Table S1-Primer sequences for qPCR.

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
36B4	TGGCCA ATAAGGTGCCAGCTGCTG	CTTGTCTCCAGTCTTTATCAGCTGCAC
Arginase	ATGGAAGAGACCTTCAGCTAC	GCTGTCTTCCCAAGAGTTGGG
CD11c	ACACAGTGTGCTCCAGTATGA	GCCCAGGGATATGTTCACAGC
Clec7a	AGGTTTTTCTCAGTCTTGCCTTC	GGGAGCAGTGTCTCTTACTTCC
Cxcl10	CCAAGTGCTGCCGTCATTTTC	GGCTCGCAGGGATGATTTCAA
Elovl5	ATGGAACATTTCGATGCGTCA	GTCCCAGCCATACAATGAGTAAG
F4/80	CTTTGGCTATGGGCTTCCAGTC	GCAAGGAGGACAGAGTTTATCGTG
Fads2	AAGGGAGGTAACCAGGGAGAG	CCGCTGGGACCATTTGGTAA
GAPDH	AATGTGTCCGTCGTGGATCT	CATCGAAGGTGGAAGAGTGG
IFNγ	TCAAGTGGCATAGATGTGGAAGAA	TGGCTCTGCAGGATTTTCATG
IKKe	ACAAGGCCCGAAACAAGAAAT	ACTGCGAATAGCTTCACGATG
IL-1β	AAATACCTGTGGCCTTGGGC	CTTGGGATCCACACTCTCCAG
IL-6	CCAGAGATACAAAGAAATGATGG	ACTCCAGAAGACCAGAGGAAAT
iNOS	GAGGCCCAGGAGGAGAGAGATCCG	TCCATGCAGACAACCTTGGTGTTG
KC	ACTGCACCCAAACCGAAGTC	TGGGGACACCTTTTAGCATCTT
MIP-1a	TTCTCTGTACCATGACACTCTGC	CGTGGAATCTTCCGGCTGTAG
MCP-1	AGGTCCCTGTCATGCTTCTG	GCTGCTGGTGATCCTCTTGT
MMP13	TGTTTGCAGAGCACTACTTGAA	CAGTCACCTCTAAGCCAAAGAAA
MMR	CTCGTGGATCTCCGTGACAC	GCAAATGGAGCCGTCTGTGC
NCoR	TGCGTCAGCTTTCTGTGATTCCACC	TGATTTCTGCCTCTGCGTTTTCCAT
NF-kB	ATGGCAGACGATGATCCCTAC	CGGAATCGAAATCCCCTCTGTT
Scd2	GCATTTGGGAGCCTTGTACG	AGCCGTGCCTTGTATGTTCTG
TBK1	ACTGGTGATCTCTATGCTGTCA	TTCTGGAAGTCCATACGCATTG
TNFα	CCAGACCCTCACACTCAGATC	CACTTGGTGGTTTGCTACGAC
Ym1	GGGCATACCTTTATCCTGAG	CCACTGAAGTCATCCATGTC

Supplementary figure legends

Figure S1- Related to Figure 3 Inflammation in other tissues. (A) Serum TNFα level in WT and KO mice after LPS injection. (B) Inflammation in BAT, subcutaneous fat and perirenal fat. (C) Inflammation in liver. Values are expressed as mean ± s.e.m. *P<0.05, **P<0.01 for KO versus WT.

Figure S2- Related to Figure 4 Consequences of NCoR deletion on TLR4-dependent gene expression (A) Box-and-whisker plots of normalized distribution of GRO-Seq tag densities across gene bodies for TLR4 hypo-responsive genes in untreated and KLA-treated WT and MNKO macrophages. Boxes encompass the 25^{th} to 75^{th} % changes. Whiskers extend to 10^{th} and 90^{th} percentiles. The median normalized tag distibution is indicated by the central horizontal bar. (B) Normalized distribution of HDAC3 ChIP-Seq tag density (from Mullican, et al, 2011) at NCoR bound regions (Barish et al., 2012) in primary macrophages. (C) ChIP for HDAC3 at the indicated genomic locations in WT and MNKO macrophages.

Figure S3- Related to Figure 6 Relationship of expression of enzymes producing ω3 FAs and POA and inflammation in WT and MNKO macrophages (A) Measurement of siRNA knockdown efficiencies for *Scd2, Elovl5, Fads2* in untreated or KLA-treated WT and MNKO macrophages. (B) Effect of siRNA knockdown of *Scd2* and *Fads2* on expression levels of *Abca1*, *Abcg1*, *Serpine1*, and *Ccl12* genes in untreated and KLA-treated WT and MNKO macrophages. Values are expressed as mean ± s.e.m. * P<0.05 for target specific siRNA (*Scd2*, *Elovl5*, or Fads2) versus siCTL in S3A, or KLA-treated target specific siRNA (*Scd2*, *Elovl5*, or Fads2) versus siCTL in S3B-C.

Figure S4- Related to Figure 7 Relationship of ω3 FAs, NF-κB complex activity and MNKO phenotype (A) Measurement of NF-κB-driven luciferase reporter activity, using constructs with NF-κB-bound regions from MNKO hypo-responsive genes (*Nos2* and *Cxcl10*) or a consensus

NF-κB response element, in untreated and KLA-treated WT and MNKO macrophages. B) Significantly enriched motifs at genomic locations identified by p65 ChIP-Seq in KLA-treated WT and MNKO macrophages. (C) Normalized distribution of H3K4me2 ChIP-Seq tag density at MNKO hypo-responsive genes in KLA-treated WT and MNKO macrophages. (D) UCSC genome browser image illustrating normalized tag counts for H3K4me2 ChIP-Seq, GRO-Seq, and NCoR ChIP-Seq (from Barish, et al, 2012) in WT and MNKO macrophages for the *Mmp12* locus. (E) Western blot of p-IKK and p-JNK in IP-macrophages from WT and MNKO. (F) Measurement of NF-κB-driven luciferase reporter activity, using constructs with NF-κB-bound regions from MNKO hypo-responsive genes (*Nos2* and *Cxcl10*) or a consensus NF-κB response element, in KLA-treated WT macrophages with and without ω3 fatty acid treatment as indicated. Values are expressed as mean ± s.e.m. * $P<0.05$ for KLA-treated KO versus WT, or EPA- or DHA-KLA versus KLA in S4E.

Supplementary method

ITTs, GTTs, and hyperinsulinemic euglycemic clamp study. Glucose and insulin tolerance tests were performed on 6 hr fasted mice. For GTTs, animals were IP injected with dextrose (1 g/kg, Hospira, Inc), whereas for ITTs 0.5 units/kg of insulin (Novolin R, Novo-Nordisk) was IP injected. Blood was drawn at 0, 15, 30, 60, and 120 minutes after dextrose or 0, 15, 30, 60 and 90 minutes after insulin injection. Mouse clamps were performed as previously described (He et al., 2003; Li et al., 2010; Lu et al., 2010). Briefly, dual catheters (MRE-025, Braintree Scientific) were implanted in the right jugular vein and tunneled subcutaneously and exteriorized at the back of the neck. The mice were allowed to recover for 3 to 4 days before the clamp procedure. After 6 h fasting, the clamp experiments began with a constant infusion (5 μCi/hr) of D-(3-3H) glucose (Du Pont-NEN, Boston, MA). After 90 min of tracer equilibration and basal sampling at t = –10 and 0 min, glucose (50% dextrose, variable infusion; Abbott) and tracer (5 μCi/hr) plus insulin (6 mU/kg/min) were infused into the jugular vein. Blood from the tail vein was drawn at 10-min intervals and analyzed for glucose to maintain the integrity of the glucose clamp. Blood was taken at t = –10, 0 (basal), 110, and 120 (end of experiment) min to determine glucose-specific activity, insulin, and free fatty acids (FFA). Steady-state conditions (120 mg/dl ± 5 mg/dl) were confirmed at the end of the clamp by ensuring that glucose infusion and plasma glucose levels were maintained constant for a minimum of 30 min. HGP and GDR were calculated in the basal

state and during the steady-state portion of the clamp. Tracer-determined rates were quantified by using the Steele equation (Steele, 1959). At steady state, the rate of glucose disappearance, or total GDR, is equal to the sum of the rate of endogenous glucose productions (HGP) plus the exogenous (cold) GIR. The IS-GDR is equal to the total GDR minus the basal glucose turnover rate.

SVCs isolation, and FACS analysis. SVCs isolation and FACS analysis were performed as previously described (Li et al., 2010). Briefly, epididymal fat pads were weighed, rinsed three times in PBS, and then minced in FACS buffer (PBS + 1% low endotoxin BSA). Tissue suspensions were treated with collagenase (1 mg/ml, Sigma-Aldrich) for 30 minutes, and then were filtered through a 100 □m filter (BD Biosciences). After centrifugation at 500 *g* for 5 min, the supernatant containing adipocytes was removed and the pallet containing SVCs fraction was incubated with RBC lysis buffer (eBioscience) for 5 min followed by another centrifugation (300 *g*, 5 min) and resuspension in FACS buffer. SVCs were incubated with Fc Block (BD Biosciences) for 20 min at 4 °C before staining with fluorescently labeled primary antibodies or control IgGs for 30 min at 4 °C. F4/80-APC FACS antibody was purchased from AbD Serotec (Raleigh, NC); FITC-CD11b and PE-CD11c FACS antibodies were from BD Biosciences. Cells were gently washed twice and resuspended in FACS buffer with propidium iodide (Sigma). SVCs were analyzed using a FACSAria flow cytometer (BD Biosciences). Unstained, single stains and Fluorescence Minus One controls were used for setting compensation and gates. The events were first gated based on Forward-area *versus* Side scatter-area as well as Side scatter-height *versus* Side scatter-width and Forward scatter-height *versus* Forward scatter-width for a total of three dual parameter plots to gate out aggregates and debris. Single color controls were used to calculate compensation using the FACSDiva software. A plot of Forward scatter *versus* propidium iodide was used as the fourth gate to identify individual, live cells. To measure markers with the maximum sensitivity, each fluorochrome was plotted *versus* propidium iodide, and polygons were drawn, angled with the aid of the Fluorescence Minus One controls.

Phenotypic evaluation of mice. Male control (n = 10) and MNKO mice (n = 10) were fed with 60% high fat diet (HFD) for 17 weeks, with or without 3 weeks of TZD treatment (rosiglitazone 3 mg per kg per d). Plasma insulin was measured by ELISA kits from ALPCO. Plasma FFA levels were measured enzymatically using a kit from WAKO Chemicals. Serum IL-6, KC, MIP-1α and MCP-1 levels were measured using a multiplex Luminex assay (Millipore /Linco research).

Immunohistochemistry. Epi-WAT was fixed and embedded in paraffin and sectioned. Adipose sections from at least 4 mice per group were incubated with anti-F4/80 antibody (Abcam) at a

1:50 dilution o/n at 4 degrees. Subsequently, a biotinylated anti-rat secondary antibody (Pharmingen) was used at 1:100 dilution, followed by 1:500 HRP-Streptavidin (Jackson) and development in substrate chromogen. Slides were counterstained with Mayer's and mounted with Vectashield mounting media. Brightfield photographs were taken of 3 representative fields per slide using a microscope .

***In vitro* chemotaxis assay.** *In vitro* chemotaxis assay was performed as previously described (Oh et al., 2010). Briefly, mouse thioglycollate-elicited peritoneal macrophages were isolated from WT and MNKO mice. For the migration *per se*, 100,000 IPMacs from WT mice were used per condition. The IPMacs were placed in the upper chamber of an 8 μm polycarbonate filter (24-transwell format; Corning, Lowell, MA), whereas primary adipocyte conditioned medium was placed in the lower chamber. After 3 hr of migration, cells were fixed in formalin and stained with 4′, 6-diamidino-2-phenylindole and observed. *In vivo* LPS administration. Briefly, after 6 hours of fasting, WT or MNKO male mice fed a chow diet were injected IP with LPS (1mg/kg) or saline. Blood was then collected for serum TNFα measurement before and 2 hours after injection.

2-Deoxyglucose (2-DOG) uptake. Mouse thioglycollate-elicited peritoneal macrophages were isolated from WT and MNKO mice and cultured with DMEM (4.5 g/L glucose) with 10% FBS. After 48 hours, cells were serum starved in DMEM with 0.5% FBS for overnight, then stimulate the cells with LPS (100 ng/ml) for 2 hours. The conditioned medium was collected after stimulation. L6 cells were treated with conditioned medium for 12 hours prior to performing the 2-deoxyglucose (2-DOG) uptake assay. The assay for glucose uptake was performed as previously described (Garvey et al., 1985; Nguyen et al., 2005).

Cell Culture and Reagents. Mouse thioglycollate-elicited peritoneal macrophages and bone marrow derived macrophages were obtained and cultured as described previously (Heinz et al., 2010). For TLR studies, cells were cultured in medium containing RPMI 1640 (Invitrogen) serum free or supplemented with either 0.5% heat-inactivated FBS (Hyclone) or 10% heat-inactivated FBS (Hyclone) for 24 hr, then stimulated with Pam3CSK4 (300 ng/ml), PolyI:C (50 ng/ml), or KLA (100 ng/ml) for 6hr. For Trichostatin A (TSA) experiments, cells were pretreated with either vehicle (DMSO) or 400 nM TSA for 2hr, then treated with KLA (100 ng/ml) for 6hr. For ω3 fatty acid experiments, cells were pretreated with either vehicle (ethanol) or 50-100 μM specified ω3-FAs (EPA or DHA) for 1hr, then treated with KLA (100 ng/ml) for 6hr. For NF-κB inhibitor experiments, cells were pretreated with either vehicle (DMSO) or 30 μM NF-κB Activation Inhibitor II (JSH-23, Calbiochem) for 1hr, then treated with KLA (100 ng/ml) for 6hr. Kdo2-

Lipid A (KLA) was purchased from Avanti Polar Lipids. Poly (I:C) was purchased from GE Healthcare Bioscience. Pam3CSK4 was purchased from InvivoGen. TSA was purchased from Sigma.

siRNA Knockdown. Thioglycollate-elicited peritoneal macrophages were plated at 7.5 x 10^5 cells per well of a 24-well plate in growth medium containing RPMI 1640 (with L-glutamine) (Invitrogen) plus 10% heat-inactivated FBS (Hyclone) without antibiotics. Cells were transfected with non-targeting control or Dharmacon siGenome SMARTpool siRNA (Thermo Fisher Scientific) using Deliver X transfection reagent (Panomics) according to the manufacturer's instructions. For ELOVL5, FADS2, SCD2, and NCoR siRNA experiments, 48hr post-transfection, cells were changed to growth medium containing RPMI 1640 (Invitrogen) supplemented with supplemented with 0.5% heat-inactivated FBS (Hyclone). At 72 hr post-transfection, cells were treated for 6hr with vehicle (PBS) or 100 ng/ml KLA (Avanti Polar Lipids). Dharmacon siGenome SMARTpool siRNAs for non-targeting control #2 (D-001206-14), Scd2 (M-045507-01), Elovl5 (M-063970-00), Fads2 (M-049816-00), Hdac3 (M-043553-01) and NCoR (M-058556-01) were purchased from Thermo Fisher Scientific.

Reporter gene activity assays. For transfections of RAW264.7 mouse macrophage cell line, cells were seeded at 200,000 cells per well in 24-well tissue culture plates. Transfection of the RAW264.7 cells was achieved using Superfect reagent (Qiagen) according to manufacturer's recommendation. RAW264.7 cells were cotransfected with 400ng indicated promoter-driven firefly luciferase expression plasmid. At 24 hr post-transfection cells were switched to growth medium containing RPMI 1640 (with L-glutamine) (Invitrogen) plus 0.5% heat-inactivated FBS (Hyclone) and 100 U penicillin/streptomycin (Invitrogen). For KLA-response studies, at 48hr post-transfection, cells were treated with vehicle (DMSO or ethanol), 400 μM Trichostatin A (TSA from Sigma), or 50-100 μM specified ω3-FAs (DHA and EPA, Cayman Chemical) for 4hr, followed by 100ng/ml KLA overnight. Cells were lysed and firefly luciferase activity was measured using a Veritas microplate luminometer (Turner Biosystems) according to manufacturer's protocol. A Beta-galactosidase expression vector was cotransfected (5ng/well) as an internal control. Relative light units (RLU) were given as transformed ratio of firefly luciferase to Beta-galactosidase. Values are the mean ratio of three independent experiments performed in triplicate. For transfections of primary macrophages from WT and MNKO mice, cells were transfected using the Amaxa Mouse Macrophage Nucleofector Kit (Lonza), using 1,000,000 cells per well in 24-well tissue culture plates. Transfections were carried out according to manufacturer's instructions.

RNA analysis. Total RNA was isolated from cells and purified using RNeasy columns and RNase free DNase digestion according to the manufacturer's instructions (Qiagen). RNA was analyzed for purity using the Agilent 2100 Bioanalyser (Agilent). For quantitative PCR analysis, either 1µl of cDNA or ChIP DNA was used for real time PCR using gene- or locus-specific primers (primer sequences indicated in Supplementary Table S1). Quantitative-PCR (SYBR GreenER) analysis was performed on an Applied Biosystems 7300 Real-time PCR system (Invitrogen). The sequences of qPCR primers used for mRNA quantification in this study were obtained from PrimerBank (Spandidos et al., 2010).

Chromatin Immunoprecipitation (ChIP) and ChIP-Seq Libraries. For ChIP of HDAC3 4 x 10^7 macrophages were used per ChIP, as described previously (Mullican et al. Genes&Development 2011). For ChIP of p65 and H4K5Ac, 2-4 x 10^7 macrophages were used per ChIP, as described previously with modifications (Heinz et al., 2010). Briefly, for p65 ChIP cells were first crosslinked in 2mM disuccinimidyl glutarate (Pierce) in PBS for 30 minutes, then subsequently in 1% formaldehyde (Sigma) in PBS for 10 minutes all at room temperature. For H3K9/14Ac ChIP cells were crosslinked in 1% Formaldehyde in PBS for 10 minutes at room temperature. The reactions were quenched by adding glycine (Sigma) to a final concentration of 125 mM. The cells were immediately centrifuged (5 min, 700x g, 4°C) and washed twice with ice-cold PBS. Cells were resuspended in swelling buffer (10 mM HEPES/KOH pH7.9, 85 mM KCl, 1 mM EDTA, 0.5% IGEPAL CA-630 (Sigma), 1x protease inhibitor cocktail (Roche), 1 mM PMSF) for 5 minutes. Cells were spun down and resuspended in 400 µl lysis buffer (50 mM Tris/HCl pH 7.4@20°C, 1% SDS, 0.5% Empigen BB (Sigma), 10 mM EDTA, 1x protease inhibitor cocktail (Roche), 1 mM PMSF)) and chromatin was sheared to an average DNA size of 100-400 bp by administering 6 pulses of 10 seconds duration at 12 W power output with 30 seconds pause on wet ice using a Misonix 3000 sonicator. The lysate was cleared by centrifugation (5 min, 16000 x g, 4°C), and 400 µl supernatant was diluted 2.5-fold with 750 µl dilution buffer (20 mM Tris/HCl pH 7.4@20°C, 100 mM NaCl, 0.5% Triton X-100, 2 mM EDTA, 1x protease inhibitor cocktail (Roche)). The diluted lysate was pre-cleared by rotating for 1 hr at 4°C with 120 µl 50% CL-4B sepharose slurry (Pharmacia; before use, 100 µl CL-4B sepharose were washed twice with TE buffer, blocked for > 30 min at room temperature with 0.5% BSA and 20 µg/ml glycogen in 1 ml TE buffer, washed twice with TE and brought up to the original volume with TE). The beads were discarded, and 1% of the supernatant were kept as ChIP input. The protein of interest was immunoprecipitated by rotating the supernatant with 30 µl Dynabeads Protein G-coated with specific antibody or species-specific IgG overnight at 4°C

(Dynabeads from Invitrogen). For preparation of Dynabead-antibody complex, Dynabeads Protein G and 5 μg specific antibody were incubated in 0.5% BSA/PBS for 1 hr at 4°C on rotator, then washed twice with 0.5% BSA/PBS and brought up to the original volume with 0.1% BSA/PBS. The beads were collected by magnet, the supernatant discarded, and resuspended in 500 μl wash buffer I (WB I) (20 mM Tris/HCl pH 7.4@20°C, 150 mM NaCl, 0.1% SDS, 1% Triton X-100, 2 mM EDTA). The beads were washed four times each with WB I (20 mM Tris/HCl pH 7.4@20°C, 150 mM NaCl, 0.1% SDS, 1% Triton X-100, 2 mM EDTA), WB II (10 mM Tris/HCl pH 7.4@20°C, 250 mM LiCl, 1% IGEPAL CA-630, 0.7% Na-deoxycholate, 1 mM EDTA), and twice each with TE plus 0.2% triton X-100 and TE plus 50mM NaCl. Immunoprecipitated chromatin was eluted twice with 100 μl elution buffer each (TE, 2% SDS) into fresh tubes for 30 min and 10 min, respectively, eluates were pooled, the Na^+ concentration was adjusted to 300 mM with 5 M NaCl and crosslinks were reversed overnight at 65°C in a hybridization oven. The samples were sequentially incubated at 37°C for 1 hr each with 0.33 mg/ml RNase A and 0.5 mg/ml proteinase K. The DNA was isolated using the ChIP DNA Clean & Concentrator (Zymo Research) according to the manufacturer's instructions. Antibodies against p65 (sc-372) were purchased from Santa Cruz Biotechnology. Antibodies against H4K5Ac (07-327) were purchased from Millipore. Antibodies against HDAC3 (ab7030) were purchased from Abcam.

For H3K4me2-MNase ChIP, 20 million cells were resuspended in 900 ul of MNase digestion buffer (50 mM Tris/HCl pH7.6, 1 mM CaCl2, 10% Triton X-100 (Sigma), 1x protease inhibitor cocktail, 1 mM PMSF). Samples were split into aliquots of 10million cells for digestion. MNase (7.5-12.5 U; Worthington) diluted in 0.1% BSA was added to samples and incubated at 37□C for 5 minutes. Stop buffer was then added to each reaction (120 μl per sample; 10 mM Tris/HCl pH7.6, 50 mM EDTA, 200 mM EGTA, 1x protease inhibitor cocktail (Roche), 1 mM PMSF). Samples were sonicated on Bioruptor for three cycles for 30 seconds on, 30 seconds off, intensity set to medium. Aliquots were recombined and moved to G2 dialysis cassette (Pierce). Dialysis was performed in RIPA buffer (10 mM Tris/HCl pH7.6, 1 mM EDTA, 1 mM EGTA, 0.1% SDS, 0.1% Na-Deoxycholate, 1% Triton X-100, 1x protease inhibitor cocktail (Roche), 1 mM PMSF) at 4□C for 2 hours. Meanwhile Protein G Dynabeads were pretreated with the H3K4me2 antibody as above. After dialysis, samples were recovered from cassette and span down at 13,000 rpm, 4□C for 10 minutes. Sample was mixed with 50 ul of the Dynabead-H3K4me2 antibody mix and rotated overnight at 4□C. Beads were washed twice with each buffer by rotating in 1 ml buffer at 4□C for 5 minutes: RIPA buffer (10 mM Tris/HCl pH7.6, 1 mM EDTA, 1 mM EGTA,

0.1% SDS, 0.1% Na-Deoxycholate, 1% Triton X-100, 1x protease inhibitor cocktail (Roche), 1 mM PMSF), LiCl buffer (0.25 M LiCl, 1% NP40, 1% NaDOC), TE plus 0.2% triton X-100 and TE plus 50mM NaCl. Immunoprecipitated chromatin was eluted twice at 37□C for 1h with 100 µl elution buffer (TE, 0.3% SDS, 250 mM NaCl, 0.5 mg/ml RNaseA) followed by overnight proteinase K treatment. DNA was isolated using the ChIP DNA Clean & Concentrator (Zymo Research) according to the manufacturer's instructions. Antibodies against H3K4me2 (07-030) were purchased from Millipore. The ChIP-seq libraries were performed as previously described (Escoubet-Lozach et al., 2011). Previously published datasets utilized for NCoR and SMRT ChIP-Seq were taken from Gene Expression Omnibus website, deposited as GSE27060 (Barish et al., 2012).

Preparation of GRO-Seq Libraries. GRO-Seq libraries were prepared from 1-7 biological replicates per condition. Global run-on (Core et al., 2008) and library preparation for sequencing (Ingolia et al., 2009) were done as described. The detailed protocol as described in (Wang et al., 2011) was performed with minor modifications. Briefly, nuclei were extracted from 12 million cells grown on 10 cm plates and after run-on reaction the RNA was extracted with Trizol LS Reagent (Invitrogen, Carlsbad, CA, USA). RNA was treated with TURBO DNase (Ambion), fragmented using RNA Fragmentation Reagents (Ambion) and purified by running through P-30 column (Bio-Rad, Hercules, CA, USA). Fragmented RNA was dephosphorylated with PNK (New England Biolabs, Ipswich, MA, USA) followed by heat-inactivation. Dephosphorylation reactions were purified using anti-BrdU beads (SantaCruz Biotech, Santa Cruz, CA, USA) and precipitated overnight. Poly(A)-tailing and cDNA synthesis was performed the next day as described in (Wang et al., 2011). However, for reverse transcription oligos with custom barcodes (underlined) were used : 5'PhosCA/TG/AC/GTGATCGTCGGACTGTAGAACTCT/ idSp/CAAGCAGAAGACGGCATACGATTTTTTTTTTTTTTTTTTTVN-3'. After cDNA synthesis, Exonuclease I (New England Biolabs; 30 min) was used to catalyze the removal of excess oligo. Enzyme was inactivated and RNA hydrolyzed by alkaline treatment (100 mM NaOH) and heat (25 min, 95°C). The cDNA fragments of were purified on a denaturing Novex 10% polyacrylamide TBE-urea gel (Invitrogen). The recovered cDNA was circularized, linearized, amplified for 10-14 cycles. The final product was ran on Novex 10%TBE gel, gel purified and cleaned-up using ChIP DNA clean & Concentrator Kit (Zymo Research Corporation, Irvine, CA, USA).

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