**Treatment conditions**

**ChIP-seq** and gene expression measurements were performed in macrophages differentiated with differentiated with L929 supernatant (source of M-CSF), on the 6th day cells were exposed to IL-4 (20ng/ml) for the indicated period of time. **ATAC-seq** experiments were carried out using the IL-4 concentrations described above. **Gene expression experiments** used the same cytokine concentration and Rosiglitazone (RSG) was used in a 1uM concentration for 3 hours.Gain of function experiments used doxycycline (1 µg/ml) and GM-CSF (50 ng/ml) for 5 days followed by IL-4 exposure for 1 day (20ng/ml). Inhibitor treatments against BRD4 (JQ1) and STAT6 (AS1517499) were used in concentrations of 500 nM and 1 µM, respectively. For these experiments dimethyl sulfoxide (DMSO) was used as vehicle control.

**RNA-seq**

Approximately 2.5ug was used for library preparation with TruSeq RNA Sample Preparation Kit (Illumina). Poly-A tailed RNA molecules were pulled down with poly-T oligo attached magnetic beads. Following purification, mRNA was fragmented with divalent cations at 85 °C, and then cDNA was generated by random primers and SuperScript II enzyme (Life Technologies). Second strand synthesis was performed followed by end repair, single ‘A’ base addition and ligation of barcode-indexed adaptors to the DNA fragments. Adapter-specific PCRs were performed to generate sequencing libraries. Libraries were size selected with E-Gel EX 2% agarose gels (Life Technologies) and purified by QIAquick Gel Extraction Kit (Qiagen). Libraries were sequenced on HiSeq 2500 instrument. Two biological replicates were sequenced.

**Generation of ES derived myeloid progenitors**

Inducible Egr2-expressing murine embryonic stem cells were maintained and expanded in knockout DMEM (Thermo-Fischer Scientific), 15% FBS (Thermo-Fischer Scientific), 1000 U/ml LIF (Merck), 50 U/mL penicillin and 50 mg/mL streptomycin (Merck) in presence of 300µg/ml G418 for chemical reselection of transgenic ES cells (Bencsik et al. 2016).

Murine ES cells were co-cultured with OP9 feeder cells for 5 days in α-MEM (Thermo-Fisher Scientific), 20% FBS (Thermo-Fisher Scientific), 50 U/mL penicillin and 50 mg/mL streptomycin (Merck). 5 day differentiated ES derived cells were further cultured with OP9 feeder cells in α-MEM (Thermo-Fisher Scientific), 20% FBS (Thermo-Fisher Scientific), 50 U/mL penicillin and 50 mg/mL streptomycin (Merck), 50 ng/ml GM-CSF (PeproTech) and 50 µM 2-ME (Merck) for an additional 5 days in the presence or absence of doxycycline (1µg/ml). On day 10, cells were harvested, and MACS purified using CD45 MicroBeads (Miltenyi) according to the manufacturer’s recommendations.

**ATAC-seq**

Cells were scraped and counted to achieve 50k/ml in ice-cold PBS. Cell suspension was further diluted to 25k/ml and nuclei were isolated with ATAC-LB (10mM Tris-HCl pH7.4, 10mM NaCl, 3mM MgCl2, 0.1% IGEPAL). Nuclei from 25k cells were used for tagmentation using Nextera DNA Library Preparation Kit (Illumina) from two biological replicates. After tagmentation DNA was purified with MinElute PCR Purification Kit (Qiagen). Tagmented DNA was amplified with Kapa Hifi Hot Start Kit (Kapa Biosystems) using 14 PCR cycles. Amplified libraries were purified again with MinElute PCR Purification Kit. Fragment distribution of libraries was assessed with Agilent Bioanalyzer and libraries were sequenced on a HiSeq 2500 platform.

**Monocyte isolation and differentiation:**

Monocyte separation was carried out using CD14 MicroBeads (Miltenyi Biotec) according to the manufacturer's instructions. Monocytes were cultured and differentiated to macrophages by their attachment to cell culture plate in RPMI 1640 supplemented with 10% FBS, 2 mM glutamine, penicillin and streptomicyn for the indicated time (Liu et al. 2008; Czimmerer et al. 2018). Cells were stimulated as indicated with IL-4 (20 ng/ml) for the time specified within the figure legends.

**RNA-seq mapping and gene expression quantification**

Rsubread’s *FeatureCounts (Liao et al. 2019)* function was used to quantify the reference transcriptome (Gencode: M21) and generate raw count table (*useMetaFeatures=TRUE* and *allowMultiOverlap=TRUE*). Genes with at least 10 Counts Per Million mapped read (CPM) in two samples were considered expressed. To determine differentially expressed genes at FDR 5% and fold change > 1.5, we used the *limma-voom (Law et al. 2014)* model, through the *DEApp (Li and Andrade 2017)* *shiny* API. Principal component analyses (PCA), correlation heatmaps and boxplots were created with R and *ggplot2* ([https://ggplot2.tidyverse.org](https://ggplot2.tidyverse.org/)). Annotation of enhancers to differentially expressed genes was based on linear proximity (+/- 100 kilobase) to the transcription start sites (TSSs). Coverage profiles represents Reads Per Kilobase Million (RPKM) values, calculated using deeptools2 *bamCoverage (Ramirez et al. 2016)* and visualized in IGV (Robinson et al. 2011). Supplementary table S3 contains the expressed genes with additional statistics, while Supplementary table S4 lists the EGR2-dependent transcription factors.

**ATAC-seq and ChIP-seq analyses**

Reads were mapped to the mouse reference genome (mm10) using the default parameters of *BWA MEM* aligner (<https://arxiv.org/abs/1303.3997>). Low mapping quality reads (MAPQ<10), reads mapping to ENCODE mouse blacklisted (Amemiya et al. 2019) regions and duplicated reads were discarded from the downstream analyses, using *samtools rmdup (Li et al. 2009)* and *bedtools intersectBed (Quinlan and Hall 2010)*. Open chromatin regions or putative binding sites were determined using *MACS2(Zhang et al. 2008)* at 5% false discovery rate (FDR). Coverage profiles were calculated using deeptools2 *bamCoverage* (*--binSize 10 --smoothLength 40 --normalizeUsing RPGC –effectiveGenomeSize 2652783500*). Normalized bigwig files were visualized in IGV. ChIP-seq read density profiles for region set summits were calculated using deeptools2 *computeMatrix* *(-a 2000 -b 2000 --binSize 10*) and *plotHeatmap* functions. Boxplot values represents the mean CPM of replicates generated using *edgeR (Robinson et al. 2010)*. Genomic annotation of peaksets was calculated using HOMER (Heinz et al. 2010) and plotted in R.

**P300 differential binding analysis**

To determine differentially bound regions at FDR 5% and fold change > 1.5, we used the *limma-voom (Law et al. 2014)* model, through the *DEApp (Li and Andrade 2017)* *shiny* API. Supplementary table S1 contains the P300 consensus peak set with statistics and normalized read intensities for the individual datasets. Mouse peak coordinates were mapped to the human genome (*hg19*) using the UCSC *liftOver* tool (minMatch=0.75). Conservation level of the mapped regions was determined using the *GenomicScores* package by calculating the mean phastCons score (*phastCons100way.UCSC.hg19*) for each region.

**Analyses of publicly available single cell RNA-seq data**

Cells with less than 200 genes detected or greater than 5% mitochondrial RNA content were excluded from the analyses. Clustering was performed on log normalized UMI counts and variance stabilizing transformation was used to call the most variable genes. We calculated z-scores for the differentially expressed genes and used them to input into PCA analysis. Clusters were identified using shared nearest neighbor (SNN) based clustering based on the first 10 PCs with k = 15 and resolution = 0.2. The same principal components were used to generate the UMAP projections, which were generated with a minimum distance of 0.1 and 30 neighbors (Becht et al. 2018). Expression of macrophage markers was plotted using log normalized expression values.

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