**Supplemental Materials and Methods**

*Healthy donors and patients with SLE*

Buffy coats from 72 healthy female blood donors genotyped on the Immunochip (Illumina) were obtained from Uppsala Bioresource. The blood donors were selected based on their genotype of the *STAT4* risk allele rs7574865 and consisted of 24 homozygous protective (G/G), 24 heterozygous (G/T) and 24 homozygous risk (T/T) individuals. The three groups were age-matched G/G=53(25-79) years, G/T=52 (22-68) years, T/T=49(26-70) years (median(range)). STAT4 phosphorylation data from patients with SLE and their plasma levels of IFN-α are previously published.1

*Cells*Peripheral blood mononuclear cells (PBMCs) were prepared through Ficoll density-gradient centrifugation and viability frozen in FCS with 10% DMSO (SigmaAldrich). Memory CD8+ T cells were isolated from PBMCs (human memory CD8+ T cell isolation kit, Miltenyi). Cells from individuals that contained >80% CD3+CD8+CD45RO+CD57- cells and >80% viable cells were used. Cells were cultured at 37 °C in 5% CO2 using RPMI1640 medium supplemented with 10% FCS, 2mM Glutamine, hepes and pest (Invitrogen). PBMCs were pre-activated with 1.5% phytohemagglutinin (PHA, Gibco) and 2.5 ng/ml IL-2 (Miltenyi) for 70-72 hours. After washing, cells were rested 4 hours before being re-stimulated with IL-12 (Peprotech) or phorbol 12-myristate-13-acetate (PMA) together with the calcium-ionophore A23187 (both Sigma Aldrich). When indicated, cells were pre-activated 24 h with 100 U/ml IFNα2b (IntronA, Schering-Plough) or 1 ng/ml TNF-α (Peprotech) and washed once with 1x PBS before PHA/IL-2 activation.

 *STAT4 and STAT1 mRNA expression*

0.5-1x105 memory CD8+ T cells were either left unstimulated, or stimulated with PHA and IL-2 for 6 h in U-bottomed 96-well microplates. mRNA was isolated with RNEasy micro plus kit and cDNA was synthesized using the QuantiTect reverse transcription kit (Qiagen). Quantitative real-time reverse transcription–polymerase chain reaction (qRT-PCR) was performed using SYBR Green reagents and a 7500 RT-PCR system (Applied Biosystems). *STAT4alfa* and *STAT4beta* isoform expression was determined using STAT4alfa forward primer: 5′-CATCTCAACAATCCGAAGTGATTCA-3′, STAT4beta forward primer: 5′-TGACCTTGTTATCTCTTTAAGCCGA-3′ and the common reverse primer: 5′-GTCAGAGTTTATCCTGTCATTCAGCAG-3′. QuantiTect primer assays was used to determine expression of *STAT1alfa* (Hs\_STAT1\_va.1\_SG) and *RPL13a* (Hs\_RPL13A\_1\_SG). Expression levels were normalized to the expression of the reference gene *RPL13A* (2^-(Ctgene of interest-Ctreference gene)).

*Phosphorylation of STAT4*

PHA/IL-2 pre-activated cells were stimulated with or without 50-100 ng/ml IL-12 for 20 minutes. Cells were fixed in 2% paraformaldehyde (PFA) and surface stained for CD4 and CD8. Following permeabilization with Perm Buffer III (BD Biosciences), cells were stained for additional surface markers and phosphorylated STAT4 (pY693) using PE-labelled anti-pSTAT4 mAb (38p-STAT4, BD Biosciences). IL-12-induced pSTAT4 was determined by subtracting the median fluorescence intensity (MFI) of unstimulated cells from the MFI of IL-12-stimulated cells.

*IFN-γ production*

PHA/IL-2 pre-activated cells were stimulated with or without 5 ng/ml IL-12 for 15 hours in the presence of GolgiPlug (BD Biosciences) the last 12 hours. After staining for cell surface markers cells were fixed in PFA, permeabilized with 0.5% saponin (SigmaAldrich) and then stained with a PE-labelled anti-IFN-γ mAb (B27, BD Biosciences). IL-12-specific IFN-γ production was determined by subtracting the frequency of IFN-γ+ cells in unstimulated cells from that of the IL-12-stimulated cells.

*Fluorescently labelled antibodies*

Fluorescently labelled antibodies to CD3 (UCHT-1), CD4 (SK3 or RPA-T4), CD8 (SK1 or RPA-T8), CD45RA (HI100), CD45RO (UCHL1), CD56 (N901) and CD57 (HCD57 or TB01) were used.

*Flow cytometry*

Flow cytometry data was collected using a FACSCantoII instrument with FACSDiva software version 7.0 (BD, Biosciences) and analyzed using FlowJo software version 10.0.8 (Tree Star).

*Statistics*

Comparisons between two genotype groups were performed with Mann-Whitney U tests. One sample t tests were used to analyze whether the mean ratio of IL-12-induced pSTAT4 between IFN-α or TNF-α pre-activated cells and non-activated cells was significantly different from 1. For comparisons across all three genotype groups, Spearman’s correlation tests were used. All tests were two-tailed and a *P* value <0.05 was considered significant.

**Supplementary reference:**

1. Hagberg N, Joelsson M, Leonard D, et al.: The STAT4 SLE risk allele rs7574865[T] is associated with increased IL-12-induced IFN-gamma production in T cells from patients with SLE. Ann Rheum Dis. 2018 Jul;77(7):1070-1077.