Online supplementary materials and methods

Study design

The overall objectives were to explore the pathogenic mechanisms of RASFs through elucidating the genetic contribution to molecular regulatory networks under inflammatory condition. First, we quantified mRNA expression by RNA sequencing and compared transcriptome of SFs between the 10 conditions (i.e., non-stimulated, IFN-α, IFN-γ, TNF-α, IL-1β, IL-6/sIL-6R, IL-17, TGF-β1, IL-18 or 8-mix) and the diseases (i.e., RA, OA). We next performed cis-eQTL analysis to evaluate the effect of genetic variants on gene expressions in stimulated SFs and five major immune cell subsets ($CD4^+$ T cells, $CD8^+$ T cells, B cells, NK cells, monocytes) from the same patient. In addition, we examined candidate causal genes among RA risk loci in SFs. Focusing on eQTL variants in LD with GWAS top-associated loci, we assessed the biological role of the CD40-CD40L pathway in SFs by transcriptomic analysis of RASFs stimulated with a 2-trimer form of the CD40 ligand and IFN-γ as a representative example. Next, in order to elucidate the link between RA genetic risk and transcriptomic and epigenomic perturbations of stimulated SFs, we performed a gene-set enrichment analysis with RA-associated genetic loci and assessed the enrichment of GWAS top-associated loci in regulatory regions (SEs or TEs) identified with ChIP sequencing. Furthermore, we combined the 3D genome architectures (chromatin loops detected by Hi-C analysis), the position of SEs, promoter regions (defined with H3K4me3 ChIP sequencing analysis) in SFs under 3 different conditions: non-stimulated, TNF-α or the 8-mix. To reveal candidate modulators crucial for SE formation, especially in the 8-mix, we integrated motif analysis to focus on SE-contacted TFs that were also enriched in 8-mix SEs and compared them with TEs or stimulated SEs. Finally, the promising pathogenic TFs (i.e., MTF1, RUNX1)

in RASFs were silenced with siRNAs to validate transcriptomic effects, and the impact of MTF1 inhibitor was assessed by *in vitro* and *in vivo* assay.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Human participants and sample collection

Synovial tissues were obtained from RA and OA patients (n = 30 each) undergoing joint replacement surgery at the University of Tokyo Hospital, Japan. RA patients fulfilled the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) criteria for the classification of RA.[1] Patient characteristics are summarized in online supplementary table 5. This study was approved by the Ethics Committees of the University of Tokyo (G3582), RIKEN and the indicated medical institutions. Written informed consent was obtained from each subject in accordance with the Declaration of Helsinki. Fresh synovial tissues were minced and digested with 0.1% collagenase (Worthington) at 37℃, in 5% CO_2 for 1.5 h and SFs were cultured in Dulbecco's modified Eagle's medium (DMEM; SIGMA) supplemented with 10% fetal bovine serum (FBS; BioWest), 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin (all from Invitrogen). SFs from passage 2 or 3 were used for RNA sequencing, ChIP sequencing, Hi-C and functional studies after removal of macrophages by magnetic separation with CD14 microbeads (Miltenyi Biotec). The purity of SFs was tested by flow cytometry

analysis (MoFlo XDP; Beckman Coulter). SFs were stained with CD14-, Thy-1 (CD90)-specific monoclonal antibodies (clone IDs: M5E2, 5E10, respectively, all from BioLegend). Most cells (>99%) had the surface marker for fibroblasts (Thy-1) but not CD14.

We collected peripheral blood from the same patients. PBMCs were isolated using Ficoll-Paque density gradient centrifugation followed by staining with CD3-, CD4-, CD8-, CD14-, CD19- and CD56-specific monoclonal antibodies (clone IDs: UCHT1, OKT4, RPA-T8, M5E2, HIB19 and HCD56, respectively, all from BioLegend). Five immune cell populations were sorted by flow cytometry (MoFlo XDP; Beckman Coulter) using the following gating strategy: $CD4^+$ T cells: $CD3^+CD4^+CD8^-CD19^-$; $CD8^+$ T cells: $CD3^+CD4^-CD8^+CD19^-$; B cells: $CD3^-CD19^+$; NK cells: $CD3^-CD14^-CD19^-CD56^+$; and monocytes: $CD3^-CD14^+CD19^-$. There were 3×10^5 cells in each population.

RNA sequencing

Purified SFs (2×10^4 cells/well) were seeded with DMEM (10% FBS, 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin) into a 24-well flat-bottom plate (Corning) and incubated at 37°C, in 5% CO_2. After 12 h, one of the following was added: 100 U/mL IFN-α (HumanZyme), 200 U/mL IFN-γ, 10 ng/mL TNF-α, 10 ng/mL IL-1β, 200 ng/mL IL-6/sIL-6R, 10 ng/mL IL-17 (all from PeproTech), 10 ng/mL TGF-β1 (R&D), 100 ng/mL IL-18 (MBL). Alternatively, cells were treated with "8-mix" (a mixture of the above 8 cytokines that simulated synergistic inflammation in arthritic joints).

These 8 cytokines were selected by a literature search (PubMed) for 1) cytokines mainly secreted by immune cells

and involved in pathological phenotype formation of SFs, 2) cytokines mainly secreted by SFs and acting as autocrine, and 3) existing therapeutic targets. The number of papers was greatest in IFN-γ, IFN-α, TNF-α, IL-1β, IL-17A, IL-18 and TGF-β1 for 1), in IL-6 for 2) and in TNF-α, IL-1β and IL-6 for 3). The cells were stimulated for an additional 24 h at 37°C, in 5% CO_2.

Total RNA from SFs and freshly sorted PBMCs was isolated using AllPrep DNA/RNA/miRNA Universal Kit (Qiagen). Libraries for RNA sequencing were prepared using TruSeq Stranded mRNA Library Prep Kit (Illumina). RNA sequencing was carried out on Illumina HiSeq 2500 (read length of 125 bp, paired end).

Bioinformatic analysis of RNA sequencing data

RNA sequencing reads were aligned to the human genome assembly hg19/GRCh37 excluding minor haplotypes, random and unknown sequences. Alignment of the reads was performed by STAR (version 2.5.3) (Key resources information) based on the GENCODE v27 (GRCh37 version) annotation. We only utilized reads that were uniquely mapped (corresponding to a mapping quality of 255 for BAM files) and properly paired for further analysis.

Gene-level read counts were quantified with HTSeq (version 0.6.0) (Key resources information) based on the GENCODE v27, with strand-specific assay mode and the other default parameters. Transcript-level quantifications were calculated with RSEM (version 1.3.0) (Key resources information).

We assessed the quality of each RNA sequencing sample by calculating the mean expression correlation coefficient with other samples with the same stimulatory conditions, equivalent to D statistics as described elsewhere.[2] All samples satisfied more than 10 million uniquely mapped read counts. We excluded samples the D

77 statistics of which were lower than 0.9, resulting in 29 excluded samples (4 non-stimulated, 4 in TNF-α, 3 in IFN-α,
78 2 in IFN-γ, 6 in IL-1β, 4 in TGF-β1, 2 in IL-17, 3 in 8-mix and 1 $CD8^+$ T cell). The remaining 856 samples were
79 utilized for the analysis.

80 Differential expression analysis was performed with the edgeR package (Key resources information) with
81 gene-level count data. For each comparison, genes whose expression was less than 10 in more than 90% of samples
82 were excluded. Gender was included as a covariate for all the comparative analyses. RUVseq R package (Key
83 resources information) was utilized for finding hidden factors using 1000 nonvariable genes with conditions as
84 negative control genes and unstimulated samples as negative control samples. Gender and 3 RUV factors were
85 considered covariates in differential expression analysis. Genes with FDR less than 0.05 in the glml RT test
86 implemented in edgeR were regarded as differentially expressed genes (DEGs).

87 Gene set enrichment of DEGs to "C2 canonical pathway" gene sets in MSigDB (Key resources information) was
88 analyzed using the clusterProfiler package (Key resources information).

89 MAGMA software (Key resources information) was applied for gene-set analysis of GWAS data. We utilized RA
90 GWAS summary statistics of European ancestry or East Asian ancestry and performed gene set enrichment analysis
91 following the instruction by the authors.[3] Briefly, we carried out “gene analysis” for GWAS summary statistics
92 using the 1000 genomes LD panels (European panel for European GWAS and East Asian panel for East Asian
93 GWAS) and GENCODE v27 gene annotation. Then we carried out “gene-set analysis” using log-fold change of
94 gene expression between conditions as gene covariate and performed enrichment analysis.

95

ChIP sequencing

Purified SFs (1×10^5 cells/well) were seeded with DMEM (10% FBS, 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin) into 6-well flat-bottom plates (Corning) and incubated at 37°C, in 5% CO_2. After 12 h, 100 U/mL IFN-α, 200 U/mL IFN-γ, 10 ng/mL TNF-α, 10 ng/mL IL-1β, 200 ng/mL IL-6/sIL-6R, 10 ng/mL IL-17, 10 ng/mL TGF-β1, 100 ng/mL IL-18 or 8-mix was added. The cells were stimulated for additional 24 h at 37°C, in 5% CO_2.

Pooled SFs and freshly sorted PBMCs from RA or OA patients (n = 20 each) were cross-linked with 1% formaldehyde for 15 min at room temperature. Chromatin was prepared from pellets of SFs (1×10^7 cells) and PBMCs (2×10^7 cells) using a CHIP-IT High Sensitivity Kit and CHIP-IT PBMC Kit (both from Active Motif), respectively. Sonication was carried out by Covaris S2 (Covaris). The shearing efficiency was analyzed by agarose gel electrophoresis after RNase treatment, reversion of crosslinking and purification of DNA. Sheared chromatin (3 µg) was immunoprecipitated using 4 µL of each rabbit polyclonal antibody (H3K4me1, H3K4me3, H3K27ac, all from Active Motif). Sheared chromatin was used as the input DNA. Immunoprecipitated DNA was quantified with the Qubit dsDNA HS Kit (Invitrogen). Libraries for ChIP sequencing were prepared using TruSeq ChIP Library Prep Kit (Illumina) with 5 ng of DNA fragments. DNA size selection (250 - 300 bp) was carried out by BluePippin (Sage Science). ChIP sequencing was carried out on an Illumina HiSeq 2500 (read length of 50 bp, single end).

Bioinformatics analysis of ChIP sequencing data

Sequencing reads from each ChIP sequencing sample were mapped to human genome assembly hg19/GRCh37

using Bowtie2 (Key resources information). PCR duplicates were removed, and only uniquely mapped reads were used for peak calling. MACS 2.0 (Key resources information) was used to detect peaks which were enriched in immunoprecipitated samples over the input. Peak calling was performed with narrow peak mode for H3K4me3 and H3K27ac and broad peak mode for H3K4me1.

NSC and RSC were calculated by cross-correlation analysis following ENCODE guidelines and samples with NSC less than 1.1 or RSC less than 1 were removed from the analysis.[4] Also, samples with <10 million effective sequence reads were removed. As a result, 4 samples (RA_CD8_H3K27ac, OA_CD8_H3K27ac, OA_IL17_H3K27ac and RA_CD8_H3K4me3) were excluded and the remaining 86 samples were utilized for further analysis.

SEs were identified with the Rank Ordering of Super-Enhancers (ROSE) algorithm (Key resources information) based on the H3K27ac ChIP sequencing signal with default parameters.

Differentially bound peak analysis for each condition was performed with HOMER software (Key resources information) with fold-enrichment threshold of 2 and Poisson enrichment *P* value threshold of 0.0001.

Motif enrichment analysis was performed with HOMER software. As motifs of some TFs associated with SEs were not included in the HOMER database, we customized motif reference with MotifDb software (Key resources information) for SE associated genes only with *homo sapiens* data.

Library construction for Hi-C

Purchased RASFs (n = 7, Articular Engineering) were used to generate an *in situ* Hi-C library as previously

described with minor modifications.[5] Briefly, SFs (1×10^5 cells/well) were seeded with DMEM (10% FBS, 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin) into 6-well flat-bottom plates and incubated at 37°C, in 5% CO_2. After 12 h, either 10 ng/mL TNF-α or 8-mix was added, and the cells were stimulated for an additional 24 h at 37°C, in 5% CO_2. Pooled SFs (2.8×10^6 cells) were cross-linked with 1% formaldehyde for 10 min at room temperature. The nuclei were permeabilized, and DNA was digested with 100 units of Mbo I restriction enzyme (NEB). The ends of restriction fragments were labeled with biotinylated nucleotides (dATP; Invitrogen), and proximity ligation was performed. After reversal of crosslinks, ligated DNA was purified and sheared to a length of roughly 400 base pairs with Covaris S2 (Covaris), at which point ligation junctions were pulled down with streptavidin beads (Invitrogen). Sequencing libraries were prepared with a Nextera Mate Pair Sample Preparation Kit (Illumina) and sequenced using a HiSeq series (read length of 150 bp, paired-end read).

Bioinformatics analysis of Hi-C data

Sequencing reads from 3 samples were mapped to human genome assembly hg19/GRCh37 using BWA-mem which is implemented in JUICER software (ver 1.8.9) (Key resources information). Loops were called using HiCCUPS software (Key resources information) implemented in JUICER with resolution of 5 kbp, 10 kbp and 25 kbp and merged loops were used for downstream analysis.

SNP typing and imputation

Genomic DNA from whole blood was isolated using QIAamp DNA Blood Midi Kit (Qiagen). Genotyping was

153 performed using Infinium OmniExpressExome BeadChips (Illumina).

154 Quality control of the genotyping data was performed using PLINK 1.90 (Key resources information), with a SNP
155 call rate > 0.99, HWE < 1×10^{-6} and sample call rate > 0.98. For genome-wide imputation, 595693 post-QC SNPs
156 were pre-phased using SHAPEIT (Key resources information) and imputation was performed using IMPUTE2
157 (Key resources information) with the 1000 Genomes Phase 3 panel as reference. Post-imputation QC was
158 performed using SNPTEST (Key resources information). Genotyped and imputed autosomal SNPs or indels with
159 MAF ≥ 0.05 were used for cis-eQTL analysis (6124313 variants in total).

160

161 **Cis-eQTL analysis**

162 For cis-eQTL analysis, genes detected in at least half of the samples under at least 1 condition were included. The
163 counts per million (CPM) matrix was normalized between samples using TMM as implemented in edgeR software,
164 normalized across samples using an inverse normal transform and normalized using PEER (Key resources
165 information) with 15 hidden confounders, and the residuals were used for analysis. We used QTLtools (Key
166 resources information) conditional pass for tissue-by-tissue eQTL analysis. In addition, to improve analytical ability,
167 we jointly analyzed the RA and OA samples. We performed a meta-analysis across SFs in various stimulatory
168 conditions and PBMC samples for eQTLs by utilizing Meta-Tissue software (Key resources information), a linear
169 mixed model that allows for heterogeneity in effect sizes across conditions. Cis-eQTL analysis was performed for
170 variants with MAF ≥ 0.05 within a 1 Mb window around each gene.

171 For each eQTL, we estimated the posterior probability that the effect is shared in each tissue (*m*-value) along with

tissue-by-tissue eQTL analysis *P* value.

For comparison of eQTL effect sizes between RA and OA samples, we performed a likelihood ratio test between the 2 nested models using the R anova function (two-sided). The null model, H_0, and alternative model, H_1 are detailed in the following equations:

$$H_0 : E \approx I + \beta_1 G + \beta_2 D$$

$$H_1 : E \approx I + \beta_1 G + \beta_2 D + \beta_3 D \times G$$

where E is the normalized eGene expression, I is the intercept, G is the eVariant genotype, D is the disease term (RA or OA), and β_1, β_2 and β_3 are the regression coefficients.

At first, we tested all of genome-wide significant eQTL variants (2,114,141 variants, FDR < 0.1 or *m*-value > 0.9) for disease interaction, which resulted in 6 loci achieving genome-wide significance (FDR < 0.1, the upper panel of online supplementary figure 2C). Second, when we limited our analyses to genome-wide significant eQTL variants which overlap with histone marks (244,195 variants which overlap with H3K4me3, H3K27ac or H3K4me1 peaks), 8 loci achieved genome-wide significance (FDR < 0.1, the middle panel of online supplementary figure 2C). Finally, when we limited our analyses to genome-wide significant eQTL variants which overlap with differential peaks in any of the histone marks between RA and OA (4,087 variants), 12 loci achieved genome-wide significance (FDR < 0.1, the lower panel of online supplementary figure 2C). We considered these 12 loci as disease-specific eQTLs.

GWAS enrichment analysis

In order to calculate GWAS variant enrichment for epigenomic marks, we prepared 10,000 sets of randomly sampled variants that were matched to GWAS variants for distance from the nearest TSS, minor allele frequency (MAF), gene density and the number of LD variants ($r^2 \geq 0.5$) using SNPSNAP (Key resources information). We counted the number of GWAS variants or randomly selected variants whose LD ($r^2 \geq 0.8$) variants or itself coincided with epigenomic marks. We calculated the empirical *P* value by comparing the number of GWAS variants that tagged epigenomic marks against the number of randomly selected variants that tagged epigenomic marks. We pruned GWAS variants such that no 2 variants were within 1 Mb of one another, and all GWAS variants within the extended MHC region (25 - 35 Mb on chromosome 6) were removed from the analysis.

Population enrichment score

In order to assess the abundance of SF populations reported in the single-cell transcriptome based analysis,[6] we calculated the population enrichment score of each SFs sample. We used “top 20 marker genes for each single-cell RNA sequencing cluster” of 4 SF clusters from the article and calculated the enrichment score of these gene sets using GSVA software (Key resources information) with normalized CPM.

cDNA synthesis and qRT-PCR

Purified RASFs (2×10^4 cells/well) were seeded with DMEM (10% FBS, 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin) into 24-well flat-bottom plates and incubated for 12h at 37°C, in 5% CO_2. In *in vitro* inhibition studies of Brd4 or MTF-1, the cells were pretreated with JQ1 (Sigma; 50 - 5000 ng/mL) or

APTO-253 (Medchemexpress; 1 - 4 μg/mL) for 6 h and incubated with 8-mix cytokines for an additional 24 h at 37°C, in 5% CO_2.

Total RNAs were extracted with RNeasy Micro Kit (Qiagen) and were reverse-transcribed to cDNA with random primers (Invitrogen), dNTP mixture (Takara), ribonuclease inhibitor (Promega) and SuperScript III (Invitrogen). Quantitative real-time PCR (qRT-PCR) was performed using CFX Connect Real-Time PCR Detection System (Bio-Rad) with QuantiTect SYBR Green PCR Kit (Qiagen). The primer pairs used in this study are shown in online supplementary table 6. Relative expression was calculated based on the abundance of control *GAPDH*.

Human IL-6 and CCL5 ELISA

The concentration of IL-6 and CCL5 in supernatants of SFs was measured using the Human IL-6 Uncoated ELISA Kit (Invitrogen) and Human CCL5/RANTES Quantikine ELISA Kit (R&D), respectively, according to the manufacturer's instruction.

Knockdown assay

Purchased RASFs were used for knockdown assays. Cells (4×10^5 cells/target) were transfected with 300 nM ON-TARGET plus siRNA targeting *MTF1, RUNX1, SNAI1* or *TCF4* (all from Dharmacon) using a Human Dermal Fibroblast Nucleofector Kit (Lonza) according to the manufacturer's instructions. SiGENOME Non-Targeting Control Pool (300 nM, Dharmacon) was used as a transfection control. Transfected cells (4×10^4 cells/well) were seeded with DMEM (10% FBS, 100 μg/mL L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin) into

24-well flat-bottom plates and incubated at 37°C, in 5% CO_2. After 6 h, cells were stimulated with 8-mix cytokines for an additional 6 h. Total RNA was isolated using AllPrep DNA/RNA/miRNA Universal Kit. Libraries for RNA sequencing were prepared using TruSeq Stranded mRNA Library Prep Kit. mRNA sequencing was carried out on Illumina MiSeq (read length of 150 bp, paired end).

CD40 stimulation assay

Purchased RASFs (n = 3) were used in the CD40 stimulation assay. RASFs (2×10^4 cells/well) were seeded with DMEM (10% FBS, 100 µg/mL L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin) into 24-well flat-bottom plates and incubated at 37°C, in 5% CO_2. After 12 h, cells were stimulated with 1 - 10 ng/mL CD40L (ENZ) and 200 U/mL IFN-γ or 8-mix cytokines for an additional 24 h. RNA extraction, cDNA synthesis and RT-PCR was performed as described above. Total RNA was isolated using AllPrep DNA/RNA/miRNA Universal Kit. Libraries for RNA sequencing were prepared using TruSeq Stranded mRNA Library Prep Kit. The mRNA sequencing was carried out on Illumina MiSeq (read length of 150 bp, paired end).

Mice and induction of CIA

DBA/1J male mice (6 weeks) were purchased from Japan SLC. To induce CIA, bovine type II collagen (CII; Chondrex) was emulsified in equal volume of Complete Freund's Adjuvant (CFA; Chondrex). Mice were intradermally injected with the emulsion (100 µL) containing 100 µg CII. Twenty-one days later, a secondary injection was given at the same concentration of CII emulsified in Incomplete Freudn's Adjuvant (IFA; Chondrex).

Mice were examined every day for clinical signs of arthritis after the first injection. The severity of arthritis was assessed by qualitative clinical score determined as follows: 0 = normal paw; 1 =one toe inflamed and swollen; 2 = >1 toe, but not entire paw inflamed and swollen, or mild swelling of entire paw; 3 = entire paw inflamed and swollen; 4 = very inflamed and swollen or ankylosed paw. Each paw was scored individually and totaled them for each mouse (a maximum of 16 points). All procedures were performed in accordance with National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and approved by the ethics committee of the University of Tokyo Institutional Animal Care and Use Committee.

Treatment of CIA

In the treatment experiment, following the onset of arthritis (clinical score >1), CIA mice were randomized into 2 groups and intravenously injected with either control (10% DMSO and 18% SBE-β-CD) or 15 mg/kg APTO-253 in 10% DMSO and 18% SBE-β-CD for twice per day for 2 consecutive days per week for 14 days. In the prophylaxis experiment, on the same day as the second immunization, CIA mice were randomized into 2 groups and intravenously injected with either control (10% DMSO and 18% SBE-β-CD) or 15 mg/kg APTO-253 in 10% DMSO and 18% SBE-β-CD for twice per day for 2 consecutive days per week for 14 days.

Histological assessment

Mice were killed on day 15 after the start of treatment. Four paws were surgically removed and fixed in 4% paraformaldehyde, decalcified in 20% EDTA and embedded in paraffin. Then, the sectioned tissues were stained

with haematoxylin and eosin (H&E) and Safranin O for histopathology. Synovial tissue thickening, mononuclear cell infiltration, pannus invasion, and cartilage damage were graded. For synovial tissue thickening, scores were: 0, no changes (thickness less than 0.7 mm at the patellar tendon); 1; mild changes (0.7-1.0 mm); 2, moderate changes (1.0-2.0 mm); 3, severe changes (2.0 mm and more). For mononuclear cell infiltration, scores were: 0, no changes (no infiltration); 1, mild changes (less than 150 cells in 0.07μm2); 2, moderate changes (150-300 cells); 3, severe changes (300 cells or more). For pannus invasion, scores were: 0, no pannus; 1, mild changes (pannus invasion within the cartilage); 2, moderate changes (pannus invasion into the cartilage/subchondral bone transition); 3, severe changes (pannus invasion into the subchondral bone). For cartilage damage, scores were: 0, no destruction; 1, minimal erosion limited to single spots; 2, slight to moderate erosion in a limited area; 3, more extended erosions; 4, general destruction.

Statistical analysis

For *in vitro* analysis, statistical significance and analysis of variance (ANOVA) between indicated groups were analyzed by R (ver 3.4.1). A comparison of more than 2 group means was analyzed by Tukey's multiple comparison tests. A comparison of 2 group means was analyzed by paired t-test or Mann–Whitney U test. Statistically significant differences were accepted at $P < 0.05$ for all tests. Data in the bar charts were expressed as means ± standard deviation (SD).

For large-scaled data analysis including differentially expressed gene analysis and eQTL analysis, multiple test correction was performed with B-H method to obtain corrected q-values. For epigenome mark enrichment analysis

284 and transcriptome enrichment analysis with MAGMA, Bonferroni-corrected significance threshold was applied.

285

286 **Key resources information**

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Rabbit polyclonal anti- H3K4me1	Active Motif	Cat#39298; RRID: AB_2615075
Rabbit polyclonal anti- H3K4me3	Active Motif	Cat#39160; RRID: AB_2615077
Rabbit polyclonal anti- H3K27ac	Active Motif	Cat#39134; RRID: AB_2561016
Mouse monoclonal anti- CD3 (clone: UCHT1)	BioLegend	Cat#300419; RRID: AB_439780
Mouse monoclonal anti- CD4 (clone: OKT4)	BioLegend	Cat#317433; RRID: AB_11150413
Mouse monoclonal anti- CD8 (clone: RPA-T8)	BioLegend	Cat#301007; RRID: AB_314125
Mouse monoclonal anti- CD14 (clone: M5E2)	BioLegend	Cat#301823; RRID: AB_893253
Mouse monoclonal anti- CD19 (clone: HIB19)	BioLegend	Cat#302211; RRID: AB_314241
Mouse monoclonal anti- CD56 (clone: HCD56)	BioLegend	Cat#318331; RRID: AB_10898118
Mouse monoclonal anti- CD90 (Thy1) (clone: 5E10)	BioLegend	Cat#328107; RRID: AB_893438
Biological Samples		
Synovial specimen of human rheumatoid arthritis	This paper	N/A
Synovial specimen of human osteoarthritis	This paper	N/A
Peripheral blood of human rheumatoid arthritis	This paper	N/A
Peripheral blood of human osteoarthritis	This paper	N/A
Chemicals, Peptides and Recombinant Proteins		
Human IFN-α 2A	HumanZyme	Cat#HZ-1066; GenPept: P01563
Human IFN-γ	PeproTech	Cat#300-02; GenPept: P01579

Human TNF-α	PeproTech	Cat#300-01A; GenPept: P01375
Human IL-1β	PeproTech	Cat#200-01B; GenPept: P01584
Human IL-6	PeproTech	Cat#200-06; GenPept: P05231
Human sIL-6R	PeproTech	Cat#200-06R; GenPept: P08887
Human TGF-β1	R&D	Cat# 240-B-002/CF; GenPept: P01137
Human IL-17	PeproTech	Cat#200-17; GenPept: Q16552
Human IL-18	MBL	Cat#B001-5; GenPept: Q14116
JQ1	Sigma-Aldrich	Cat#SML1524; CAS: 1268524-70-4
MEGACD40L	ENZ	Cat#ALX-522-110-C010
APTO-253	Medchemexpress	Cat#HY-16291; CAS: 916151-99-0
Bovine Type II Collagen	Chondrex	Cat#20022
Complete Freund's Adjuvant	Chondrex	Cat#7001
Incomplete Freund's Adjuvant	Chondrex	Cat#7002
Critical Commercial Assays		
AllPrep DNA/RNA/miRNA Universal Kit	QIAGEN	Cat#80224
RNeasy Micro Kit	QIAGEN	Cat#74004
TruSeq Stranded mRNA Library Prep Kit	Illumina	Cat#RS-122-2101/2102
ChIP-IT High Sensitivity	Active Motif	Cat#53040
ChIP-IT PBMC	Active Motif	Cat#53042
TruSeq ChIP Library Preparation Kit	Illumina	Cat#IP-202-1012/1024
Nextera Mate Pair Sample Preparation Kit	Illumina	Cat#FC-132-1001
Human Dermal Fibroblast Nucleofector Kit	Lonza	Cat#VPD1001
Human IL-6 Uncoated ELISA Kit	Invitrogen	Cat#88-7066
Human CCL5/RANTES Quantikine ELISA Kit	R&D	Cat#DRN00B

Deposited Data		
Read counts data of RNA sequencing	This paper	NBDC: hum0207.v1.RNA.v1
eQTL summary	This paper	NBDC: hum0207.v1.eQTL.v1
Peaks data of ChIP sequencing	This paper	NBDC: hum0207.v1.ChIP.v1
Chromatin loops data of Hi-C	This paper	NBDC: hum0207.v1.HiC.v1
Experimental Models: Cell Lines		
Synovial fibroblasts of human rheumatoid arthritis	Articular Engineering	Cat#CDD-H-2910-RA
Experimental Models: Organisms/Strains		
Mouse: DBA/1J Jms Slc	SLC	RRID: MGI:5651994
Oligonucleotides		
ON-TARGET plus siRNA targeting MTF1	Dharmacon	Cat#L-020078-00-0005
ON-TARGET plus siRNA targeting RUNX1	Dharmacon	Cat#L-003926-00-0005
ON-TARGET plus siRNA targeting SNAI1	Dharmacon	Cat#L-010847-01-0005
ON-TARGET plus siRNA targeting TCF4	Dharmacon	Cat#L-004594-00-0005
SiGENOME Non-Targeting Control Pool #1	Dharmacon	Cat#D-001206-13-05
Software and Algorithms		
R3.4.1	R Core team, 2016	https://www.R-project.org
Python 2.7	Python Software	https://www.python.org/
STAR (version 2.5.3)	Dobin et al, 2012	https://github.com/alexdobin/STAR

HTSeq (version 0.6.0)	Anders et al, 2014	https://github.com/simon-anders/htseq
RSEM (version 1.3.0)	Li et al, 2011	https://github.com/deweylab/RSEM
RUVseq (version 1.10.0)	Risso et al, 2014	https://github.com/drisso/RUVSeq
edgeR (version 3.18.1)	Robinson et al, 2010	https://bioconductor.org/packages/release/bioc/html/edgeR.html
MAGMA (version 1.07)	de Leeuw C et al, 2015	https://ctg.cncr.nl/software/magma
Bowtie2 (version 2.3.4.2)	Langmead et al, 2009	https://github.com/BenLangmead/bowtie2
MACS 2.0 (version 2.1.1)	Zhang et al, 2008	https://github.com/taoliu/MACS
ROSE	Whyte et al, 2013	http://younglab.wi.mit.edu/super_enhancer_code.html
HOMER (version 4.9.1)	Heinz et al, 2010	http://homer.ucsd.edu/homer/
MotifDb (version 1.18.0)	Shannon et al, 2019	http://bioconductor.org/packages/release/bioc/html/MotifDb.html
BWA (version 0.7.17)	Li et al, 2009	https://github.com/lh3/bwa
JUICER (version 1.5)	Durand et al, 2016	https://github.com/aidenlab/juicer
HiCCUPS	Rao et al, 2014	https://github.com/aidenlab/juicer/wiki/HiCCUPS
PLINK (v1.90b4.4)	Purcell et al, 2007	https://github.com/chrchang/plink-ng/

SHAPEIT (v2.r904)	Delaneau et al, 2012	https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html
IMPUTE2 (version 2.3.2)	Howie et al, 2009	https://mathgen.stats.ox.ac.uk/impute/impute_v2.html
SNPTEST (version 2.5.4)	Marchini et al, 2007	https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html
Meta-Tissue (version 0.5)	Sul et al, 2013	http://genetics.cs.ucla.edu/metatissue/
PEER (version 1.0)	Stegle et al, 2010	https://github.com/PMBio/peer/wiki
QTLtools	Delaneau, 2017	https://qtltools.github.io/qtltools/
SNPSNAP	Pers et al, 2014	https://data.broadinstitute.org/mpg/snpsnap/
GSVA (version 1.24.2)	Hänzelmann et al, 2013	https://bioconductor.org/packages/release/bioc/html/GSVA.html
BEDTools (version 2.26.0)	Quinlan et al, 2010	https://github.com/arq5x/bedtools2
MSigDB (version 7.1)	Liberzon et al, 2011	https://www.gsea-msigdb.org/gsea/msigdb/index.jsp
clusterProfiler (version 3.16.1)	Yu et al, 2012	https://bioconductor.org/packages/release/bioc/html/clusterProfiler.html
Other		
Human CD14 MicroBeads	Miltenyi Biotec	Cat#130-050-201
Mbo I	NEB	Cat#R0147S
Biotin-14-dATP	Invitrogen	Cat#19524016

DynabeadsTM MyOne™ Streptavidin T1	Invitrogen	Cat#65601
SuperScript III Reverse Transcriptase	Invitrogen	Cat#18080093
Random Primers	Invitrogen	Cat#48190011
dNTP Mixture	Takara	Cat#4030
RNasin® Plus Ribonuclease Inhibitor	Promega	Cat#N2611
QuantiTect SYBR Green PCR Kit	QIAGEN	Cat#204143

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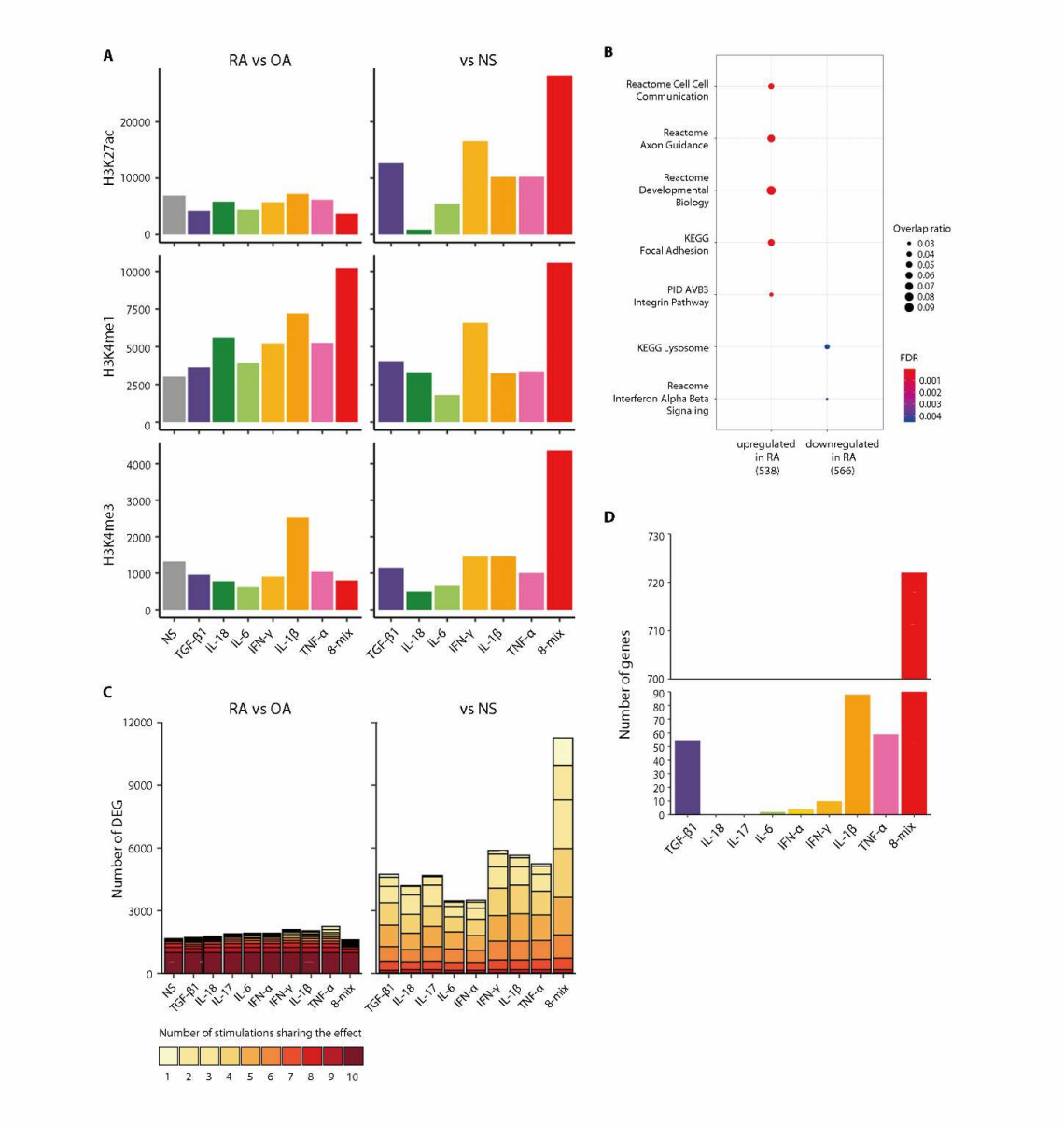
Online supplementary note 1. The estimated enrichment of SF populations revealed by single-cell RNA sequencing analysis of freshly isolated SFs.

Fan Zhang *et al* reported three sublining subpopulations, namely $CD34^{+}$ (F1), HLA-DRA^{hi} (F2) and $DKK3^{+}$ (F3), and one lining subpopulation (F4) based on single-cell RNA sequencing.[6] To elucidate the association between transcriptional changes of activated SFs and those 4 fractions, we applied "top 20 marker genes for each single-cell RNA sequencing cluster" for enrichment score calculation, and the population enrichment score of our stimulated SFs was calculated using GSVA software.[7] F4 is the population most abundant in the lining of OA synovium, and interestingly, the F4 score was higher in OASFs irrespective of the stimulation (online supplementary figure 11). In contrast, F2 is the major IL-6 producer in the sublining, and the F2 score was strongly upregulated under IFN-γ, IFN-α, IL-6 or 8-mix stimulation and showed no difference between RA and OA. Accordingly, we surmised that the F4 population was quantitatively stable between the diseases, although the F2 population might be inducible under inflammation.

Online supplementary note 2. Contribution of each cytokine to 8-mix condition.

The epigenomic modifications in the 8-mix were deciphered into additive effects of 8 stimulations and non-additive effects, which might be the consequence of cytokine synergy. The additive effect largely consisted of changes induced by the combination of 3 or 4 kinds of cytokines including IL-1β, IFN-α and/or IFN-γ (online supplementary figure 12). A part of non-additive H3K27ac peaks formed distinct SEs (figure 5B), and some RA risk loci including rs28411352 overlapped with those SEs.

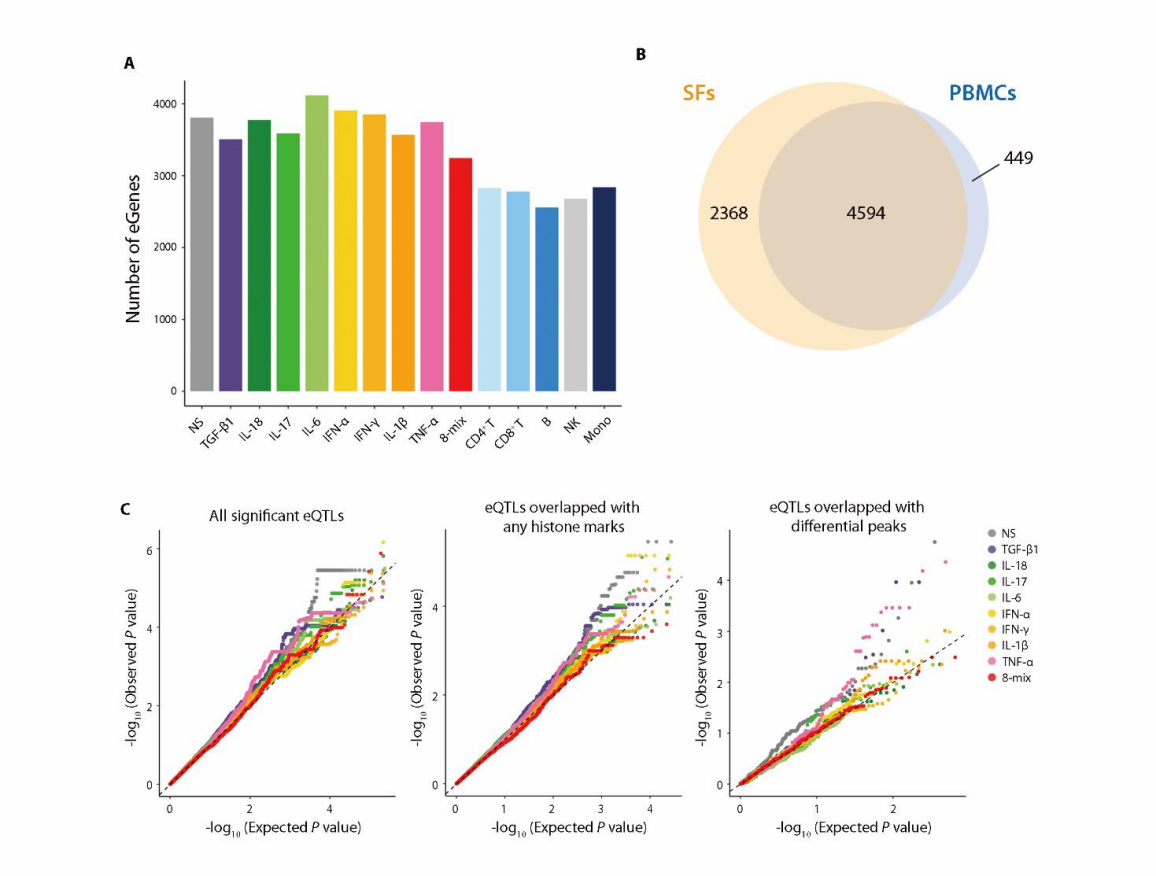


Online supplementary figure 1. Overview of transcriptomic and epigenomic signatures in RASFs under stimulatory conditions.

(**A**) The number of differential peaks from ChIP sequencing. Left, RA vs OA; Right, stimulated SFs vs non-stimulated SFs. (**B**) Significantly enriched pathways for differentially expressed genes comparing RASFs and

OASFs under non-stimulated condition. (**C**) The number of differentially expressed genes from RNA sequencing. Left, RA vs OA; Right, stimulated SFs vs non-stimulated SFs. Bar plots are colored by the number of stimulations sharing the effects. Left, RA vs OA; Right, stimulated SFs vs non-stimulated SFs. (**D**) The number of genes for which the response to stimulation were significantly different between RASFs and OASFs (FDR < 0.05). For each stimulation, gene expression was analyzed with non-stimulated SFs, and disease-stimulation interaction term was tested for significance.

SFs, synovial fibroblasts; RA, rheumatoid arthritis; OA, osteoarthritis; NS, non-stimulated; DEG, differentially expressed genes.



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323 **Online supplementary figure 2. Summary of the results of cis-eQTL analysis in stimulated SFs and PBMCs**

324 **from RA and OA patients.**

325 (**A**) The number of eGenes in stimulated SFs and PBMCs. (**B**) A Venn diagram representing the overlap of eGenes

326 in SFs (in any condition) and PBMCs. (**C**) Distribution of disease-eQTL interaction *P* values compared to expected

327 null distribution. When analyses were limited to eQTL variants overlapping with differential epigenome peaks

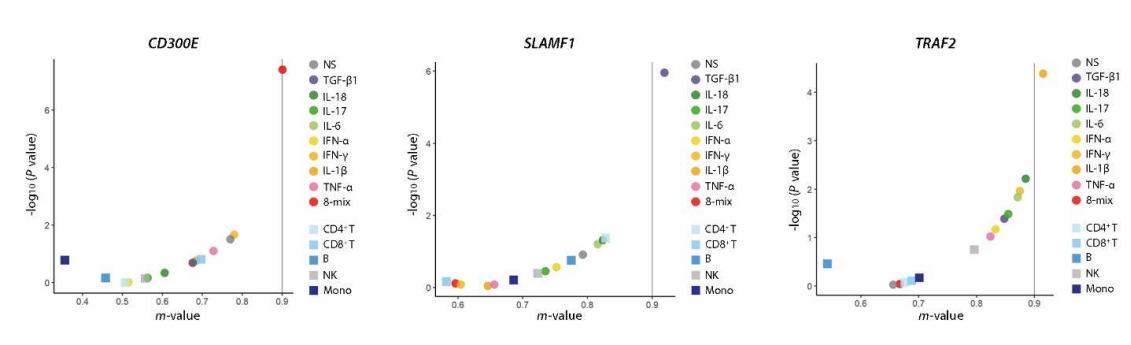
328 between RA and OA (right panel), the interaction becomes more obvious compared to when analyses were

329 performed with eQTL variants overlapping with any histone marks (middle) or all of the eQTL variants (left).

330 SFs, synovial fibroblasts; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; OA, osteoarthritis;

331 NS, non-stimulated; eQTL, expression quantitative trait locus.

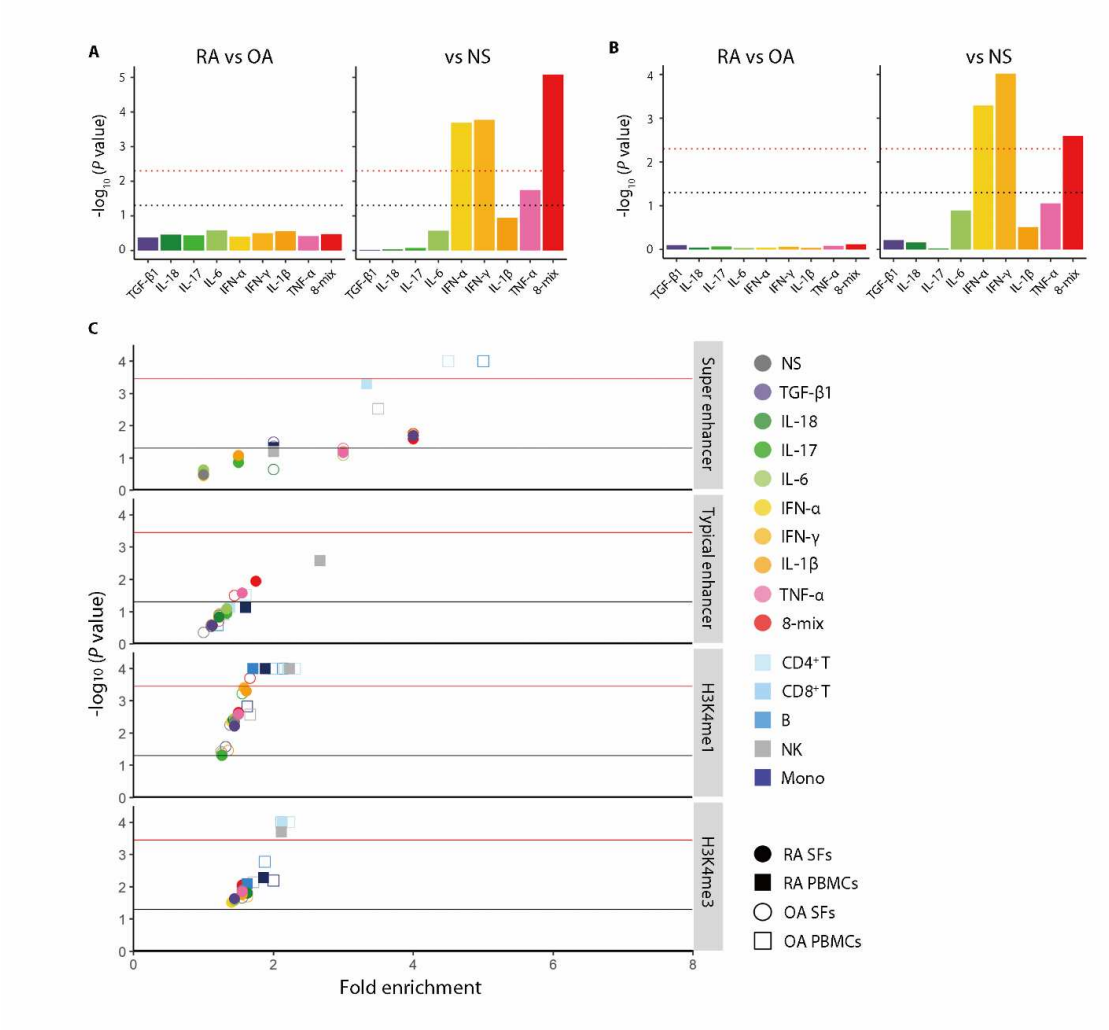
332



Online supplementary figure 3. Representative examples of eQTL in stimulated SFs.

(**A** to **C**) Examples of stimulation-specific eQTLs. A dot plot of cis-eQTL meta-analysis posterior probability *m*-value and tissue-by-tissue analysis -$\log_{10}$ *P* value for rs8069701-*CD300E* (**A**), chr1:160179300-*SLAMF1* (**B**) and rs914744-*TRAF2* (**C**) are shown.

SFs, synovial fibroblasts; NS, non-stimulated; eQTL, expression quantitative trait locus.



Online supplementary figure 4. Polygenic association between differentially expressed genes and RA risk variants, and GWAS-super-enhancers enrichment analysis in Type 1 diabetes mellitus.

(**A, B**) Polygenic association analysis of differentially expressed genes with RA genetic risk using EUR GWAS (**A**) and EAS GWAS (**B**) data. Association *P* values were calculated with MAGMA. The red dotted lines and the black dotted lines are the cutoff for Bonferroni significance and $P = 0.05$, respectively. (**C**) Enrichment of type 1 diabetes mellitus risk loci in transcriptional regulatory regions of stimulated SFs and PBMCs. Active enhancers were

346 classified into super-enhancers (SEs) and typical-enhancers (TEs) following standard ROSE algorithms. The red

347 solid lines and the black solid lines are the cutoff for Bonferroni significance and $P = 0.05$, respectively.

348 SFs, synovial fibroblasts; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; OA, osteoarthritis;

349 NS, non-stimulated; SE, super enhancer; TE, typical enhancer; GWAS, genome-wide association study.

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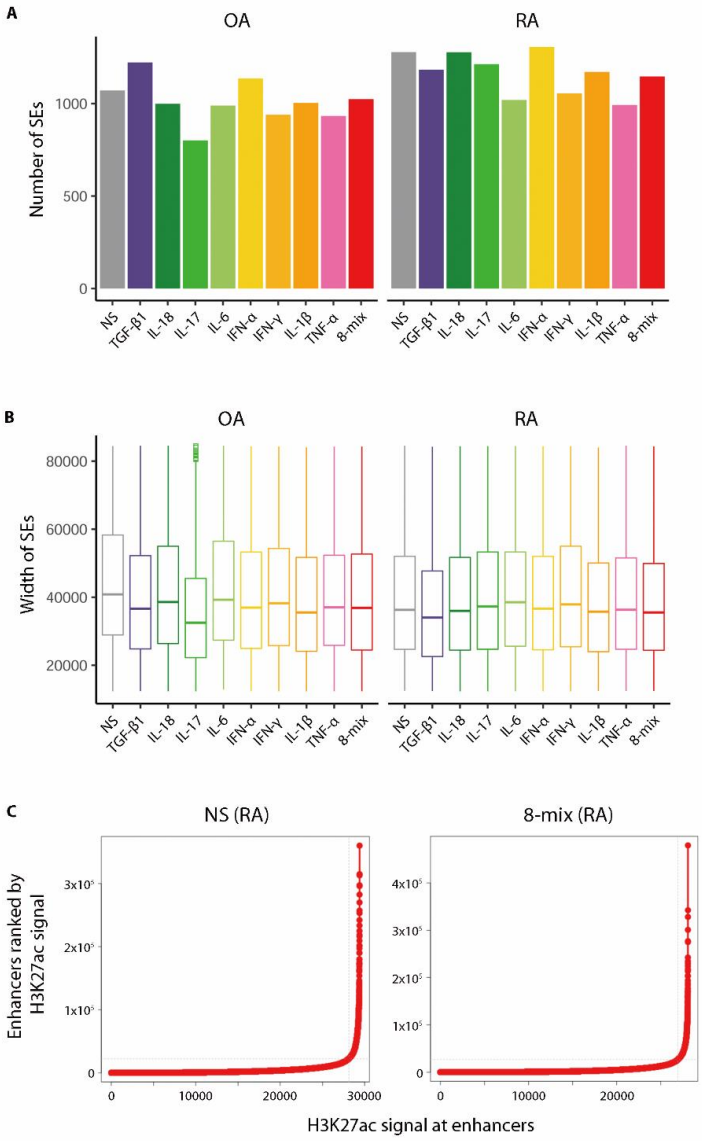


351

352 **Online supplementary figure 5. Comparison of the number and width of SEs in SFs among different**

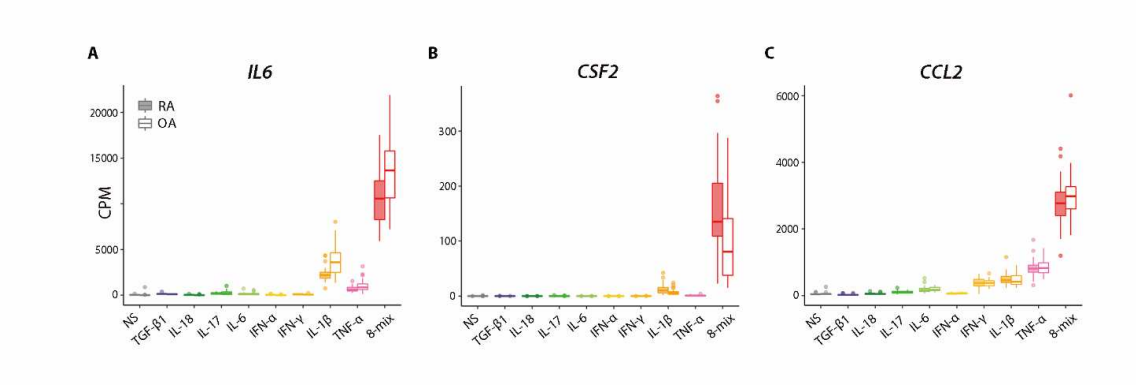
353 **stimulatory conditions.**

354 (**A**) The number of SEs of each stimulated SFs. (**B**) The width of SEs of each stimulated SFs. Boxes, interquartile

355 range; whiskers, distribution. (**C**) Distribution of SEs based on H3K27Ac signals and enhancer ranks in

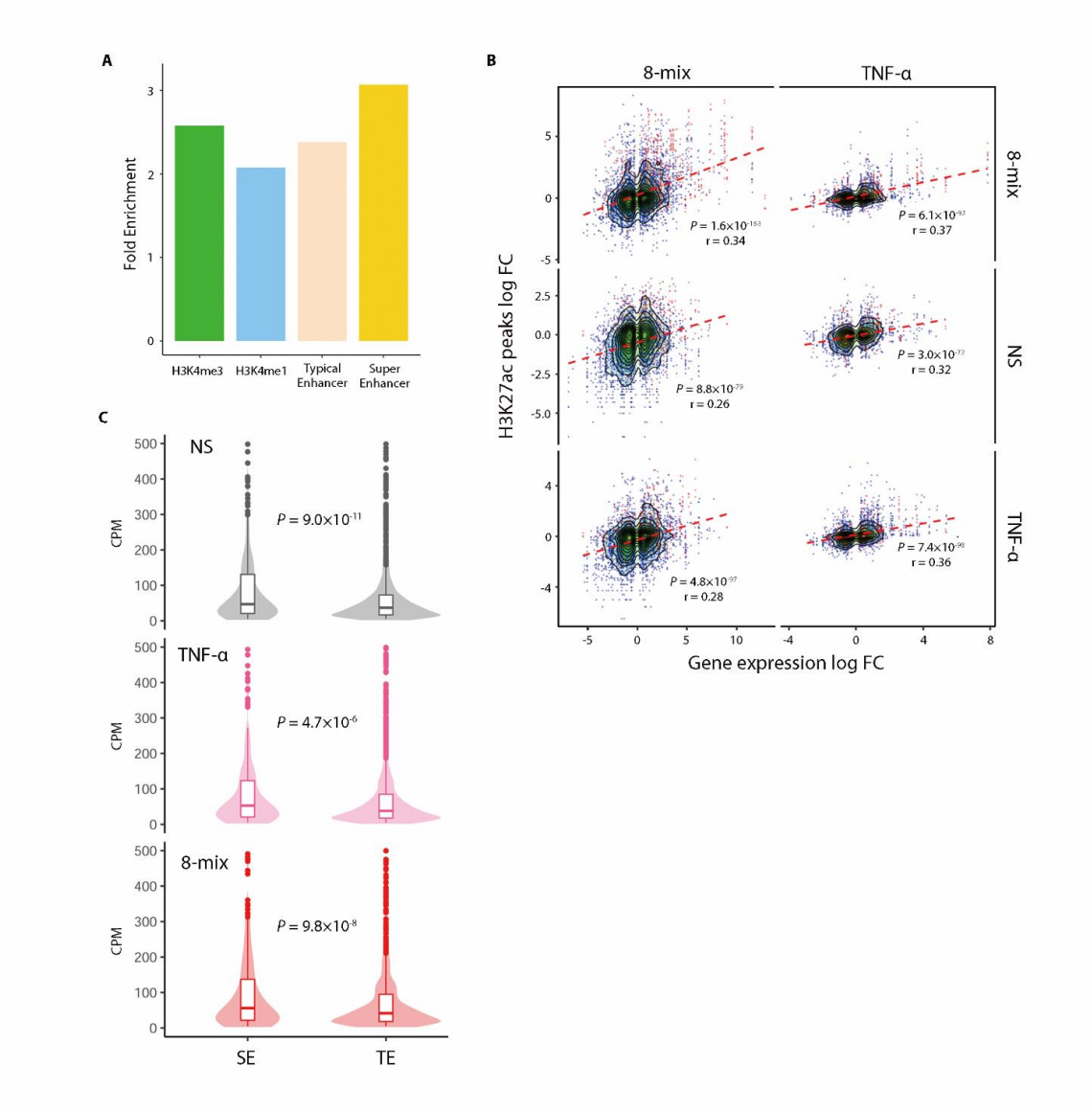
non-stimulated (left) and 8-mix stimulated (right) RASFs.

SFs, synovial fibroblasts; RA, rheumatoid arthritis; OA, osteoarthritis; NS, non-stimulated; SE, super enhancer.



Online supplementary figure 6. Synergistic effect of cytokines on epigenomic modifications and inflammatory gene expression.

(**A** to **C**) Transcript abundances of representative RA pathogenic genes, *IL6* (**A**), *CSF2* (**B**) and *CCL2* (**C**) from RNA sequencing data in stimulated SFs. Boxes, interquartile range; whiskers, distribution; dots, outliers. SFs, synovial fibroblasts; RA, rheumatoid arthritis; OA, osteoarthritis; NS, non-stimulated; CPM, counts per million.



367

368 **Online supplementary figure 7. The relevance among Hi-C loop, SEs and gene expression levels.**

369 (**A**) The enrichment of Hi-C loop anchors with epigenome status (H3K4me3 peaks, H3K4me1 peaks, TEs and SEs).

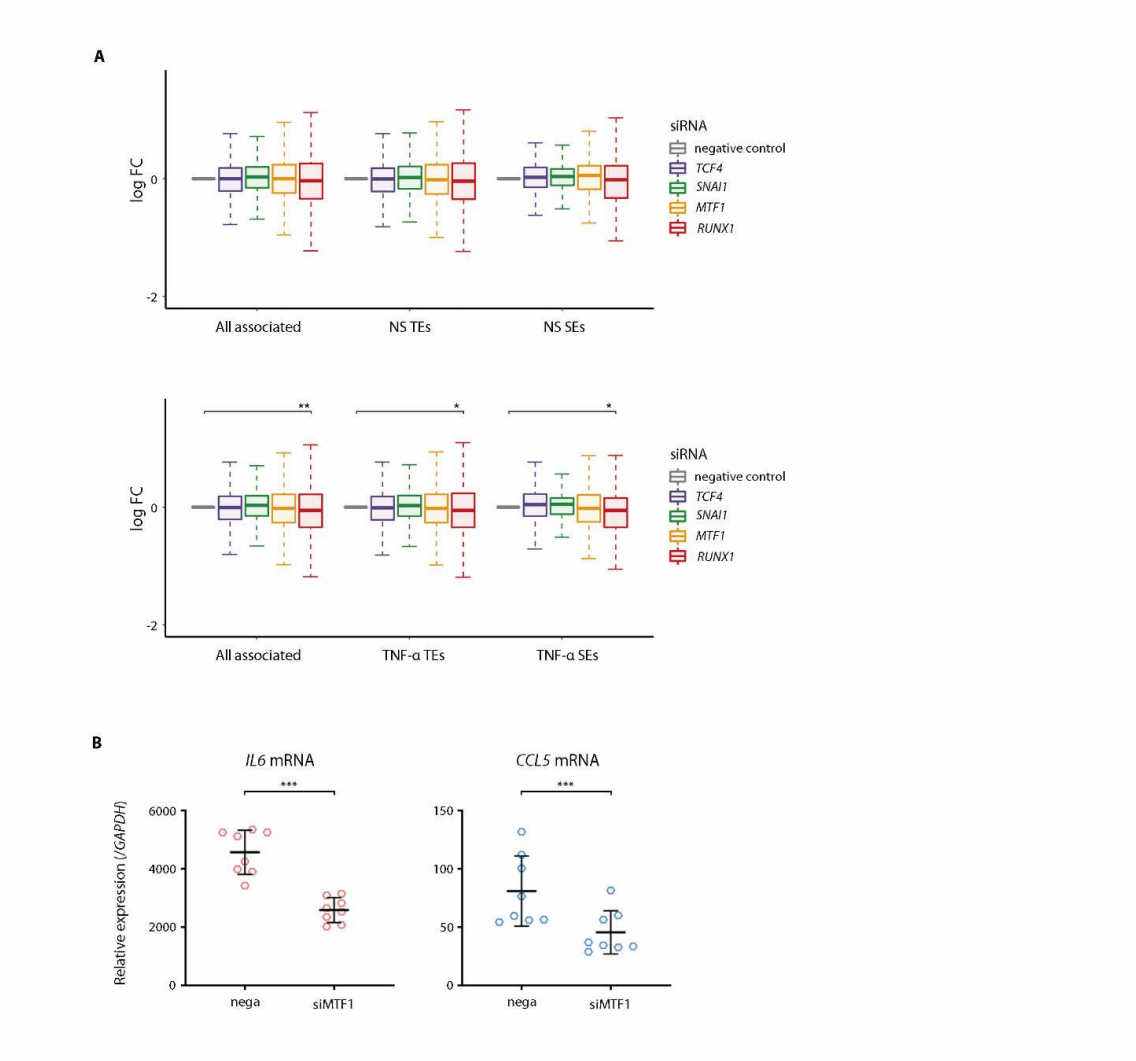
370 Fold change was calculated compared with randomly selected loci from the whole genome. (**B**) Comparison of

371 H3K27ac peak fluctuation and its associated gene expression fluctuation. Associated gene for each H3K27ac peak

372 was determined with Hi-C loops. Fold change between RA and OA samples are compared. In the left panel, genes

and H3K27ac peaks were connected with Hi-C loops in 8-mix stimulated SFs. In the right panel, genes and H3K27ac peaks were connected with Hi-C loops in TNF-α stimulated SFs. Top, comparison in 8-mix stimulated SF samples; middle, comparison in non-stimulated SF samples; bottom, comparison in TNF-α stimulated SF samples. *P* values and ρ were calculated using Spearman's test. Red dot, SE-contacting genes; Blue dot, TE-contacting genes. (**C**) Transcript abundances of TE or SE-contacting genes from RNA sequencing data for stimulated SFs. Boxes, interquartile range; whiskers, distribution; dots, outliers; density plot, frequency. *P* values were calculated with Student t test.

SFs, synovial fibroblasts; RA, rheumatoid arthritis; OA, osteoarthritis; NS, non-stimulated; SE, super enhancer; TE, typical enhancer; CPM, counts per million.



383

384 **Online supplementary figure 8. Transcription factors associated with SEs formation in 8-mix stimulated SFs.**

385 (**A**) Expression of non-stimulation or TNF-α TE or SE-contacting genes in transcription factors (*TCF4*, *SNAI1*,

386 *MTF1* and *RUNX1*) -depleted SFs relative to control SFs. Boxes, interquartile range; whiskers, distribution. *P*

387 values were calculated using a paired t test (*$P < 0.05$, **$P < 0.01$). (**B**) Transcript abundances of *IL6* and *CCL5*

388 from qRT-PCR data in *MTF1*-depleted SFs (n = 8). Horizontal crossbars, mean; error bars, SD. *P* values were

389 calculated using a paired t test (***$P < 0.001$).

390 SFs, synovial fibroblasts; NS, non-stimulated; SE, super enhancer; TE, typical enhancer.

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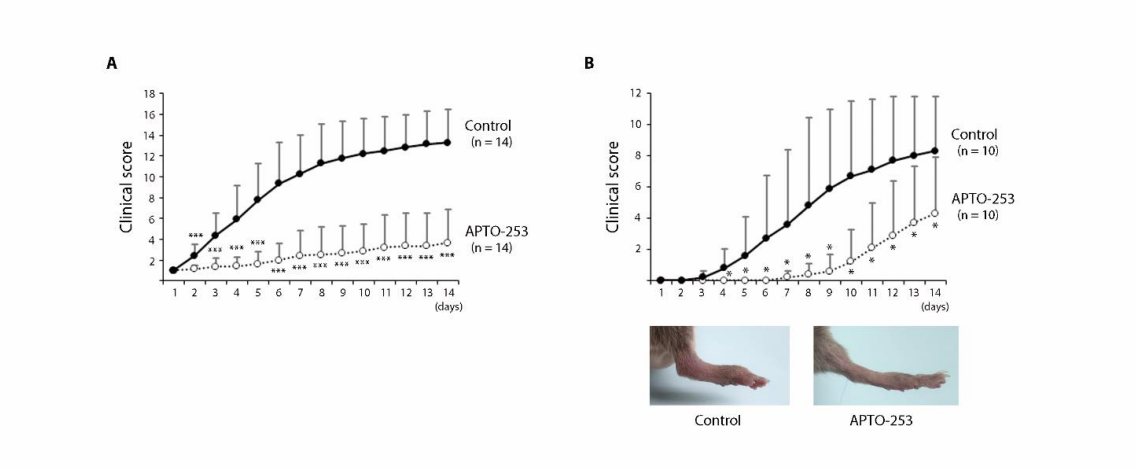

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393 **Online supplementary figure 9. Preventive effect of APTO-253 on CIA model.**

394 (**A**) The replication of therapeutic effect of APTO-253 on CIA model (also see figure 8). Dots, mean; Error bars,

395 SD. *P* values were calculated using a Mann–Whitney U test (***, $P < 0.001$).

396 (**B**) On the same day as the second immunization, CIA mice were intravenously injected with either control or 15

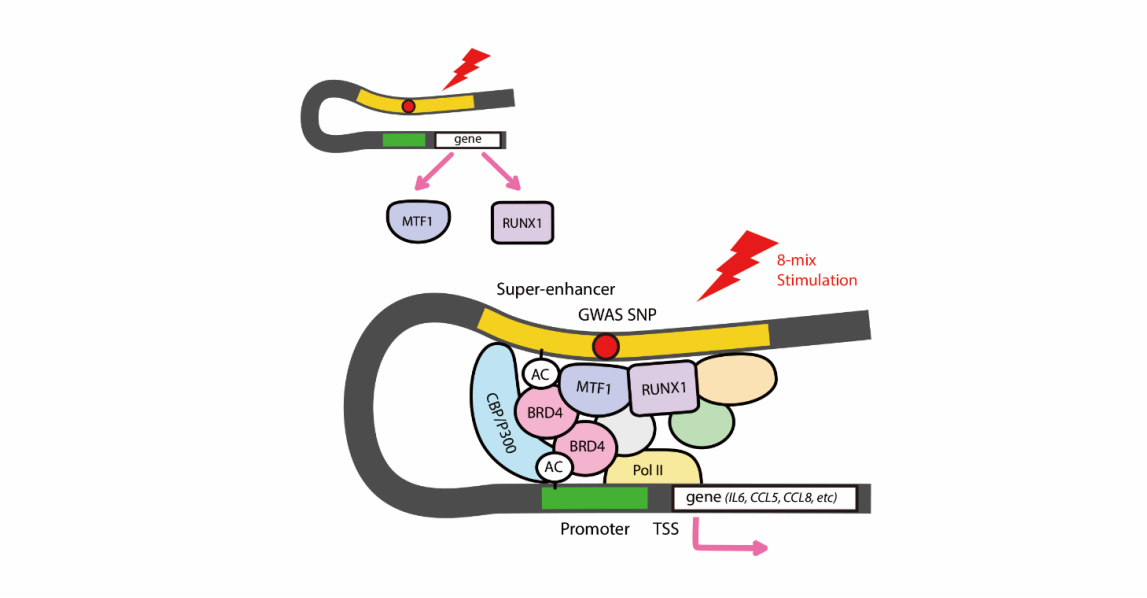
397 mg/kg APTO-253 for twice per day for 2 consecutive days per week. Clinical scores in each group and

398 representative pictures of hind paw. Dots, mean; Error bars, SD. *P* values were calculated using a Mann–Whitney

399 U test (*, $P < 0.05$).

400 CIA, collagen-inducer arthritis.

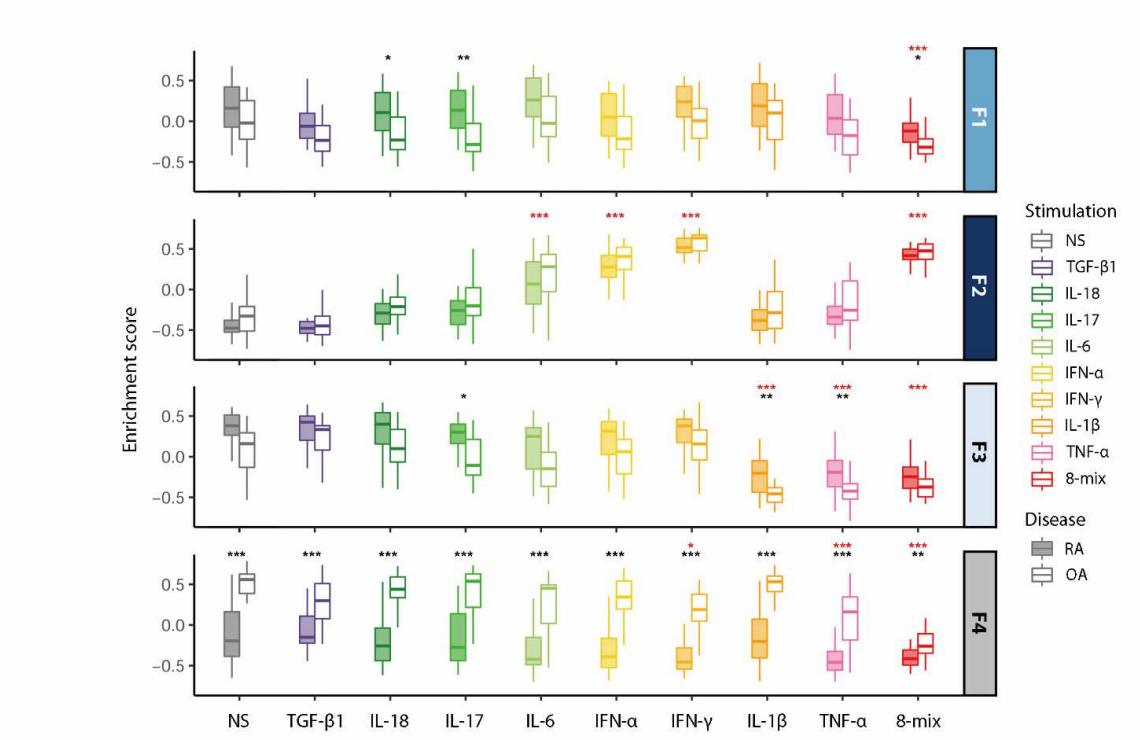
401



Online supplementary figure 10. A Graphical summary of the present study.

The authors conducted integrated analysis of stimulated SFs and demonstrated chromatin remodeling in the presence of synergistic proinflammatory cytokines. The dynamic changes with super-enhancer formation are associated with RA heritability. Transcription factors including MTF1 and RUNX1 could to be crucial for structural arrangement and the marked increase in the expression of pathogenic molecules from SFs.

SFs, synovial fibroblasts; RA, rheumatoid arthritis; TSS, transcriptional start site; GWAS, genome-wide association study.



411

412 **Online supplementary figure 11. The estimated enrichment of SF populations revealed by single-cell RNA**

413 **sequencing analysis of freshly isolated SFs.**

414 The population enrichment score of our stimulated SFs was calculated using GSVA software. Fan Zhang *et al*

415 reported three sublining subpopulations, namely $CD34^{+}$ (F1), $HLA\text{-}DRA^{hi}$ (F2) and $DKK3^{+}$ (F3), and one lining

416 subpopulation (F4) based on single-cell RNA sequencing.[6]

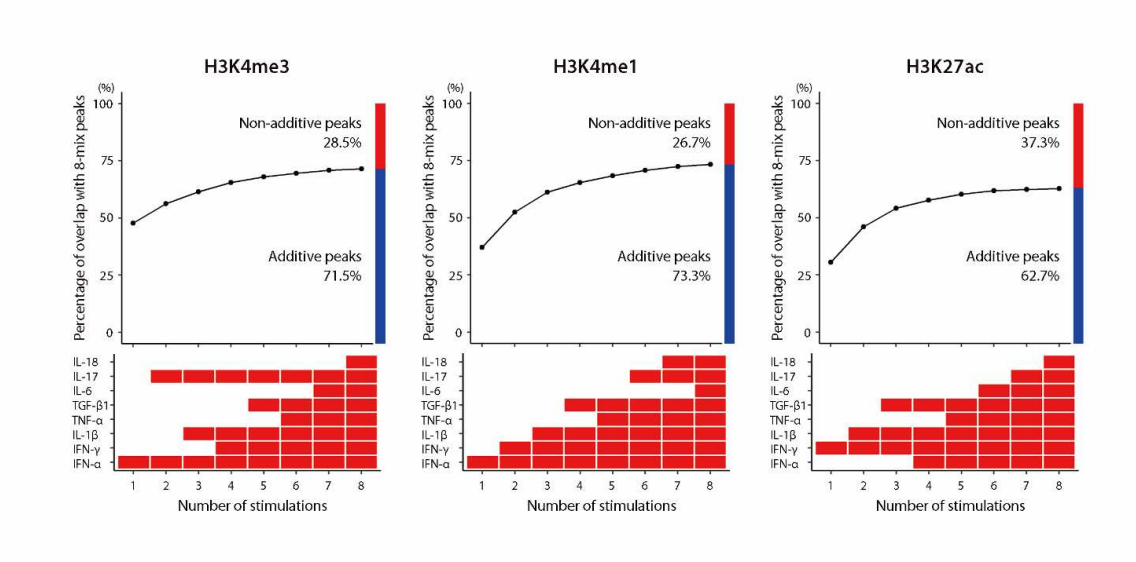
417 We applied "top 20 marker genes for each single-cell RNA sequencing cluster" for enrichment score calculation.

418 *P* values were calculated using a paired t test (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, red, comparison between

419 stimulation and non-stimulation; black, comparison between RA and OA). Boxes, interquartile range; whiskers,

distribution.

RA, rheumatoid arthritis; OA, osteoarthritis; NS, non-stimulation; F1-4, Fraction 1-4.



Online supplementary figure 12. Contribution of each cytokine to 8-mix condition.

To decipher epigenomic modulations by the 8-mix into each cytokine, we compared the overlap of 8-mix-induced peaks with the union of the individual cytokine simulation-induced peaks. All of the combinations of 1 - 8 cytokines were tested, and the combinations which accounted for the largest fraction of 8-mix-induced peaks are plotted. The percentage of peak overlap between 8-mix-induced peaks and the best combination of individual cytokine-induced peaks (upper plot) and the combination of cytokines (lower panel) are shown.

Online supplementary table 1. Summary of differentially expressed genes (Separate file).

Log fold changes and *P* values of comparisons between RA and OA or between stimulation and non-stimulation are listed for all the analyzed genes. NA values indicates that the genes are not expressed highly enough for comparisons.

Online supplementary table 2. Disease-specific cis-eQTL signals (Separate file).

List of the eQTLs whose effect sizes showed significant interactions with disease term. All the listed variants overlap with differential epigenome peaks between RA and OA.

Online supplementary table 3. Colocalization of RA GWAS and cis-eQTL signals (Separate file).

The list of cis-eQTL top variants which are in LD with RA GWAS top-associated loci. Variant pairs with $R^2 > 0.6$ in EUR or EAS population in 1000G phase 3 data are listed. The RA GWAS top-associated SNP was downloaded from the NHGRI-EBI GWAS Catalog.[8] EFO_0000685 was downloaded on 11/09/2018.

eQTL, expression quantitative trait locus; GWAS, lead variant in genome-wide association study; R^2, r square values between eQTL top variant and GWAS top-associated SNP in EUR or EAS population (the larger one is written); method, eQTL analysis method for the indicated top eQTL variant; MT, meta-tissue analysis; TBT, tissue-by-tissue analysis

Online supplementary table 4. Summary of SE-contacted genes (Separate file).

449 **Online supplementary table 5. Characteristics of patients for RNA sequencing.**

	RA (n=30)	OA (n=30)
Age, years (range)	70 (52-80)	73 (54-88)
Female, n (%)	26 (86.7)	24 (80.0)
Serological markers		
Rheumatoid factor-positive, n (%)	25 (83.3)	0 (0)
Anti-CCP autoantibody-positive, n (%)	21 (70.0)	0 (0)
Disease activity, n (%)		
High (DAS-ESR >5.1)	6 (20.0)	n/a
Moderate (DAS-ESR 3.2-5.1)	20 (66.7)	n/a
Low/Remission (DS-ESR <3.2)	4 (13.3)	n/a
Steinbrocker Stage, n (%)		
Ⅰ	0 (0)	n/a
Ⅱ	3 (10.0)	n/a
Ⅲ	11 (36.7)	n/a
Ⅳ	16 (53.3)	n/a
Steinbrocker Class, n (%)		
Ⅰ	0 (0)	n/a
Ⅱ	17 (56.7)	n/a
Ⅲ	11 (36.7)	n/a
Ⅳ	2 (6.7)	n/a
Treatment, n (%)		
csDMARDs		
MTX	14 (46.7)	0 (0)
BUC	5 (16.7)	0 (0)
IGU	4 (13.3)	0 (0)
SASP	5 (16.7)	0 (0)
TAC	5 (16.7)	0 (0)
Glucocorticoids	21 (70.0)	0 (0)
boDMARDs		
TNFi	6 (20.0)	0 (0)
ABT	2 (6.7)	0 (0)
TCZ	2 (6.7)	0 (0)

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451

RA, rheumatoid arthritis; OA, osteoarthritis; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; MTX, methotrexate; BUC, bucillamine; IGU, iguratimod; SASP, salazosulfapyridine; TAC, tacrolimus; boDMARDs, biological originator disease-modifying antirheumatic drugs; TNFi, tumour necrosis factor inhibitors; ABT, abatacept; TCZ, tocilizumab; n/a, not applicable.

456 **Online supplementary table 6. Sequences of primer pairs used in qRT-PCR.**

Target	Sequence (Forward)	Sequence (Reverse)
IL6	5'- GCCTTCGGTCCAGTTGCCTT -3'	5'- AGTGCCTCTTTGCTGCTTTCAC -3'
CCL5	5'- AGTGTGTGCCAACCCAGAGAAGAA -3'	5'- TGTGGTAGAATCTGGGCCCTTCAA -3'
MTF1	5'- GCCCCAGTAATGGCTGTGAG -3'	5'- TCCTCTGATCCATTGTGTTGTGG -3'
RUNX1	5'- TCCACTGCCTTTAACCCTCA -3'	5'- AGGTGAAATGGGCGTTGCT -3'
SNAI1	5'- TATGCTGCCTTCCCAGGCTTG -3'	5'- ATGTGCATCTTGAGGGCACCC -3'
TCF4	5'- TCCAGGTTTGCCATCTTCAGT -3'	5'- GCCTGGCGAGTCCCTATTG -3'
GAPDH	5'- GAAGGTGAAGGTCGGAGTC -3'	5'- GAAG ATGGTGATGGGATTTC -3'

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