**Supplementary Methods**

**Chromatin Immunoprecipitation (ChIP)**

ChIP was performed using the Transcription factor ChIP Kit (Diagenode) according to manufacturers instructions. Briefly, at least six biological replicates of each experiment (harvest from at least 6 T150 flasks of cells) were crosslinked with a final concentration of 1% formaldehyde (Sigma-Aldrich) for 10 minutes. Fixation was stopped with 0.125M glycine and washed twice with ice-cold PBS. Collected cells were lysed with the provided buffers and dissolved in shearing buffer to a final concentration of 1x10e6cells per ChIP reaction. Shearing was performed using the BioruptorTM (Diagenode) at 4°C and 35-50 sonication cycles (30s on/ 30s off). Shearing conditions were optimized for differentiated THP1 cells and tested for shearing efficiency by agarose gel electrophoresis. The following antibodies were used: anti-LXRα (Abcam, ab 41902), anti-RXRα (Santa Cruz Biotechnology, sc-774), anti-H3K4me3 (Diagenode, pAB-003-050), anti-H4K20me1 (Abcam, ab9051) and negative control IgG (Diagenode, kch-819-015). For each ChIP 2 – 4 µg antibody were used. After washing and reverse crosslinking of precipitated samples, DNA purification was performed with the QIAquick PCR purification kit (Qiagen) according to the manufacturers instructions. Each LXRα ChIP reaction was performed at least in quadruplicates and pooled at the DNA purification step. H3K4me3 and H4K20me1 ChIP reactions were processed in duplicates. DNA quantification was performed with Quant-it Picogreen dsDNA Kit (Invitrogen) according to the manual. Enrichment was measured as described above by quantitative real-time q-PCR with primers flanking new or known response elements and non target control regions applying at least 20pg sample/PCR. The relative occupancy of the immunoprecipitated factor at a locus was estimated using following equation 2e(ct Input – ct ChIP). Ct input and ChIP are the threshold cycles of PCR done in triplicates on DNA samples from input and ChIP. LXRα ChIP qPCR was normalized against IgG ChIP qPCR of the same locus.

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| ID | Name | Forward primer | Reverse primer |
| 1 | ABCA1\_1 | CCCAGCTTCCCCATCTGCGC | CCGGAGGTGGGGTGCCCAAT |
| 2 | ABCA1\_2 | CTCACTCTCGCTCGCAATTA | ACGTGCTTTCTGCTGAGTGA |
| 3 | ABCA1\_3 | CGGGCTCATGCTCCACTCGG | GCCGATTGCCCCACATCCCT |
| 4 | LXRα\_1 | CATCTGTTTCGGTCTCTTTGG | GCAGATGCTCCAGTCCAGAT |
| 5 | ACCA1\_1 | CGCCCCTGTCTCCCACCTCA | TCGGAGGTGAACGGCCTGGA |
| 6 | FASN | CGGGGTTACTGCCGGTCATCG | GTGGGTGGACGTCCGTCTCG |
| 7 | SREBF1 | CCGCCTTTAACCCGCTCGGTG | CCCTTTAACGAAGGGGGCGGG |
| 8 | ABCA1\_4 negative control site | AGAGCGGACCCCAAAGCTGGT | GGCAGTGTGTCCAGGGCTTCC |
| 9 | LXRα\_2 negative control site | GGATTACAGACCCGCATCAC | CCAGCAATGGTGTGTTGAAA |
| 10 | ACCA1\_2 negative control site | TGCCACTGATCCACGATGTTGCC | AGTGGTCTTGGGAAAGAGCAGGC |
| 11 | ABCG1\_Prom | TGCTTTACGCCCAGTGACTT | CTGTGTAATGCTACAGGGAGGA |
| 12 | ABCG1\_Enh. | CCAGCTGGTAATGGCTTGTAG | CTGTCTGTCAACCCCTCTGG |
| 13 | COL4A1 | ACTTGCACCACACTCACACA | CTCCGGCTAAGTGTGTGTGT |
| 14 | IGFBP4 | TAGGGAAGCGGCTTTTCCTC | CACCTCAAGGGATCACTGCA |
| 15 | MYLIP | GCCCGATAGTAACCTCTGCC | AGGCTGAAGAAACTGACCAAGT |
| 16 | PBX4 | AAGGAGTTCAAGGCCATGCTT | GAAAGTGGATGCGGCATTGT |
| 17 | PARP1 | TCATTTGAGTCCCTGTGCAGT | TAATCGCATAGTCCCCCAGC |
| 18 | APOC1\_1 | GCCAGCCAACCTAGAGTCTG | ATCACTACATCCGTCCCCCA |
| 19 | APOC1\_2 | GCCGAACTAGAGTCTGAGGC | AATTCCTTCCCCACCAGCTG |
| 20 | H19 | CTGGTCTGTGCTGGCCACGG | GCACCTTGGCTGGGGCTCTG |
| 21 | ACTB | CCATTGGCAAGAGCCCGGCT | GACACCCCACGCCAGTTCGG |

**ChIP-sequencing**

For deep sequencing ChIP samples (10-15ng of pooled DNA derived from individual CHIP experiments) were first amplified using the ChIP-Seq Sample Prep Kit (Illumina) according to the manufacturers instructions. Sequence reads of 36bp were obtained using the second generation Genome Analyzer IIx. and the Solexa Analysis Pipeline (Illumina). Unfiltered 36bp sequence reads were uniquely mapped to the human genome assembly (February 2009, GRCh37/hg19) using Bowtie (13) allowing for two mismatches along each tag. LXRα sequencing of macrophages and T0901317 treated macrophages was performed twice in biological duplicates. Sequencing data was submitted to www.ebi.ac.uk/ena/data/view/ERP001502. 25bp resolution LXRα binding profiles were generated genome-wide using the MACS tool (14) with the option –wig. Resulting wiggle files (.wig) were converted to the bigWig format using the program wigToBigWig (66). Normalized signal profiles were generated using makeUCSCfile using the Hypergeometric Optimization of Motif EnRichment (HOMER) software (58). Resulting bedGraph files (.bg) were converted to the bigWig format using the program bedGraphToBigWig (66). BigWig files were uploaded to a webserver and visualized as custome track in the UCSC Genome Browser (67). The program bigWigSummary (66) was used to retrieve signals from wiggle or bedGraph files based on genomic coordinates of LXRα peak intervals or intervals of open chromatin. The exact command used for this step is:bigWigSummary density.bigwig <chr> <start> <end> 1 type=mean. Where the density.bigwig is a bigwig file generated from filtered sequence alignments, <chr> is the chromosome, and <start> and <end> are the starting and ending positions of the interval, respectively. For visualization of selected loci the UCSC extracted tags of loci were normalized against IgG control lane tags of same loci and visualized with GraphPad Prism 5.0.

**Peak calling and filtering**

Peak identification was performed using the model based-analysis of ChIP-seq algorithm (MACS, Zhang et al., 2008) with aligned sequencing tags in BED format from LXRα-ChIP and IgG-ChIP experiments. The MACS version 1.0.1 was accessed via Galaxy (https://main.g2.bx.psu.edu). The following peak calling parameters were used: p-value cut-off = 10e-5, effective genome size = 2.7e9, bandwidth = 300 and m-fold = 5. Additionally, three levels (1kb, 5kb, 10kb) of regions around the peak regions were used to calculate the maximum lambda as local lambda. To determine a stringent peak set for downstream analyses of LXRα ChIP-seq lanes, we applied filtering for false positives. We discarded all peaks with a tag/length enrichment ratio <0.07 and peaks with less or equal number of tags as in the IgG control lane. For improved quality assessment we performed k-means clustering of our LXRα ChIP-seq data in SeqMiner (16, 68) and discarded all cluster with control data mean density >0.25. Additionally we removed cluster manually after individual genome browser observation (69). Macrophages treated with T0901317 and vehicle control, respectively were LXRα ChIPed and sequenced in two biological replicates. After replicate analysis and for final data assessment we combined all tags and repeated the peak calling and filtering procedure as described above.

**Differential binding**

For better comparison between different ChIP-seq lanes and to detect differential LXRα binding across investigated cell models we performed LXRα peak enrichment normalization (15) for all cell models. In brief, we compiled all independently MACS called and filtered LXRα peaks from all cell models and computed the union genomic regions of all peak coordinates with significant LXRα enrichment (2652 genomic regions). Than we scored each region for each sample and normalized the LXRα peak heights with quantile normalization. After computing the log2 fold change between the peak heights we could categorize three different LXRα peak sets based on a change of 1.5 fold.

**Formaldehyde Assisted Isolation of Regulatory Elements (FAIRE)**

Chromatin accessibility has been described as dramatically predetermining for transcription factor binding (43). To assess the relative openness of chromatin at LXRα binding sites and at transcriptional start sites (TSS) of potential target genes, we performed FAIRE (21) followed by sequencing and qPCR validation. In brief, cells were cross-linked and chromatin was fragmented as described above for the ChIP assay. The input control sample of FAIRE was reverse crosslinked over night at 65°C and 600rpm using a thermo shaker (TS-100, Biolabo Scientific Instruments) followed by incubation for 2h at 55°C and 500 rpm in the presence of 20μg Proteinase K (Invitrogen, 25530-049), whereas the FAIRE-sample stayed crosslinked and was just diluted with water. Chromatin of both samples was extracted from the aqueous phase by the phenol/chloroform procedure. As DNA in nucleosome depleted (regulatory active) regions is less likely crosslinked with proteins, we find these chromatin fragments in the aqueous phase and enrich therefore open and regulatory active chromatin regions. As control we analyzed the total chromatin and could calculate the enrichment ratio of open chromatin compared to total chromatin.

**FAIRE-sequencing**

Sequencing and mapping of FAIRE enriched chromatin was processed as described for ChIP-seqencing above. Aligned sequencing tags were converted to a continuous wiggle track with 25 bp resolution using F-Seq (70) and further processed with the Unix command ’sed’ and the program wigToBigWig (66). Further visualization as described for ChIP-seq above. For relative openness analysis of the three defined LXRα peak sets (2652 genomic regions), the individual cell model enrichment intensities were extracted from BigWig files, quantile normalized and averaged for each genomic region.

**Response elements cloning**

For the In-Fusion™ cloning of LXRα/RXRα response elements (RE) the appropriate primer extensions were used to enable cloning into the prepared pGL4.31[luc2P/GAL4UAS/Hygro] vector (Promega) and to derive the desired RE–constructs. PCR was performed in 50µl reaction mixes using Expand High Fidelity polymerase according to the manufacturer’s instructions (Roche) with 30pmol of each primer (Pr1099 and Pr1050), appended with the In-FusionTM extensions as appropriate, and 2µL of the RE oligo DNA (0.1µM) as template per reaction. The resulting PCR products were size-checked by agarose gel electrophoresis and purified using the Invisorb® DNA CleanUp Kit (STRATEC Molecular GmbH). Purified PCR products were eluted in 30µl of Buffer EB, 10mM Tris pH 8.0 buffer and yields assessed by nanodrop. Prior to their use in In-Fusion™ reactions, pGL4.31 vector was prepared by digestion with KpnI and NheI. The restriction digest was followed by agarose gel electrophoresis, gel extraction and purification before elution in 10mM Tris pH 8.0 buffer. About 50ng of purified PCR product and 100ng of the appropriately linearized pGL4.31 vector were mixed in the tubes of an In-FusionTM Dry- Down 8-tube stripe and incubated at 37°C for 15min, followed by 50°C for 15min. 5µL of each reaction was used to transform *E. coli* Stellar™ Competent Cells (Clontech). Transformants were selected by plating on culture plates (LB Agar, ampicillin) and incubation overnight at 37°C. To quickly screen the transformants for inserts of correct sizes a colony PCR protocol was performed using the standard pGL4.31 vector primers. Seven transformants for every RE were checked and their PCR products analysed on an agarose gel. Two likely candidate clones for every RE were set up in cultures overnight at 37°C for plasmid preparation (QIAprep® Spin Miniprep Kit). The integrity of all RE-clones was verified by sequencing before large-scale plasmid preparations were performed.

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| Graph ID | Name | DNA ologonucleotide (5 x sequence) |
| 1 | ABCA1 | GCGCAGAGGTTACTATCGGTCAAAGC |
| 2 | SREBF1 | GCTGCGGGGTTACTGGCGGTCATTCA |
| 3 | FASN | GCTGCGGGGTTACTGCCGGTCATTCA |
| 4 | MYLIP | GCTGAGAGGTTACTATCGGGCATTCA |
| 5 | DR4 motif set 1 | GCTGCGAGGTTACTCCAGGTCATTCA |
| 6 | DR4 motif set 2 | GCTGCGGGGTTACTGCAGGTCATTCA |
| 7 | Mutated DR4 | GCTGCGGGGTTACGGCCGGTCATTCA |
| 8 | Mutated DR4 | GCTGCGGGGTTAGAGCCGGTCATTCA |
| 9 | Mutated DR4 | GCTGCGGGGTTACAGCCGGTCATTCA |
| 10 | Mutated DR4 | GCTGCGGGGTTAGTGCCGGTCATTCA |
| 11 | Mutated DR4 | GCTGCGGGATCACTGCAGGTCATTCA |
| 12 | Mutated DR4 | GCTGCGGGATTACTGCCGGTCATTCA |
| 13 | Mutated DR4 | GCTGCGAAAATACTGCAGGTCATTCA |
| 14 | Mutated DR4 | GCTGCGGGGTTCCTGCCGGTCATTCA |

**LXRα and RXRα cloning**

Full length LXRα and RXRα were cloned from cDNA fragments that corresponded to the open reading frames (ORF) of LXRα and RXRα (Source BioScience clone IRATp970C0271, Gene ID: 7376 and clone IOH39435, Gene ID: 6256). Fragments were amplified by PCR using primers 659-660 and 669 -670, respectively. Both PCR products were cloned into the vector pBIND (Promega) using restriction enzymes BamHI and BmtI. The resulting plasmids were introduced into *Escherichia coli* SCS1 cells. After sequence confirmation the prepared maxipreps (Qiagen) were used for reporter gene assays.

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| Name | Forward primer | Reverse primer |
| Pr1099- Pr1050 | TGGCCTAACTGGCCGGTACCGAGTTTCTAGATGAA | TTTTATAGCCCCCCGCTAGCGTCTTGCTGCGGGG |
| pGL4.31 | TACGGGAGGTATTGGACAGG | TCGATATGTGCGTCGGTAAA |
| 669-670 | ATAGGCTAGCCAGCTTGAAGCAAGCCTCCTGAAAGATGGACACCAAACATTTCCTG | GCGGCCGCTCTAGACTAAGTCATTTGGTGCGGC |
| 659-660 | ATAGGCTAGCCAGCTTGAAGCAAGCCTCCTGAAAGATGCCCCACTCTGCTGG | AGTCGACGGATCCTCATTCGTGCACATCCCA |

**Dual Luciferase Reporter Gene Assay**

For reporter gene analysis HEK293T cells were plated on a white, clear bottom 384 well plate (Greiner) at a density of 1x105 cells/ml and cultivated in DMEM media (Invitrogen) supplemented with 10% FBS for 24h prior to transfection. Transfection was carried out with 0.25% Lipofectamine (Invitrogen) in Optimem media (Invitrogen). HEK293T cells were co-transfected with the pGL4.31- LXRE- Luc (100ng), pBIND-LXRα and pBIND-RXRα (each 20ng) for 4h under a humidified atmosphere of 5% CO2 and 95% air at 37°C. Afterwards transient transfected HEK293T cells were treated with 10µM T0901317 in DMEM media supplemented with 10% FBS for 24h. After the incubation period cells were washed twice with PBS and harvested for luciferase reporter gene assay applying the Dual Luciferase Reporter System (Promega) according to provided instructions. Measurement of bioluminescence was carried out with the POLARstar Omega Microplate reader (BMG Labtech). Activity was expressed as relative luciferase unit (RLU) and finally visualized as fold change of T0901317 treatment vs. vehicle control.

**Genome-wide gene expression analysis**

Total RNA was isolated from four biological replicates using RNeasy mini kit (Qiagen) following the manufacturers instructions. An additional on-column DNAse digestion step (DNase-Set, Qiagen) was included. RNA quantity and integrity was checked by Nanodrop (ND-100 Spectrophotometer) and agarose gel electrophoresis, respectively. High quality RNA was utilized for whole genome microarray analysis. Microarray analyses were performed according to instructions of Illumina‘s TotalPrep RNA Amplification Kit followed by hybridisation on HumanHT-12 v3/v4 Expression BeadChips (Illumina). Scanning was performed with Illumina‘s BeadStation 50 (Illumina) platform and reagents. Samples were processed in biological quadruplicates. Basic expression data analysis was carried out using BeadStudio 3.1 (Illumina Software). Raw data were background-subtracted and normalized using the cubic spline algorithm. Processed data were then filtered for significant detection (P-value <0.01) and differential expression vs. vehicle treatment according to the Illumina T-test error model and were corrected according to the Benjamini-Hochberg procedure (P-values <0.05). For LXR knockdown analysis we filtered for significant detection (P-value <0.01) in control siRNA samples. Normalized T0901317 treated knockdown and control siRNA samples to vehicle control (DMSO) or to foam cells. Statistical analysis of knockdown was performed by using a two-tailed Students-T-test. Significance refers to LXR siRNA versus control siRNA with correction according to the Benjamini-Hochberg procedure (P-values <0.05). Bead array data were validated by using quantitative real-time PCR. Gene expression data were submitted in MIAME-compliant form to the ArrayExpress database under accession number E-MTAB-1106 (www.ebi.ac.uk/arrayexpress).

**Supplementary references**

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