Supplemetary Figure 1.

A

Cluster 1 (Cl1)

Motif	p-value	T%	Bg%
PU.1	1e-92	22.20	3.33
NR half	1e-75	25.09	5.50
PU.1::IRF	1e-25	4.34	0.36
TRE	1e-22	9.77	2.60
C/EBP	1e-18	3.38	0.32
IRF	1e-15	2.65	0.25
ETS	1e-14	8.81	3.07
DR2	1e-13	4.70	1.07

Cluster 2 (Cl2)

Motif	p-value	T%	Bg%
DR1	1e-93	22.44	3.32
TRE	1e-68	20.12	3.79
EGR2	1e-67	28.05	7.60
PU.1	1e-42	14.39	3.05
CRE	1e-26	11.71	3.14
DR1	1e-21	4.39	0.52
NR site	1e-20	4.02	0.45

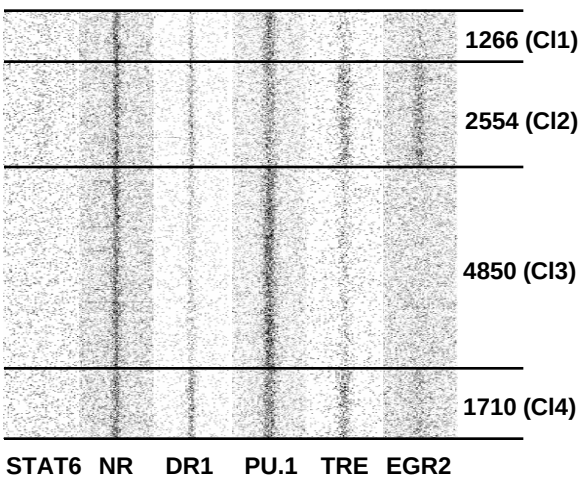
Cluster 3 (Cl3)

Motif	p-value	T%	Bg%
NR half	1e-175	42.33	7.13
PU.1	1e-168	37.05	5.35
DR4	1e-46	3.36	0.03
PU.1::IRF	1e-25	2.04	0.03
TRE	1e-25	10.79	2.90
RUNX	1e-20	4.56	0.59

Cluster 4 (Cl4)

Motif	p-value	T%	Bg%
DR1	1e-143	22.53	1.86
PU.1	1e-103	32.87	7.41
TRE	1e-66	13.36	1.60
C/EBP	1e-25	1.63	0.02
EGR2	1e-14	7.67	2.45
RUNX	1e-14	3.25	0.46

B

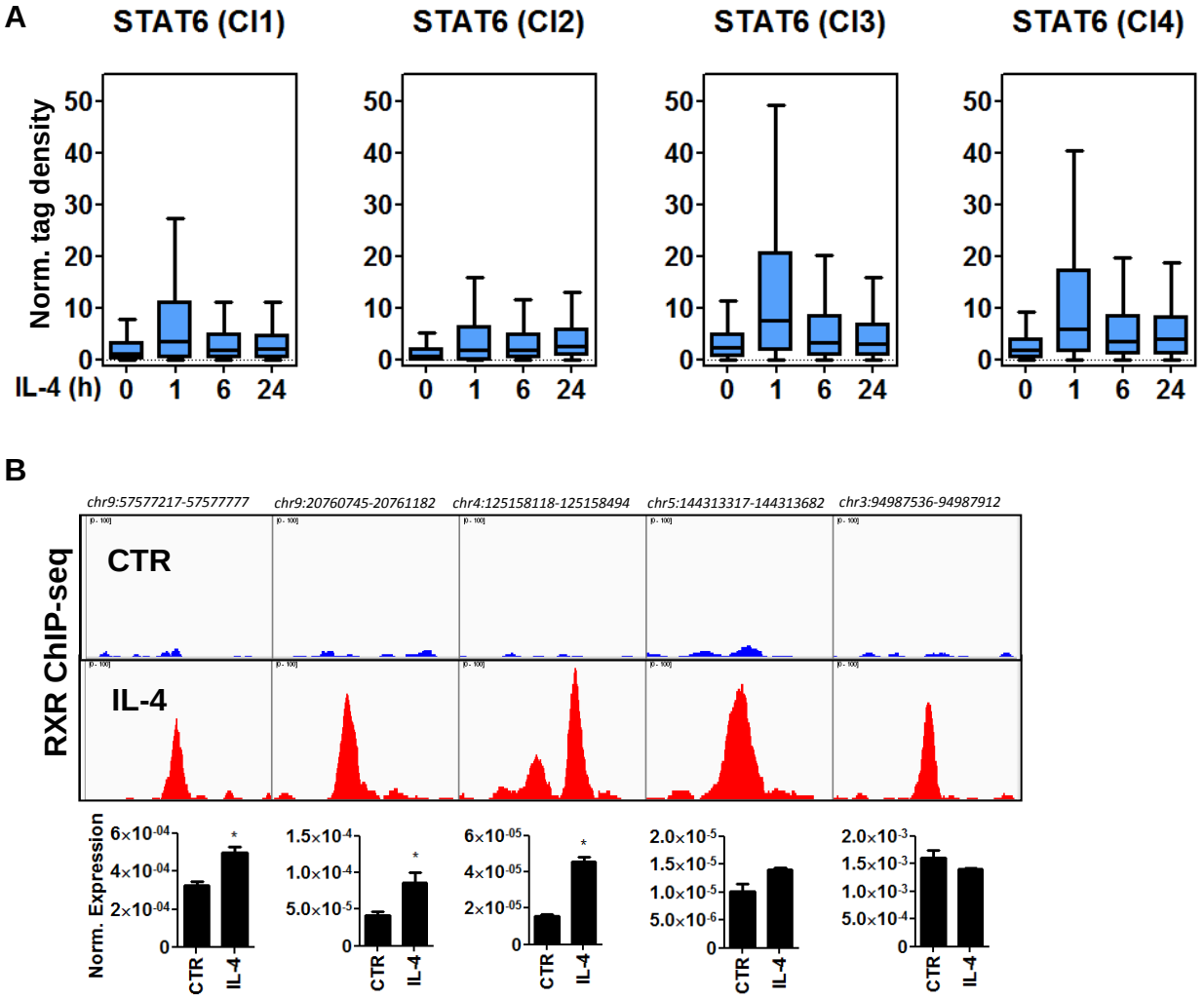


STAT6 (1h IL-4)

STAT6	1e-304	49.23	4.77

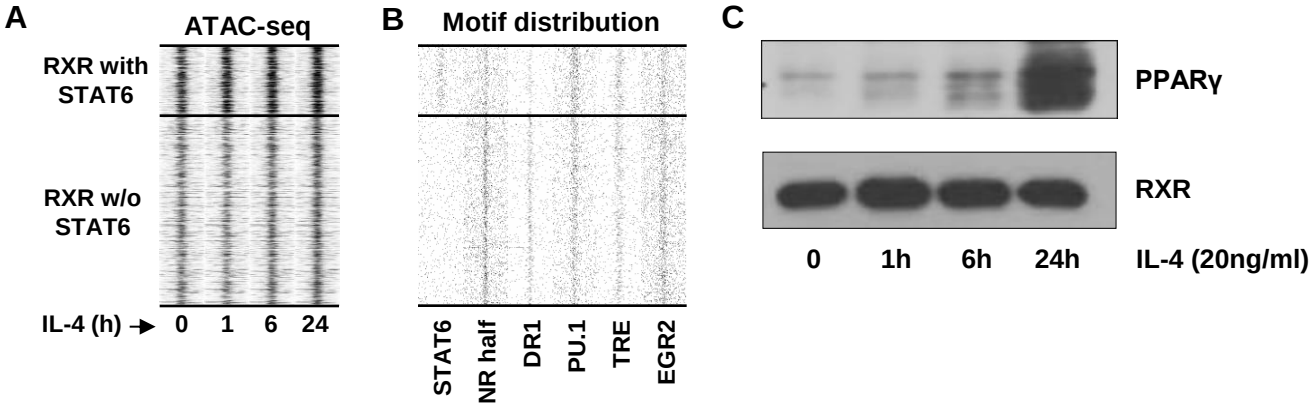
Supplementary Figure 1. Related to Figure 1.
A, *De novo* motif discovery results in the four clusters as shown on Figure 1 panel B. Motif logos, names, p-values and the percentages of motif hits either on RXR (target) peaks (T%) or a random background (Bg%) is presented. Motifs used to generate motif distribution plots are highlighted in blue. B, Distribution of motifs around RXR peaks. 1.5-kb regions are represented in 30-bp bins. STAT6 motif matrix was obtained from a STAT6 ChIP-seq sample treated with IL-4 for an hour.

Supplemetary Figure 2.



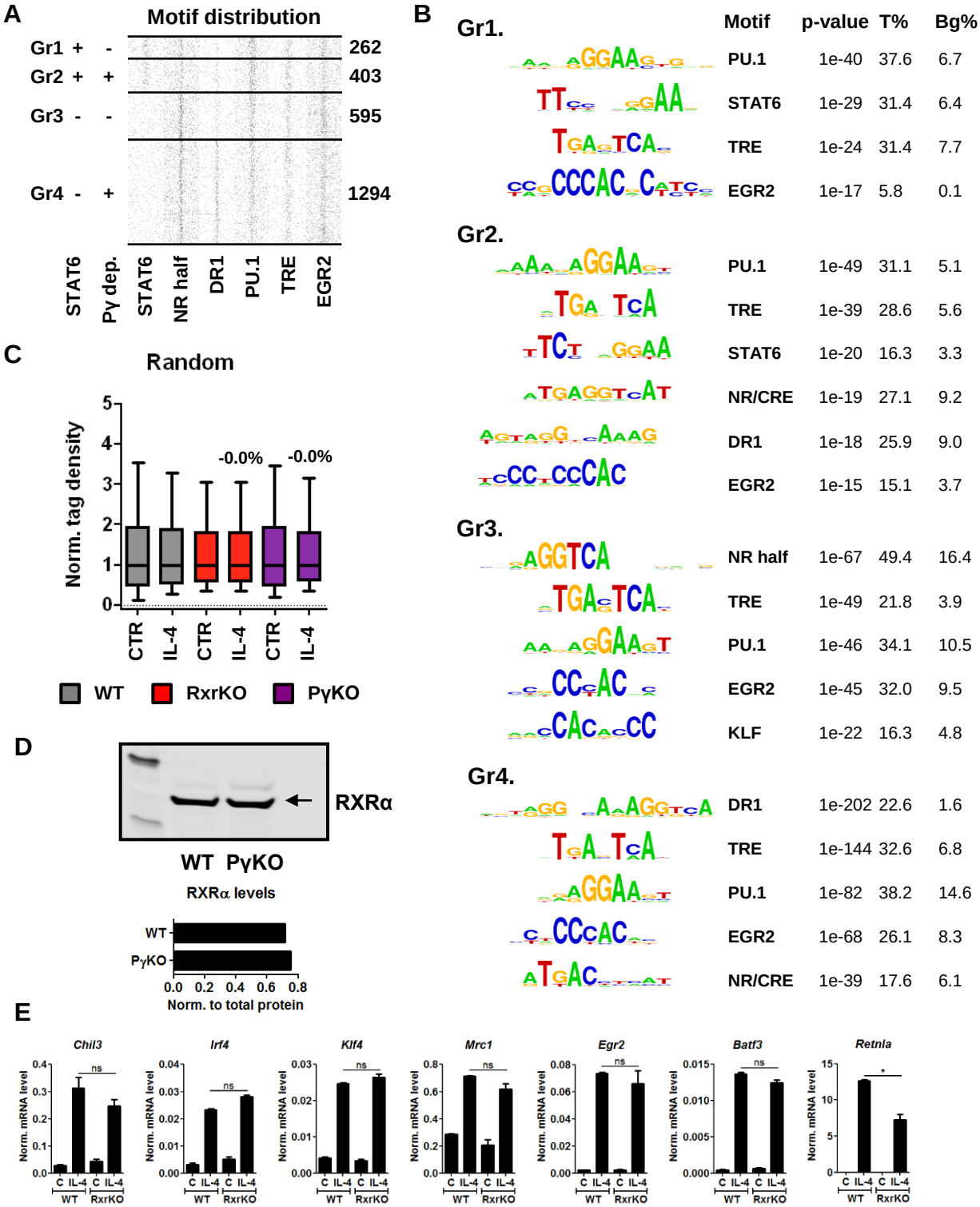
Supplementary Figure 2. Related to Figure 2.
A, Box plots depicting the normalized read enrichments (Norm. tag density) for STAT6 obtained from ChIP-seq experiments. Clusters established on Figure 1 panel B are shown, and the time points of IL-4 stimulation are also indicated (h – hours). B, IGV genom browser images of five *de novo* RXR-bound genomic regions (top). Enhancer RNA measurements next to the detected peaks in control (CTR) and IL-4 stimulated macrophages. Changes were considered significant at $p<0.05$ using two-tailed unpaired t test (n=3). Normalized expression to *Ppia* is presented on the y axis (Norm. Expression).

Supplemetary Figure 3.



Supplementary Figure 3. Related to Figure 3.
A, Read distribution plot of the indicated ATAC-seq experiments in the *de novo*, IL-4/STAT6-dependent RXR cluster separated based on STAT6 binding (h – hours). B, Distribution of the indicated motifs around RXR peaks of the *de novo* cluster. 1.5-kb regions are represented in 30-bp bins. C, Western blot analysis of PPARγ and RXR expression at the indicated time points after IL-4 exposure.

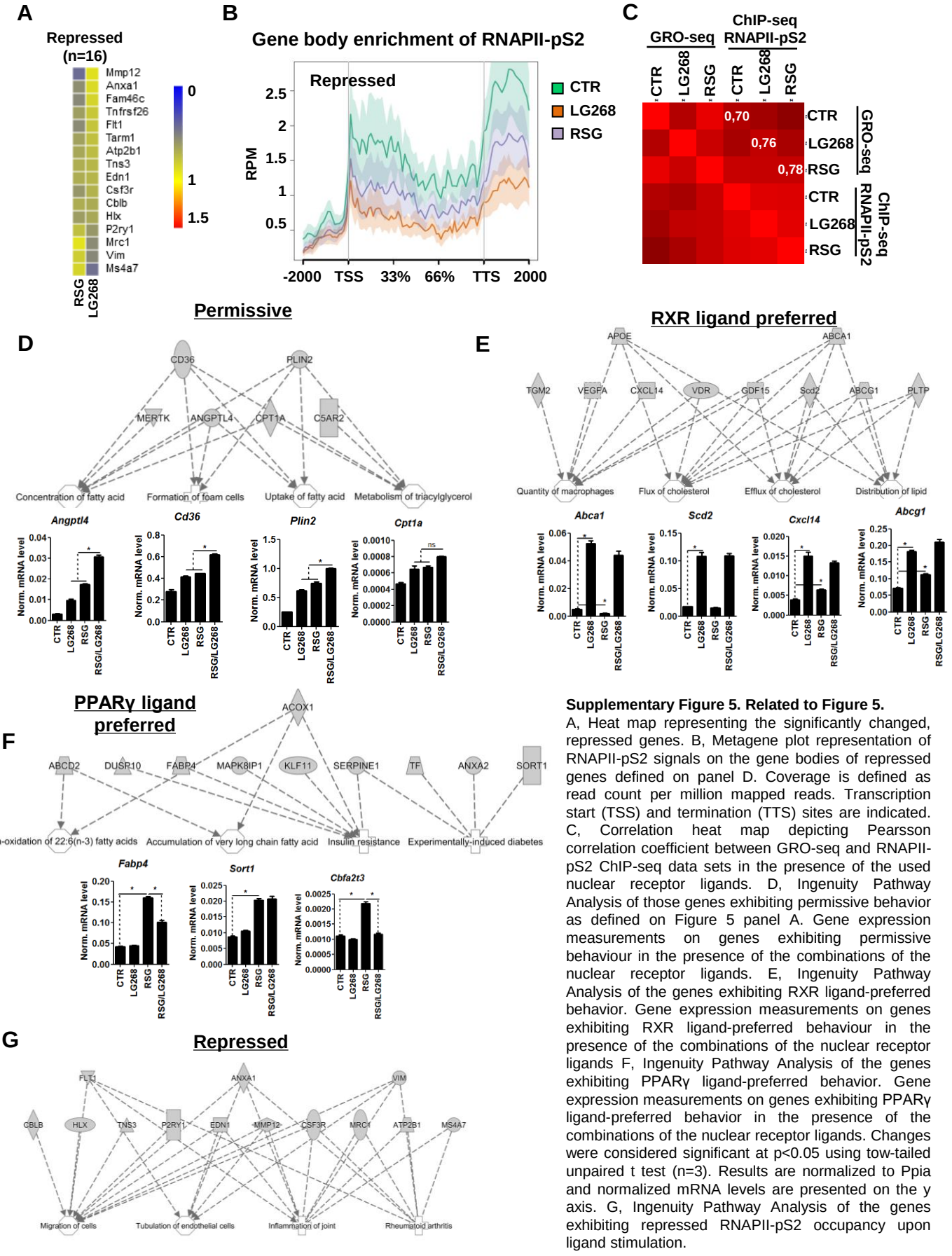
Supplementary Figure 4.



Supplementary Figure 4. Related to Figure 4.

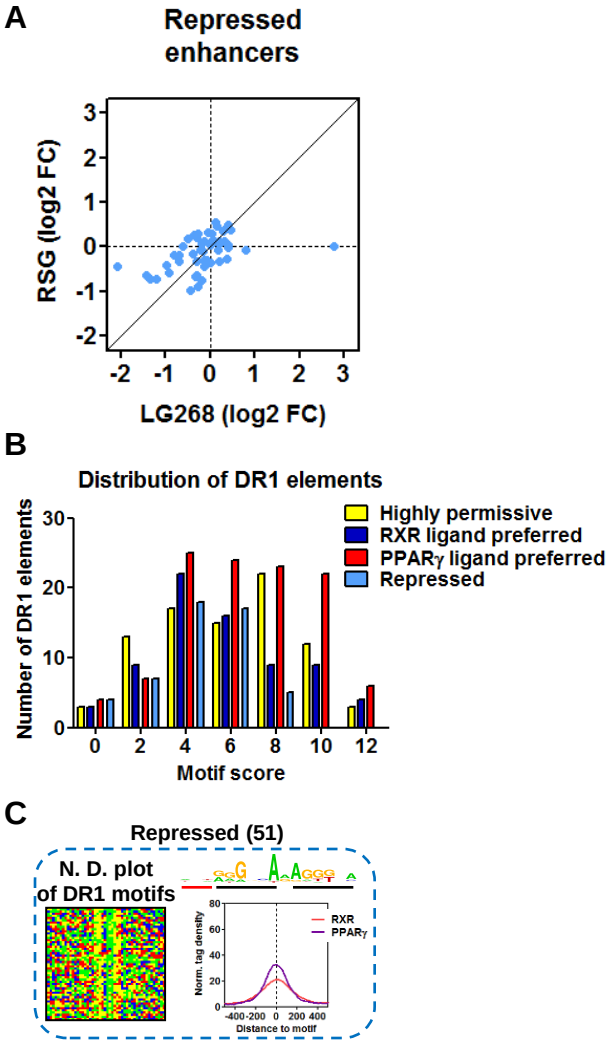
A, Distribution of the indicated motifs around the RXR peaks of the *de novo* cluster (Gr1-4.). 1.5-kb regions are represented in 30-bp bins. B, *De novo* motif analysis in the four groups. Motif logos, names, p-values and the percentages of motif hits either on RXR (target) peaks (T%) or a random background (Bg%) is presented. C, Box plot depicting the normalized tag density of ATAC-seq data for a random set of open chromatin regions (n=7248 – every 10th region showing read enrichment throughout the genome). Percentages represent the contribution of the *knocked-out* nuclear receptor to chromatin openness, calculated based on the median values for the IL-4-treated samples. D, Western blot of RXRα levels from wild type (WT) and *Pparg knockout* (PγKO) macrophage protein extracts (top). Normalized levels of RXRα to total protein (Norm. to total protein). E, Gene expression measurements from wild type (WT) and *Rxra/b knockout* (RxrKO) macrophages in the absence (C) or presence of IL-4. Results were normalized to *Ppia* and normalized mRNA level is presented on the y axis (Norm. mRNA level). Changes were considered significant at $p<0.05$ using tow-tailed unpaired t test (n=3).

Supplementary Figure 5.



Supplementary Figure 5. Related to Figure 5.
A, Heat map representing the significantly changed, repressed genes. B, Metagene plot representation of RNAPII-pS2 signals on the gene bodies of repressed genes defined on panel D. Coverage is defined as read count per million mapped reads. Transcription start (TSS) and termination (TTS) sites are indicated. C, Correlation heat map depicting Pearsson correlation coefficient between GRO-seq and RNAPII-pS2 ChIP-seq data sets in the presence of the used nuclear receptor ligands. D, Ingenuity Pathway Analysis of those genes exhibiting permissive behavior as defined on Figure 5 panel A. Gene expression measurements on genes exhibiting permissive behaviour in the presence of the combinations of the nuclear receptor ligands. E, Ingenuity Pathway Analysis of the genes exhibiting RXR ligand-preferred behavior. Gene expression measurements on genes exhibiting RXR ligand-preferred behaviour in the presence of the combinations of the nuclear receptor ligands F, Ingenuity Pathway Analysis of the genes exhibiting PPARγ ligand-preferred behavior. Gene expression measurements on genes exhibiting PPARγ ligand-preferred behavior in the presence of the combinations of the nuclear receptor ligands. Changes were considered significant at $p<0.05$ using tow-tailed unpaired t test (n=3). Results are normalized to Ppia and normalized mRNA levels are presented on the y axis. G, Ingenuity Pathway Analysis of the genes exhibiting repressed RNAPII-pS2 occupancy upon ligand stimulation.

Supplementary Figure 6.



Supplementary Figure 6. Related to Figure 6.
A, Scatter plots depicting RNAPII-pS2 signal on individual enhancers from the repressed enhancer group in the presence of rosiglitazone (RSG) and LG268. Log_2 fold change over control is presented. B, Bar graph depicting DR1 motif distribution based on motif scores within the enhancer groups defined on Figure 6. C, Nucleotide distribution plot of repressed PPARγ:RXR-bound genomic regions along with the DR1 motif enriched (left). Normalized tag density for PPARγ and RXR binding is also represented as a boxplot and histogram (right).