JAK phosphatase and negatively regulates cytokine receptor signalling. *Nature* 409, 349–354
24. Yamada, T. *et al.* (2002) CD45 controls interleukin-4-mediated IgE class switch recombination in human B cells through its function as a Janus kinase phosphatase. *J. Biol. Chem.* 277, 28830–28835
25. Simoncic, P.D. *et al.* (2002) The T cell protein tyrosine phosphatase is a negative regulator of janus family kinases 1 and 3. *Curr. Biol.* 12, 446–453
26. Ali, S. *et al.* (2003) SHP-2 regulates SOCS-1-mediated Janus kinase-2 ubiquitination/degradation downstream of the prolactin receptor. *J. Biol. Chem.* 278, 52021–52031
27. O'Shea, J.J. *et al.* (2013) Janus kinase inhibitors in autoimmune diseases. *Ann. Rheum. Dis.* 72 (Suppl. 2), 111–115
28. Ng, S.L. *et al.* (2011) IkappaB kinase epsilon (IKKε) regulates the balance between type I and type II interferon responses. *Proc. Natl. Acad. Sci. U. S. A.* 108, 21170–21175
29. Tenoever, B.R. *et al.* (2007) Multiple functions of the IKK-related kinase IKKepsilon in interferon-mediated antiviral immunity. *Science* 315, 1274–1278
30. Steen, H.C. *et al.* (2013) Identification of STAT2 serine 287 as a novel regulatory phosphorylation site in type I interferon-induced cellular responses. *J. Biol. Chem.* 288, 747–758
31. Ooi, E.L. *et al.* (2014) Novel antiviral host factor, TNK1, regulates IFN signaling through serine phosphorylation of STAT1. *Proc. Natl. Acad. Sci. U. S. A.* 111, 1909–1914
32. Jiang, L.J. *et al.* (2011) RA-inducible gene-I induction augments STAT1 activation to inhibit leukemia cell proliferation. *Proc. Natl. Acad. Sci. U. S. A.* 108, 1897–1902
33. Hou, J. *et al.* (2014) Hepatic RIG-I predicts survival and interferon-alpha therapeutic response in hepatocellular carcinoma. *Cancer Cell* 25, 49–63
34. Staab, J. *et al.* (2013) CDK8 as the STAT1 serine 727 kinase? *JAKSTAT* 2, e24275
35. Bancerek, J. *et al.* (2013) CDK8 kinase phosphorylates transcription factor STAT1 to selectively regulate the interferon response. *Immunity* 38, 250–262
36. Choudhury, G.G. (2004) A linear signal transduction pathway involving phosphatidylinositol 3-kinase, protein kinase Cepsilon, and MAPK in mesangial cells regulates interferon-gamma-induced STAT1alpha transcriptional activation. *J. Biol. Chem.* 279, 27399–27409
37. Nguyen, H. *et al.* (2001) Roles of phosphatidylinositol 3-kinase in interferon-gamma-dependent phosphorylation of STAT1 on serine 727 and activation of gene expression. *J. Biol. Chem.* 276, 33361–33368
38. Uddin, S. *et al.* (2002) Protein kinase C-delta (PKC-delta) is activated by type I interferons and mediates phosphorylation of Stat1 on serine 727. *J. Biol. Chem.* 277, 14408–14416
39. Deb, D.K. *et al.* (2003) Activation of protein kinase C delta by IFN-gamma. *J. Immunol.* 171, 267–273
40. Ramsauer, K. *et al.* (2002) p38 MAPK enhances STAT1-dependent transcription independently of Ser-727 phosphorylation. *Proc. Natl. Acad. Sci. U. S. A.* 99, 12859–12864
41. Branger, J. *et al.* (2003) Inhibition of coagulation, fibrinolysis, and endothelial cell activation by a p38 mitogen-activated protein kinase inhibitor during human endotoxemia. *Blood* 101, 4446–4448
42. Wu, T.R. *et al.* (2002) SHP-2 is a dual-specificity phosphatase involved in Stat1 dephosphorylation at both tyrosine and serine residues in nuclei. *J. Biol. Chem.* 277, 47572–47580
43. Xu, D. and Qu, C.K. (2008) Protein tyrosine phosphatases in the JAK/STAT pathway. *Front. Biosci.* 13, 4925–4932
44. ten Hoeve, J. *et al.* (2002) Identification of a nuclear Stat1 protein tyrosine phosphatase. *Mol. Cell. Biol.* 22, 5662–5668
45. David, M. *et al.* (1995) Differential regulation of the alpha/beta interferon-stimulated Jak/Stat pathway by the SH2 domain-containing tyrosine phosphatase SHPTP1. *Mol. Cell. Biol.* 15, 7050–7058
46. He, R.J. *et al.* (2014) Protein tyrosine phosphatases as potential therapeutic targets. *Acta Pharmacol. Sin.* 35, 1227–1246
47. Ungureanu, D. *et al.* (2005) SUMO-1 conjugation selectively modulates STAT1-mediated gene responses. *Blood* 106, 224–226
48. Qureshi, S.A. *et al.* (1995) Tyrosine-phosphorylated Stat1 and Stat2 plus a 48-kDa protein all contact DNA in forming interferon-stimulated-gene factor 3. *Proc. Natl. Acad. Sci. U. S. A.* 92, 3829–3833
49. John, J. *et al.* (1991) Isolation and characterization of a new mutant human cell line unresponsive to alpha and beta interferons. *Mol. Cell. Biol.* 11, 4189–4195
50. Kimura, T. *et al.* (1996) Essential and non-redundant roles of p48 (ISGF3 gamma) and IRF-1 in both type I and type II interferon responses, as revealed by gene targeting studies. *Genes Cells* 1, 115–124
51. Levy, D.E. *et al.* (1990) Synergistic interaction between interferon-alpha and interferon-gamma through induced synthesis of one subunit of the transcription factor ISGF3. *EMBO J.* 9, 1105–1111

52. Bell, O. *et al.* (2011) Determinants and dynamics of genome accessibility. *Nat. Rev. Genet.* 12, 554–564
53. Cui, K. *et al.* (2004) The chromatin-remodeling BAF complex mediates cellular antiviral activities by promoter priming. *Mol. Cell. Biol.* 24, 4476–4486
54. Yan, Z. *et al.* (2005) PBAF chromatin-remodeling complex requires a novel specificity subunit, BAF200, to regulate expression of selective interferon-responsive genes. *Genes Dev.* 19, 1662–1667
55. Huang, M. *et al.* (2002) Chromatin-remodelling factor BRG1 selectively activates a subset of interferon-alpha-inducible genes. *Nat. Cell. Biol.* 4, 774–781
56. Ni, Z. *et al.* (2005) Apical role for BRG1 in cytokine-induced promoter assembly. *Proc. Natl. Acad. Sci. U. S. A.* 102, 14611–14616
57. Bhattacharya, S. *et al.* (1996) Cooperation of Stat2 and p300/CBP in signalling induced by interferon-alpha. *Nature* 383, 344–347
58. Paulson, M. *et al.* (2002) IFN-Stimulated transcription through a TBP-free acetyltransferase complex escapes viral shutoff. *Nat. Cell. Biol.* 4, 140–147
59. Shakespear, M.R. *et al.* (2011) Histone deacetylases as regulators of inflammation and immunity. *Trends Immunol.* 32, 335–343
60. Chang, H.M. *et al.* (2004) Induction of interferon-stimulated gene expression and antiviral responses require protein deacetylase activity. *Proc. Natl. Acad. Sci. U. S. A.* 101, 9578–9583
61. Gao, B. *et al.* (2013) Inhibition of histone deacetylase activity suppresses IFN-gamma induction of tripartite motif 22 via CHIP-mediated proteasomal degradation of IRF-1. *J. Immunol.* 191, 464–471
62. Nusinzon, I. and Horvath, C.M. (2003) Interferon-stimulated transcription and innate antiviral immunity require deacetylase activity and histone deacetylase 1. *Proc. Natl. Acad. Sci. U. S. A.* 100, 14742–14747
63. Falkenberg, K.J. and Johnstone, R.W. (2014) Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. *Nat. Rev. Drug Discov.* 13, 673–691
64. Klampfer, L. *et al.* (2004) Requirement of histone deacetylase activity for signaling by STAT1. *J. Biol. Chem.* 279, 30358–30368
65. Sakamoto, S. *et al.* (2004) Histone deacetylase activity is required to recruit RNA polymerase II to the promoters of selected interferon-stimulated early response genes. *J. Biol. Chem.* 279, 40362–40367
66. Litvak, V. *et al.* (2012) A FOXO3-IRF7 gene regulatory circuit limits inflammatory sequelae of antiviral responses. *Nature* 490, 421–425
67. Zhang, J.J. *et al.* (1998) Ser727-dependent recruitment of MCM5 by Stat1alpha in IFN-gamma-induced transcriptional activation. *EMBO J.* 17, 6963–6971
68. DaFonseca, C.J. *et al.* (2001) Identification of two residues in MCM5 critical for the assembly of MCM complexes and Stat1-mediated transcription activation in response to IFN-gamma. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3034–3039
69. Zhu, M. *et al.* (1999) Functional association of Nmi with Stat5 and Stat1 in IL-2- and IFNgamma-mediated signaling. *Cell* 96, 121–130
70. Lau, J.F. *et al.* (2003) Role of metazoan mediator proteins in interferon-responsive transcription. *Mol. Cell. Biol.* 23, 620–628
71. Kadota, S. and Nagata, K. (2014) Silencing of IFN-stimulated gene transcription is regulated by histone H1 and its chaperone TAF-I. *Nucleic Acids Res.* 42, 7642–7653
72. Tahk, S. *et al.* (2007) Control of specificity and magnitude of NF-kappa B and STAT1-mediated gene activation through PIASy and PIAS1 cooperation. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11643–11648
73. Liu, B. *et al.* (2001) A transcriptional corepressor of Stat1 with an essential LXXLL signature motif. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3203–3207
74. Mostafavi, S. *et al.* (2016) Parsing the interferon transcriptional network and its disease associations. *Cell* 164, 564–578
75. Morrow, A.N. *et al.* (2011) A novel role for IFN-stimulated gene factor 3II in IFN-gamma signaling and induction of antiviral activity in human cells. *J. Immunol.* 186, 1685–1693
76. Fink, K. and Grandvaux, N. (2013) STAT2 and IRF9: beyond ISGF3. *JAKSTAT* 2, e27521
77. Cheon, H. *et al.* (2013) IFNbeta-dependent increases in STAT1, STAT2, and IRF9 mediate resistance to viruses and DNA damage. *EMBO J.* 32, 2751–2763
78. Sung, P.S. *et al.* (2015) Roles of unphosphorylated ISGF3 in HCV infection and interferon responsiveness. *Proc. Natl. Acad. Sci. U. S. A.* 112, 10443–10448
79. Fish, E.N. *et al.* (1999) Activation of a CrkL–stat5 signaling complex by type I interferons. *J. Biol. Chem.* 274, 571–573
80. Xu, L. *et al.* (2016) IFN regulatory factor 1 restricts hepatitis E virus replication by activating STAT1 to induce antiviral IFN-stimulated genes. *FASEB J.* 30, 3352–3367
81. Harada, H. *et al.* (1994) Structure and regulation of the human interferon regulatory factor 1 (IRF-1) and IRF-2 genes: implications for a gene network in the interferon system. *Mol. Cell. Biol.* 14, 1500–1509
82. Ivashkiv, L.B. and Donlin, L.T. (2014) Regulation of type I interferon responses. *Nat. Rev. Immunol.* 14, 36–49
83. Grandvaux, N. *et al.* (2002) Transcriptional profiling of interferon regulatory factor 3 target genes: direct involvement in the regulation of interferon-stimulated genes. *J. Virol.* 76, 5532–5539
84. Collins, S.E. *et al.* (2004) Innate cellular response to virus particle entry requires IRF3 but not virus replication. *J. Virol.* 78, 1706–1717
85. Bartee, E. *et al.* (2009) The addition of tumor necrosis factor plus beta interferon induces a novel synergistic antiviral state against poxviruses in primary human fibroblasts. *J. Virol.* 83, 498–511
86. Wang, W. *et al.* (2016) Convergent transcription of interferon-stimulated genes by TNF-alpha and IFN-alpha augments antiviral activity against HCV and HEV. *Sci. Rep.* 6, 25482
87. Mestan, J. *et al.* (1988) Antiviral activity of tumour necrosis factor. Synergism with interferons and induction of oligo-2′,5′-adenylate synthetase. *J. Gen. Virol.* 69, 3113–3120
88. Lee, J. *et al.* (2015) TNF-alpha induced by hepatitis C virus via TLR7 and TLR8 in hepatocytes supports interferon signaling via an autocrine mechanism. *PLoS Pathog.* 11, e1004937
89. Ruby, J. *et al.* (1997) Antiviral activity of tumor necrosis factor (TNF) is mediated via p55 and p75 TNF receptors. *J. Exp. Med.* 186, 1591–1596
90. Seo, S.H. and Webster, R.G. (2002) Tumor necrosis factor alpha exerts powerful anti-influenza virus effects in lung epithelial cells. *J. Virol.* 76, 1071–1076
91. Mestan, J. *et al.* (1986) Antiviral effects of recombinant tumour necrosis factor *in vitro*. *Nature* 323, 816–819
92. Uddin, S. *et al.* (2000) The Rac1/p38 mitogen-activated protein kinase pathway is required for interferon alpha-dependent transcriptional activation but not serine phosphorylation of Stat proteins. *J. Biol. Chem.* 275, 27634–27640
93. Li, Y. *et al.* (2005) Activation of mitogen-activated protein kinase kinase (MKK) 3 and MKK6 by type I interferons. *J. Biol. Chem.* 280, 10001–10010
94. Wu, T. *et al.* (1994) Interferon-gamma induces the synthesis and activation of cytosolic phospholipase A2. *J. Clin. Invest.* 93, 571–577
95. Peppelenbosch, M.P. (1995) Rac mediates growth factor-induced arachidonic acid release. *Cell* 81, 849–856
96. Young, P.R. (2013) Perspective on the discovery and scientific impact of p38 MAP kinase. *J. Biomol. Screen.* 18, 1156–1163
97. Li, Y. *et al.* (2004) Role of p38alpha Map kinase in type I interferon signaling. *J. Biol. Chem.* 279, 970–979
98. Uddin, S. *et al.* (1999) Activation of the p38 mitogen-activated protein kinase by type I interferons. *J. Biol. Chem.* 274, 30127–30131
99. Lee, Y.B. *et al.* (2000) p38 map kinase regulates TNF-alpha production in human astrocytes and microglia by multiple mechanisms. *Cytokine* 12, 874–880

100. Hu, J. *et al.* (2001) ERK1 and ERK2 activate CCAAAT/enhancer-binding protein-beta-dependent gene transcription in response to interferon-gamma. *J. Biol. Chem.* 276, 287–297
101. Lucas-Hourani, M. (2013) Inhibition of pyrimidine biosynthesis pathway suppresses viral growth through innate immunity. *PLoS Pathog.* 9, e1003678
102. Pan, Q. *et al.* (2012) Mycophenolic acid augments interferon-stimulated gene expression and inhibits hepatitis C virus infection *in vitro* and *in vivo*. *Hepatology* 55, 1673–1683
103. Chung, D.H. *et al.* (2016) Discovery of a broad-spectrum antiviral compound that inhibits pyrimidine biosynthesis and establishes a type 1 interferon-independent antiviral state. *Antimicrob. Agents Chemother.* 60, 4552–4562
104. Wang, Y. *et al.* (2016) Cross talk between nucleotide synthesis pathways with cellular immunity in constraining hepatitis E virus replication. *Antimicrob. Agents Chemother.* 60, 2834–2848
105. Testoni, B. *et al.* (2016) Ribavirin restores IFNalpha responsiveness in HCV-infected livers by epigenetic remodelling at interferon stimulated genes. *Gut* 65, 672–682
106. Neuzil, K.M. *et al.* (1995) Safety and pharmacokinetics of vitamin A therapy for infants with respiratory syncytial virus infections. *Antimicrob. Agents Chemother.* 39, 1191–1193
107. Bocher, W.O. *et al.* (2008) All-trans retinoic acid for treatment of chronic hepatitis C. *Liver Int.* 28, 347–354
108. Cho, N.E. *et al.* (2016) Retinoid regulation of antiviral innate immunity in hepatocytes. *Hepatology* 63, 1783–1795
109. Bitetto, D. *et al.* (2013) Vitamin A deficiency is associated with hepatitis C virus chronic infection and with unresponsiveness to interferon-based antiviral therapy. *Hepatology* 57, 925–933
110. Debing, Y. and Neyts, J. (2014) Antiviral strategies for hepatitis E virus. *Antiviral Res.* 102, 106–118
111. Loutfy, M.R. *et al.* (2003) Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA* 290, 3222–3228
112. Lasfar, A. *et al.* (2016) IFN-lambda therapy: current status and future perspectives. *Drug Discov. Today* 21, 167–171
113. Miller, C.H. *et al.* (2009) Clinical use of interferon-gamma. *Ann. N. Y. Acad. Sci.* 1182, 69–79
114. Lau, J.Y. *et al.* (1991) A randomised controlled trial of recombinant interferon-gamma in Chinese patients with chronic hepatitis B virus infection. *J. Med. Virol.* 34, 184–187
115. Muir, A.J. *et al.* (2006) Interferon gamma-1b for the treatment of fibrosis in chronic hepatitis C infection. *J. Viral. Hepat.* 13, 322–328
116. Chan, H.L. *et al.* (2016) Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: a randomized phase 2b study (LIRA-B). *J. Hepatol.* 64, 1011–1019
117. Muir, A.J. *et al.* (2014) A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J. Hepatol.* 61, 1238–1246
118. Hernandez, P.P. *et al.* (2015) Interferon-lambda and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection. *Nat. Immunol.* 16, 698–707
119. Pott, J. *et al.* (2011) IFN-lambda determines the intestinal epithelial antiviral host defense. *Proc. Natl. Acad. Sci. U. S. A.* 108, 7944–7949
120. Schoggins, J.W. *et al.* (2011) A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature* 472, 481–485
121. Asselah, T. *et al.* (2008) Liver gene expression signature to predict response to pegylated interferon plus ribavirin combination therapy in patients with chronic hepatitis C. *Gut* 57, 516–524
122. Dill, M.T. *et al.* (2012) Interferon-gamma-stimulated genes, but not USP18, are expressed in livers of patients with acute hepatitis C. *Gastroenterology* 143, 777–786
123. Crow, Y.J. and Manel, N. (2015) Aicardi-Goutières syndrome and the type I interferonopathies. *Nat. Rev. Immunol.* 15, 429–440
124. Bennett, L. *et al.* (2003) Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J. Exp. Med.* 197, 711–723
125. Mandl, J.N. *et al.* (2008) Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and non-pathogenic AIDS virus infections. *Nat. Med.* 14, 1077–1087
126. Mullen, L.M. *et al.* (2015) Pattern recognition receptors as potential therapeutic targets in inflammatory rheumatic disease. *Arthritis Res. Ther.* 17, 122
127. Kaplan, D.H. *et al.* (1996) Identification of an interferon-gamma receptor alpha chain sequence required for JAK-1 binding. *J. Biol. Chem.* 271, 9–12
128. Qing, Y. *et al.* (2005) Role of tyrosine 441 of interferon-gamma receptor subunit 1 in SOCS-1-mediated attenuation of STAT1 activation. *J. Biol. Chem.* 280, 1849–1853
129. Sadzak, I. *et al.* (2008) Recruitment of Stat1 to chromatin is required for interferon-induced serine phosphorylation of Stat1 transactivation domain. *Proc. Natl. Acad. Sci. U. S. A.* 105, 8944–8949