Supplemental methods

Purification of transcription factories and co-immunoprecipitations

The active sites of transcription (i.e., transcription factories) can be purified as multi-MDa nucleoprotein complexes using an established protocol (Melnik et al. 2016). In brief, approximately 15 million HUVECs grown to confluence in 15-cm plates are harvested in a "physiological" buffer (PB) that allows retention of essentially all transcriptional activity. Intact nuclei are next collected by mild treatment with NP-40 and centrifugation, treated with DNase I to release most chromatin (the "chromatin" fraction), pelleted, washed, and resuspended in a nuclear lysis buffer on ice. Subsequently, treatment with a mixture of Group-III caspases and vigorous shaking releases >6 MDa-large complexes into the supernatant. This represents the "factory" fraction, is diluted to 500 µl using PB, and incubated in the presence of 6 µg of a rabbit polyclonal RELA antibody (Active motif; 39369) overnight at 4°C on a rotator. Immunoselected complexes are captured on magnetic protein G beads (Active motif; 53014), washed 5x in ice-cold PB, and released by mixing with standard 1x SDS loading buffer and boiling (5 min, 98°C). Finally, co-immunoprecipitating proteins are resolved on SDS-PAGE gradient gels (4-15%, Bio-Rad; 4568083), and visualized by western blotting. The antibodies used here are mouse monoclonals raised against c-FOS (Developmental Studies Hybridoma Bank; PCRP-FOS-1A7), and TBP (Abcam; ab818), and rabbit polyclonals against JUN (Santa Cruz Biotech.; sc-1694X) and histone H3 (Santa Cruz Biotech.; sc-10809).

Whole-genome chromosome conformation capture (Hi-C) and analysis

Hi-C was performed using 35 million HUVECs stimulated for 30 min with TNF as described (Belton et al. 2012). In brief, nuclei were isolated, treated overnight with 800 units *Hind*III (New England Biolabs), overhangs were filled-in with biotin and ligated under dilute conditions, before being sonicated to ~800 bp, and biotinylated 3C junction being selected on streptavidin beads. After washing non-captured DNA away, end-repair and ligation of Illumina linkers was performed, and the library was sequenced (in two replicates) on a HiSeq2000 platform to generate a total of 200 million read pairs (100 bp in length). The resulting reads were then mapped to the reference genome (hg18) iteratively (to ensure maximum recovery of uniquely mapped pairs) using BWA (Li and Durbin 2009). The .BAM files containing mapped reads were merged, duplicates were removed using Picard tools (http://picard.sourceforge.net/) and the output converted into BEDPE format using BEDTools (Quinlan and Hall 2010). Then, custom R scripts were used to bin the genome into equally-sized bins (25-250 kbp), assigned reads to bins, and normalize read counts to library size. Next, the HiTC package (Servant et al. 2012) was used to annotate and correct matrices for biases in genomic features (Yaffe and Tanay 2011), and visualize 2D heat maps. Finally, topologically-associating domain (TAD) boundaries were identified at a resolution of 100 kbp using "HiCseg" and default parameters (Lévy-Leduc et al. 2014).

Chromatin interaction analysis with paired-end tag sequencing (ChIA-PET)

ChIA-PET was performed in HUVECs stimulated with TNF for 0 or 30 min (Papantonis et al. 2012; Li et al. 2014). In brief, HUVECs were cross-linked using 10 mM ethyl-glycol-*bis*-succinimidylsuccinate (EGS; Thermo Scientific) in 50% glacial acetic acid (45 min) and then in 1% paraformaldehyde (20 min) at room temperature, quenched (5 min) in 2.5 M glycine, harvested, sonicated (Branson), and complexes were immunoprecipitated using the Pd75C9 antibody directed against the phospho-Ser2/-Ser5 heptad repeats in the C-terminus of the largest catalytic subunit of RNA polymerase II (a gift by Hiroshi Kimura). Chromatin captured on magnetic beads was processed as described (Li et al. 2014), and digested with *Mme*I (New England Biolabs). Finally, libraries were sequenced on a GAII analyzer (Illumina) and

resulting paired-end tags (PETs) were analyzed. Libraries yielded ~35x10^6 20-bp paired-end reads each, of which ~10.8x10^6 were successfully aligned to the human genome (see **Supplemental Fig. S3A**). For stringency, we only analyzed interactions supported by ≥3 PETs (Li et al. 2014).

Differential motif and co-binding analysis in DHS footprints

DNase-seq raw reads from HUVECs were obtained (GEO accession: GSM816646) and aligned to the human genome (hg18). Footprints were predicted using the HINT method (Gusmao et al. 2016) and extended by 5 bp up- and downstream. Then, motif-predicted binding sites (MPBSs) were determined by performing motif search inside footprints overlapping "with" or "without" RELA peaks against position frequency matrices obtained from public databases (Robasky et al. 2011; Mathelier et al. 2014). MPBSs were used to assess the enrichment of transcription factor binding sites using an approach based on the Fisher's exact test as described (Lin et al. 2015). All tools used here are available as part of the Regulatory Genomics toolbox (http://www.regulatory-genomics.org). *De novo* motif analysis was performed via MEME (Bailey et al. 2009) with variable cutoffs (FDR<0.001 returned a 5'-RKRNHTYYCH-3' consensus for "without" sites, while an FDR <0.0001 gave a 5'-GGRRYTYYCC-3' motif at "with" sites).

JDP2 knock-down using siRNA

HUVECs are seeded at 8000/cm^2 in 6-well plates and grown to ~80% confluency. For transfection, 1,5 µl of 20µM siRNA (Sigma-Aldrich) are added to 125µl OptiMEM in one tube, and 6µl RNAiMAX to 125µl OptiMEM (Life Technologies) in another. The contents of the two tubes are mixed, incubated for 20 min at room temperature, and added dropwise in 800µl EndoPAN 3 (PAN Biotech) complemented with 3% FBS in the absence of antibiotics. Following 24-h incubation, fresh medium is added to the cells, and they are grown for another 36 h, before transferring into starvation media for an overnight incubation and stimulation for 30 min with TNF. Finally, cells are harvested in 500 µl of Trizol (Life Technologies), RNA is purified using the Direct-zol RNA kit (Zymo Research; including an on-column DNase treatment), reverse-transcribed using Superscript II as per manufacturer's instructions (Life Technologies) and used in RT-qPCR. The knock-down was performed in three independent replicates using a "scrambled" control (sense – UUGUACUACACAAAAGUACUG[dT][dT], antisense – CAGUACUUUUGUGUAGUACAA[dT][dT]) or an siRNA oligo targeting *JDP2* at exon 3 (sense – GACUGUGGAGGAGCUGAAA[dT][dT], antisense – UUUCAGCUCCUCCACAGUC[dT][dT]; Sigma-Aldrich). PCR primer sequences are available on request.

Oligonucleotides

All oligonucleotides used in qPCR were designed in Primer3Plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) using its default "qPCR" settings; optimal length was set to 20-22 nt, melting temperature to 62°C, and amplimer length to 100-250 bp. Sequences are available on request.

Statistical analysis

P-values (two-tailed) derived from unpaired Student's *t*-tests were calculated using GraphPad and deemed significant when <0.01 (http://www.graphpad.com). Spearman's correlation coefficients were calculated using standard commands in R.

Supplemental references

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