Supplementary Methods

A. Measurement of the Kynurenine/Tryptophan (KYN/TRP) Pathway Metabolites

LC-MS/MS analysis of KYN, TRP, and kynurenic acid (KA)

KYN-D_4, TRP-D_5, and KA-D_5 were used as internal standards (IS). Serum samples were prepared for analysis by a transfer of 10 µL sample, followed by the addition of 90 µL precipitation solution (acetonitrile/H_2O 8:2 with 0.1% formic acid and 0.01% ascorbic acid) containing IS. After vortexing, samples were centrifuged for 5 minutes at 4°C and 13,000 rpm, and 10 µL of supernatant was diluted 10-fold with 90 µL of ultrapure water with 0.1% (v/v) formic acid and 0.01% (w/v) ascorbic acid.

Samples were injected by a SIL20-AD autosampler (Shimadzu, Japan) onto an Atlantis T3 C18 High Performance Liquid Chromatography (HPLC) column (2.1*150 mm, 3.0 µm particle size; Waters, USA), held at 25°C. Mobile phase A consisted of ultrapure water with 0.1% FA. Mobile phase B was acetonitrile with 0.1% FA. Elution of the compounds was performed using a linear gradient at a flow rate of 0.2 mL/minute using the Infinity 1290 HPLC system (Agilent, USA). The HPLC system was connected to a QTrap 5500® mass spectrometer (Sciex, USA) equipped with a Turbo Ion Spray interface.

The acquisitions on the QTrap® 5500 were performed in positive ionization mode, with optimized settings for the analytes. The instrument was operated in multiple reaction-monitoring (MRM) mode. Data were calibrated and quantified using the Analyst™ data system (Sciex, version 1.5.2).

LC-MS/MS analysis of quinolinic acid (QA)

QA-D_3 was used as an IS. Serum samples were prepared for analysis by a transfer of 10 µL sample, followed by the addition of 40 µL precipitation solution (acetonitrile/H_2O 8:2) containing IS. After vortexing, samples were centrifuged for 5 minutes at 4°C and 13,000 rpm, and 5 µL of supernatant was diluted with 50 µL of ultrapure water with 0.1% (v/v) formic acid and 0.01% (w/v) ascorbic acid.

Samples were injected by a SIL 10ADvp autosampler (Shimadzu, Japan) onto a Synergi Max-RP HPLC column (3.0*100 mm, 2.5 µm particle size; Phenomenex, USA), held at 20°C. Mobile phase A consisted of ultrapure water with 0.2% TFA. Mobile phase B was acetonitrile with 0.2% TFA. Elution of the compound was performed using a linear gradient at a flow rate of 0.3 mL/minute using the LC-20ADxr HPLC system (Shimadzu, Japan). The HPLC system was connected to an API 4000® triple quadrupole mass spectrometer (Sciex, USA) equipped with a Turbo Ion Spray interface.

The acquisitions on the API 4000® mass spectrometer were performed in positive ionization mode, with optimized settings for the analytes. The instrument was operated in MRM mode. Data were calibrated and quantified using the Analyst™ data system (Sciex, version 1.4.2).

B. RNA Sequencing (RNAseq)

RNA isolation and quality control measures

De-identified, blinded whole blood samples in PAXgene Blood RNA tubes were received by Cold Spring Harbor Laboratory, and left out overnight at room temperature. RNA was extracted using the PAXgene RNA Kit, according to instructions exactly as written in the manufacturer's protocol. A subset of the samples was tested for quality determined by RNA Integrity Number (RIN) score using the RNA Nano Kit on a BioAnalyzer by Agilent Technologies.

After the blood RNA extraction, quality control was performed on all the RNA samples using the RNA assay for Qubit fluorometer (Thermo Fisher Scientific). A subset of the samples was run using the Agilent Femto RNA assay.

Library Preparation and RNAseq Technique

The kapa mRNA HyperPrep kit Illumina Platforms were used for library preparation. This protocol is suitable for the construction of high-quality libraries from 50 ng to 1 ug of total intact RNA. The amount of starting material was 100 ng high quality RNA in 50uL of RNase-free water, and fragment sizes of ~ 450 base

pair were targeted (6 minutes at 85ºC incubation). For the library amplification step, 13 cycles of PCR were performed.

Post-enrichment, the libraries were evaluated using the DNA HS assay on Qubit and the DNA HS Bioanalyzer assay, and then libraries were pooled based on nM concentration. The final pools were quantified using the kapa qPCR library quantification protocol, and then loaded on the Illumina NextSeq500 instrument. Sequencing runs were performed as single-end 76 base pair high outputs.

C. Identification of Interferon-Stimulated Genes (ISG)

Identification of ISG in the Interferome Database (Rusinova I et al Interferome v2.01, 2013)[1]

The filter in Interferome was set as previously described in Chiche et al[2], "Supplemental Methods, Interferome database:" experiment type: *in vitro*, species: human, organ: all except fetal brain, embryo, umbilical vein. Genes were defined as ISG if they were responsive to at least one type of interferon (IFN) with fold change (FC) expression > 2 compared to baseline after *in vitro* stimulation with IFN, as previously described (Chiche et al).

D. IFN scores

IFN scores were derived using methods for quantification of ISG expression and ISG selection:

1. Quantification of individual ISG expression:

   - Z-scores of normalized and variance stabilized gene expression were calculated as:

$$\frac{\text{Expression of the gene of interest} - \text{HC mean expression of the gene of interest}}{\text{HC standard deviation (SD) of the expression of the gene of interest}}$$

   - The "Z-IFN score" for each subject was then calculated as the mean of Z-scores for each of the genes of interest for each subject.

2. ISG selection:

   The "ISGs of interest" used to compute an IFN score for each subject were selected by 2 approaches:

   - **Approach 1** included 110 ISG reported by Arazi et al in their studies of single cell RNAseq analysis of IFN response in infiltrating cells in lupus nephritis. Of these 110 ISGs, 96 are co-expressed in the IFN modules reported by Chiche et al.
   - **Approach 2** included 19 ISGs from the 110 ISG included in Approach 1 that are more responsive to type I IFN than type II IFN, according to the modules of co-expressed ISG described in Chiche et al. (Module 1.2).

References

1. Rusinova I, Forster S, Yu S, et al. Interferome v2.0: an updated database of annotated interferon-regulated genes. *Nucleic Acids Res* 2013;41:D1040-6.
2. Chiche L, Jourde-Chiche N, Whalen E, et al. Modular transcriptional repertoire analyses of adults with systemic lupus erythematosus reveal distinct type I and type II interferon signatures. *Arthritis Rheumatol* 2014;66:1583-95.