SUPPLEMENTAL EXPERIMENTAL PROCEDURES

Data can be browsed with dedicated databrowsers on the ImmGen website ("Cytokines" pages) and have been deposited at the NCBI Gene Expression Omnibus under GSE75306

Mice and treatments

C57BL/6J and *Tyk2* spontaneous mutant B10.Q (JAX 2024), (5 weeks old males) were purchased from the Jackson Laboratory (Bar Harbor, USA). *Ifnar1* deficient mice were obtained from the Jackson Laboratory, then maintained on the B6 background. Mice were analyzed unchallenged, or after subcutaneous injection of 10,000U IFNα (Recombinant Mouse IFN Alpha A3, R&D, cat # 12100-1), 2 hrs prior to sacrifice unless otherwise specified. Tofacitinib (Pfizer, Cambridge, MA) was administered by oral gavage, 25 mg/kg in 0.5% methyl cellulose, twice daily.

Gene expression profiling

Immunocytes were sorted to high purity by flow cytometry according to ImmGen SOP ((Heng et al., 2008) and www.immgen.org), RNA was prepared from Trizol lysates and used for gene expression profiling on Affymetrix MoGene ST1.0 microarrays (Expression Analysis, Durham, NC).

Time course analysis. Microarray data was generated for 28 consecutive time points after IFN treatment (10^4 units injected subcutaneously) and baseline gene expression data measured in biological triplicate. From the 28 time points IFN treated data, we excluded 5 arrays with low dynamic range (<79), and only analyzed the data for following time points: (0.25hr, 0.5hr, 0.75hr, 1hr, 1.25hr, 1.5hr, 2.25hr, 2.75hr, 3hr, 3.5hr, 5hr, 5.5hr, 6hr, 6.5hr, 7hr, 8hr, 9hr, 10hr, 11hr, 12hr, 13hr, 14hr, 15hr). Data were first normalized with RMA, and we quantified the log2 fold change (FC) for each time point with respect to baseline, using the average of the three baseline replicates. Our initial analysis indicated that response to IFN data is consistent with an impulse-like function (Chechik and Koller, 2009), and therefore to reduce unwanted inter-sample heterogeneity, we smoothed the FC data for each gene (across the 23 time points) using the moving average smoothing approach (implemented in MATLAB). To define kinetic metrics, robust ISGs were selected as having a FC>2 for two consecutive time points and FC>2.5 for at least one time point, resulting in 182 analyzed ISGs. For each of these induced genes we defined three key parameters based on the shape of the response curve (FC) across the 24 time points: time to ½ onset, slope of onset, and maximum. Slope of onset was estimated as the slope of the line between FC at ½ onset and maximum onset.

Dose response. The IFN dose response experiments were performed in vitro. Splenic B cells were isolated by negative selection (Stemcell Technologies, EasySep kit #19854) from 6 week-old C57BL/6J male mice, washed and cultured in RPMI 1640 supplemented with 10% (vol/vol) FBS, L-glutamate, and pen/strep in round bottom 96-well plates at 10^5 cells/well. IFN was added at 10 fold serial concentrations (1000U/ml, 100U/ml, 10U/ml, 1U/ml and 0.1U/ml) in triplicate. After 2 hrs culture at 37 °C, cells were transferred into Trizol for RNA preparation and expression profiling. To estimate the "Effective Dose 50" (ED_{50}) for each gene, we first computed a "baseline normalized" percentage of maximum response at each IFN dose per gene (performed in log space, by subtracting the mean of baseline expression level of each gene from its expression level at different IFN doses (Fig. 1G)). We then estimated ED50 values per gene (in log space), by fitting a linear model to the two dose values bracketing 50% maximum response.

Profiling and analysis of Ifnar1 and Tyk2-deficient mice. Gene expression profiles were generated in triplicate from sorted splenic B cells and peritoneal macrophages as above, from unchallenged mice or 2 hrs after injection of IFNα, processed and normalized per above. ISGs most sensitive to tonic IFN were defined (Fig. 2B) as those with the largest WT/*Ifnar1*-KO, normalized for intrinsic responsiveness to IFN (log2(foldchange(WT/*Ifnar1*-KO)) > log2(foldchange(WT+IFN / WT))/4 , with tonic-insensitive ISGs defined as log2(foldchange(WT/*Ifnar1*-KO)) < log2(foldchange(WT+IFN / WT))/6.

Effects of JAK inhibitor. Gene expression profiles were pooled from several experiments (n=4 to 7 per group) involving paired Tofacitinib or vehicle-treated mice (treatments ranging from 3 hrs to 7 days were combined, as effects were comparable with respect to ISG inhibition), with or without 2 hrs IFN administration. After normalization with the RMA algorithm (Irizarry et al., 2003), data were preprocessed by removing unexpressed, discarding transcripts with high inter-replicate coefficient of variation (typically *Sno* loci), and by using residuals to a linear model fit to sample's dynamic range (to smooth artefactual variance due to different signal intensities, which can become an issue in cases of low true variance). Drug effects at baseline were quantified, independently for each cell-type, as the mean FoldChange between Tofa- and vehicle-treated mice. For inhibition of the IFN response in challenged mice, the inhibition index was computed for each cell-type, as (log2(x/y) –

log2(z/y))/log2(x/y); where x is the mean of IFN only datasets, y the mean of baseline and z the mean of IFN+Tofa datasets (0= no inhibition, 1 full inhibition).

Chromatin accessibility (ATACseq)

ATACseq libraries were constructed as previously reported (Buenrostro et al., 2013). Specifically, 50,000 primary B cells sorted as above were spun down by centrifugation at 500g for 5min, washed once with 50uL of cold PBS and suspended in 50uL of cold hypotonic lysis buffer (10mM Tris-Cl PH7.4, 10mM NaCl, 3mM MgCl2 and 0.1% NP40) by gentle pipetting. After immediate centrifugation at 500g for 10mn, the pellet was re-suspended in 50uL of transposition reaction mix (2.5uL Tagment DNA Enzyme in 50uL of 1xTagment DNA Buffer, Nextera DNA Sample Prep Kit, Illumina, CA, USA) and incubated for 30mn at 37°C to be tagged and fragmented. The DNA was purified by MinElute PCR Purification Kit (Qiagen, Hilden, Germany) and kept at -80°C until the library preparation.

To construct libraries, the 1st round of PCR was performed in 50uL using NEBNext High-Fidelity 2X PCR Master Mix (New England Biolabs, MA, USA) with a set of primers (1.25uM each) designed by (Buenrostro et al., 2013) with following thermal cycles: 30 sec hot-start at 98°C, followed by 9 cycles [98°C for 10 sec, 63°C for 30 sec and 72°C for 30 sec] and a final extension at 72°C for 5mn. The PCR products were purified and size-selected by Agencourt AMPure XP beads (Beckman Coulter, CA, USA) (0.6x and 1.6x vol. for removing long and short fragments respectively). Then to avoid an over amplification, which can produce more GC bias, 1/10 of the libraries were subjected to qPCR (StepOnePlus Real-Time PCR System, Life Technologies, CA, USA) employing SYBR GreenI (final 0.6x SYBR GreenI, Life Technologies) and the same PCR mix as in the 1st round of PCR. After running the qPCR (30sec at 98°C, followed by 25 cycles [98°C for 10 sec, 63°C for 30 sec and 72°C for 30 sec]), amplification curves were examined. The remaining libraries were subjected to the 2nd round of PCR with following thermal cycles: 30 sec hot-start at 98°C, followed by 5 cycles [98°C for 10 sec, 63°C for 30 sec and 72°C for 30 sec] and a final extension at 72°C for 5mn. The libraries were purified by Agencourt AMPure XP beads and 50bp, single-end reads were sequenced on an Illumina HiSeq2500 in a Rapid run mode.

After trimming low quality reads by sickle1.2 (https://github.com/najoshi/sickle) and adapter sequence by cutadapt1.2.1 (Martin, 2015), short reads were mapped to mm10 by bowtie1.1.1 with –m 1 option to avoid non-unique alignments (Langmead et al., 2009). Then, duplicated reads and reads mapped to mitochondrial DNA (16.0~22.4%) were removed using Picard Tools (http://broadinstitute.github.io/picard). The aligned results from the same condition were merged by samtools merge and peaks were determined by macs applying options --nomodel --shift 5 --extsize 170 --keep-dup 1 --SPMR -q 0.01 (samtools1.1 and macs2.1.0) (Li et al., 2009; Zhang et al., 2008; Li et al., 2009; Zhang et al., 2008). Identified peaks from 2 conditions were merged by BEDTools mergeBed and the number of reads within peaks were counted from each aligned result before merging by BEDTools coverageBed (BEDTools2.19.0) (Quinlan and Hall, 2010). The number of reads in peaks were normalized by quantile-normalization and region length to calculate signal densities, which were employed to plot the ATACseq signals. To calculate the distance between the summit and TSS, a region summit was assigned to the position of the highest signal within a peak. Positions for refGenes were downloaded February 2015 from UCSC table browser (http://genome.ucsc.edu), and overlapping between refGenes and ATACseq peaks, as well as the distances from a summit of ATACseq region to the closest TSS of ISG were determined on galaxy website (https://usegalaxy.org/). ATACseq peaks which overlapped with the TSS(s) of a gene were defined as TSS-peaks. To visualize the representative ATACseq signals, datasets were normalized by quantile normalization taking every 10bp bin, converted into bigwig format and visualized by IGV software (Robinson et al., 2011). 1731 ISGs including those identified in B cells (expression FC>1.2 in consecutive 3 time points in time-course data, 1281 genes, or significantly induced at 2hrs, FC>1.2 P-Val<0.05, 761 genes) and other cell types (11 cell-set data, 975 genes) formed the set used to calculate the distance between IFN-induced ATACseq peaks and the closest ISG. To examine the bias by tonic sensitivity in the transcript-ATAC plots (Figure 4D), P-values were calculated by Wilcoxon signed-rank test between the ATACseq signals for tonic sensitive or insensitive genes and expression matched non-ISG genes (1000 random draws of the reference genes, and the median in the plots).

Chromatin ImmunoPrecipitation by Sequencing (ChIP-seq)

After the splenocytes from control or IFN-treated mice were dissociated and fixed by 1% Formaldehyde (Formaldehyde 16%, Methanol-Free, Fisher Scientific, PA, USA) at room temperature for 10mn with gentle rocking, B cells were negatively isolated using EasySep Mouse B cell Isolation Kit. For PolII and H3K4me1 ChIPs, approximately 2x10^{7}cells were spun down, snap frozen by liquid nitrogen and kept at -80°C prior to use. For Stat1 and Stat2 ChIPs, cells were processed without freezing.

ChIP-seq libraries were constructed as previously reported (Rahl et al., 2010). Specifically, for PolII ChIPs, the cell pellets were thawed on ice, suspended in 1ml of lysis buffer 1 (50mM HEPES pH 7.2, 140mM NaCl, 1mM EDTA, 10% glycerol, 0.5% NP40, 0.25% TritonX100 and cOmplete EDTA-free protease inhibitor cocktail, Roche Diagnostics, Basel, Switzerland) and incubated for 10mn at 4°C with a gentle rocking. After spinning 5mn at 1350g, the pellets were re-suspended in 1ml of hypertonic buffer (10mM Tris-Cl pH 8.0, 200mM NaCl, 1mM EDTA pH 8.0, 0.5mM EGTA pH 8.0 and cOmplete EDTA-free) and incubated 10mn at room temperature with a gentle rocking, followed by a 5mn centrifugation at 1350g. Then the pellets were re-suspended in 900uL of sonication buffer (50mM HEPES pH 7.2, 140mM NaCl, 1mM EDTA pH 8.0, 1mM EGTA pH 8.0, 0.1% Na-Deoxycholate, 0.1% SDS and cOmplete EDTA-free) and sonicated for 24cycles [on-5sec and off-15sec] on ice at 30% output (S-4000 and Microtip probe #418, MISONIX, CT, USA). TritonX100 was added to a final concentration of 1% to the sonicated lysates and centrifuged 15mn at 16,000g for clearing cell debris. The cleared lysates were rotated overnight at 4°C with 100uL of Dynabeads Protein G (Life Technologies) pre-incubated with 10ug of antibody (anti-PolII: N-20, Santa Cruz Biotechnology). Beads were washed 7 times with RIPA buffer (50mM HEPES pH 7.2, 300mM LiCl, 1mM EDTA, 1% NP40 and 0.7% Na-Deoxycholate) and once with TNE (10mM Tris-Cl pH 8.0, 50mM NaCl and 1mM EDTA pH 8.0). Bound complexes were eluted into elution buffer (50mM Tris-Cl pH 8.0, 10mM EDTA pH 8.0 and 1% SDS) by incubating 15mn at 65°C, vortexing every 2mn. Crosslinks were reversed by incubating the eluted DNA at 65°C for 10hrs. Then, RNA and protein were digested by RNaseA (PureLink RNaseA, Life technologies) and ProteinaseK (Proteinase K, recombinant, PCR Grade, Roche Diagnostics) respectively. DNA was isolated by phenol chloroform extraction employing MaXtract High Density tubes (QIAGEN) followed by ethanol precipitation.

For H3K4me1 ChIPs, we used the sonication buffer (10mM Tris-Cl pH 8.0, 100mM NaCl, 1mM EDTA pH 8.0, 0.5mM EGTA pH 8.0, 0.1% Na-Deoxycholate, 0.5% N-lauroylsarcosine and cOmplete EDTA-free), anti-H3K4me1 antibodies (1:1 mixture of ab8895, abcam and 07-436, EMD Millipore) and RIPA buffer (50mM HEPES pH 7.2, 100mM LiCl, 1mM EDTA, 1% NP40 and 0.7% Na-Deoxycholate).

For Stat1 and Stat2 ChIPs, approximately $3x10^7$ fixed and negatively isolated B cells were incubated in lysis buffer 1 and hypertonic buffer, without freezing the cells. After a centrifuge, cell pellets were re-suspended in 1ml of sonication buffer (50mM HEPES pH 7.2, 140mM NaCl, 1mM EDTA pH 8.0, 1mM EGTA pH 8.0, 0.1% Na-Deoxycholate, 0.1% SDS and cOmplete EDTA-free), transferred into a milliTUBE (1ml, Covaris, MA, USA) and sonicated on Covaris S2 Focused-Ultrasonicator (Covaris) with a following condition: Duty Cycle 5%, Intensity 4, Cycles per Burst 200, Power mode Sweeping, AFA Intensifier No Intensifier and Process time 18mn. TritonX100 was added to a final concentration of 1% to the sonicated lysates. Approximately 350uL of the cleared lysates were used for a ChIP with 35uL of Dynabeads Protein G and 35uL of Dynabeads Protein A pre-incubated with 10ug of each antibody (anti-Stat1: sc-592, Santa Cruz Biotechnology and anti-Stat2: #07-140, EMD Millipore).

For library construction, the ends of immunoprecipitated DNA were repaired by End-It DNA End-Repair Kit (Epicentre, WI, USA) followed by a single adenine nucleotide overhang attachment, which allows the directional ligation, using Klenow fragment (Klenow Fragment 3'>5' exo-, New England Biolabs). The adaptor oligo mix (final 33.3 nM, sequences are listed below) was ligated by T4 DNA Ligase (LigaFast Rapid DNA Ligation System, Promega, WI, USA). DNA was purified with 1.8x vol. Agencourt AMPure XP beads between these steps. Then the adapter ligated DNA was amplified by PCR in 50uL employing NEBNext High-Fidelity 2X PCR Master Mix and a set of indexed primers (0.5uM each, sequences are listed below) by following thermal cycles: 30 sec hot-start at 98°C, followed by 8 cycles [98°C for 10 sec, 63°C for 30 sec and 72°C for 30 sec] and a final extension at 72°C for 5mn. To optimize the amplification, 1/10 of the post-PCR mixtures were diluted with a PCR cocktail containing NEBNext High-Fidelity 2X PCR Master Mix, primers and SYBR GreenI (final 0.6x) and subjected to qPCR (30sec at 98°C, followed by 25 cycles [98°C for 10 sec, 63°C for 30 sec and 72°C for 30 sec]). After amplification curves were checked, the remaining post-PCR mixtures were further amplified by achieving additional PCR of 4~11 cycles. Libraries were purified and size-selected using Agencourt AMPure XP beads (1.25x vol. to remove short fragments). 50bp, single-end reads were sequenced on an Illumina HiSeq2500 in a Rapid run mode for PolII and H3K4me1 and 50bp+41bp paired-end reads were sequenced on an Illumina NextSeq 500 in a High Output mode for Stat1 and Stat2.

After trimming low quality reads by sickle1.2 and adapter sequence by cutadapt1.2.1 (Martin, 2015), short reads were mapped to mm10 by bowtie 1.1.1 with –m 1 option, extended and piled-up by macs2.1.0 with options --nomodel --extsize 290 (for PolII and H3K4me1) --keep-dup 1 -B --SPMR. To normalize the PolII datasets, signals for every 10bp bin over each chromosome were taken and normalized by quantile normalization. Signals over TSS (-50bp to +200 bp of TSS) and gene-body (+200bp from TSS to gene end) were counted as the PolII on TSS and genebody respectively. For Stat2 analysis, mapped reads in each ATAC peak were counted by bedtools 2.23.0. The

datasets were converted into bigwig format and visualized by IGV software to show representative distribution of each factor.

Adaptor oligos (same as Multiplexing Adapters from Illumina)
5'ACACTCTTTCCCTACACGACGCTCTTCCGATCT
5'p-GATCGGAAGAGCACACGTCT
PCR Primers (modified from Illumina Multiplexing PCR Primers, under lines indicate the indexing part)

PE1.0 (common primer)
5'AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCT
PE2.1
5'CAAGCAGAAGACGGCATACGAGATCGTGATGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.2
5'CAAGCAGAAGACGGCATACGAGATACATCGGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.3
5'CAAGCAGAAGACGGCATACGAGATGCCTAAGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.4
5'CAAGCAGAAGACGGCATACGAGATTGGTCAGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.5
5'CAAGCAGAAGACGGCATACGAGATCACTGTGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.6
5'CAAGCAGAAGACGGCATACGAGATATTGGCGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.7
5'CAAGCAGAAGACGGCATACGAGATGATCTGGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.8
5'CAAGCAGAAGACGGCATACGAGATTCAAGTGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.9
5'CAAGCAGAAGACGGCATACGAGATCTGATCGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.11
5'CAAGCAGAAGACGGCATACGAGATGTAGCCGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.12
5'CAAGCAGAAGACGGCATACGAGATTACAAGGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.13
5'CAAGCAGAAGACGGCATACGAGATTTGACTGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.18
5'CAAGCAGAAGACGGCATACGAGATGCGGACGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT
PE2.24
5'CAAGCAGAAGACGGCATACGAGATGCTACCGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCT

ATACseq-enriched TF binding site motif analysis

To simplify the motif analysis and interpretation, we focused on ATAC peaks that overlapped a TSS and neighboring region ("TSS peaks"). 8,510 peaks were mapped to a unique TSS, and a total of 8,324 unique genes were assigned at least one ATAC TSS peak. Of the 102 ISGs in the regulatory network, 81 were assigned an ATAC TSS peak. To identify motifs associated with each TSS peak, we used the FIMO algorithm (http://web.mit.edu/meme_v4.9.0/doc/fimo.html). FIMO assigns a score, and a corresponding p-value, for the match between an input sequence and a given position-weight-matrix (PWM) representing a motif. In this analysis, we considered 263 known PWMs defined by the HOMER database (http://homer.salk.edu/homer/motif/motifDatabase.html), and assigned a score for each of these 263 PWMs to each TSS peak. We only considered motif scores with $p<10^{-4}$ (the default p-value threshold used by FIMO). We used the hypergeometric test to identify significantly enriched PWMs in various ISG lists. To identify enriched PWMs for general ISGs, we defined as background all non-ISG genes with detectable TSS ATAC peaks.

Regulatory network inference from cross-species datasets

Defining the set of regulators. Potential regulators were defined as all kinases and phosphatases, annotated by the kinome database (Manning et al., 2002), and all transcription factors and co-factors as defined by the AnimalTFDB database (http://www.bioguo.org/AnimalTFDB/). This definition resulted in a set of 1,152 potential regulators.

Defining the set of targets. We identified a set of targets to be included in the analyses by aiming to satisfy two criteria: inference of a species shared network (i.e., avoiding the potential for identifying regulatory links only supported by one species), and maximizing the coverage of represented target genes across different cell types. To do so, potential targets were identified using fold change calculations for mouse and human data in T cells and in DCs (as these two cell types also represent the majority of ImmVar cell types). Targets were required to be induced in T cells of human and T cells of mouse, or DCs of human and DCs of mouse (AND operation used between species, and OR operation used between cell types). For each cell type, FC > 2 in one species and at least FC > 1.5 in the second species was required. This resulted in 110 potential target genes.

Constructing the cross-species IFN regulatory network. 12 datagroups were used to construct the IFN regulatory network (Table S3A). Following the approach of Wang et al (Wang et al., 2009), each data group was first used independently to construct a co-expression matrix between all potential regulators (r:regulators) and potential targets (t:targets), resulting in twelve matrices of size r-by-t. These co-expression matrices were then z-score transformed across each column, so Z^k_{ij} represents the strengths of the association between regulator i and target gene j in dataset k. A final combined network, Z*, was computed by taking the element-wise average of all the z-score matrices, and a corresponding p-value was computed for each edge (Wang et al., 2009). An 0.01 FDR threshold was used to identify significant regulatory links. Regulators that linked to less than five targets (at 0.01 FDR), or targets that linked to less than two regulators (at 0.01 FDR) were excluded from the network. The LAS biclustering algorithm (Shabalin et al., 2015) was applied to this network to identify regulatory clusters.

Expanding the regulatory network to large set of ISGs with cell-specificity. The regulatory clusters were extended to a larger set of ISGs as follows. First, 818 IFN induced genes (FC>2) in mouse or human (union of those induced in T cells and DCs) were initially used to construct a combined regulator-to-target co-expression network. Then, each of these 818 genes was assigned to one of the 5 regulatory clusters, or "none" (if we could not make a high-confidence prediction about regulatory cluster memberships), based on the inferred network. In particular, the predictions were made based on the average co-expression between each of these target genes and regulators of each of the biclusters identified above (i.e., the smaller high-confidence network). In this way, a total of 629 target genes were assigned to five regulatory clusters (the remaining ISGs with lower confidence predictions were not considered). Cluster sizes varied between 106 and 173 (Table S3G).

RNAi knockdown and validation of predicted network links

RNAi knockdown data, as processed 'Z-score', have been reported (Chevrier et al., 2011). Among the regulatory and target genes tested in this dataset, 20 regulators and 16 target genes overlapped with those in our high-confidence IFN regulatory network. To compute AUROCs (Figure S5F), the RNAi z-scores were binarized using 6 different thresholds (3, 5, 10, 20, 30, 50), and accordingly 6 different vectors of binary link labels, with increasing confidence on the predicted associations between pairs of regulators and targets, were created. Then AUROC metric was used to assess the predictability of these binary link labels from the links predicted by our network.

Network overlap with interferon signatures in human diseases

We collated (Table S4A) genesets reported as differentially expressed in whole blood or PBMCs in a number of studies encompassing diverse conditions: acute or chronic microbial infection (Berry et al., 2010; Bolen et al., 2013; Dunmire et al., 2014; Fink et al., 2007; Smeekens et al., 2013); Common Variable Immunodeficiency (CVID); HIV patients non-responsive to antiviral therapy (Park et al., 2013; Wu et al., 2008); chronic autoimmune diseases (SLE, RA, Sjogren's syndrome) (Baechler et al., 2003; Bennett et al., 2003; Greenberg et al., 2005; Emamian et al., 2009) or MS patients insensitive to interferon therapy (Bustamante et al., 2013); recurrent major depression (Mostafavi et al., 2014); an ISG signature which predict a favorable outcome of early febrile Dengue infection (Nascimento et al., 2009). Several signatures from vaccination studies were also included (Li et al., 2014). Interferon "disease signatures" were retrieved from supplementary tables of 18 relevant publications (Table S4A). Only studies performed using blood expression data (whole blood, or whole PBMC) were included. These disease signatures were converted to binary vectors, based on presence/absence of our ISGs in the IFN regulatory network. To be more inclusive in terms of human ISG representation, we extended our list of ISGs to 124 genes by including additional ISGs induced in human CD4+ T cells (FC>1.5) (Tables S3D-F).

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