

Supplementary table 1. List of NGS samples

Cell type	Treatment / differentiation time	Antibody / Method	Replicate	BioProject	SRA experiment	GEO series	GEO sample	Citation
Bone marrow-derived macrophage	24h IL-4	PPAR γ	rep1	PRJNA318630	SRX3097650	GSE115083	GSM3164887	Daniel and Nagy et al. NAR. 2018. PMID: 29506156
Bone marrow-derived macrophage	24h IL-4	PPAR γ	rep2	PRJNA318630	SRX3097649	GSE115083	GSM3164888	
Bone marrow-derived macrophage	24h IL-4	RXR	-	PRJNA318630	SRX6750742	GSE142249	GSM4223704	
Bone marrow-derived macrophage	-	PU.1	-	PRJNA318630	SRX1716779	GSE107456	GSM2867721	Daniel and Nagy et al. NAR. 2018. PMID: 29506156
Bone marrow-derived macrophage	1h IL-4	PU.1	-	PRJNA318630	SRX1716764	GSE107456	GSM2867722	
Bone marrow-derived macrophage	6h IL-4	PU.1	-	PRJNA318630	SRX1716766	GSE107456	GSM2867723	
Bone marrow-derived macrophage	24h IL-4	PU.1	-	PRJNA318630	SRX1716812	GSE107456	GSM2867724	
Bone marrow-derived macrophage	-	ATAC-seq	-	PRJNA318630	SRX1716809	GSE107456	GSM2867754	Daniel and Nagy et al. Immunity. 2018. PMID: 30332629
Bone marrow-derived macrophage	1h IL-4	ATAC-seq	-	PRJNA318630	SRX1716803	GSE107456	GSM2867755	
Bone marrow-derived macrophage	6h IL-4	ATAC-seq	-	PRJNA318630	SRX1716805	GSE107456	GSM2867756	
Bone marrow-derived macrophage	24h IL-4	ATAC-seq	-	PRJNA318630	SRX1716804	GSE107456	GSM2867757	
Bone marrow-derived macrophage	24h IL-4 + 1h veh	RNAPII-pS2	rep1	PRJNA318630	SRX3097634	GSE107456	GSM2867748	Daniel and Nagy et al. Immunity. 2018. PMID: 30332629
Bone marrow-derived macrophage	24h IL-4 + 1h veh	RNAPII-pS2	rep2	PRJNA318630	SRX3097633	GSE107456	GSM2867749	
Bone marrow-derived macrophage	24h IL-4 + 1h RSG	RNAPII-pS2	rep1	PRJNA318630	SRX3097632	GSE107456	GSM2867750	
Bone marrow-derived macrophage	24h IL-4 + 1h RSG	RNAPII-pS2	rep2	PRJNA318630	SRX3097631	GSE107456	GSM2867751	
Bone marrow-derived macrophage	-	RNA-seq	rep1	PRJNA318630	SRX1924028	GSE106706	GSM2845676	Czimmerer et al. Immunity. 2018. PMID: 29343442
Bone marrow-derived macrophage	-	RNA-seq	rep2	PRJNA318630	SRX1924029	GSE106706	GSM2845677	
Bone marrow-derived macrophage	-	RNA-seq	rep3	PRJNA318630	SRX1924041	GSE106706	GSM2845678	
Bone marrow-derived macrophage	-	RNA-seq	rep4	PRJNA318630	SRX1924053	GSE106706	GSM2845679	
Bone marrow-derived macrophage	1h IL-4	RNA-seq	rep1	PRJNA318630	SRX1924065	GSE106706	GSM2845680	
Bone marrow-derived macrophage	1h IL-4	RNA-seq	rep2	PRJNA318630	SRX1924077	GSE106706	GSM2845681	
Bone marrow-derived macrophage	1h IL-4	RNA-seq	rep3	PRJNA318630	SRX1924082	GSE106706	GSM2845682	
Bone marrow-derived macrophage	1h IL-4	RNA-seq	rep4	PRJNA318630	SRX1924083	GSE106706	GSM2845683	
Bone marrow-derived macrophage	3h IL-4	RNA-seq	rep1	PRJNA318630	SRX1924040	GSE106706	GSM2845695	
Bone marrow-derived macrophage	3h IL-4	RNA-seq	rep2	PRJNA318630	SRX1924042	GSE106706	GSM2845696	
Bone marrow-derived macrophage	3h IL-4	RNA-seq	rep3	PRJNA318630	SRX1924043	GSE106706	GSM2845697	
Bone marrow-derived macrophage	3h IL-4	RNA-seq	rep4	PRJNA318630	SRX1924044	GSE106706	GSM2845698	
Bone marrow-derived macrophage	6h IL-4	RNA-seq	rep1	PRJNA318630	SRX1924050	GSE106706	GSM2845703	
Bone marrow-derived macrophage	6h IL-4	RNA-seq	rep2	PRJNA318630	SRX1924051	GSE106706	GSM2845704	
Bone marrow-derived macrophage	6h IL-4	RNA-seq	rep3	PRJNA318630	SRX1924052	GSE106706	GSM2845705	
Bone marrow-derived macrophage	6h IL-4	RNA-seq	rep4	PRJNA318630	SRX1924054	GSE106706	GSM2845706	
Bone marrow-derived macrophage	24h IL-4	RNA-seq	rep2	PRJNA318630	SRX1924032	GSE106706	GSM2845688	
Bone marrow-derived macrophage	24h IL-4	RNA-seq	rep3	PRJNA318630	SRX1924033	GSE106706	GSM2845689	
Bone marrow-derived macrophage	24h IL-4	RNA-seq	rep4	PRJNA318630	SRX1924034	GSE106706	GSM2845690	
E14-derived adipocyte	Day 21	PPAR γ	rep1	PRJNA318630	SRX6750743	GSE142249	GSM4223705	
E14-derived adipocyte	Day 21	PPAR γ	rep2	PRJNA318630	SRX6750744	GSE142249	GSM4223706	
E14-derived adipocyte	Day 30	RXR	-	PRJNA318630	SRX6750745	GSE142249	GSM4223707	
3T3-L1-derived adipocyte	Day 7	C/EBP α	-	PRJNA299295	SRX1357062	GSE74189	GSM1913007	Lai B et al. NAR. 2017. PMID: 28398509
3T3-L1-derived adipocyte	Day 7	C/EBP β	-	PRJNA299295	SRX1357066	GSE74189	GSM1913011	

Supplementary Figure 1.

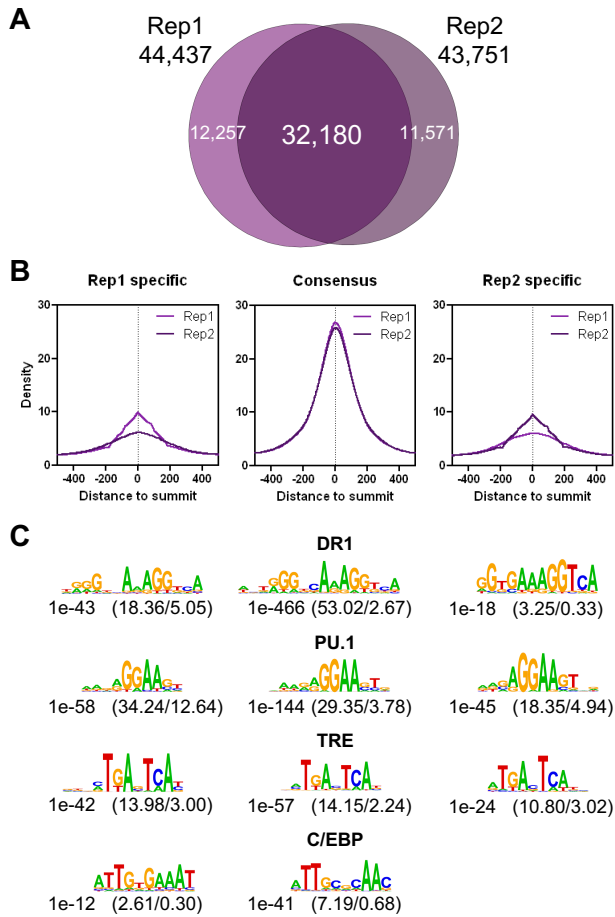
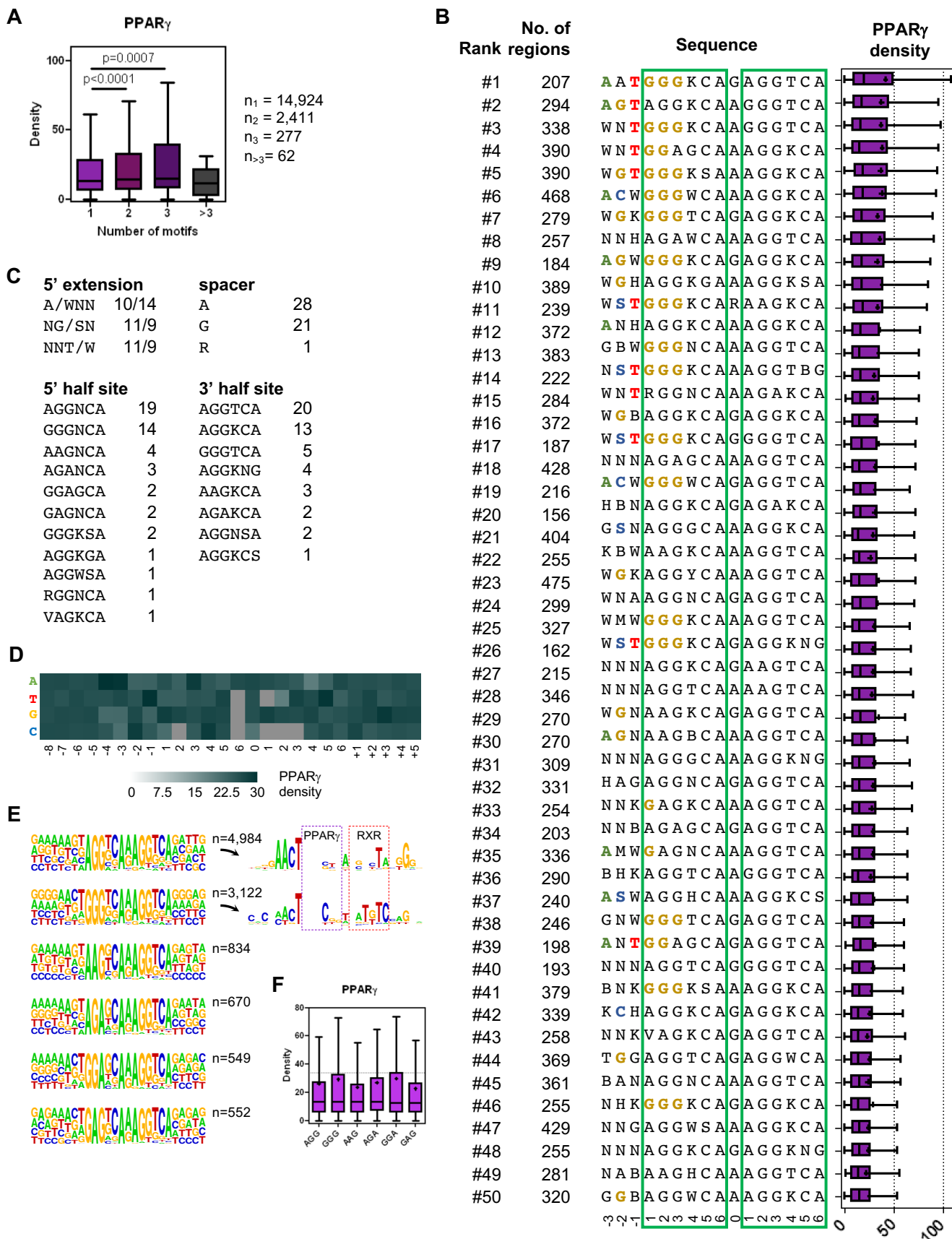


Figure S1. Overview of the PPAR γ cistrome of alternatively polarized macrophages. **(A)** The overlap of the PPAR γ peak sets determined from two biological replicates. **(B)** The average PPAR γ ChIP-seq coverage relative to the summit position of the overlapping (consensus) and replicate specific peak sets, depicted in 10-bp resolution. **(C)** The *de novo* motifs enriched in the top 1,000 peaks of the consensus and replicate-specific peak sets. P-values and target/background percentages are indicated.

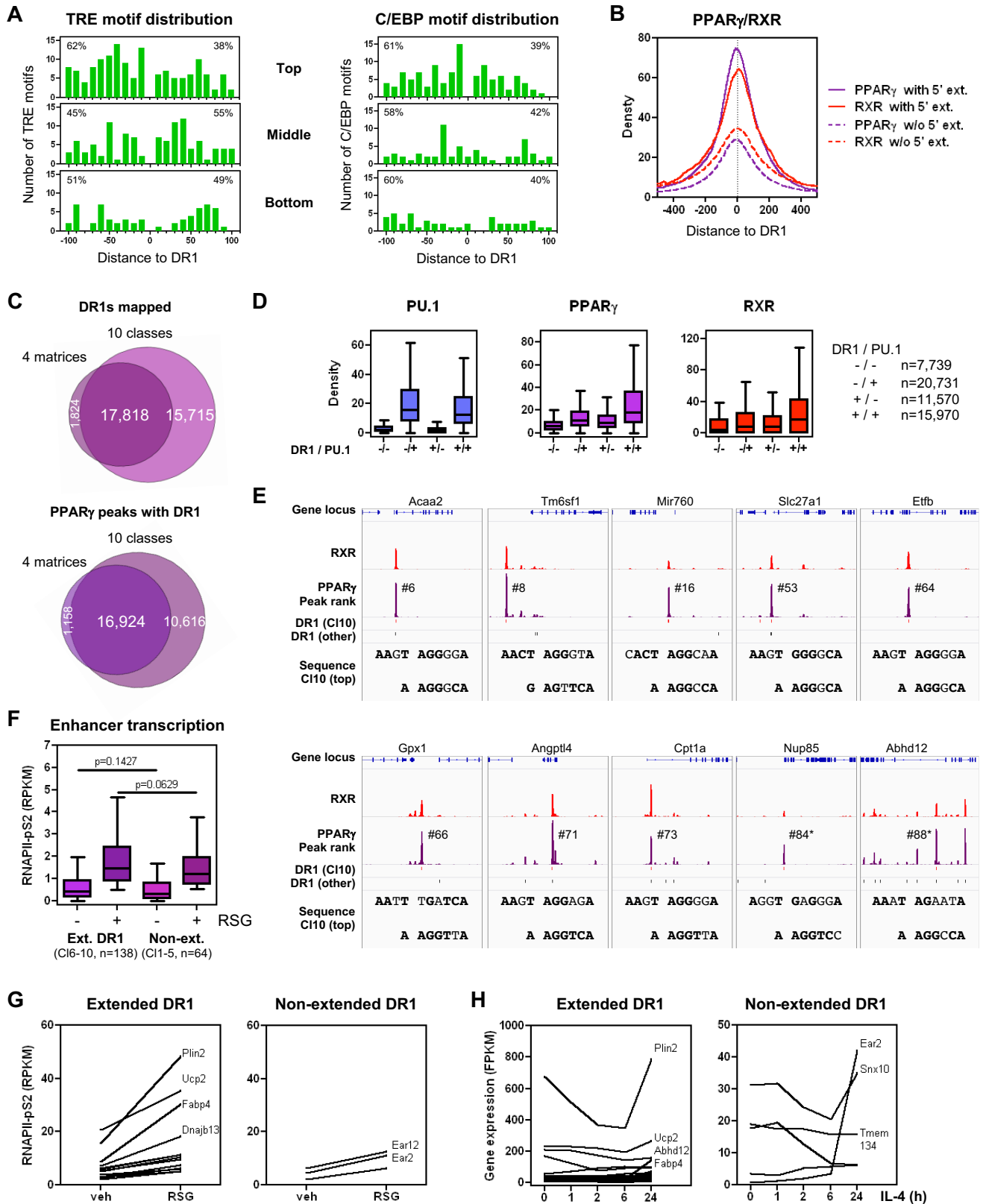
Supplementary Figure 2.



Supplementary Figure 2.

Figure S2. Identification of the extensions of PPREs. **(A)** PPAR γ ChIP-seq densities at those PPAR γ binding sites harboring the indicated number of DR1s. P-values were determined by two-tailed unpaired t-tests. **(B)** The consensus sequence of DR1 clusters, determined by k-means clustering (k=50) of the single DR1 sequences per PPAR γ binding site (n=14,924) and ranked by the per cluster upper quartile of the PPAR γ ChIP-seq densities. Half sites and the nucleotides specific for the top clusters are highlighted. The box plot shows the PPAR γ ChIP-seq densities of each DR1 motif cluster (right). **(C)** A summary of the sequence composition of the 50 clusters. **(D)** A heat map representing the average PPAR γ ChIP-seq density of all DR1s harboring the indicated nucleotide (axis Y) at the indicated position (axis X). **(E)** The nucleotide frequencies of those single DR1s starting with 5'-AGG-3', 5'-GGG-3', 5'-AAG-3', 5'-AGA-3', 5'-GGA-3', or 5'-GAG-3' trinucleotides (left), and the result of Nucleotide Contribution Analysis for the most frequent ones (right). **(F)** The PPAR γ ChIP-seq densities at those DR1s starting with the indicated nucleotide trimers.

Supplementary Figure 3.



Supplementary Figure 3.

Figure S3. Characterization of the unbalanced PPREs. **(A)** TRE (left) and C/EBP motif distribution (right) around the top, middle, and bottom 500 DR1s according to the PPAR γ ChIP-seq densities, depicted in 10-bp resolution. **(B)** The average PPAR γ and RXR ChIP-seq coverage of the extended (Ext4) and non-extended (Ext0) DR1s, depicted in 10-bp resolution. **(C)** Venn diagrams representing the overlap between the DR1s mapped by using the initial 4 motif matrices (Figure 1B) or those of the 10 classes (top), and the overlap between the PPAR γ ChIP-seq peaks having DR1s mapped by using the initial 4 motif matrices or those of the 10 classes (bottom). **(D)** PU.1, PPAR γ , and RXR ChIP-seq densities at the PPAR γ binding sites having or lacking DR1 and/or PU.1. **(E)** Genomic view of the top 10 PPAR γ (purple) ChIP-seq peaks with Class 10 DR1 together with the RXR coverage (red). The locus, the peak rank according to the peak score, the mapped Class 10 (red) or other (black) PPREs, and the sequence of Class 10 elements are included. **(F)** The RNAPII-pS2 ChIP-seq densities (RPKM) at extended (Classes 6-10) or non-extended (Classes 1-5) ligand-responsive DR1s in the presence or absence of Rosiglitazone (RSG). Fold difference (FD) > 1.5; Coverage > 0.5 RPKM. **(G)** The RNAPII-pS2 ChIP-seq densities (RPKM) of direct PPAR γ target genes associated with extended (left) or non-extended DR1(s) (right) in the presence or absence of RSG. Genes are shown over 5 RPKM “expression” and 1.5 FD. **(H)** Expression changes of the identified genes associated with extended (left) or non-extended DR1(s) (right) upon IL-4 treatment at the indicated time points, determined with RNA-seq. Genes are shown over 5 FPKM expression.

Supplementary Figure 4.

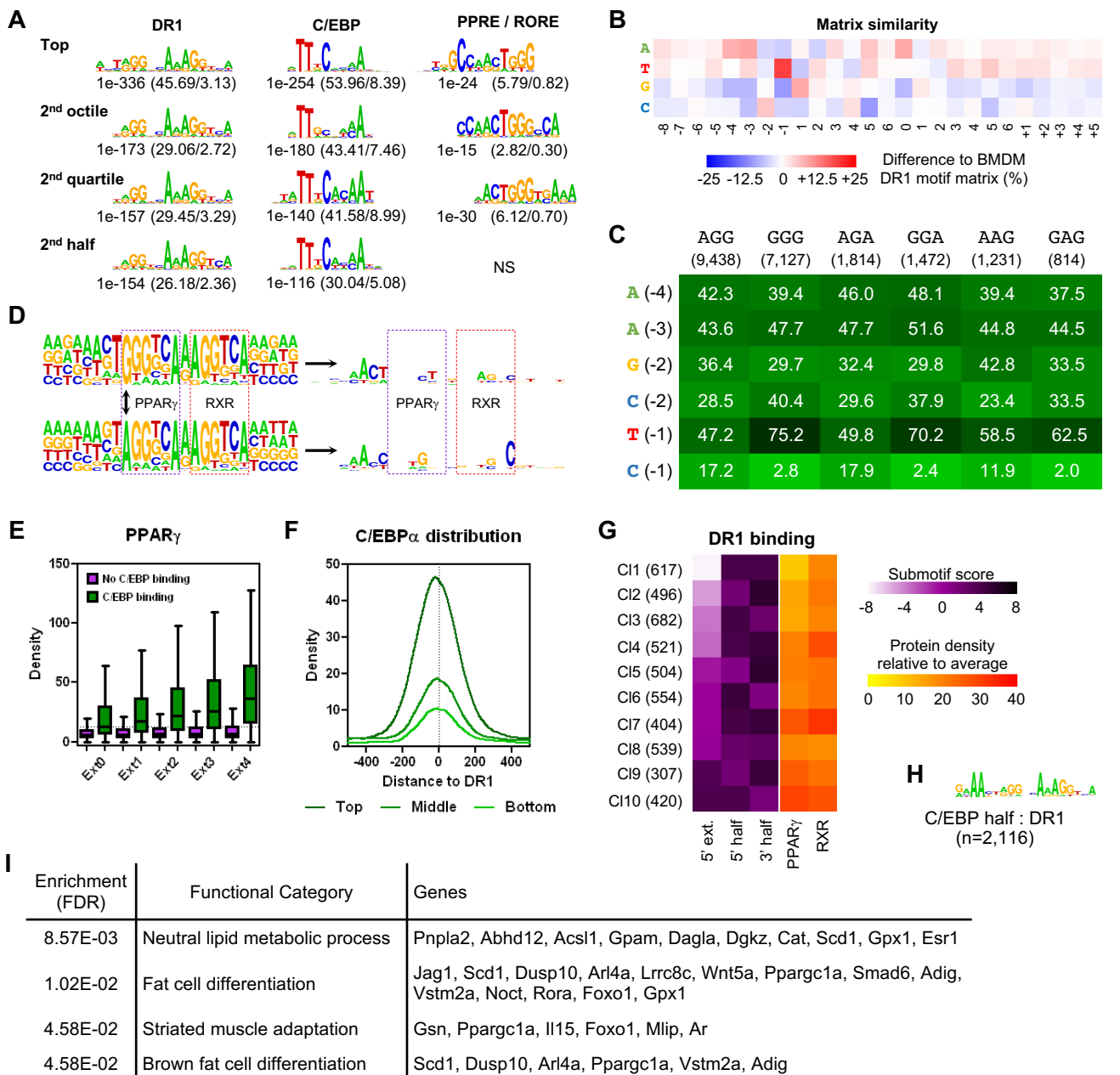


Figure S4. Characterization of the factors determining the adipocyte PPAR_γ cistrome. **(A)** The *de novo* motifs enriched in the top 1,000 peaks of all, the 2nd octile, the 2nd quartile, and the bottom half of the consensus adipocyte PPAR_γ peak set. P-values and target/background percentages are indicated. **(B)** The differences between the adipocyte- and macrophage-specific nucleotide frequencies within the single DR1 sequences per PPAR_γ binding site. **(C)** Concomitance of the indicated nucleotides at the indicated positions (A-A-G/C-T/C) within the 5' extension (left) and the DR1s starting with the indicated trinucleotides (top), as expressed in percentage. **(D)** The nucleotide frequencies of the single DR1s starting with 5' 'A' or 'G' (left), and the result of Nucleotide Contribution Analysis (right). The PPAR and RXR half sites are highlighted with purple and red dashed lines, respectively. **(E)** The dependence of PPAR_γ binding on the presence (green) or absence of C/EBP α/β (purple) and the strength of the 5' extension (Ext0-4). Extensions were discriminated by the number of those nucleotides matching with the 5'-AACT-3' sequence. **(F)** The average C/EBP α ChIP-seq coverage around the top, middle, and bottom 500 PPREs according to the PPAR_γ ChIP-seq densities, depicted in 10-bp resolution. **(G)** Correlation between the average sub-motif score (5' extension, 5' half, and 3' half) and the PPAR_γ/RXR ChIP-seq density of the 10 motif classes determined by k-means clustering (k=10), depicted in the presence of C/EBP. **(H)** A composite element containing a downstream C/EBP half site and a DR1 separated by two spacer nucleotides. **(I)** A table representing the top GO categories associated to C/EBP:DR1 composite elements.