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## Endoplasmic reticulum stress actively suppresses hepatic molecular identity in damaged liver

Vanessa Dubois <sup>1,|</sup>, Céline Gheeraert <sup>1,§</sup>, Wouter Vankrunkelsven <sup>2,§</sup>, Julie Dubois-Chevalier <sup>1,\*</sup>, Hélène Dehondt <sup>1,\*</sup>, Marie Bobowski-Gerard <sup>1</sup>, Manjula Vinod <sup>1</sup>, Francesco Paolo Zummo <sup>1</sup>, Fabian Güiza <sup>2</sup>, Maheul Ploton <sup>1</sup>, Emilie Dorchies <sup>1</sup>, Laurent Pineau <sup>1</sup>, Alexis Boulinguez <sup>1</sup>, Emmanuelle Vallez <sup>1</sup>, Eloise Woittrain <sup>1</sup>, Eric Baugé <sup>1</sup>, Fanny Lalloyer <sup>1</sup>, Christian Duhem <sup>1</sup>, Nabil Rabhi <sup>3</sup>, Ronald E. van Kesteren <sup>4</sup>, Cheng-Ming Chiang <sup>5</sup>, Steve Lancel <sup>1</sup>, Hélène Duez <sup>1</sup>, Jean-Sébastien Annicotte <sup>3</sup>, Réjane Paumelle <sup>1</sup>, Ilse Vanhorebeek <sup>2</sup>, Greet Van den Berghe <sup>2</sup>, Bart Staels <sup>1</sup>, Philippe Lefebvre <sup>1,§</sup>, Jérôme Eeckhoutte <sup>1,§</sup>,  
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<sup>1</sup> Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-EGID, F-59000 Lille, France.

<sup>2</sup> Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, B-3000 Leuven, Belgium.

<sup>3</sup> Univ. Lille, UMR 8199 - EGID, CNRS, Institut Pasteur de Lille, F-59000 Lille, France.

<sup>4</sup> Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands

<sup>5</sup> University of Texas Southwestern Medical Center, Simmons Comprehensive Cancer Center, Department of Biochemistry, and Department of Pharmacology, Dallas, TX 75390, USA.

| Present address: Clinical and Experimental Endocrinology, Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), KU Leuven, B-3000 Leuven, Belgium.

§,\* Contributed equally

§ Joint senior authors

# Corresponding author

### CORRESPONDING AUTHOR

Dr. Jérôme Eeckhoutte

INSERM UMR 1011-Bâtiment J&K

Université de Lille, Faculté de Médecine de Lille-Pôle Recherche

Boulevard du Professeur Leclerc

59045 Lille cedex

France

Tel : 33(0)3 20 97 42 20 / Fax : 33(0)3 20 97 42 01

E-mail: [jerome.eeckhoute@inserm.fr](mailto:jerome.eeckhoute@inserm.fr)

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## **ABSTRACT**

Liver injury triggers adaptive remodeling of the hepatic transcriptome for repair/regeneration. We demonstrate that this involves particularly profound transcriptomic alterations where acute induction of genes involved in handling of endoplasmic reticulum stress (ERS) is accompanied by partial hepatic dedifferentiation. Importantly, widespread hepatic gene downregulation could not simply be ascribed to cofactor squelching secondary to ERS gene induction, but rather involves a combination of active repressive mechanisms. ERS acts through inhibition of the liver identity (LIVER-ID) transcription factor (TF) network, initiated by rapid LIVER-ID TF protein loss. In addition, induction of the transcriptional repressor NFIL3 further contributes to LIVER-ID gene repression. Alteration to the liver TF repertoire translates into compromised activity of regulatory regions characterized by the densest co-recruitment of LIVER-ID TFs and decommissioning of BRD4 super-enhancers driving hepatic identity. While transient repression of the hepatic molecular identity is an intrinsic part of liver repair, sustained disequilibrium between the ERS and LIVER-ID programs is linked to liver dysfunction as shown using mouse models of acute liver injury and livers from deceased human septic patients.

## **KEYWORDS**

Liver injury / endoplasmic reticulum stress / cell identity / transcriptional ecosystem / super-enhancer / PAR-bZIP / NFIL3 / sepsis

## INTRODUCTION

The liver exerts instrumental homeostatic and detoxifying functions. This organ is also characterized by a unique capacity to regenerate (Abu Rmilah et al., 2019). Studies in mice subjected to liver regeneration subsequent to partial hepatectomy (PHx), a model of liver resection which is a frequent clinical practice to remove liver tumors (Liu et al., 2015a), have identified a role for endoplasmic reticulum stress (ERS) in this process (Argemi et al., 2017, Liu et al., 2015b). ERS, which results from the accumulation of unfolded/misfolded proteins in the ER lumen, triggers the unfolded protein response (UPR), aimed at restoring ER homeostasis. The UPR is controlled by three major ERS sensors, namely the endoplasmic reticulum to nucleus signaling 1 (ERN1/IRE1), eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3/PERK) and activating transcription factor 6 (ATF6) (Almanza et al., 2019). Signalling triggered by these sensors leads to activation of the X-box-binding protein 1 (XBP1S), ATF4 and ATF6 transcription factors (TFs) and subsequent collaborative induction of ERS handling genes such as ER chaperones (Almanza et al., 2019, Vihervaara et al., 2017). Additional, non-transcriptional effects of the UPR involved in alleviating ERS also comprise the regulation of protein synthesis (mRNA translation) and degradation (Almanza et al., 2019). However, it has become clear that ERS bears functions beyond proteostasis *per se* (Hetz, 2012). For instance, liver regeneration upon PHx requires transient ERS to induce genes involved not only in proteostasis but also in acute-phase and DNA damage responses (Argemi et al., 2017, Liu et al., 2015b). Moreover, ERS has been linked to the (patho)physiological control of lipid and glucose metabolism in the liver (Rutkowski, 2019). The molecular mechanisms involved in ERS-mediated control of liver metabolic functions are still poorly defined. TFs activated by the UPR (including XBP1S, ATF4, DDIT3/CHOP, ATF6) can directly bind to and modulate expression of specific metabolic genes. In addition, a handful of liver-enriched TFs display reduced expression or activity upon ERS through ill-defined mechanisms (Rutkowski, 2019). In general, while gene silencing substantially contributes to ERS-induced transcriptional regulation, the mechanisms accounting for these downregulations are seldom defined (Almanza et al., 2019, Vihervaara et al., 2018). Hence, ERS-induced transcriptional

remodelling, especially gene downregulation, remains to be fully understood and its relevance towards liver pathophysiology to be better defined.

We and others have reported that hepatic gene transcription relies on networks of highly interconnected TFs (Kyrnizi et al., 2006), which are co-recruited to *cis*-regulatory modules (CRMs) (Dubois-Chevalier et al., 2017), a conclusion corroborated by several studies in other systems reporting that extensive collaboration of TFs at CRMs is essential for their activities (e.g. (Levo et al., 2017)). These findings point to a requirement for a comprehensive assessment of changes in global TF expression/activity induced by (patho)physiological signals when aiming to define how transcriptional outputs are controlled. Here, we have used a functional genomics approach to characterize the molecular mechanisms responsible for hepatic gene transcriptional alterations triggered by ERS and to define how this relates to liver damage in mouse models of acute liver injury and livers from deceased human septic patients.

## RESULTS

### **Acute ERS recapitulates the loss of hepatic molecular identity observed following liver PHx through extensive and preferential repression of liver identity genes**

The hepatic response to ERS was defined using transcriptomic analysis of mouse primary hepatocytes (MPH) treated with thapsigargin for 4h (Appendix Fig.S1A). In addition to induction of the UPR (hereafter referred to as the ERS UP genes), we found a substantial fraction of regulated genes (~45%) downregulated upon ERS in MPH (ERS DOWN genes) (Appendix Fig.S1A). This regulatory pattern was conserved when analyzing the mouse liver transcriptome 8h after a single intraperitoneal injection of tunicamycin, another ERS-inducing drug (Appendix Fig.S1B-C) (Arensdorf et al., 2013). Moreover, transcriptomic data mining using Short Time-series Expression Miner (STEM) (Ernst et al., 2005, Rib et al., 2018), a tool defining the preferential dynamic patterns of gene expression, confirmed that transient ERS occurs upon PHx (Fig.1A and Appendix Fig.S2) (Liu et al., 2015b, Reimold et al., 2000). Strikingly, unlike ERS UP genes, which are mostly involved in

housekeeping functions, ERS DOWN genes are linked to liver-specific functions (e.g. coagulation, xenobiotic drug metabolism) (Fig.1B). Concomitant to transient ERS, mouse liver regeneration following PHx has been linked to transient decrease in metabolic gene expression (Argemi et al., 2017, White et al., 2005). We found this was related to ERS DOWN genes being transiently downregulated upon liver PHx (Fig.1A). As the transcriptome of cells has been proposed to be ruled by ecosystem-like equilibriums where resources required to induce novel programs are used at the expense of established ones (Silveira & Bilodeau, 2018), we monitored the extent of transcriptomic alterations triggered by PHx or chemically-induced ERS compared to physiological transcriptomic changes unrelated to liver injury, i.e. triggered by fasting to feeding transition in mice (Benegiamo et al., 2018, Kalvisa et al., 2018). Bagplots (bivariate boxplots showing fold-changes in expression relative to baseline mouse liver gene expression levels) revealed that downregulation of the hepatic program upon PHx and ERS was associated with more complex and widespread transcriptomic alterations including a greater induction of genes expressed at low/moderate levels in the healthy mouse liver (Fig.1C).

To further characterize the impact of PHx and ERS on the hepatic transcriptional program, we defined cell identity genes, i.e. master liver transcriptional regulators and effector genes. Identity genes establish/maintain tissue-specific functions and distinguish themselves by broad H3K4me3 domains encompassing the transcription start site, a feature functionally related to high transcriptional expression and consistency (Benayoun et al., 2014). We defined liver identity (LIVER-ID) genes as those displaying this epigenetic feature preferentially in liver (Appendix Fig.S3A and Table EV1). We verified that LIVER-ID genes displayed expression levels which are higher (Fig.1D), liver-specific (Fig.1E), and linked to hepatic functions when compared to non-LIVER-ID genes, i.e. ubiquitously labelled with broad H3K4me3 (UBQ genes) or lacking liver broad H3K4me3 (Other genes) (Appendix Fig.S3B). LIVER-ID genes were transiently downregulated upon liver PHx (Fig.1F) as well as upon ERS both *in-vitro* in MPH and *in-vivo* in mouse liver (Fig.1G-H and Appendix Fig.S3C-D). LIVER-ID gene repression was specific and not linked to their high expression levels which could make

them more prone to repression, since ERS-mediated repression did not correlate with basal hepatic gene expression (Appendix Fig.S3E). Note that while microarray-based transcriptomic analyses reliably define fold-changes, this technology under-estimates their magnitude (Dallas et al., 2005). This notion should be taken into account when interpreting microarray-based results throughout the study. In particular, LIVER-ID genes were enriched among genes which were the most repressed by ERS (Fig.1I-K). Reciprocal induction of ERS UP genes and downregulation of LIVER-ID genes was validated using RT-qPCR in MPH (Fig.1L and Appendix Fig.S3F-G) and mouse liver (Fig.1M and Appendix Fig.S3F). Interestingly, ERS DOWN genes correspond to genes induced during hepatic differentiation, based on whole liver (Fig.1N and Appendix Fig.S3H) (Li et al., 2009) or hepatobiliary single-cell (Fig.1O and Appendix Fig.S3I-J) (Yang et al., 2017) transcriptomic data obtained at different developmental stages.

Altogether, these data point to loss of hepatic molecular identity upon liver PHx, which can be recapitulated by acute ERS acting as a widespread repressor of the liver transcriptional program.

#### **Acute ERS triggers a global loss of activity of the LIVER-ID TF network and its densely co-bound CRMs**

To define how liver molecular identity loss is induced by ERS at the transcriptional regulatory level, we monitored changes in CRM activities in MPH using alterations to H3K27 acetylation (H3K27ac) levels as a surrogate. H3K27ac ChIP-seq assays identified regions with increased (62%) or decreased (38%) H3K27ac signal intensities (denoted H3K27ac UP or H3K27ac DOWN), respectively (Appendix Fig.S4A and Dataset EV1). Genes linked to H3K27ac UP regions were significantly enriched in ERS UP genes, while ERS DOWN genes were more strongly linked to H3K27ac DOWN regions (Fig.2A). In line, LIVER-ID genes were most significantly linked to H3K27ac DOWN regions (Fig.2B).

Locus overlap analysis (LOLA) (Sheffield & Bock, 2016) was next used to compare genomic localization of H3K27ac regions with the chromatin binding sites (cistromes) of mouse TFs (657 cistromes) from the Gene Transcription Regulation Database (GTRD) (Yevshin et al., 2017). We found that 81% of the mouse hepatic TF cistromes comprised in this database (61 out of 75 cistromes)



belonged to the cluster displaying the strongest overlap with H3K27ac DOWN regions (Appendix Fig.S4B and Table EV2), suggesting these regions might be characterized by dense hepatic TF co-recruitment. In line, monitoring the co-recruitment patterns of 47 transcriptional regulators in mouse liver (Dubois-Chevalier et al., 2017) revealed that H3K27ac DOWN regions were uniquely characterized by a node of highly co-recruited transcriptional regulators, which was not found for H3K27ac UP or unchanged regions (Fig.2C). Moreover, several of these regulators were defined as LIVER-ID TFs (Fig.2C, panel d), i.e. TFs comprised within the previously described LIVER-ID gene list (Appendix Fig.S5 and Table EV1; 43 TFs).

Additional analyses of hepatic enhancers indicated that the extent of LIVER-ID TF co-binding positively associated with their chance of being inactivated by ERS, as judged through their overlap with H3K27ac DOWN regions (Fig.2D). Importantly, this could not be attributed to any single LIVER-ID TF. Indeed, this pattern was observed for each individual LIVER-ID TF, when focusing on its specific set of bound CRMs. Additionally, lack of several individual LIVER-ID TFs was linked to reduced propensity for ERS-mediated repression. Thus, deficiency in activity of a single LIVER-ID TF could not explain ERS-induced loss of H3K27ac at mouse CRM but rather pointed to ERS-mediated inactivation being linked to a concomitant impaired activity of several LIVER-ID TFs (Fig.2D). This led us to investigate whether ERS is linked to a coordinated and global loss of master hepatic TF activities. In line with this hypothesis, we found that LIVER-ID TFs mostly belonged to ERS DOWN genes (Fig.2E and Appendix Fig.S6A-B). Similar conclusions were reached when defining LIVER-ID TFs based on high and specific expression in the human liver (D'Alessio et al., 2015) or on reconstructed gene regulatory networks (Zhou et al., 2017), which largely overlap with our epigenetically-defined LIVER-ID TF list (Appendix Fig.S6C-D), hence supporting the robustness of our findings. RT-qPCR assays confirmed ERS-mediated downregulation of LIVER-ID TFs in mouse AML12 hepatocytes, MPH and mouse liver (Fig.2F and Appendix Fig.S6E-G). LIVER-ID TF gene downregulation in MPH was blunted by pre-treating the cells with the chemical chaperone 4-phenylbutyrate (PBA), which, as expected, alleviated ERS response as judged through lower induction of ERS UP genes (Fig.2G). The diminished

LIVER-ID TF gene expression induced by ERS was accompanied by loss of LIVER-ID TF activity as evidenced by a drastic decrease in both nuclear and chromatin-bound levels of HNF4A, NR1H4/FXR and FOXA2/HNF3B (Fig.2H-I), which have well-established hepatic functions and were used as examples in these analyses.

These data indicate that ERS triggers a global impairment of LIVER-ID TF expression/activities. Among LIVER-ID TF with decreased expression, HLF (Fig.2F and Appendix Fig.S6E-F) belongs to the PAR-bZIP family together with TEF, DBP and NFIL3. While HLF, TEF and DBP behave as transcriptional activators, repressive functions have been ascribed to NFIL3 thereby establishing a balance in the transcriptional regulation of shared target genes (e.g. (Mitsui et al., 2001)). Recently, NFIL3 has been found to be induced upon ERS in mouse pancreatic islets (Ohta et al., 2017). Interestingly, acute hepatic ERS triggers a switch in the expression profile of the PAR-bZIP TF family members including strong induction of *Nfil3* levels (Fig.3A-B and Appendix Fig.S7A-D) and chromatin binding (Fig.3C). This switch in expression of the PAR-bZIP TF family members was also observed upon liver PHx (Appendix Fig.S7E). Transcriptomic analyses of the liver of *Nfil3*<sup>-/-</sup> (NFIL3 KO) mice subjected to ERS (Appendix Fig.S8) revealed that repression of LIVER-ID gene expression was blunted in NFIL3 KO mice, as illustrated by GSEA showing enrichment of LIVER-ID genes in NFIL3 KO compared to WT livers subjected to acute ERS (Fig.3D). Further investigation of the genes contributing the most to this enrichment, i.e. LIVER-ID genes less efficiently repressed by ERS in NFIL3 KO compared to WT mice (Table EV3), revealed “Drug metabolism and cytochrome P450” as the main pathway (Fig.3D). Several of these genes are involved in xenobiotic metabolism (*Gsta3*, *Adh1*, *Cyp3a11*, *Fmo5* and *Ugt2b1*), a liver function previously defined as being critically regulated by the PAR-bZIP TF family (Gachon et al., 2006). Additional cytochrome P450-related liver functions are also less repressed by ERS in NFIL3 KO mice (Table EV3). Blunted ERS-mediated repression in NFIL3 KO mouse livers of specific genes related to xenobiotic metabolism is shown in Fig.3E. In addition to the features defining the highest sensitivity to ERS-mediated repression (i.e. dense LIVER-ID TF co-recruitment and, as described hereafter, overlap with BRD4 SE), these genes are bound by NFIL3 at CRMs which

are specifically active in hepatocytes when compared to the non-parenchymal cells (NPC) (Fig.3F and Appendix Fig.S9).

Altogether, these data reveal that acute ERS profoundly remodels the liver TF repertoire where a global loss of LIVER-ID TF expression is reinforced, within the PAR-bZIP TF family, by induction of the transcriptional repressor NFIL3.

### **Acute ERS triggers decommissioning of BRD4 at super-enhancers (SE) and preferentially represses SE-associated genes**

We next investigated how compromised LIVER-ID TF expression/activities translate into loss of the hepatic transcriptional program. TFs activate target gene expression through recruitment of transcriptional coactivators. Among those, BRD4 has been identified as crucial to establish and maintain transcriptomic cellular identity (Di Micco et al., 2014, Lee et al., 2017). BRD4 recruitment to CRMs requires EP300-mediated protein acetylation, including acetylation of H3 at K27 (Roe et al., 2015). Considering that LIVER-ID TFs target EP300 at liver CRMs to catalyze H3K27ac (Thakur et al., 2019), through their interaction with EP300 (Appendix Fig.S10A) (Eeckhoutte et al., 2004, Kemper et al., 2009, von Meyenn et al., 2013), we hypothesized that the ERS-mediated decrease in LIVER-ID TFs and H3K27ac might culminate into compromised BRD4 recruitment at CRMs. Using CHIP-qPCR, we found that ERS decreased BRD4 binding at H3K27ac DOWN CRMs in MPH and mouse liver (Fig.4A and Appendix Fig.S10B). This decrease could not be ascribed to reduced BRD4 expression levels upon ERS (Fig.4B and Appendix Fig.S10C).

To verify the importance of BRD4 loss with regards to expression of LIVER-ID genes, MPH were treated with the BRD4 inhibitors JQ1, which impedes recognition of acetylated proteins by the BRD4 bromodomain, and MZ1, which targets BRD4 for degradation (Zengerle et al., 2015) (Fig.4B). Both treatments severely compromised basal expression of LIVER-ID genes, which could moreover not be further repressed by ERS (Fig.4C and Appendix Fig.S11). The decreased LIVER-ID gene expression observed upon BRD4 inhibition was not kinetically preceded by decreased protein expression of the LIVER-ID TFs HNF4A, NR1H4/FXR and FOXA2/HNF3B (Appendix Fig.S12), indicating

it was most likely a direct consequence of deficient BRD4-mediated gene transcription. Activation of canonical ERS UP genes was also blunted, although these genes appeared less sensitive to BRD4 inhibition (Fig.4C and Appendix Fig.S11). MPH treatment with C646, an inhibitor of the EP300 histone acetyltransferase, also reduced basal expression of LIVER-ID genes and blocked further repression by ERS (Appendix Fig.S13), while treatment with the histone deacetylase (HDAC) inhibitor trichostatin A impeded their repression by ERS (Appendix Fig.S14).

BRD4 control of cell identity is linked to its recruitment at CRMs densely co-bound by master TFs, organized in clusters defining so called super-enhancers (SE) (Whyte et al., 2013). BRD4 SE (defined using mouse liver BRD4 ChIP-seq data (Kim et al., 2018)) largely overlapped LIVER-ID domains (i.e. liver preferential broad H3K4me3 regions as defined above) (Appendix Fig.S15A). Interestingly, LIVER-ID domains overlapping BRD4 SE showed stronger binding of EP300 and LIVER-ID TFs (Appendix Fig.S15B) together with stronger H3K27ac basal levels in MPH, which displayed a more pronounced decrease upon acute ERS (Fig.4D). Accordingly, LIVER-ID domains overlapping BRD4 SE showed enrichment for H3K27ac DOWN regions (Appendix Fig.S15C) and their associated genes (Appendix Fig.S15D). In line, genes associated with both LIVER-ID domains and BRD4 SE showed the highest basal and most liver-specific expression (Appendix Fig.S15E). Importantly, these genes were more strongly downregulated by ERS (Fig.4E).

Altogether, these data point to BRD4 SE decommissioning as central to LIVER-ID gene expression loss upon acute ERS in hepatocytes. In this context, BRD4 SE defines a subset of LIVER-ID genes with greatest sensitivity to acute ERS-mediated repression.

#### **Loss of liver identity is initiated by a rapid decrease in LIVER-ID TF protein levels upon acute ERS**

Kinetic experiments in MPH indicated that the decrease of LIVER-ID TF expression triggered by ERS precedes that of non-TF LIVER-ID genes (Fig.5A), consistent with impairment of the hepatic TF network driving subsequent loss of liver CRM activities and target gene expression. LIVER-ID TFs are organized as an interdependent transcriptional network involving auto- and cross-regulatory loops (Kyrnizi et al., 2006) at BRD4 SE (Appendix Fig.S16). Therefore, we reasoned that any alteration to

LIVER-ID TF protein levels could serve as an initial trigger which would secondarily be amplified by decreased expression of their encoding genes. Interestingly, further analyses of the kinetics of LIVER-ID TF loss of expression upon acute ERS revealed that the decrease in protein levels of HNF4A, NR1H4/FXR and FOXA2/HNF3B was already effective 1h after induction of ERS, at a time when mRNA levels are still unchanged (Fig.5B-C and Appendix Fig.S17). While promoting translation of specific ERS-induced genes such as *Atf4*, ERS is also known to trigger global translation inhibition through the EIF2AK3/PERK pathway (Almanza et al., 2019). We therefore hypothesized that ERS may modulate LIVER-ID TF activities by inhibiting their translation. In line with this hypothesis, treatment of MPH with the EIF2AK3/PERK signaling inhibitor ISRIB dampened loss of NR1H4 after 1h of ERS (Fig.5D-E). Since translational inhibition could not alone account for acute ERS-induced LIVER-ID TF loss, and since ERS may modulate TF activities by inducing their degradation as shown for FOXO1 (Zhou et al., 2011) and CREB3L3 (Wei et al., 2018), we investigated a role for proteasomal degradation in LIVER-ID TF loss. We observed that treatment with the proteasome inhibitor MG132 blunted repression of LIVER-ID TFs, especially that of HNF4A, in MPH subjected to 1h of ERS (Fig.5F-G and Appendix Fig.S18A). Since proteasomal degradation of HNF4A can be induced by the SRC kinase (Chellappa et al., 2012) following liver PHx (Huck et al., 2019) and since ERS has been reported to activate SRC through its interaction with ERN1/IRE1a in HeLa cells (Tsai et al., 2018), we monitored SRC activation in MPH subjected to ERS using phosphorylation levels of SRC at Y416 (p-Y416-SRC) as a marker. We found that ERS leads to SRC activation in MPH, which could be prevented by treatment with its inhibitor PP2 (Fig.5H). Importantly, this was associated with a dampening of ERS-mediated degradation of HNF4A (1h after ERS induction) (Fig.5F and I and Appendix Fig.S18B) and of subsequent (4h after ERS induction) LIVER-ID TF gene repression (Fig.5J).

These data indicate that ERS triggers loss of hepatic identity through a global impairment of LIVER-ID TF expression/activities, involving EIF2AK3/PERK and SRC-dependent rapid decrease in their protein levels.

**Sustained loss of LIVER-ID genes and concomitant induction of ERS gene expression in**

## **dysfunctional mouse and human livers**

To assess whether similar responses occur upon acute liver injury, we performed experiments on injured/dysfunctional livers of mice subjected to bacterial injection (sepsis<sup>BIM</sup> model) (Paumelle et al., 2019). Our results show that sepsis triggers profound alterations in the liver transcriptome (Appendix Fig.S19A) compatible with loss of hepatic molecular identity (Fig.6A compared to 1C). Indeed, sepsis also decreased expression of LIVER-ID genes (Fig.6B and Appendix Fig.S19B-F), concomitant with an enrichment for ERS UP genes among the most strongly upregulated genes in septic mouse livers (Fig.6C). Similar observations were made when mining the transcriptomic response occurring in other mouse models of liver damage including drug-induced liver injury (Appendix Fig.S20). Overall, impaired LIVER-ID gene expression in injured livers was linked to partial hepatic dedifferentiation as judged using principal component analysis (Fig.6D). Indeed, the transcriptome of injured livers resembles more that of newborn livers than that of mature adult livers, in line with postnatal liver maturation being linked to significant transcriptomic changes (Fig.1N) (Bhate et al., 2015, Peng et al., 2017).

Further mining the transcriptional changes induced by sepsis, we observed that genes significantly modulated by ERS in MPH (from Fig.1) showed a similar regulation pattern in liver (Fig.6E, Appendix Fig.S21A-B) or purified hepatocytes (Appendix Fig.S21C-E) from septic mice. Importantly, LIVER-ID TF expression was globally compromised (Fig.6F-G and Appendix Fig.S21F-G), accompanied by a switch in expression of the PAR-bZIP TF family members (Appendix Fig.S22A) and reduced expression of genes involved in xenobiotic metabolism (Appendix Fig.S22B). Pre-treatment of septic mice with the ERS inhibitor tauroursodeoxycholic acid (TUDCA) blunted ERS and displayed hepatoprotective effects, as indicated by reduced XBP1S (Fig.6H-I and Appendix Fig.S22D) and decreased levels of circulating liver serum aminotransferases (Fig.6J), respectively. Interestingly, TUDCA concomitantly allowed to protect from a general loss of LIVER-ID TF expression (Fig.6H-I and Appendix Fig.S22D-E), pointing to the functional link between ERS and loss of LIVER-ID gene expression in injured liver.

To monitor ERS and LIVER-ID gene expression upon liver recovery, we made use of a second sepsis mouse model (denoted sepsis<sup>CLP</sup>), which combines caecal ligation and puncture to induce sepsis with intravenous fluid resuscitation in order to mimic the clinical setting encountered in intensive care units (ICUs) (Derde et al., 2017). Indeed, this model allows an assessment of transcriptional changes in both the acute and post-acute resolutive phase (3 days after CLP) of liver injury (Thiessen et al., 2017). ERS gene upregulation and LIVER-ID TF repression, together with a switch in PAR-bZIP TF expression, was observed in the acute phase of sepsis (10h after CLP) (Fig.7A and Appendix Fig.S22F). At later time points, transcriptional changes were blunted with most genes returning to near baseline levels 3 days after CLP (Fig.7A). Hence, reminiscent of liver regeneration following PHx, loss of molecular identity together with ERS gene induction transiently co-occur in the mouse liver upon sepsis. This indicated that ERS resolution was phased with recovery of the LIVER-ID program. To further assess the functional relationship between recovery from ERS and loss of liver identity, we mined mouse liver transcriptomic data obtained from tunicamycin-injected WT or *Atf6*<sup>-/-</sup> (*Atf6* KO) mice, the latter being characterized by an inability to resolve ERS (Arensdorf et al., 2013). Indeed, while ERS UP genes have returned to baseline levels 34h after ERS in WT mice, their decreased expression is only partial in *Atf6*<sup>-/-</sup> mice leading to sustained ERS UP gene levels (Fig.7B). This was accompanied by a failure of ERS DOWN and LIVER-ID genes to fully return to baseline levels in *Atf6*<sup>-/-</sup> compared to WT mice (Fig.7C). This indicated that sustained ERS impedes re-establishment of the LIVER-ID program. To define if sustained loss of LIVER-ID gene expression is linked to liver dysfunction, we mined transcriptomic data from hepatocyte-specific HNF4A KO mice subjected to PHx, since these mice fail to recover ultimately leading to their death (Fig.7D) (Huck et al., 2019). Importantly, we found that this was linked to sustained downregulation of LIVER-ID genes and TFs 5 days after PHx (Fig.7D) at a time when the hepatic program is normally re-established (Fig.1A). These data therefore indicate that LIVER-ID TF re-expression is critically required to preclude detrimental consequences of liver injury.

Despite intense ICU care, septic patients frequently present with liver failure leading to their

death (Nessler et al., 2012). Interestingly, livers from deceased septic humans displayed downregulation of LIVER-ID TF encoding genes and concomitant upregulation of ERS UP genes when compared to control donors (undergoing elective restorative rectal surgery) (Appendix Fig.S23A-B). Moreover, correlative analyses revealed that LIVER-ID TFs behave as a group of genes with strong positive correlation, which are overall inversely correlated with ERS UP genes (including *NFIL3*), in livers of septic humans (Fig.7E). To further assess whether loss of hepatic molecular identity might contribute to human liver dysfunction, we compared LIVER-ID TF gene expression levels between livers from deceased septic patients with serum bilirubin levels below ( $Bil < 2$ ) or above ( $Bil > 2$ ) 2mg/dL (i.e. the most commonly used cut-off in clinics to define liver dysfunction in septic patients (Vincent et al., 1996)). We observed a stronger overall decrease in LIVER-ID TF gene expression in the  $Bil > 2$  group (Fig.7F), differences being the most pronounced for *NR1I2/PXR* and *HLF* (Fig.7G). This was associated with a more pronounced switch in the expression of the PAR bZIP TF family in the  $Bil > 2$  group compared to the  $Bil < 2$  group (Appendix Fig.S23C). While ERS gene induction was present in the two groups, *DDIT3/CHOP* was only upregulated in the  $Bil > 2$  group, suggestive of a more severe ERS and/or of activation of additional detrimental signaling pathways which would add up to ERS in patients with liver dysfunction (Fig.7H).

Altogether, these data indicate that sustained loss of LIVER-ID TF expression linked to persistent ERS gene induction is detrimental to liver function recovery, which may relate to liver dysfunction in septic patients.

## DISCUSSION

ERS had previously been shown to repress a handful of genes involved in liver metabolic functions (Chikka et al., 2013). Here, we have redefined the paradigm related to acute ERS-induced changes in the liver by pointing to a more global loss of molecular identity and partial hepatic dedifferentiation, which we found to be characteristic of acute liver injury. As discussed hereafter and detailed in Fig.8A, loss of LIVER-ID gene expression results from several ERS-induced



signaling pathways, consistent with signalling from the different sensors of ERS being activated in liver injury (Wang et al., 2020) and functionally intermingled (Fig.5 and Appendix Fig.S24) (Brewer, 2014). Importantly, the relevance of our findings is indicated by several lines of evidence defining chemically-induced ERS as appropriate for the study of pathophysiological ERS-induced transcriptional regulations. First, repression of LIVER-ID genes was observed both with tunicamycin and thapsigargin, ruling out any drug-specific artifact (e.g. Appendix Fig.S3G). Second, this repression was readily linked to ERS and not any other potential drug-related effect as it was blunted by *i)* cycloheximide (Appendix Fig.S25A), which, by inhibiting protein synthesis, alleviates ERS and decreases UPR gene expression (Harding et al., 2000) ; *ii)* the chemical chaperone PBA (Fig.2G) ; and *iii)* inhibitors of the different ERS sensors (Fig.5D-E and Appendix Fig.S24). Third, chemically-induced ERS recapitulated both induction of the different arms of the UPR (Fig.1L-M and 6F) and the overall preferential downregulation of LIVER-ID genes observed in injured liver (Fig.1,6 and Appendix Fig.S19C-F). Fourth, this repression of LIVER-ID genes was not artificially linked to strong chemically-induced ERS. Indeed, dose-response experiments showed that ERS-mediated repression was proportional to the ERS intensity, i.e. not requiring maximal ERS response (Appendix Fig.S25B). Moreover, induction of *Klf9*, recently described as a marker of strong ERS (Fink et al., 2018), was not stronger in the chemically-induced ERS models (Appendix Fig.S25C). Fifth, inhibition of SRC kinase prevents HNF4A degradation both following acute ERS (Fig.5F,I and S18) and liver PHx (Huck et al., 2019).

In addition to translation inhibition induced by EIF2AK3/PERK, our study points to Initial loss in LIVER-ID TF expression involving ERS-mediated proteasomal degradation events. In particular, we report a role for SRC kinase mediated proteasomal degradation of HNF4A. These findings, which are in contrast with a previous study suggesting that HNF4A protein levels were not modulated by ERS (Arendsdorf et al., 2013), are of importance when taking into account HNF4A's requirement for maintaining/establishing the LIVER-ID TF network and hepatocyte identity (Fig.7D) (Huck et al., 2019, Lau et al., 2018, Thakur et al., 2019). Additional mechanisms directing LIVER-ID TFs towards

degradation most probably co-occurs such as those triggered by interaction with XBP1S (Zhou et al., 2011). More generally, our findings are however in line with a recent study indicating that targets of endoplasmic reticulum-associated protein degradation also include TFs and epigenetic regulators (Wei et al., 2018). Loss of LIVER-ID TF expression is further amplified by their transcriptional downregulation being linked to their organization as an interdependent transcriptional network where LIVER-ID TF encoding genes form auto- and cross-regulatory loops (Appendix Fig.S16) (Fig.8A). The hepatic TF network increases in complexity and stability during development making LIVER-ID TF gene expression more robust to alterations in single TF expression/activity in the adult liver (Kyrmizi et al., 2006). Our finding that deletion of HNF4A dramatically impacts re-expression of the other LIVER-ID TFs involved in termination of liver regeneration following PHx (Fig.7D) indicates that liver stress/injury decreases the hepatic core TF network robustness. This is most probably linked to the global loss of LIVER-ID TF expression jeopardizing cross-regulatory loops therefore rendering hepatocytes more sensitive to loss of activities of individual TFs (Felix & Barkoulas, 2015, Gjuvsland et al., 2007). ERS-induced transcriptional downregulation of LIVER-ID TFs/genes involves decommissioning of BRD4 at LIVER-ID TF densely co-bound CRMs organized into SE. Importantly, this implies that not all LIVER-ID genes are equally sensitive to ERS-mediated repression defining partial hepatic dedifferentiation as being linked to preferential repression of highly expressed SE-associated LIVER-ID genes. TF recruitment complexity and SE have both been positively associated with particularly strong activity of regulatory regions important for cell identity (Santiago-Algarra et al., 2017, Whyte et al., 2013). In this context, we show that a widespread decrease in LIVER-ID TFs accounts for the breadth of detrimental transcriptional effects of ERS/liver injury on hepatic molecular identity.

Contrary to a recent study suggesting that BRD4 is required for establishment but not maintenance of cell identity (Lee et al., 2017), and in line with other previous reports (Di Micco et al., 2014), our work indicates a role for BRD4 in maintenance of mature hepatocyte molecular identity. ERS-induced loss of hepatic molecular identity is accompanied by BRD4 redistribution towards ERS

gene regulatory regions. Competition for transcriptional resources has been proposed to rule transient transcriptional adaptations to environmental disturbances in a model referred to as transcriptional ecosystem (Silveira & Bilodeau, 2018). In line, we have found that stressed/injured liver requires to enhance expression of an exceptionally large spectrum of genes, which may trigger hepatocytes to temporarily decommission highly active regulatory regions to supply the required transcriptional resources (Fig.8A-B). Squelching (competition between TFs for limited cofactor amounts) has been proposed, but never firmly proven, to be a driving force in cofactor redistribution responsible for trans-repression (Schmidt et al., 2016). This was for instance suggested as an explanation for transcriptional repression induced by tumor necrosis factor (Schmidt et al., 2015). In the context of acute ERS, our study points to a cascade of molecular events described here above involving early loss of LIVER-ID TF expression/activities, indicating repression of LIVER-ID gene expression does not rely *per se* on squelching i.e. ERS TFs competing off BRD4 binding from fully active LIVER-ID TFs. Together with the role of NFIL3, our data rather indicate that ERS-mediated repression is an active process and not an indirect consequence of ERS gene induction. While squelching on its own cannot explain loss of LIVER-ID gene expression, our data do not entirely rule out that competition for BRD4 might further contribute to LIVER-ID gene downregulation.

Our data using several models of liver injury and genetically deficient mice have established that the hepatic and ERS transcriptional programs are in competitive equilibrium with direct relevance towards the liver's ability to recover from injury. Indeed, while transient loss of hepatic molecular identity is linked to stress/injury handling, detrimental effects occur if the hepatic transcriptional program cannot be re-established. In line with loss of LIVER-ID TF expression being instrumental in triggering liver injury, forced hepatic expression of HNF4A or FOXA2 has been shown to be protective (Huck et al., 2019, Wang et al., 2017). Predictive models of transcriptomic regulation where alternative programs are in competitive equilibrium postulate that cessation of environmental disturbances would allow cells to restore their normal transcriptional program as the default one (Silveira & Bilodeau, 2018) (Fig.8B). The kinetic and feedback mechanisms allowing re-establishment

of the hepatic identity upon recovery from liver injury remain to be fully defined but critically require LIVER-ID TFs (re-expression (Fig.7A-D). Interestingly, ERS-induced loss of molecular identity is not restricted to the liver (Appendix Fig.S26 and Table EV4), but whether this mechanism is globally involved in organ repair and/or dysfunction beyond liver remains to be defined. The mechanisms leading to organ dysfunction in sepsis are still incompletely understood. Cell death has been ruled out as a potential main contributor (Takasu et al., 2013). In this context, our results obtained from the livers of deceased septic patients point to sustained loss of LIVER-ID TFs as a likely contributor to human liver dysfunction (Fig.8B). Switch in expression of the PAR-bZIP family members may relate to compromised xenobiotic metabolism associated with poor outcome in treated critically-ill septic patients (Gachon et al., 2006, Woznica et al., 2018) while loss of PPARA may impede liver's ability to adapt its metabolic activities during sepsis (Paumelle et al., 2019). While our data indicate that acute ERS directly represses LIVER-ID gene expression (events occurring in MPH in the absence of detectable activation of regulatory regions involved in the hepatic inflammatory response (Appendix Fig.S27)), additional signals including inflammatory cytokines (Brown et al., 2014) most probably combine with ERS during sepsis to trigger the exceptionally large alterations to the hepatic transcriptional equilibrium we observed in this condition.

## **MATERIALS AND METHODS**

### **Cell culture**

The immortalized mouse hepatocyte cell-line AML12 was obtained from ATCC (CRL-2254) and cultured as previously described (Ploton et al., 2018). Mouse primary hepatocytes (MPH) were prepared from livers of 10 weeks-old male C57BL/6J mice (Charles River) as described in (Bantubungi et al., 2014) and grown on collagen-coated plates in serum-free William's medium (Ploton et al., 2018). Non-parenchymal cells (NPC) from the same livers were obtained by differential centrifugation. Briefly, liver homogenates obtained after perfusion were pressed through a 70  $\mu$ m cell strainer and centrifugated for 5 min at 27g. Pellets from this first centrifugation were washed and

centrifuged twice again for 5 min at 27g to obtain the MPH fraction. Supernatants from the first centrifugation were collected and centrifuged for 5 min at 400g to obtain the NPC fraction. Separation of MPH and NPC was confirmed by monitoring expression of selected marker genes (Appendix Fig.S2D). Acute endoplasmic reticulum stress (ERS) treatment in MPH is defined as 4h treatment with 1 $\mu$ M thapsigargin. Vehicle (0.04% DMSO) was used as control. In all figures from this study, ERS in MPH is defined as 4h treatment with 1 $\mu$ M thapsigargin unless indicated otherwise (shorter or longer treatment times with different concentrations were also used in some experiments as specifically indicated in the figures and their legends). Experiments involving MZ1 or JQ1 were performed by pre-treating MPH for 3h with 0.01, 0.1 or 1 $\mu$ M MZ1 or 1h with 500nM JQ1 before addition of 1 $\mu$ M thapsigargin for 4h. Experiments involving C646 were performed by co-treating MPH with 5, 10 or 20 $\mu$ M C646 and 1 $\mu$ M thapsigargin for 4h. Experiments involving trichostatin A were performed by co-treating MPH with 1 $\mu$ M trichostatin A and 1 $\mu$ M thapsigargin for 4h. Experiments involving cycloheximide were performed by co-treating MPH with 0, 1 or 10 $\mu$ g/mL cycloheximide and 1 $\mu$ M thapsigargin for 4h. Experiments involving PBA, ISRIB, MG132 or PP2 were performed by pre-treating MPH for 30 min with 5mM PBA, 1 $\mu$ M ISRIB, 10 $\mu$ M MG132 or 10 $\mu$ M PP2 before addition of 1 $\mu$ M thapsigargin for 1h or 4h. Experiments involving inhibitors of the three arms of the UPR were performed by pre-exposing AML12 cells to 30 $\mu$ M STF083010, 200 $\mu$ M ISRIB or 100 $\mu$ M AEBSF for 2h and subsequently treating them for 4h with 1 $\mu$ M thapsigargin or 2 $\mu$ g/mL tunicamycin.

Fluorescence activated cell sorting (FACS)-isolated hepatocytes were obtained by directly running the MPH fraction into an Influx sorter (Becton Dickinson) equipped with a 200  $\mu$ m nozzle and tuned at a pressure of 3.6 psi and a frequency of 6.3 kHz. Sample fluid pressure was adjusted to reach an event rate of 2000 events/second. Hepatocytes were identified as FSChi SSChi events and sorted on a “pure” mode with 80% sorting efficiency.

HEK293 cells were grown as in (Ploton et al., 2018) and transfected using jetPEI (Polyplus Transfection) according to the manufacturer’s instructions.

## **Chemicals**

All chemicals used in this study are provided in the Reagents and Tools table.

### **Animal experiments**

Male C57BL/6J wildtype (WT) mice were purchased from Charles River at 8 weeks of age and housed in standard cages in a temperature-controlled room (22-24°C) with a 12h dark-light cycle. They had *ad libitum* access to tap water and standard chow and were allowed to acclimate for 2 weeks prior to initiation of the experimental protocol. ERS was induced by intraperitoneal injection of tunicamycin using 1 µg/g mouse *body weight* (Sigma-Aldrich, #T7765) or vehicle (150 mM dextrose) and liver was collected 8h later (5 mice per group). The *Nfil3*<sup>-/-</sup> (NFIL3 KO) mice used in this study (C57BL/6J background) were previously described (van der Kallen et al., 2015). WT littermates were used as controls. Mice of 10 weeks of age were treated with tunicamycin or vehicle as described above and liver was collected 8h after injection (8 mice per group). To induce ERS in muscle, 30 µg tunicamycin was injected intramuscularly into the gastrocnemius muscle. The contralateral leg was injected with a saline solution and used as control. Muscles were collected 24h after injection (9 mice per group).

Two different models of sepsis were used. For the bacterial injection model (BIM) of sepsis (sepsis<sup>BIM</sup>), mice were injected intraperitoneally with  $8 \times 10^8$  CFU of live *E. coli* (DH5α) bacteria or PBS (controls) and liver was collected 16h later (6 mice per group). In a separate experiment, mice were pre-treated for 4 consecutive days with tauroursodeoxycholic acid (TUDCA) (intraperitoneal injection of 500 mpk/day) or vehicle (PBS) followed by bacterial injection 2h after the last TUDCA administration on the fourth day (10 mice per group), and sacrificed 6h after bacterial injection which is sufficient to induce LIVER-ID TF loss (Appendix Fig.S22C). For the caecal ligation and puncture (CLP) model of sepsis (sepsis<sup>CLP</sup>), male C57BL/6J wildtype mice of 24 weeks of age were randomly allocated to sepsis<sup>CLP</sup> or healthy pair-fed control and sacrificed after 10h, 30h or 3 days (15 mice per group per timepoint). Mice in the sepsis<sup>CLP</sup> groups were subjected to single-puncture CLP followed by intravenous fluid resuscitation as previously described (Derde et al., 2017). Briefly, mice were anesthetized, a catheter was inserted in the central jugular vein and the surgical CLP procedure

was performed (50% ligation of the caecum at half the distance between the distal pole and the base of the caecum and a single puncture through-and-through) followed by intravenous fluid resuscitation. They received pain medication and antibiotics 6 hours after CLP and from then on every 12 hours for the remainder of the experiment and mice of the “day 3” group (prolonged phase) received parenteral nutrition from the morning after surgery to mimic the human clinical situation. The data reported for the sepsis<sup>CLP</sup> design correspond to the 10h time point (acute phase) unless indicated otherwise. Healthy pair-fed mice were used as control.

All animal studies were performed in compliance with EU specifications regarding the use of laboratory animals and approved by the Nord-Pas de Calais Ethical Committee (for ERS treatments and the sepsis<sup>BIM</sup> design) or the KU Leuven Ethical Committee (P093/2014) (for the sepsis<sup>CLP</sup> design).

### **Biochemical analyses**

Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were determined by colorimetric assays (Thermo Fischer Scientific) using serum obtained following retro-orbital blood collection.

### **Real-time quantitative PCR analyses of gene expression**

RNA extraction, reverse transcription and real-time quantitative PCR (RT-qPCR) were performed as previously described (Dubois-Chevalier et al., 2017). The primer sequences are listed in Table EV5. All primers were designed to hybridize to different exons, and generation of single correct amplicons was checked by melting curve dissociation. Murine gene expression levels were normalized using hypoxanthine guanine phosphoribosyl transferase (*Hprt*) (sepsis<sup>CLP</sup> experiments) or cyclophilin A (*PP1a*) (all other experiments) housekeeping gene expression levels as internal control. Human gene expression levels were normalized using 18S ribosomal RNA (*RNA18S5*). For gene expression analyses, *in-vitro* experiments (AML12 and MPH) were repeated at least three times (independent experiments), each experiment being performed in technical triplicates. For *in-vivo* mouse studies, we used at least 5 animals per experimental condition (genotype or treatment). The number of biological replicates is indicated in the figure legends.

## **Gene expression microarrays**

RNA was extracted from MPH treated for 4h with 1  $\mu$ M thapsigargin (3 independent experiments), livers of NFIL3 KO and WT littermates treated for 8h with 1  $\mu$ g/g tunicamycin (5 mice per genotype per treatment) or gastrocnemius muscles of WT mice treated for 24h with 30  $\mu$ g tunicamycin (treated and contralateral control muscles from 9 mice) and was checked for quantity and quality using the Agilent 2100 Bioanalyzer (Agilent Biotechnologies) before being processed for analysis using MoGene-2\_0-st Affymetrix arrays according to the manufacturer's instructions. Data were analyzed as described hereafter and have been submitted to GEO under accession number GSE122508.

## **Transcriptomic data analyses**

### *Liver-specificity index*

The liver-specificity index was calculated as the difference of normalized expression in liver and mean of normalized expression in control tissues using data from BioGPS (Table EV6).

### *Normalization of microarrays and identification of differentially expressed genes*

Raw transcriptomic data from Affymetrix microarrays were normalized with Partek Genomics Suite 6.6 using background correction by Robust Multi-array Average (RMA), quantile normalization and summarization via median-polish. Principal component analyses (PCA) were used for quality control of the data. RMA values were also used to display expression changes for selected gene sets in different figures. Differential expression analyses were performed at probeset level with Partek Genomics Suite. Dysregulated genes were defined taking into account any potential factor interaction in the original experimental design and using a Benjamini–Hochberg corrected p-value cut-off (FDR) set at 0.05.

### *Single-cell RNA-seq data analyses*

Raw counts from single-cell transcriptomic data (447 cells from E10.5 to E17.5) (Yang et al., 2017) were normalized by estimation of library size factor with DESeq 1.26.0 (Anders & Huber, 2010) according to (Brennecke et al., 2013). PCA was performed on normalized data using FactoMineR 1.41



(Lê et al., 2008). Then the average expression of ERS DOWN or ERS UP genes was projected for each cell on 2D PCA plot.

#### *Identification of preferential patterns of gene expression following partial hepatectomy*

Genes with different temporal expression profiles were identified using the Short Time-series Expression Miner (STEM v1.3.11) (Ernst et al., 2005), which fits dynamic patterns of gene expression to model profiles. Normalized gene expressions (rpkm) were obtained from (Rib et al., 2018) and average expression from replicates was used. Parameters were set at “Log normalize data”, 4 for “max unit change in model profiles between time points”, -0.05 for “minimum absolute expression change” and FDR for “Correction method”.

#### *Comparison of the breadth of transcriptomic changes occurring in the mouse liver*

To make fold-changes comparable with those obtained using RNA-seq, microarray data were normalized using the Affymetrix Power Tool (Thermo Fisher Scientific) run through the GIANT tools suite (Vandel et al., 2018) on a local instance of Galaxy (Afgan et al., 2018). Normalization was set to “scale intensity + rma” and normalization level to “probeset”. Normalized expression values retrieved for the studies which used RNA-seq (Table EV6) were  $\text{Log}_2$ -transformed. For each dataset, a single expression value per gene was defined using gene symbols as identifiers and by averaging values obtained from replicates. Fold-changes ( $\text{Log}_2$ ) were next computed on scaled data, which were obtained using the scale function of the « graphics » R package (R\_Core\_Team, 2015) on each dataset separately. This was performed using global mean (mean of all expression values under all conditions of interest in a given study) for “center” parameter and global standard deviation for the “scale” parameter. Only genes common to all analysed datasets were considered for subsequent analyses and, for each dataset, the bottom 20% genes with lowest expression in the liver were discarded. Bagplots were drawn using the "bagplot" function of the “aplpack” (v1.3.2) R package using default parameters (R\_Core\_Team, 2015). Bagplots are bivariate boxplots showing the spread of the data using a “bag” containing 50% of the data points with the largest depth (around the median) and its extension by a “loop” whose limit exclude outliers (Rousseeuw et al., 1999).

### *Comparison of the transcriptome of injured livers with that of the developing mouse liver*

Transcriptomic data of liver injuries were pooled and batch effects were corrected with the “ComBat” function of the “sva” R package (Leek et al., 2019) using the mouse liver differentiation study as the batch of reference (see Table EV6 for details regarding used datasets). Parameters were set to “mean.only=T” and “par.prior=T”. Each study was defined as a different batch where the control condition (i.e. non-injured livers) was matched to the adult liver stage of the reference dataset. Next, a PCA was computed only on the mouse liver differentiation study with the “PCA” function of FactomineR (Lê et al., 2008) (using “scale.unit=F”). Liver injury studies were considered as supplemental individuals. Finally, the first principal component (representing 63.55% of the variability of the mouse liver differentiation study) was plotted and used to project the liver injury studies. Data corresponding to prenatal mouse livers were used in the analyses but were discarded for data visualization.

### *Functional enrichment analyses*

Functional enrichment analyses were performed using the ToppGene Suite (Chen et al., 2009). KEGG Pathways with Bonferroni-corrected p-value  $<10^{-3}$  and Gene Ontology (GO) Biological Processes with Bonferroni-corrected p-value  $<10^{-6}$  were considered and similar terms were merged.

### *Gene set enrichment analyses*

Gene set enrichment analyses (GSEA) were performed using the GSEA software (v3.0) developed at the Broad Institute (Subramanian et al., 2005). We used 1000 gene-set permutations and the following settings: “weighted” as the enrichment statistic and “difference of classes” as the metric for ranking genes. Ranking was performed by the GSEA software using the average expression value per gene when multiple probesets were present in the microarray. In addition to enrichment plots, figures also provide NES and FDR, which are the normalized enrichment score and the false discovery rate provided by the GSEA software, respectively. In experiments with multiple conditions, the BubbleGUM tool (GSEA Unlimited Map v1.3.19) (Spinelli et al., 2015) was used to integrate and compare numerous GSEA results with multiple testing correction. Non-oriented GO term enrichment

analyses were performed using the “MousePath\_GO\_gmt.gmt” set of genes from the Gene Set Knowledgebase (GSKB) (Lai et al., 2016).

### **Chromatin Immunoprecipitation**

MPH ( $3 \times 10^6$  cells) were fixed for 30 min at room temperature with disuccinimidyl glutarate followed by a 10 min incubation with 1% formaldehyde and a 5 min incubation with 125 mM glycine. After two washes with ice-cold PBS, cells were scraped in PBS, pelleted by centrifugation at 400g for 5 min, resuspended in Lysis Buffer (50 mM Tris-HCl pH 8.0, 10 mM EDTA, 1% SDS and 1x PIC from Roche) and sonicated for 4 min (4 cycles 30 sec ON / 30 sec OFF using Bioruptor Pico from Diagenode). Mouse liver (200 mg of tissue) was cut in small pieces in ice-cold PBS, pressed through a 70  $\mu$ m cell strainer followed by a few passages through a 18G needle. Fixation, lysis and sonication were performed as described for MPH. Chromatin (50  $\mu$ g for H3K27ac ChIP and 200  $\mu$ g for BRD4 ChIP) was diluted 10-fold in Dilution Buffer (20 mM Tris-HCl pH 8.0, 1% Triton X-100, 2 mM EDTA, 150 mM NaCl) and incubated overnight with 2  $\mu$ g of H3K27ac antibody (Active Motif, #39685) or 3  $\mu$ g of BRD4 antibody (Bethyl Labs, #A301-985A100) at 4°C. The next day, A/G sepharose bead mix (GE Healthcare) was added during 4 hours at 4°C in presence of 70  $\mu$ g/mL yeast tRNA (Sigma-Aldrich). Beads were washed three times with RIPA buffer (50 mM HEPES pH 7.5, 1 mM EDTA, 0.7% Na Deoxycholate, 1% NP40 and 500 mM LiCl) containing 10  $\mu$ g/mL yeast tRNA and once with TE buffer (10 mM Tris-HCl pH 8.0, 1 mM EDTA). DNA was then eluted in 100 mM NaHCO<sub>3</sub> containing 1% SDS and incubated overnight at 65°C for reverse-crosslinking. DNA purification was performed using the MinElute PCR purification kit (Qiagen, #2800) and samples were subjected to qPCR analyses. The primer sequences are listed in Table EV5.

H3K27ac ChIP and input samples from MPH treated for 4h with 1  $\mu$ M thapsigargin or vehicle (0.04% DMSO) from 3 independent experiments were additionally sent for sequencing on an Illumina Hi-seq 4000 as single-end 50-base reads according to the manufacturer’s instructions. Data were analyzed as described hereafter and have been submitted to GEO under accession number GSE122508.

## ChIP-seq data analyses

ChIP-seq data quality control and uniform reprocessing including mapping to the mm10 version of the mouse genome and signal normalization have been described in (Dubois-Chevalier et al., 2017) except Bowtie 2 (sensitive mode) (Langmead et al., 2009) was used for the BRD4 ChIP-seq analyses. ChIP-seq data were visualized using the Integrated Genome Browser (IGB 9.0.1) (Freese et al., 2016).

### *Broad H3K4me3 domain identification and identity gene definition*

H3K4me3 ENCODE ChIP-seq data from several mouse tissues (Shen et al., 2012) (Table EV6) were used to call broad H3K4me3 enriched regions using MACS2 as described in (Chen et al., 2015). Broad H3K4me3 domains were defined as those spanning more than 3 times the median size of all H3K4me3 enriched regions in a given tissue. Broad H3K4me3 domains from mouse liver were separated into liver-identity (LIVER-ID) domains, which were defined as broad H3K4me3 domains specific to liver (i.e. detected in less than 25% of other analysed tissues), and in ubiquitous (UBQ) domains. LIVER-ID and UBQ domains were then assigned to genes according to overlapping TSS from the GENCODE (M9) database (Frankish et al., 2019), resulting in 621 LIVER-ID genes and 657 UBQ genes which are listed in Table EV1. TFs within these gene lists were subsequently obtained using comparison with mouse TFs listed in the Animal TFDB 2.0 (Zhang et al., 2015). Muscle-identity (MUSCLE-ID) and UBQ genes, listed in Table EV4, were defined in a similar way using H3K4me3 ChIP-seq data from the ROADMAP consortium processed by (Chen et al., 2015). Human to mouse gene name conversion was performed using the dbOrtho tool from bioDBnet (Mudunuri et al., 2009).

### *Super-enhancer identification*

To define BRD4 super-enhancers (SE), we first used MACS2 to identify enriched peaks (Effective genome size = 2150570000, Band Width = 300, mfold = 5 to 50, FDR (q-value) = 0.05, Max duplicate tags at the same location = 1) using mapped reads previously filtered to remove duplicates and reads mapping to false-positives regions we had identified in (Dubois-Chevalier et al., 2017). SE were identified by applying Rank Ordering of Super-Enhancers (ROSE) (Loven et al., 2013, Whyte et

al., 2013) on the BRD4 peak-calling results using mouse liver ChIP-seq inputs (GSE26345) as control (setting: -s 12500, -t 0).

#### *Identification of changes in H3K27ac induced by acute ERS*

Regions with significant changes in H3K27ac ChIP-seq signals induced by ERS were identified using csaw 1.6.1 (Lun & Smyth, 2014, Lun & Smyth, 2016). Mapped reads were previously filtered to remove duplicates and reads mapping to ENCODE blacklisted regions (Encode\_Project\_Consortium, 2012) or mouse ChIP-seq false-positives regions we had identified in (Dubois-Chevalier et al., 2017). The command lines and full list of used parameters are provided in Computer Code EV1. Briefly, the genome was binned and reads counted, bins with background level signal as defined using input samples were discarded before normalization using a loess regression. Finally, after dispersion estimation with the function estimateDisp, a paired-differential analysis was performed on this filtered and normalized data using glmQLFit. Bins overlapping H3K27ac peaks (broad regions called with MACS2 using a pool of all H3K27ac ChIP-seq datasets and inputs as control - parameters: q-val narrow = 0.001 and q-val broad = 0.01) were identified using findOverlaps from GenomicRanges 1.24.3 (Lawrence et al., 2013) (parameters : minoverlap=75, maxgap=0). Bins overlapping a single H3K27ac peak were combined using combineOverlaps and only merged bins with FDR  $\leq$  0.05 were considered (merged bins with FDR > 0.05 were defined as unchanged H3K27ac regions). The ratio of UP to DOWN bins in the merged regions was next calculated and H3K27ac UP or DOWN regions were defined as those having a ratio  $\geq$  2 or  $\leq$  0.5, respectively. Coordinates for H3K27ac UP, DOWN and unchanged regions are provided in Dataset EV1. The bigwig signals were computed using the loess normalized signal on each dataset and/or averaging the loess normalized signal between replicates. Genes were assigned to H3K27ac regions as follows. First, genes whose TSS from the GENCODE (M9) database (Frankish et al., 2019) directly overlaps H3K27ac regions were retrieved. In addition, distal H3K27ac were linked to potentially regulated genes using CisMapper (O'Connor et al., 2017) as previously described in (Dubois-Chevalier et al., 2017).

#### *Analyses of transcriptional regulators recruited to regions with changes in H3K27ac induced by acute*

## ERS

In order to identify TFs whose binding is enriched in H3K27ac UP and H3K27ac DOWN regions, we used Locus Overlap Analysis (LOLA 1.4.0) (Sheffield & Bock, 2016) to compare TF binding within UP, DOWN and ALL (i.e. also including H3K27ac unchanged) regions. Mouse TF binding sites were retrieved from the Gene Transcription Regulation Database (GTRD) ([http://gtrd.biouml.org/downloads/16.07/mouse\\_meta\\_clusters.interval.2017\\_03\\_10](http://gtrd.biouml.org/downloads/16.07/mouse_meta_clusters.interval.2017_03_10)) (Yevshin et al., 2017). Inputs were discarded and ChIP-seq datasets were ascribed to TFs using nomenclature information provided by the authors. A heatmap of log odds ratio was generated using the heatmap.2 function of the R package “gplots” (v3.0.1) (Warnes et al., 2016) and hierarchical clustering using the hclust function of the R package “Stats” (using Euclidean distance and ward.D2 agglomeration method) (R\_Core\_Team, 2015). A list of the TFs of each cluster is shown in Table EV2.

H3K27ac UP, DOWN or unchanged regions were overlapped with *cis*-regulatory modules (CRMs) defined in (Dubois-Chevalier et al., 2017) based on co-binding of 47 transcriptional regulators in mouse liver. Combinatorial co-binding of transcriptional regulators at H3K27ac UP, DOWN or unchanged was analyzed using multidimensional scaling (MDS) analyses as described in (Dubois-Chevalier et al., 2017). Plots were performed with the smoothScatter function of the « graphics » R package (R\_Core\_Team, 2015) using a conserved color scale.

### **Public transcriptomic and functional genomic data recovery**

Public data used in this study were downloaded from Gene Expression Omnibus (GEO) (<http://www.ncbi.nlm.nih.gov/geo/>) (Edgar et al., 2002), ENCODE (Yue et al., 2014), UCSC Genome Browser (Dreszer et al., 2012) or BioGPS (Mouse MOE430 Gene Atlas) (Wu et al., 2016) and are listed in Table EV6.

### **Human samples**

Postmortem liver biopsies from patients admitted to the intensive care unit (ICU) of Leuven University Hospital with sepsis (n=64), who died after a median ICU stay of 10 days (IQR 6-20 days), were compared with matched patients undergoing elective restorative rectal surgery (n=18). Written

informed consent was obtained from the patients or their closest family member and from the volunteers. The study protocols and consent forms were approved by the KU Leuven Institutional Review Board (ML1094, ML1820, and ML2707). Bilirubin was quantified with use of a standard routine automated assay in the University Hospital Clinical Laboratory.

### **Protein extraction**

#### *Total extracts*

MPH and AML12 cells were scraped in ice-cold PBS, pelleted by centrifugation at 400g for 5 min, lysed in Laemmli buffer 6x (175 mM Tris-HCl pH 6.8, 15% glycerol, 5% SDS, 300 mM DTT and 0.01% Bromophenol Blue) and sonicated for 10 minutes. Mouse liver was cut in small pieces in ice-cold PBS and pressed through a 70 µm cell strainer. The pellet obtained after centrifugation at 400g for 5 min was lysed and sonicated as described for MPH. Western blottings shown in this study were obtained using total cellular extracts unless indicated otherwise.

#### *Nuclear extracts*

MPH were scraped in ice-cold PBS, mouse liver was cut in small pieces in ice-cold PBS and pressed through a 70 µm cell strainer. Pellets were obtained by centrifugation at 400g for 5 min, lysed in Hypotonic Buffer (20 mM Tris-HCl pH 8.0, 10 mM NaCl, 3 mM MgCl<sub>2</sub>, 0.2% NP40 and 1x PIC from Roche) and incubated for 5 min at 4°C. Samples were centrifuged at 600g for 5 min at 4°C and supernatants constituted the cytoplasmic fraction. Nuclear pellets were lysed in Nucleus Lysis Buffer (25 mM Tris-HCl pH 8.0, 500 mM NaCl, 1 mM EDTA, 0.5% NP40 and 1x PIC from Roche). Hypotonic Buffer and Nucleus Lysis Buffer were supplemented with Phosphatase Inhibitor Cocktail (#P044 from Sigma-Aldrich) as well as with 5 mM Sodium Butyrate and 5 µM Trichostatin A for deacetylase inhibition. After incubation for 30 min at 4°C, samples were sonicated for 10 min and centrifuged at 16000g for 5 min at 4°C. Laemmli 6x was added to the supernatants which were used for Western immunoblotting.

#### *Chromatin fraction*

MPH were scraped in ice-cold PBS, pelleted by centrifugation at 400g for 5 min, lysed in

Buffer A (50 mM HEPES pH 7.5, 10 mM KCl, 1.5 mM MgCl<sub>2</sub>, 340 mM sucrose, 10% glycerol, 1 mM DTT and 1x PIC from Roche) and incubated for 10 min at 4°C. Samples were centrifuged at 1300g for 5 min at 4°C and supernatants were discarded. Nuclear pellets were washed with Buffer A and subsequently lysed in solution B (3 mM EDTA, 0.2 mM EGTA, 1 mM DTT and 1x PIC from Roche). After incubation for 30 min at 4°C, samples were centrifuged at 1700g for 5 min at 4°C and supernatants were discarded. Chromatin pellets were washed with solution B, resuspended in Buffer C (50 mM Tris-HCl pH 8.0, 1 mM MgCl<sub>2</sub> and 83 U/μL benzonase) and incubated for 20 min at 4°C. Laemmli buffer 6x was added before loading for Western immunoblotting.

### **Plasmids and *in-vitro* transcription and translation**

The pcDNA3.1-mNFIL3 (Addgene 34572) and pSGG5-hHNF4A constructs were used for *in-vitro* transcription and translation (*in-vitro* TNT) using the TnT® Quick Coupled Transcription/Translation System (Promega).

### **Western immunoblotting**

#### *Western blot assays (WB)*

One hundred μg of proteins were separated by 10% SDS-PAGE and immunodetected by Western immunoblotting using the primary antibodies listed in the Reagents and Tools table. Primary antibodies were detected using HRP-conjugated secondary antibodies (Sigma-Aldrich). Images were acquired using a G-box (Syngene, Cambridge UK) or using the iBright™ CL1500 Imaging System (Thermo Fisher Scientific). Quantifications were performed using Image Studio Lite v5.2 (LI-COR Biosciences, Lincoln, USA) and band intensities were defined using the signal value (sum of the pixel intensity in a shape minus the background value).

#### *Simple Western immunoassays (WES)*

Simple Western size-based assays were run on a WES system as recommended by the manufacturer (ProteinSimple, San Jose, USA). Protein concentrations ranged from 0.25 to 0.8 μg/μL depending on the target protein. Primary antibodies are listed in the Reagents and Tools table. Secondary antibodies were provided by the manufacturer (PS-MK14 and PS-MK15, ProteinSimple).



Data were analyzed using the Compass software (ProteinSimple). Quantifications were obtained using the area under the peak of the protein of interest.

### **Co-immunoprecipitation assays**

MPH cells were resuspended into hypotonic buffer (20 mM Tris-HCl, pH 7.5, 10 mM NaCl, 3 mM MgCl<sub>2</sub>, 0.2% NP40 and protease inhibitors) and the pellet was lysed for 30 min. After 10 min sonication (30 s on/off cycles with a Bioruptor (Diagenode) and centrifugation, 500 µg nuclear proteins from the soluble fraction were diluted with two volumes of a buffer containing 25 mM Tris-HCl pH7.5, 1 mM EDTA, 1.5 mM MgCl<sub>2</sub> and incubated overnight with 2 µg of p300 antibody (Active motif, #61401) or control mouse IgG (sc-2025, Santa Cruz). Samples were then incubated for 4h with magnetic beads (Life technologies) previously blocked with 5 mg/ml of serum albumin bovine and washed 4 times using ice-cold washing buffer containing 25 mM Tris-HCl pH7.5, 150 mM NaCl, 1 mM EDTA, 0.2% NP40 and protease inhibitors. Beads were finally eluted in Laemmli buffer 6x.

### **Statistical analyses**

Statistical analyses were performed using the Prism software (GraphPad, San Diego, CA) and R (R\_Core\_Team, 2015). The specific tests and corrections for multiple testing which were used as well as the number of samples per condition are indicated in the figure legends. In all instances, statistical significance was considered to be reached when p-values were below 0.05, which was indicated by \* or #. All bar graphs show means ± SD (standard deviations). Box plots are composed of a box from the 25<sup>th</sup> to the 75<sup>th</sup> percentile with the median as a line and min to max as whiskers.

### **DATA AVAILABILITY**

The datasets produced in this study are available in the following databases:

- Chip-Seq data: Gene Expression Omnibus GSE122613

(<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE122613>)

- Transcriptomic data: Gene Expression Omnibus GSE122508

(<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE122508>).

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## CONFLICT OF INTERESTS

BS is consultant for Genfit SA. The remaining authors declare no competing financial interest.

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## FIGURE LEGENDS

**Figure 1. Acute ERS triggers massive transcriptomic alterations characterized by repression of LIVER-ID genes and loss of hepatic molecular identity.**

**(A)** Top 2 significantly overrepresented expression patterns for ERS UP and ERS DOWN genes following PHx. Data show changes in expression at 4, 10, 48h and 1 week after PHx (0h) for genes comprised within each model profile of dynamic expression identified by STEM. The complete set of identified model profiles is provided in Appendix Fig.S2.

**(B)** Functional enrichment analyses were performed using ERS UP (*upper panels*) or ERS DOWN (*lower panels*) genes and the ToppGene Suite. KEGG Pathways with Bonferroni-corrected p-value  $<10^{-3}$  were considered and similar terms were merged.

**(C)** Bagplots showing the breadth of transcriptomic changes for the indicated datasets. Genes were positioned based on their basal expression levels in the control conditions and their FC ( $\text{Log}_2$ ) in the indicated (patho)physiological context. The dark blue area is the “bag” (50% of the data points

around the median, which is indicated by a red cross) while the light blue area delimits the “loop” (see Materials and Methods for details). Red dots are outliers.

**(D-E)** Box plots showing normalized expression in liver (D) and liver-specificity index (E) of LIVER-ID genes, UBQ genes and other genes. Liver-specificity index was calculated as the difference of normalized expression in liver (2 replicates) and mean of normalized expression in control tissues (2 replicates per tissue) using data from BioGPS (Table EV6) and is reported as  $\text{Log}_2$ . Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-way ANOVA with Welch’s correction and Dunnett’s Modified Tukey-Kramer pairwise multiple comparison test was used to assess statistical significance, \*P < 0.05.

**(F)** Similar analyses as in (A) using LIVER-ID genes.

**(G-H)** Box plots showing  $\text{Log}_2$  FC ERS/Control in MPH (3 independent experiments) (G) or mouse liver (3 mice per group) (H) for LIVER-ID genes, UBQ genes and other genes. Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-way ANOVA with Welch’s correction and Dunnett’s Modified Tukey-Kramer pairwise multiple comparison test was used to assess statistical significance, \*P < 0.05.

**(I)** Enrichment plots from gene set enrichment analyses (GSEA) performed using LIVER-ID genes as the gene set and transcriptomic changes induced by acute ERS in MPH (*upper panel*) or mouse liver (*lower panel*) as the ranked gene list. NES and FDR (as in all subsequent GSEA panels) are the normalized enrichment score and the false discovery rate provided by the GSEA software, respectively.

**(J-K)** Genes repressed by ERS in MPH (3 independent experiments) (J) or mouse liver (3 mice per group) (K) were ranked based on their  $\text{Log}_2$  FC ERS/Control and divided into quartiles (increased repression from Q1 to Q4). The fraction of LIVER-ID genes in the 4 quartiles was defined and is displayed relative to that obtained for Q1 arbitrarily set to 1. The bar graphs show means  $\pm$  SD (standard deviations). Chi-square test with BH correction for multiple testing was used to assess statistical significance, \*P < 0.05.

**(L-M)** RT-qPCR analyses of selected ERS UP and LIVER-ID genes monitoring expression changes induced by acute ERS in MPH (3 to 9 independent experiments) (L) or mouse liver (5 to 7 mice per group) (M). The bar graphs show means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean  $\text{Log}_2$  FC ERS/Control is statistically different from 0, \*P < 0.05. Panel (L) is also displayed in Appendix Fig.S3G.

**(N)** Heatmaps showing normalized expression of ERS UP and ERS DOWN genes from MPH (*upper panel*) or mouse liver (*lower panel*) in mouse liver at the indicated stages of development.

**(O)** Average expression of ERS DOWN genes from MPH in single-cells from the hepatobiliary lineage. See Materials and Methods together with Appendix Fig.S3I for details regarding data processing. The hepatoblast-to-hepatocyte and hepatoblast-to-cholangiocyte differentiation paths are indicated with arrows.

**Figure 2. Acute ERS compromises LIVER-TF expression and activities of their densely co-bound hepatic CRMs.**

**(A)** Comparison of transcriptomics (data from 3 independent experiments) and H3K27ac ChIP-seq (data from 3 independent experiments) from MPH. Genes were assigned to H3K27ac regions as described in Material and Methods. The number of ERS DOWN genes is indicated relative to the number of ERS UP genes for the 3 categories of H3K27ac regions. The bar graph shows means  $\pm$  SD (standard deviations). Fisher's exact test with BH correction for multiple testing was used to assess statistical significance, \*P < 0.05, #P < 0.05.

**(B)** Similar analyses to (A). The number of LIVER-ID and UBQ genes is indicated relative to the number of other genes for the 3 categories of H3K27ac regions. The H3K27ac ChIP-seq data were obtained from 3 independent MPH experiments. The bar graph shows means  $\pm$  SD (standard deviations). Chi-square test with BH correction for multiple testing was used to assess statistical significance, #P < 0.05.

**(C)** Multidimensional scaling (MDS) was performed as described in Materials and Methods and transcriptional regulator co-recruitment was depicted using density plots for regions with increased

(a), decreased (b) or unchanged (c) H3K27ac levels in MPH upon acute ERS. The boxed area (d) represents a subset of transcriptional regulators (TR) with a high degree of co-binding in H3K27ac DOWN regions. LIVER-ID TFs are depicted in red.

**(D)** Heatmaps showing the percentage of enhancers overlapping H3K27ac down regions. Enhancers were first split into those bound or not by a given LIVER-ID TF (right) and then based on co-binding of additional LIVER-ID TFs (defining 3 subgroups with 0-2, 3-5 or 6-8 co-bound additional LIVER-ID TFs).

**(E)** Enrichment plots from GSEA performed using LIVER-ID TFs as the gene set and transcriptomic changes induced by acute ERS in MPH (*upper panel*) or mouse liver (*lower panel*) as the ranked gene list.

**(F)** RT-qPCR analyses of selected LIVER-ID TFs monitoring expression changes induced by acute ERS in MPH (4 to 7 independent experiments). The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean  $\text{Log}_2$  FC ERS/Control is statistically different from 0, \*P < 0.05. This graph is also displayed in Appendix Fig.S6E.

**(G)** RT-qPCR analyses of selected ERS UP and LIVER-ID TF genes monitoring expression changes induced by 4h ERS in MPH pre-treated or not for 30min with 5mM PBA (3 independent experiments). Mean  $\text{Log}_2$  FC ERS/Control are shown. The bar graph shows means  $\pm$  SD (standard deviations). Two-way ANOVA with Bonferroni's post-hoc test was used to assess statistical significance, \*P < 0.05.

**(H-I)** Nuclear extracts (H) and chromatin fractions (I) from MPH were subjected to Western blot with antibodies against HNF4A, NR1H4/FXR, FOXA2/HNF3B or DDIT3/CHOP. LMNA or histone H3 were used as loading controls. Results obtained from 3 independent biological replicates are shown. See Appendix Fig.S6H and Ploton et al. (Ploton et al., 2018) for antibody validation.

**Figure 3. Induction of NFIL3 by acute ERS contributes to repression of genes involved in xenobiotic metabolism.**

**(A)** RT-qPCR analyses of *Hlf*, *Tef*, *Dbp* and *Nfil3* expression monitoring changes induced by acute ERS in MPH (3 to 5 independent experiments) (*left panel*) or mouse liver (5 mice per group) (*right panel*).



The bar graphs show means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean  $\text{Log}_2$  FC ERS/Control is statistically different from 0, \*P < 0.05.

**(B)** Total protein extracts from MPH (*left panel*) or mouse liver (*right panel*) were subjected to Western blot with an antibody against NFIL3. ACTB was used as loading control. See Appendix Fig.S7B for antibody validation.

**(C)** Chromatin fractions from MPH (*upper panel*) or mouse liver (*lower panel*) were subjected to Western blot with an antibody against NFIL3. Histone H3 was used as loading control.

**(D)** Enrichment scores from GSEA performed using LIVER-ID genes repressed by acute ERS in MPH (MPH ERS DOWN) as the gene set and liver transcriptomic changes induced by acute ERS and/or deletion of *Nfil3* (NFIL3 KO) as the ranked gene lists were integrated and corrected for multiple testing using the BubbleGUM tool. For the NFIL3 KO ERS vs WT ERS comparison, the Core Enrichment genes (i.e. the subset of genes that contributes most to the enrichment result) were subjected to functional enrichment analyses using the ToppGene Suite. The top ranked KEGG Pathway with its Bonferroni-corrected p-value is shown.

**(E)** Box plots showing mRNA expression for 5 genes from the Core Enrichment from D involved in xenobiotic metabolism issued from the transcriptomic analyses. Shown are  $\text{Log}_2$  FC relative to the mean normalized expression in the WT Control group (5 mice per group). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. Two-way ANOVA with Bonferroni's post-hoc test was used to assess statistical significance, \*P < 0.05.

**(F)** The Integrated Genome Browser (IGB) was used to visualize ChIP-seq profiles for NFIL3 (green) and several LIVER-ID TFs (red) in the mouse liver at the *Gsta3* gene locus. Levels of H3K27ac in MPH and cells from the non-parenchymal fraction (NPC) are shown in blue. The grey bar indicates the position of a BRD4 SE.

**Figure 4. Acute ERS triggers hepatic SE decommissioning through impaired recruitment of the cell identity maintenance cofactor BRD4.**

**(A)** BRD4 occupancy (*left panels*) and H3K27ac levels (*right panels*) at regulatory regions associated with ERS UP or LIVER-ID genes (8 regions at ERS gene loci and 10 regions at LIVER-ID gene loci, depicted in Appendix Fig.S10B and listed in Table EV5) were assessed by ChIP-qPCR in MPH (10 independent experiments) or mouse liver (10 mice per group) to define changes induced by acute ERS. Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-sample t-test with BH correction for multiple testing was used to determine if the mean  $\text{Log}_2$  FC ERS/Control is statistically different from 0, \*P < 0.05.

**(B)** *Left panel*, BRD4 mRNA (4 independent experiments) or protein expression levels (5 independent experiments; densitometric quantification of Fig.4B and Appendix Fig.S10C) in MPH subjected to acute ERS. The bar graphs show means  $\pm$  SD (standard deviations). Student's t-test was used to assess statistical significance. *Right panel*, Total protein extracts from MPH pre-treated for 3h with 0.01 $\mu$ M MZ1 followed by addition of 1 $\mu$ M thapsigargin (ERS) for 4h were subjected to Western blot with an antibody against BRD4. LMNA was used as loading control.

**(C)** Heatmaps showing  $\text{Log}_2$  FC (relative to the DMSO/Control condition) for 5 ERS UP and LIVER-ID genes issued from RT-qPCR analyses (Appendix Fig.S11) of MPH pre-treated with 500nM JQ1 (*left*) or 0.01 $\mu$ M MZ1 (*right*) followed by addition of 1 $\mu$ M thapsigargin (ERS) for 4h (3 to 6 independent experiments). Two-way ANOVA with Bonferroni's post-hoc test was used to assess statistical significance.

**(D)** Heatmaps showing average H3K27ac ChIP-seq signals in MPH at LIVER-ID domains overlapping (+) or not (-) with BRD4 SE. The arrow indicates the position of gene transcriptional start sites.

**(E)** Box plots showing  $\text{Log}_2$  FC ERS/Control in MPH (3 independent experiments) (*left panel*) or mouse liver (3 mice per group) (*right panel*) for genes associated with LIVER-ID + BRD4 SE or LIVER-ID - BRD4 SE, which are listed in Table EV1. Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. Student's t-test was used to assess statistical significance, \*P < 0.05.

**Figure 5. Loss of LIVER-ID TF protein expression is a primary event upon acute ERS.**

**(A)** RT-qPCR analyses of 21 LIVER-ID genes (12 TFs and 9 non-TFs, listed in Table EV5) in MPH which were treated with 1 $\mu$ M thapsigargin (ERS) for 4h, 8h, 16h or 24h (4 independent experiments). For each gene, the timepoint showing maximal repression by ERS was recorded. The heatmap depicts the percentage of genes maximally repressed by ERS at each timepoint.

**(B)** RT-qPCR analyses of *Hnf4a*, *Nr1h4* and *Foxa2* expression in MPH treated with vehicle (Control) or 1 $\mu$ M thapsigargin (ERS) for 1h or 4h (4 independent experiments). The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC ERS/Control is statistically different from 0, \*P < 0.05.

**(C)** Densitometric quantification of the protein expression data shown in Fig.5D, Fig.5F and Fig.S18A-B for the 1h timepoint (average of 9 biological replicates) and Fig.2H for the 4h timepoint (average of 3 biological replicates). The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC ERS/Control is statistically different from 0, \*P < 0.05.

**(D)** Nuclear extracts from MPH pre-treated for 30min with 1 $\mu$ M ISRIB followed by addition of 1 $\mu$ M thapsigargin (ERS) for 1h were subjected to Western blot with antibodies against HNF4A, NR1H4, FOXA2 or DDIT3. LMNA was used as loading control. Results obtained from 3 independent biological replicates are shown.

**(E)** Densitometric quantification of the protein expression data shown in panel (D). Repression by ERS in the ISRIB condition (average of 3 biological replicates) is shown relative to repression by ERS in vehicle condition. The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean relative repression is statistically different from 100%, \*P < 0.05.

**(F)** Nuclear extracts from MPH pre-treated for 30min with 10 $\mu$ M MG132 or 10 $\mu$ M PP2 followed by addition of 1 $\mu$ M thapsigargin (ERS) for 1h were subjected to Western blot or Simple Western immunoassay with antibodies against HNF4A, NR1H4, FOXA2 or XBP1S. LMNA was used as loading control. Results obtained from 2 independent biological replicates are shown. Additional replicates

are shown in Appendix Fig.S18A-B.

**(G)** Densitometric quantification of the protein expression data shown in panel (F) and Appendix Fig.S18A. Repression by ERS in MG132 condition (average of 4 biological replicates) is shown relative to repression by ERS in vehicle condition. The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean relative repression is statistically different from 100%, \*P < 0.05.

**(H)** (*Left*) Cytoplasmic extracts issued from the MPH used in panel (F) (2 biological replicates) were subjected to Western blot with antibodies against p-Y416-SRC or total SRC. ACTB was used as loading control. (*Right*) Densitometric quantification of the protein expression data. The bar graphs show means  $\pm$  SD (standard deviations). Two-way ANOVA with Bonferroni's post-hoc test was used to assess statistical significance.

**(I)** Densitometric quantification of the protein expression data shown in panel F and Appendix Fig.S18B. Repression by ERS in the PP2 condition (average of 4 biological replicates) is shown relative to repression by ERS in vehicle condition. The bar graph shows means  $\pm$  SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean relative repression is statistically different from 100%.

**(J)** RT-qPCR analyses of selected ERS UP and LIVER-ID TF genes monitoring expression changes induced by 4h ERS in MPH pre-treated or not for 30min with 10 $\mu$ M PP2 (3 independent experiments). Mean Log<sub>2</sub> FC ERS/Control are shown. The bar graph shows means  $\pm$  SD (standard deviations). Two-way ANOVA with Bonferroni's post-hoc test was used to assess statistical significance, \*P < 0.05.

**Figure 6. ERS contributes to LIVER-ID gene downregulation and loss of hepatic identity in septic mice.** **(A)** Similar analysis as in Fig.1C using transcriptomic data from the liver of sepsis<sup>BIM</sup> mice (16h after intraperitoneal injection of live *E. coli*).

**(B-C)** Enrichment plots from GSEA performed using LIVER-ID genes (B) or the response to ERS gene set (GO:0034976) (C) as the gene set and transcriptomic differences in sepsis<sup>BIM</sup> vs Control mouse

liver as the ranked gene list.

**(D)** Comparison of the transcriptome of the indicated liver injury models (details are provided in Appendix Fig.S20 and Table EV6) with that of the developing mouse liver performed as described in the Materials and Methods. PC1 is the first principal component which represents 63.55% of the variability within the mouse liver differentiation study. PC1 was used to project the liver injury studies. APAP, Acetaminophen overdose – Model of drug-induced acute liver injury. CCL4, Carbon tetrachloride hepatotoxicity – Model of drug-induced chronic liver injury. MCD-HF, Methionine-choline deficient diet with high fat - Model of NASH/fibrosis.

**(E)** Box plots showing Log<sub>2</sub> FC for ERS UP, DOWN or unchanged genes in sepsis<sup>BIM</sup> vs Control mouse liver (6 mice per group). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-way ANOVA with Welch's correction and Dunnett's Modified Tukey-Kramer pairwise multiple comparison test was used to assess statistical significance, \*P < 0.05.

**(F)** RT-qPCR analyses of selected ERS UP genes and LIVER-ID TFs monitoring expression changes in the liver of sepsis<sup>BIM</sup> vs Control mice (6 mice per group). The bar graph shows means ± SD (standard deviations). One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC sepsis<sup>BIM</sup>/Control is statistically different from 0, \*P < 0.05.

**(G)** Nuclear extracts from livers of control or sepsis<sup>BIM</sup> mice were subjected to Western blot or Simple Western immunoassay with antibodies against HNF4A, NR1H4 or FOXA2. LMNA was used as loading control.

**(H)** Nuclear extracts from livers of sepsis<sup>BIM</sup> mice pre-treated for 4 consecutive days with vehicle or 500 mpk TUDCA were subjected to Western blot with antibodies against HNF4A, NR1H4, FOXA2 or XBP1S. TFIIB was used as loading control. Additional mice are shown in Appendix Fig.S22D.

**(I)** Densitometric quantification of the protein expression data from 6 mice precondition shown in panel (H) (3 mice per condition) and Appendix Fig.S22D (3 additional independent mice per condition). The bar graph shows means ± SD (standard deviations). One-sample t-test with BH

correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC TUDCA/Vehicle is statistically different from 0, \*P < 0.05.

**(J)** Serum alanine aminotransferase (ALT) (*left*) and aspartate aminotransferase (AST) activities (*right*) from sepsis<sup>BIM</sup> mice pre-treated for 4 consecutive days with vehicle or 500 mpk TUDCA (10 mice per group). The bar graphs show means ± SD (standard deviations). Student's t-test was used to assess statistical significance, \*P < 0.05.

**Figure 7. Competitive equilibrium between LIVER-ID and ERS gene expression in injured mouse and human livers.**

**(A)** RT-qPCR analyses of selected ERS UP genes and LIVER-ID TFs in livers from sepsis<sup>CLP</sup> mice collected 10h, 30h or 3 days after CLP (15 mice per group) vs livers from healthy pair-fed mice (Control) (15 mice per group). The bar graph shows means ± SD (standard deviations). Wilcoxon test with BH correction for multiple testing was used to assess statistical significance, \*P < 0.05.

**(B)** Box plots showing Log<sub>2</sub> FC ERS/Control in mouse liver for ERS UP genes 8h and 34h after tunicamycin injection in WT or ATF6 KO mice (3 mice per experimental condition). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC ERS/Control is statistically different from 0, \*P < 0.05. NS, not significant.

**(C)** Similar analyses to panel (B) for ERS DOWN and LIVER-ID genes (3 mice per experimental condition). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC ERS/Control is statistically different from 0, \*P < 0.05.

**(D)** Main observations from (Huck et al., 2019) (*left*) and box plots showing Log<sub>2</sub> FC HNF4A KO/Control in mouse liver (3 mice per group) for LIVER-ID genes and TFs 5 days after PHx (*right*). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-sample t-test with BH correction for multiple testing was used to determine if the mean Log<sub>2</sub> FC HNF4A KO/Control is statistically different from 0, \*P < 0.05.

(E) Correlations of gene expressions within the critically-ill group were used to organize the analyzed genes as a network. Green bars indicate a positive correlation while red bars indicate a negative correlation. The color intensity is proportional to the correlation coefficient. The position of the genes is determined by both the directions and values of the correlation coefficients.

(F) Expression of LIVER-ID TF encoding genes from Appendix Fig.S23A was analyzed in the livers of deceased critically-ill patients with sepsis displaying agonal bilirubin levels below ( $\text{Bil} < 2$ ;  $n=34$ ) or above ( $\text{Bil} > 2$ ;  $n=28$ )  $2\text{mg/dL}$ . Median fold-change expression level of each group for the different genes has been used to generate the box plots. Expression levels in the critically-ill groups are expressed relative to those in the control group ( $n=18$ ). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. One-tailed t-test was used to assess whether expression of LIVER-ID TF encoding genes in the  $\text{Bil} > 2$  group is significantly greater than in the  $\text{Bil} < 2$  group,  $*P < 0.05$ .

(G) RT-qPCR analyses of indicated LIVER-ID TF encoding genes monitoring expression in the livers of  $\text{Bil} < 2$  ( $n=34$ ) or  $\text{Bil} > 2$  ( $n=28$ ) groups of deceased critically-ill patients with sepsis vs control donors ( $n=18$ ). Data are shown as box plots, with mRNA levels of the critically-ill groups expressed relative to those of the control group. Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. Wilcoxon test was used to assess statistically significant differences with the  $\text{Bil} > 2$  group,  $*P < 0.05$ .

(H) RT-qPCR analyses of indicated ERS UP genes performed and analyzed as in panel (G). Box plots are composed of a box from the 25th to the 75th percentile with the median as a line and min to max as whiskers. Wilcoxon test was used to assess statistically significant differences with the  $\text{Bil} > 2$  group,  $*P < 0.05$ .

**Figure 8. Summary of the molecular mechanisms involved in ERS-induced loss of hepatic molecular identity and implications for liver pathophysiology.**

(A) Model for ERS-mediated loss of hepatic identity. Initial loss in LIVER-ID TF activities involves reduced protein levels linked to PERK and SRC signaling ①, which is secondarily amplified by

decommissioning of BRD4 SE ② and impaired feedback loops within the LIVER-ID TF hepatic network ③. This consequently leads to loss of hepatic molecular identity and partial dedifferentiation of hepatocytes ③. Induction of NFIL3 operates as an additional mechanism further contributing to active repression of the LIVER-ID TF network target genes, especially those involved in xenobiotic metabolism.

**(B)** Implications of the competitive equilibrium between the hepatic and ERS transcriptional programs in liver pathophysiology. Please also refer to the discussion.



Figure 1

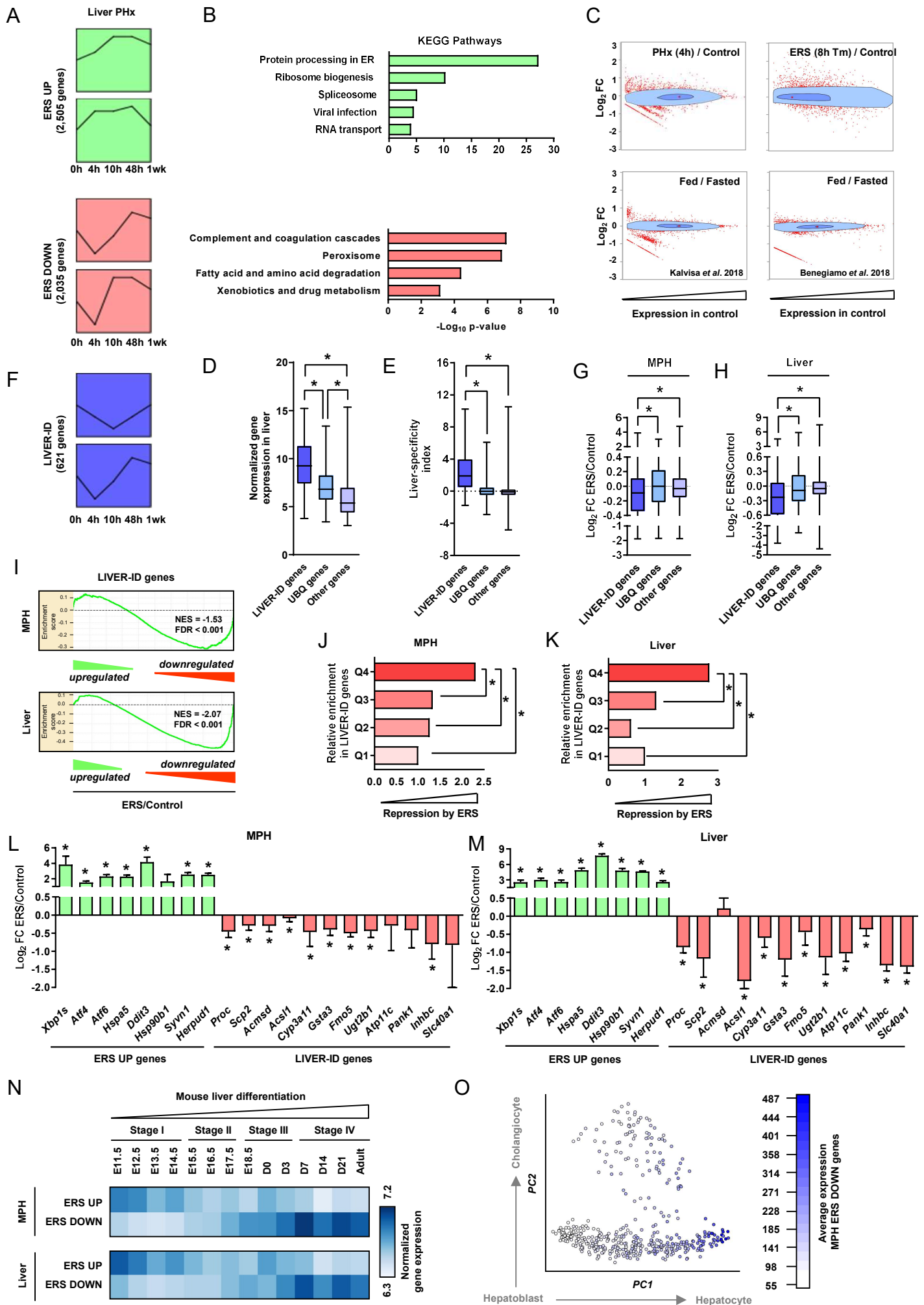


Figure 2

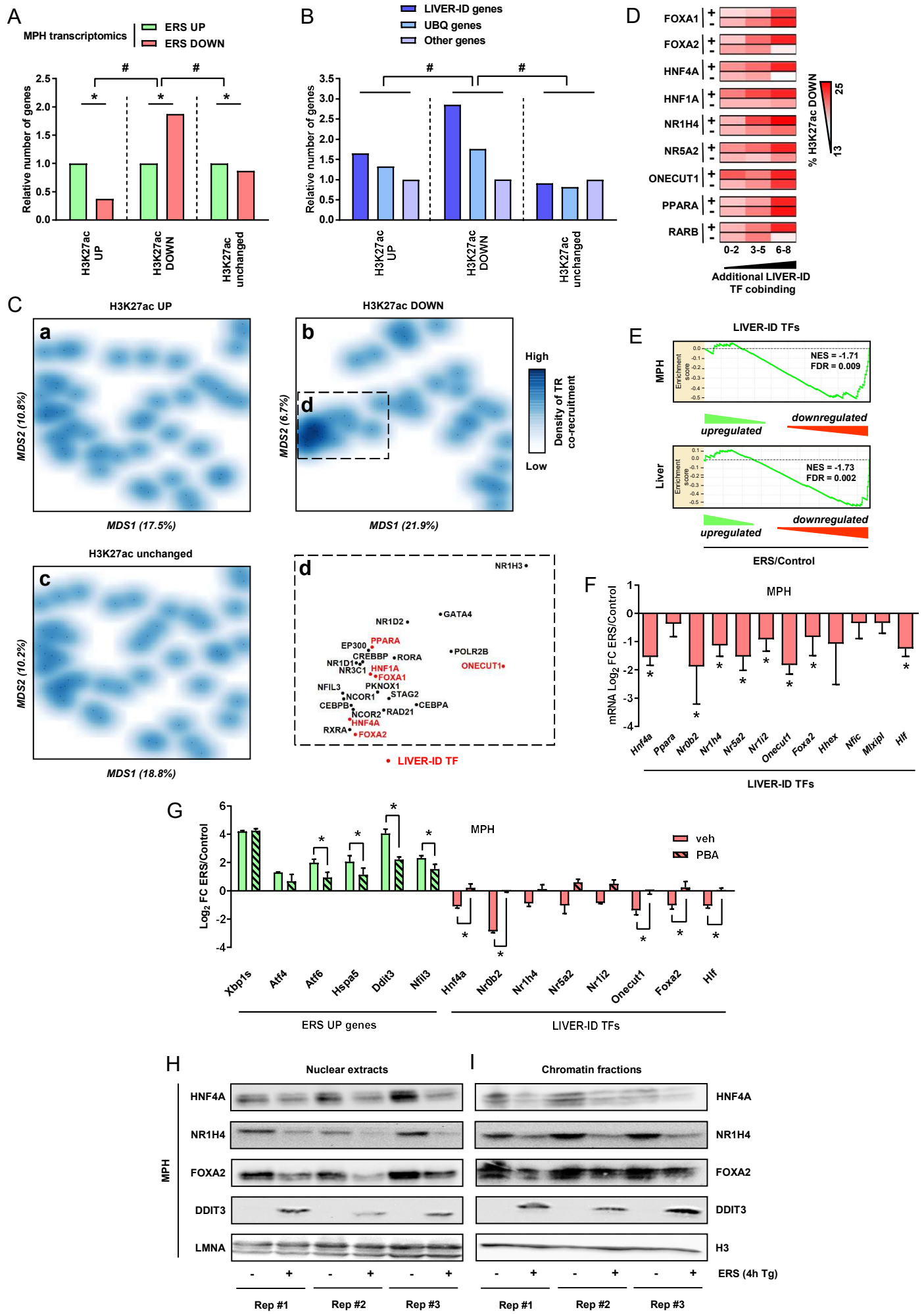


Figure 3

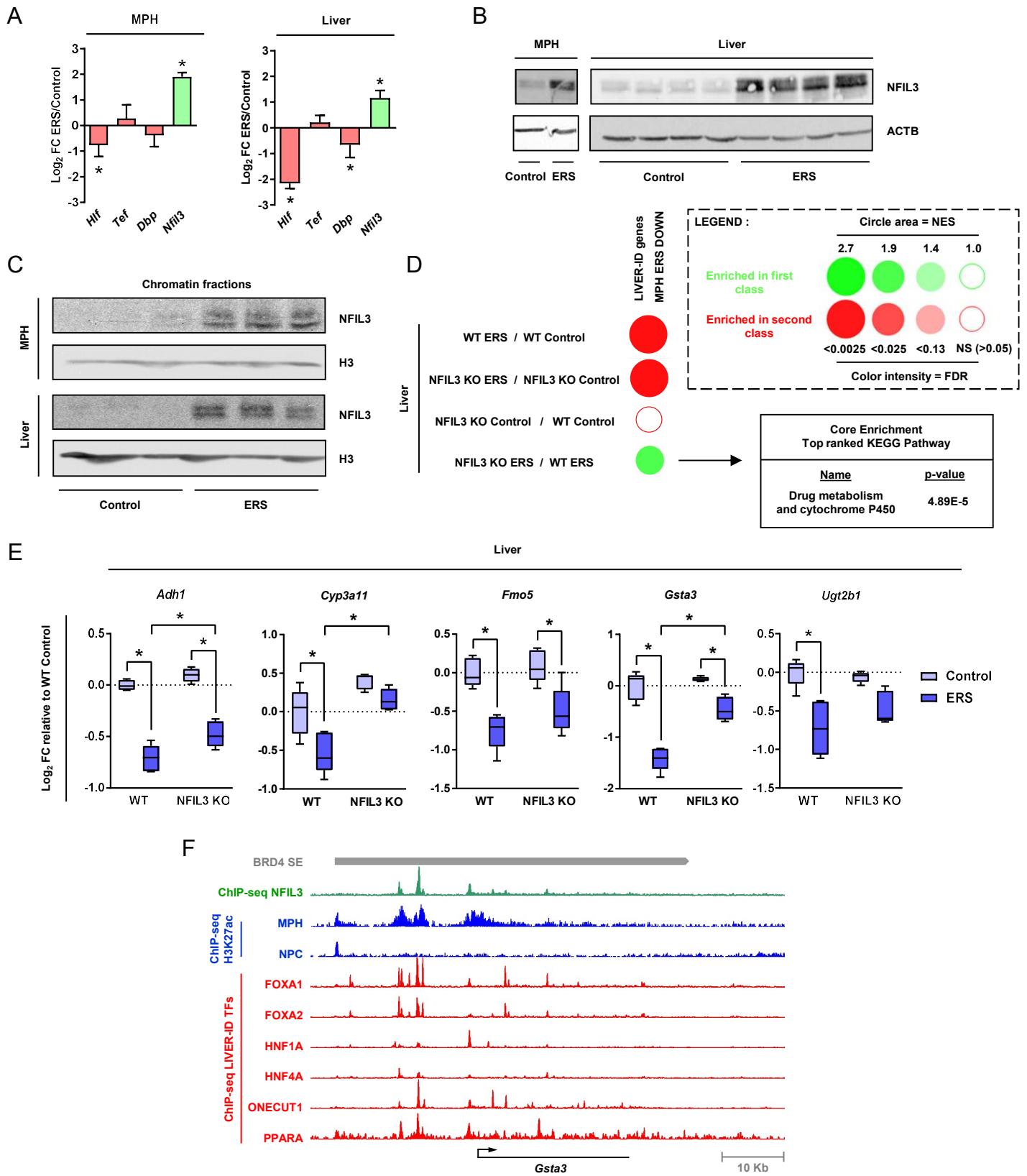
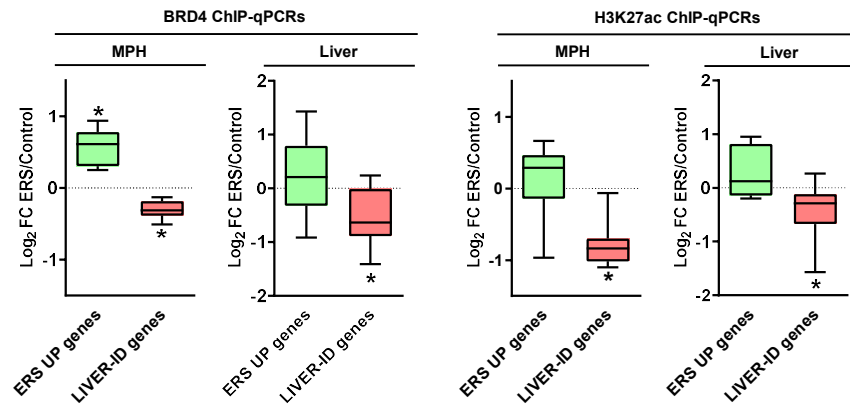
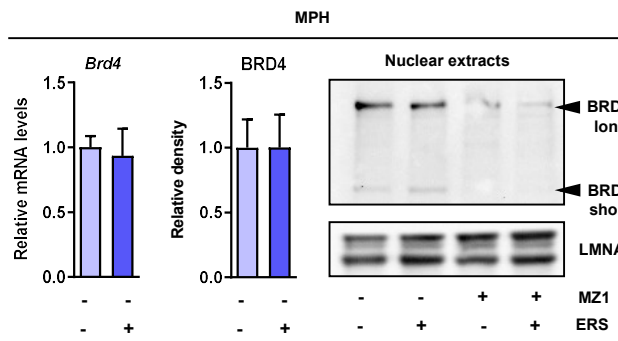


Figure 4

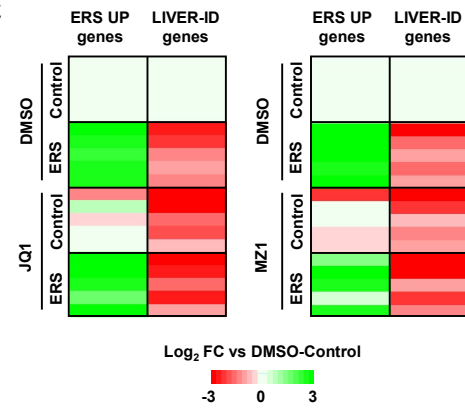
A



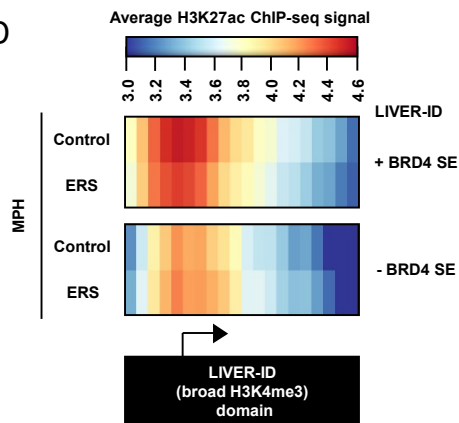
B



C



D



E

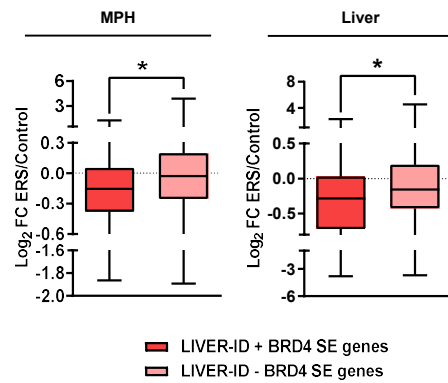


Figure 5

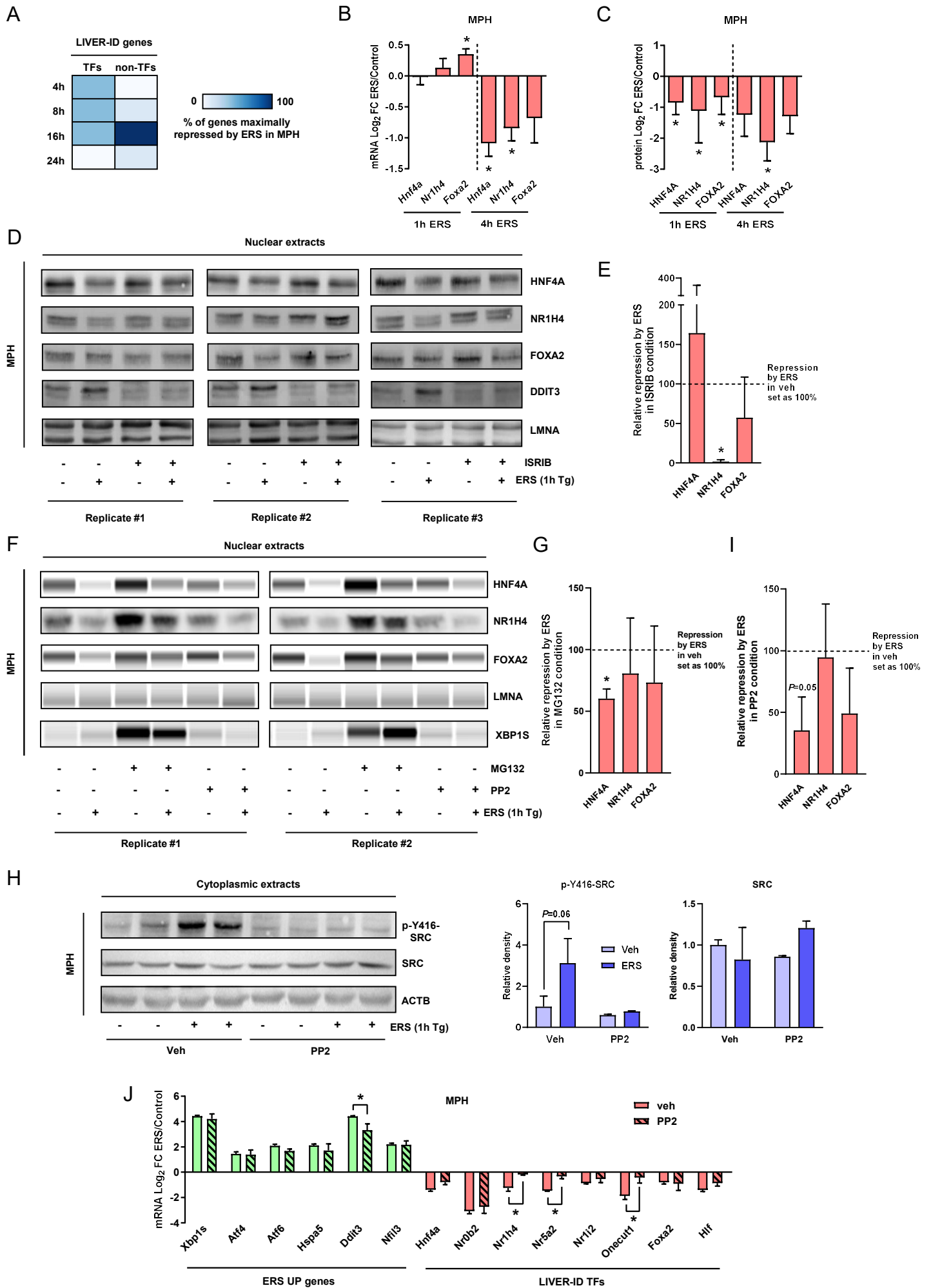


Figure 6

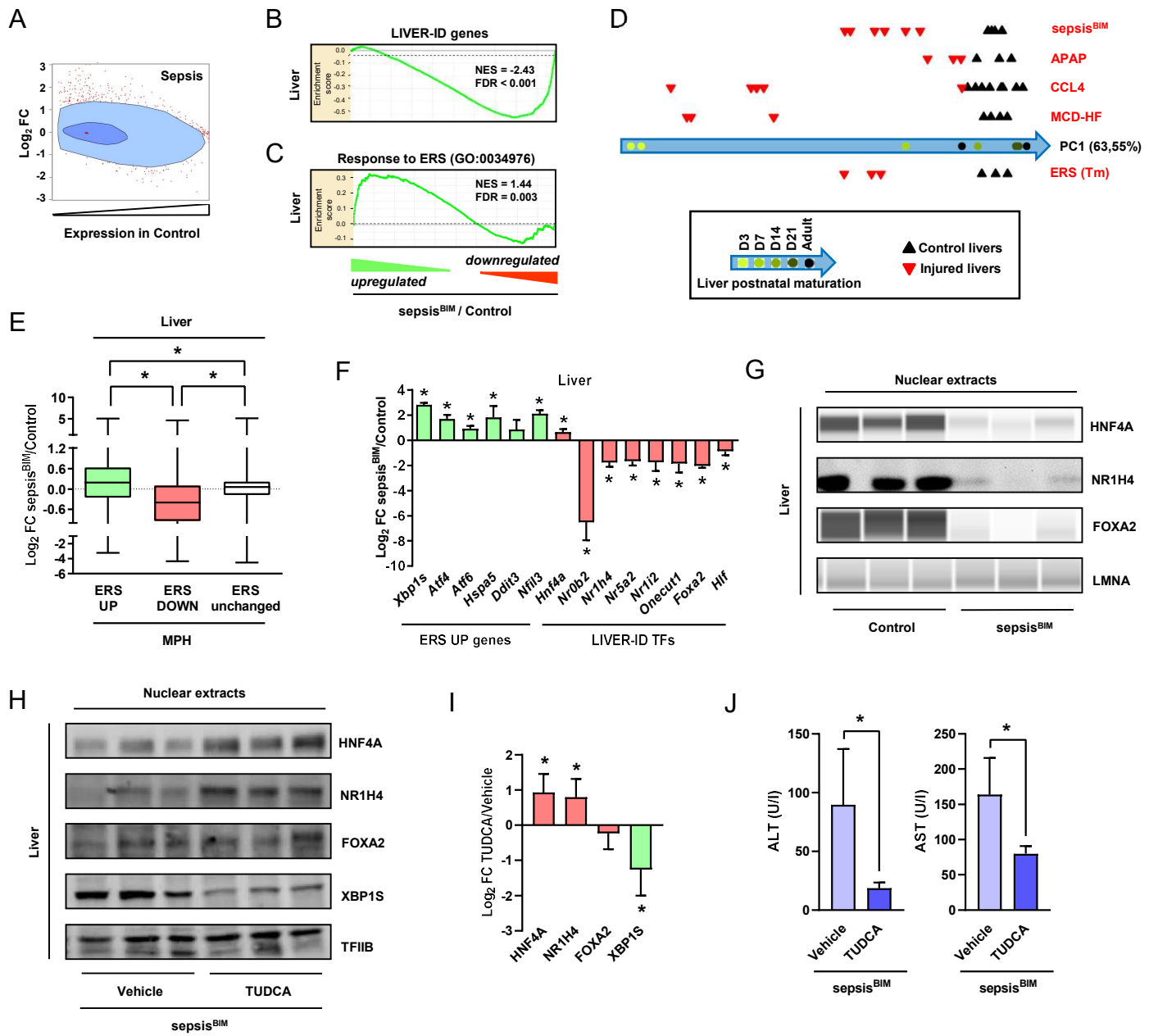


Figure 7

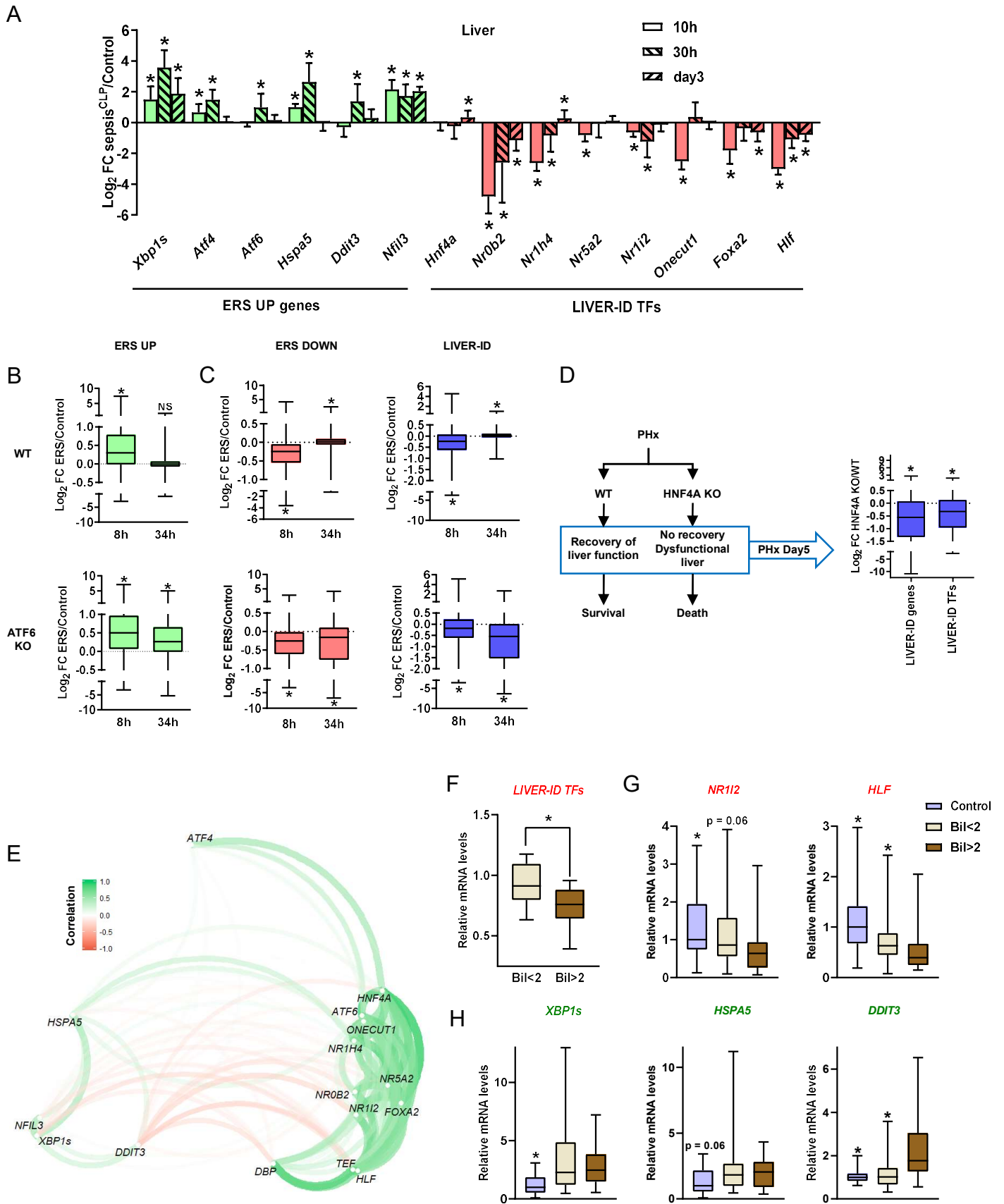
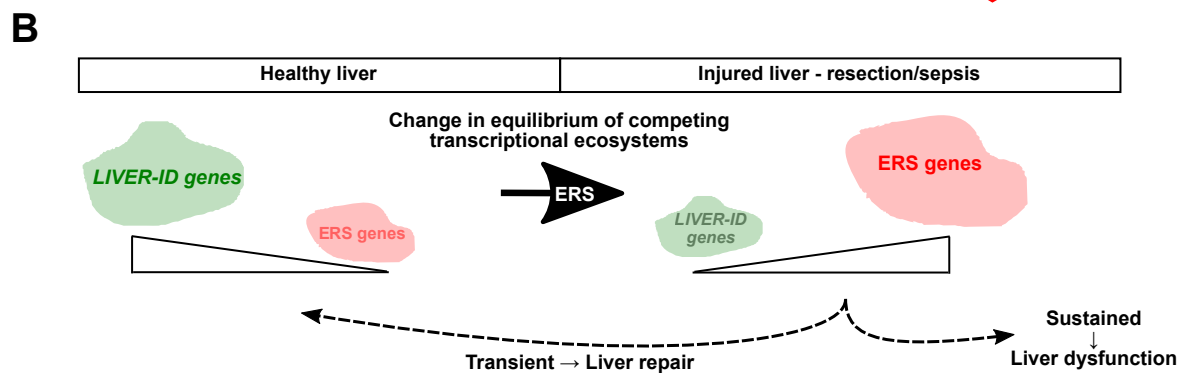
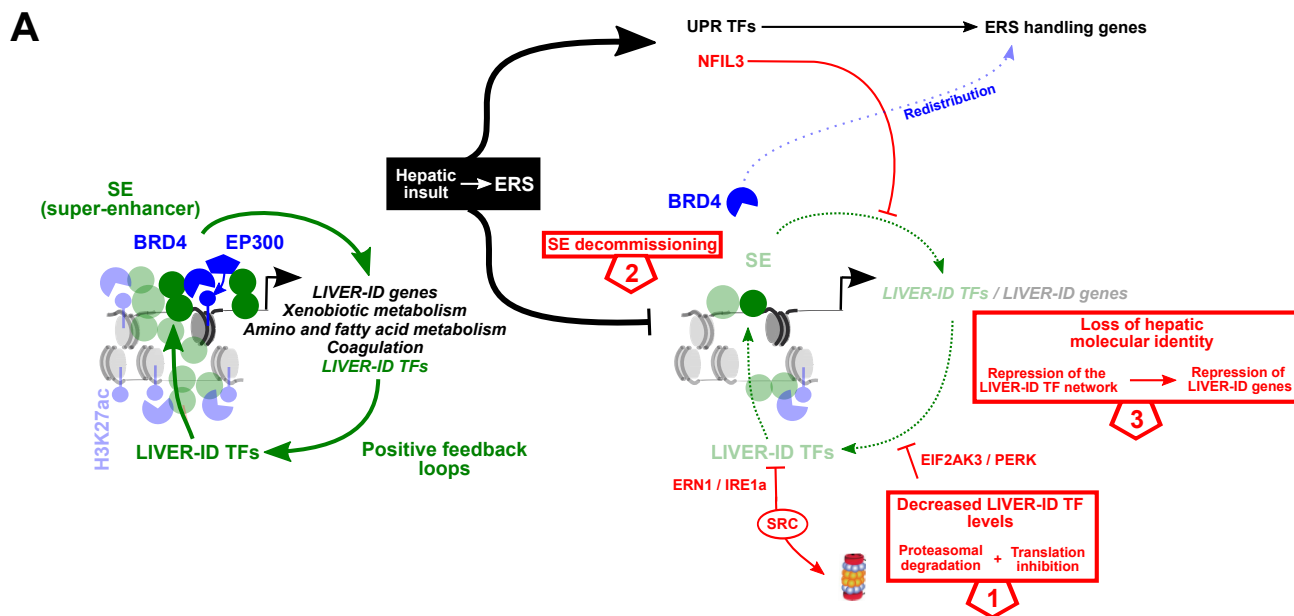


Figure 8





**Table EV1**

This table provides the list of LIVER-ID and UBQ genes.

LIVER-ID genes identified as LIVER-ID TFs and linked to BRD4 SE are indicated.

## BLUE CLUSTER

Kmt2b.EXP032360.immortalized\_brown\_preadipocytes..bed  
Smad3.EXP000858.38B9\_cells.TGF.bed  
Gata3.EXP000796.CD8\_Gata3\_KO.NULL.bed  
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Rarb.EXP032486.Liver.RA-treatment.bed  
Nr1d2.EXP031402.liver.time\_5amZT22.bed  
Ncor2.EXP032387.liver.ZT10.bed  
Rxra.EXP032521.RMKO\_314..bed  
Ar.EXP032777.caput\_epididymis.specifcicity\_affecting\_androgen\_receptor\_knock-in.bed  
Rxra.EXP032518.RFKO\_232..bed  
Ncor2.EXP032388.liver.ZT22.bed  
Nr1d1.EXP031403.liver.Rev-erb\_alpha\_KO.bed  
Trp53.EXP030949.embryonic\_stem\_ES\_cells.untreated.bed  
Cebpb.EXP031832.C57BL6J.3\_hours\_after\_partial\_hepatectomy.bed  
Rxra.EXP032520.RMKO\_225..bed  
Rxra.EXP032519.RFKO\_233..bed  
Rxra.EXP032524.RMWT\_315..bed  
Rxra.EXP032522.RFWT\_234..bed  
Hnf4a.EXP032824.colonic\_epithelial\_cells.3%\_DSS.bed  
Hnf4a.EXP031181.Mouse\_villus..bed  
Rxra.EXP032525.RMWT\_227..bed  
Ar.EXP032172.caput\_epididymis.castratedplusvehicle.bed  
Egr1.EXP031839.C57BL6J.36\_hours\_after\_partial\_hepatectomy.bed  
Rxra.EXP032523.RFWT\_235..bed  
Stat5a.EXP032418.mammary.Ezh2\_KO.bed  
Ar.EXP032175.prostate.castratedplusvehicle.bed  
Esr1.EXP030621.Liver..bed  
Nfe2.EXP031818.primary\_megakaryocytes..bed  
Trp53.EXP030950.embryonic\_stem\_ES\_cells.adriamycin.bed  
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Ar.EXP030588.Mouse\_Prostate\_Pten-ff\_R26-ERGERG..bed  
Ar.EXP030590.Mouse\_Prostate\_Pten-ff..bed  
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Nr1d2.EXP031401.liver.time\_5pmZT10.bed  
Esrra.EXP031907.liver..bed  
Kmt2b.EXP030685.mouse\_brown\_preadipocytes\_WT\_CEBPbeta\_GFP\_MLL4\_ChIP..bed  
Rxra.EXP032487.Liver.RA-treatment.bed  
Esr1.EXP032821.liver.10\_nM\_beta-estradiol\_E2.bed  
Esr1.EXP031407.uterus.vehicle.bed  
Hnf4a.EXP031182.Mouse\_villus\_Cdx2\_KO..bed  
Cebpb.EXP032041.liver.dex.bed  
Cebpb.EXP031992.mouse\_whole\_liver.Ad-lib\_fed.bed  
Cux2.EXP031264.CD-1\_Charles\_River\_female..bed  
Pparg.EXP032204.3T3-L1.adeno-LACZ.bed  
Ppara.EXP031218.liver.Control.bed  
Esr1.EXP032062.mouse\_mammary\_cells\_express\_GFP-GR\_Cherry-ER\_and\_Afos\_uni  
Elf5.EXP031810.Trophoblast\_stem\_cells..bed

Rxra.EXP032484.Liver..bed  
Cebpa.EXP031829.C57BL6J.48\_hours\_after\_partial\_hepatectomy.bed  
Rxra.EXP032105.liver..bed  
Stat5b.EXP030769.Mammary\_tissues.stat5a-null.bed  
Rela.EXP032922.C57BL6.LPS.bed  
Cebpa.EXP031830.C57BL6J.168\_hours\_after\_partial\_hepatectomy.bed  
Pparg.EXP000533.thioglycollate-elicited\_peritoneal\_macrophages.NULL.bed  
Cebpa.EXP031828.C57BL6J.36\_hours\_after\_partial\_hepatectomy.bed  
Stat5a.EXP000123.CD-1\_FL.NULL.bed  
Cebpa.EXP031826.C57BL6J.16\_hours\_after\_partial\_hepatectomy.bed  
Esr2.EXP032820.aorta.10\_nM\_beta-estradiol\_E2.bed  
Stat5a.EXP032237.mammary\_gland.day\_6\_of\_pregnancy.bed  
Cebpa.EXP031824.C57BL6J.3\_hours\_after\_partial\_hepatectomy.bed  
Cebpb.EXP032037.liver.dex\_adDN-CEBP.bed  
Nr1d1.EXP000373.liver.ZT10.bed  
Cebpb.EXP031838.C57BL6J.168\_hours\_after\_partial\_hepatectomy.bed  
Cebpb.EXP031834.C57BL6J.16\_hours\_after\_partial\_hepatectomy.bed  
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Ar.EXP032778.ventral\_prostate..bed  
Foxa1.EXP031141.CD1\_outbred\_mice..bed  
Stat5a.EXP000121.CD-1\_FH.NULL.bed  
Cebpb.EXP031831.C57BL6J.0\_hours\_after\_partial\_hepatectomy.bed  
Cebpa.EXP030885.liver\_hepatocytes..bed  
Cebpb.EXP031835.C57BL6J.24\_hours\_after\_partial\_hepatectomy.bed  
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Stat5a.EXP000120.CD-1\_MH.NULL.bed  
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Cebpb.EXP031833.C57BL6J.8\_hours\_after\_partial\_hepatectomy.bed  
TCF7L1\_M-20.EXP000273.3T3-L1.24\_hours\_of\_adipogenic\_stimuli.bed  
Foxa2.EXP030886.liver\_hepatocytes..bed  
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Ppara.EXP031219.LXRdKO\_liver.Control.bed  
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Cebpb.EXP032039.liver.veh.bed  
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## GREEN CLUSTER

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Sp1.EXP031619.F1\_CB\_trophoblast\_stem\_cells..bed  
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Runx1.EXP031139.primary\_thymocyte..bed  
Utf1.EXP030689.mouse\_embryonic\_stem\_cells.Standard\_Serum.bed  
Sp1.EXP032826.Flkplus\_cKitplus\_progenitor..bed  
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Tcf7l2.EXP031214.Hepatocytes\_isolated\_from\_adult\_liver..bed  
Creb1.EXP031994.mouse\_whole\_liver.Fasted\_24h\_Re-fed\_2h.bed  
Klf5.EXP032750.CGR8.KLF5\_overexpression.bed  
Rabbit\_anti-C-terminal\_Ikaros\_[from\_Stephen\_Smale\_Lab].EXP031844.primary\_pre-B\_Spi1.EXP031071.Fetal\_liver\_precursor\_derived\_DN1..bed  
Ctcf.EXP031030.Mouse\_spleen..bed  
Pparg.EXP031795.C3H10T12\_cells..bed  
Pou5f1.EXP032977.epiblast\_like\_cells\_EpiLC..bed  
Foxa2.EXP030604.postnatal\_day\_12\_female\_mouse\_uterus..bed  
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Ctcf.EXP032691.HPC7..bed

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Srf.EXP030897.HL-1\_cardiac\_muscle\_cell\_line..bed  
Runx2.EXP032846.mineralizing\_osteoblast..bed  
Kmt2b.EXP032320.immortalized\_brown\_preadipocytes.D7\_of\_adipogenesis\_MLL4\_KC  
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Creb1.EXP031993.mouse\_whole\_liver.Fasted\_24h.bed  
Erg.EXP030591.Mouse\_Prostate\_Pten-ff..bed  
Kmt2b.EXP032319.immortalized\_brown\_preadipocytes.D2\_of\_adipogenesis\_MLL4\_KC  
Gata2.EXP030541.Mast\_cell..bed  
Pou5f1.EXP031169.CMTi-1..bed  
Gata2.EXP032697.primary\_mast\_cells..bed  
Zfp143.EXP030478.MEF-like..bed  
Spi1.EXP000855.38B9\_cells.NULL.bed  
Klf5.EXP032748.CGR8..bed  
Runx2.EXP032844.preosteoblast..bed  
Pou5f1.EXP031878.ESC..bed  
Vdr.EXP032793.MC3T3-E1.ethanol\_vehicle.bed  
Rara.EXP032482.Liver..bed  
Rara.EXP032106.liver..bed  
Spi1.EXP031073.Fetal\_liver\_precursor\_derived\_DN2b..bed  
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Runx2.EXP032845.matrix-depositing\_osteoblast..bed  
Tbx5.EXP030898.HL-1\_cardiac\_muscle\_cell\_line..bed  
Prdm5.EXP032409.mouse\_embryonic\_fibroblast..bed  
T.EXP032929.D3..bed  
Myog.EXP010576.C2C12.EqS\_2\_0pct\_24hr.bed  
Foxo1.EXP000864.pro-B\_cell.RAG1\_KO.bed  
Zfp143.EXP030477.mESC\_J1..bed  
Ctcf.EXP010117.G1E-ER4.diffProtD\_24hr.bed  
Tfap2a.EXP032171.kidney.castratedplustestosterone.bed  
Pparg.EXP030874.3T3-L1\_adipocytes.0\_1%\_DMSO\_Vehicle\_for\_1\_hour.bed  
Tcf3.EXP032692.HPC7..bed  
Tfap2a.EXP032181.caput\_epididymis.castratedplusvehicle.bed  
Spi1.EXP032476.Pro-B\_cell..bed  
Runx2.EXP032591.MC3T3-E1.ethanol\_vehicle.bed  
Ptf1a.EXP030597.Neural\_Tube..bed  
Spi1.EXP031072.Fetal\_liver\_precursor\_derived\_DN2a..bed  
Pou5f1.EXP030812.Embryonic\_stem\_cells..bed  
TCF3.EXP030868.Telogen\_quiescent\_hair\_follicle\_stem\_cells\_HFSCs..bed  
Tet1.EXP000591.embryonic\_stem\_cells.NULL.bed  
Nanog.EXP031877.ESC..bed  
Smad3.EXP000850.MC1R20tetMyod114\_embryonic\_stem\_cells.Activin\_-Myod1\_day\_2  
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Spi1.EXP032699.primary\_mast\_cells..bed



Pou5f1.EXP032976.epiblast\_like\_cells\_EpiLC.Activin\_A.bed  
Irf8.EXP032458.dendritic\_cells..bed  
Sox9.EXP032505.hair\_follicle\_stem\_cells\_HFSCs..bed  
ikaros.EXP032480.Pre-pro-B\_cell..bed  
anti-Otx2.EXP032979.epiblast\_like\_cells\_EpiLC..bed  
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Clock.EXP032489.Liver..bed  
Irf8.EXP032460.dendritic\_cells..bed  
Tfap2a.EXP032182.caput\_epididymis.intact.bed  
Myog.EXP031958.C2C12..bed  
Nfib.EXP031855.Hair\_follicle\_stem\_cells\_HfSCs..bed  
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Esr1.EXP032992.uterine\_cells.saline\_vehicle.bed  
GFP\_Abcam\_Cambridge\_UK.EXP032498.Neural\_Retina..bed  
Ascl2.EXP032453.CD4plus\_T\_cells.Ascl2\_vector\_transfected.bed  
Spi1.EXP032329.FDCPmix..bed  
Spi1.EXP032255.Macrophage.DMSO\_7h\_Kdo2\_Lipid\_A\_KLA\_6h.bed  
Pou5f1.EXP00018.ESC.NULL.bed  
Tbx3.EXP031208.heart..bed  
Fli1.EXP031691.hemogenic\_endothelium.dox.bed  
Ctcf.EXP031037.Mouse\_intestine..bed  
Spi1.EXP031529.bone\_marrow-derived\_macrophages\_7th\_day\_of\_differentiation.IFN $\gamma$ .bed  
Pax5.EXP030466.mix\_C57BL6\_and\_129..bed  
Myog.EXP010707.C2C12.EqS\_2\_0pct\_60hr.bed  
anti-Otx2.EXP032983.embryonic\_stem\_cells\_ESC.Dox.bed  
Runx2.EXP032798.MC3T3-E1.100nM\_125OH2D3.bed  
Spi1.EXP032326.FDCPmix..bed  
Jarid2.EXP000184.Embryonic\_stem\_cells.NULL.bed  
Erg.EXP030593.Mouse\_Prostate..bed  
Spi1.EXP031526.bone\_marrow-derived\_macrophages\_7th\_day\_of\_differentiation..bed  
Spi1.EXP032242.Macrophage.none.bed  
Foxa2.EXP030601.Pancreas..bed  
Spi1.EXP032096.resting\_mature\_peripheral\_primary\_B\_cells.stimulated\_for\_3\_days.be  
Ctcf.EXP000677.Embryonic\_stem\_cells.Dnmt13a3b\_KO.bed  
Spi1.EXP031518.bone\_marrow-derived\_macrophages\_7th\_day\_of\_differentiation.stat1  
Ctcf.EXP031621.F1\_CB\_trophoblast\_stem\_cells..bed  
Pparg.EXP030875.3T3-L1\_adipocytes.1\_M\_rosiglitazone\_\_0\_1%\_DMSO\_for\_1\_hour.b  
Cebpa.EXP030872.3T3-L1\_adipocytes.0\_1%\_DMSO\_Vehicle\_for\_1\_hour.bed  
Vdr.EXP032794.MC3T3-E1.100nM\_125OH2D3.bed  
Prdm5.EXP032410.mouse\_embryonic\_fibroblast..bed  
Kmt2b.EXP032358.immortalized\_brown\_preadipocytes..bed  
Spi1.EXP032331.FDCPmix..bed  
T.EXP032913.D3..bed  
anti-Klf4.EXP032729.mESC\_J1..bed  
Tfap2c.EXP032396.ZHBTc4-TS\_cells..bed  
Myod1.EXP031190.P19\_cells..bed  
Utf1.EXP031631.Embryonic\_Stem\_Cell..bed  
Nkx2-5\_N-19.EXP031210.heart..bed  
Rara.EXP032485.Liver.RA-treatment.bed

Tcf3.EXP000868.double-positive\_T\_cell.NULL.bed  
anti-Otx2.EXP032978.epiblast\_like\_cells\_EpiLC.Activin\_A.bed  
Spi1.EXP031538.BMDM\_cells\_7th\_day\_of\_differentiation..bed  
Fli1.EXP000332.Early\_haematopoietic\_cell\_line\_derived\_from\_ES\_cells.NULL.bed  
Spi1.EXP000841.bone\_marrow-derived\_macrophages.LXRD\_KO.bed  
Tcf3.EXP000866.pre-pro-B\_cell.E2A\_KO\_1h.bed  
Meis1.EXP031130.P19\_6.all-trans\_retinoic\_acid\_RA.bed  
Spi1.EXP032095.resting\_mature\_peripheral\_primary\_B\_cells.stimulated\_for\_1\_day.bec  
Ncoa2.EXP032905.Prostate..bed  
sox2.EXP032894.D3\_Embryonic\_Stem\_Cells..bed  
Ctcf.EXP010450.CH12.None.bed  
Erg.EXP030589.Mouse\_Prostate\_Pten-ff\_R26-ERGERG..bed  
Ctcf.EXP010468.Lung.NULL.bed  
Ctcf.EXP031032.Bruce4\_embryonic\_stem\_cells..bed  
Pax5.EXP030464.C57BL6..bed  
Ctcf.EXP031029.Mouse\_lung..bed  
Srebf1.EXP032718.C57BL6.ZT18.bed  
Erg.EXP030587.Mouse\_Prostate\_R26-ERGERG..bed  
Kmt2b.EXP032317.immortalized\_brown\_preadipocytes.D7\_of\_adipogenesis.bed  
Tbx3.EXP031951.Mouse\_embryonic\_stem\_cells..bed  
anti-Klf4.EXP032727.mESC\_J1..bed  
Tfcp2l1.EXP000480.Embryonic\_stem\_cells.NULL.bed  
Ctcf.EXP010091.Heart.NULL.bed  
Ctcf.EXP010284.Kidney.NULL.bed  
Nanog.EXP031954.Mouse\_embryoid\_bodies..bed  
Ctcf.EXP031023.Mouse\_cortex..bed  
Ctcf.EXP010181.Liver.NULL.bed  
Ctcf.EXP031026.Mouse\_heart..bed  
Ctcf.EXP031028.Mouse\_liver..bed  
Ctcf.EXP010301.Cortex.NULL.bed  
Ascl1\_Abcam\_ab74065\_lot\_830280.EXP032187.Primary\_adult\_neural\_progenitor\_cell.  
Clock.EXP032488.Liver..bed  
Ctcf.EXP031027.Mouse\_kidney..bed  
Ctcf.EXP010612.MEF.NULL.bed  
Spi1.EXP000535.thioglycollate-elicited\_peritoneal\_macrophages.NULL.bed  
anti-Otx2.EXP032981.embryonic\_stem\_cells\_ESC..bed  
Gata2.EXP031715.Mouse\_uterus.P4.bed  
Cebpa.EXP030873.3T3-L1\_adipocytes.1\_M\_rosiglitazone\_\_0\_1%\_DMSO\_for\_1\_hour.t  
Ctcf.EXP031031.Mouse\_embryonic\_fibroblast..bed  
Tbx3.EXP031952.Mouse\_embryoid\_bodies..bed  
Rxra.EXP032802.MC3T3-E1\_differentiated\_for\_15\_days.100nM\_125OH2D3.bed  
Tcf3.EXP000867.pre-pro-B\_cell.E2A\_KO\_6h.bed  
Nanog.EXP031953.Mouse\_embryonic\_stem\_cells..bed  
ZNF384\_HPA004051.EXP011017.ES-E14.None.bed  
Rxra.EXP000681.F9\_embryonal\_carcinoma\_cells.6hr\_ATRA.bed  
Ebf1.EXP031258.Bone\_Marrow..bed  
Spi1.EXP031560.Myeloid\_progenitor\_cells.MSCV-IRF8\_transduced.bed  
Tal1.EXP000085.Lin-\_bone\_marrow\_hematopoietic\_progenitor\_cells.NULL.bed  
Tfap2a.EXP032167.prostate.castratedplustestosterone.bed  
Cebpb.EXP032347.immortalized\_brown\_preadipocytes..bed

Foxa2.EXP030605.day\_of\_pseudopregnancy\_2\_5\_and\_3\_5\_female\_mouse\_uterus..be  
Gata1.EXP031251.G1ME..bed  
Ebf1.EXP000188.A-MuLV\_pre\_B-cells.NULL.bed  
Ebf1.EXP032475.Pro-B\_cell..bed  
Ascl1\_ab74065.EXP030573.C57BL6\_embryonic\_fibroblasts.BAM\_factors.bed  
Anti-HA.EXP031689.differentiating\_murine\_hematopoietic\_cells.dox.bed  
Rbpjl.EXP030600.Pancreas..bed  
Smad3.EXP000852.MC1R20tetMyod114\_embryonic\_stem\_cells.-Myod1\_day\_5.bed  
GFP\_Abcam\_Cambridge\_UK.EXP032496.RPE..bed  
Pparg.EXP030809.Brown\_Adipose\_Tissue..bed  
Olig2.EXP001006.Ainv15\_ATCC\_SCRC-1029\_with\_inducible\_V5-tagged\_Olig2.plusDo:  
Nkx3-1.EXP031261.Recombinant\_inbred\_B6\_x\_129\_Nkx3-1\_plus-..bed  
Esr2.EXP032993.uterine\_cells.estradiol\_250\_ngmouse.bed  
Rxxa.EXP032801.MC3T3-E1\_differentiated\_for\_15\_days.ethanol\_vehicle.bed  
Ascl1\_ab74065.EXP030566.C57BL6\_neural\_progenitor.Ascl1.bed  
Tal1.EXP031693.differentiating\_murine\_hematopoietic\_cells..bed  
Atoh1.EXP000331.4\_P5\_cerebella\_pooled.NULL.bed  
Ar.EXP032779.ventral\_prostate.specifcicity\_affecting\_androgen\_receptor\_knock-in.bed  
Pparg.EXP030810.Epididymal\_White\_Adipose\_Tissue..bed  
Esr1.EXP031408.uterus.estradiol.bed  
Foxo3-NFL\_Brunet\_Lab\_Greer\_et\_al\_\_2007\_Pmid\_17900900.EXP032188.Primary\_ad  
Gata1.EXP011011.MEL.DMSO\_2\_0pct.bed  
Sox2.EXP031239.embryonic\_stem\_cells\_ESCs..bed  
Cebpa.EXP030889.differentiated\_3T3-L1\_cells..bed  
Arntl.EXP032491.Liver..bed  
Rxxa.EXP000679.F9\_embryonal\_carcinoma\_cells.48hr\_ethanol.bed  
Myod1.EXP000856.C2C12\_cells.NULL.bed  
Rxxa.EXP000682.F9\_embryonal\_carcinoma\_cells.24hr\_ATHA.bed  
Rxxa.EXP000683.F9\_embryonal\_carcinoma\_cells.48hr\_ATHA.bed  
Atf2.EXP033004.3T3-L1..bed  
FLAG\_and\_HA.EXP000359.mESCs.NULL.bed  
Kmt2b.EXP032359.MyoD-induced\_immortalized\_brown\_preadipocytes..bed  
Pparg.EXP000491.3T3L1\_cells.Day\_0\_of\_differentiation.bed  
Sox2\_raised\_by\_ourselves.EXP032395.ZHBTc4-TS\_cells..bed  
Arntl.EXP032490.Liver..bed  
Tbx20.EXP000266.adult\_whole\_heart.NULL.bed  
Trp53.EXP030952.embryonic\_stem\_ES\_cells.adriamycin.bed  
custom\_made\_against\_Esrrb.EXP000485.Embryonic\_stem\_cells.NULL.bed  
PR.EXP031193.uterus.oil.bed  
Srebf1.EXP032719.C57BL6.ZT22.bed  
Nr5a2.EXP000179.embryonic\_stem\_cells.NULL.bed  
Trp53.EXP032070.mouse\_embryo\_fibroblast\_MEF.0\_2ugml\_doxorubicin\_for\_6h.bed  
anti-Ascl1.EXP032949.ICR..bed  
Hnf4a.EXP032823.colonic\_epithelial\_cells.water\_only.bed  
Esr1.EXP031898.mammary\_gland..bed  
Pparg.EXP000494.3T3L1\_cells.Day\_3\_of\_differentiation.bed

## PURPLE CLUSTER

Cebpb.EXP032901.BV2..bed  
Gata1.EXP031087.Megakaryocyte\_Progenitor\_Cell\_Line\_G1ME..bed  
Nkx3-1.EXP031262.Recombinant\_inbred\_B6\_x\_129..bed  
Nkx2-1.EXP031891.mixed\_129B6..bed  
Hsf1.EXP031482.striatal\_cells\_derived\_from\_wild\_type\_HdhQ7Q7\_embryonic\_mice.ce  
Kmt2b.EXP032316.immortalized\_brown\_preadipocytes.D2\_of\_adipogenesis.bed  
Cebpb.EXP010773.C2C12.EqS\_2\_0pct\_60hr.bed  
Nkx2-1.EXP031892.mixed\_129B6..bed  
Pparg.EXP000041.3T3-L1\_adipocytes.NULL.bed  
Cdx2.EXP032548.ESC\_Ainv15\_ATCC\_SCRC-1029.plusDox\_plusFGF.bed  
Rela.EXP030425.primary\_bone\_marrow-derived\_macrophages.Dexamethasone\_treat  
Myod1.EXP032355.MyoD-induced\_immortalized\_brown\_preadipocytes..bed  
Spi1.EXP032895.BV2..bed  
Myog.EXP010753.C2C12.EqS\_2\_0pct\_7d.bed  
Pbx1.EXP033034.3T3-L1..bed  
Neurod1.EXP000434.hand-picked\_pancreatic\_islets.NULL.bed  
Klf5.EXP033033.3T3-L1..bed  
Cebpa.EXP032345.immortalized\_brown\_preadipocytes..bed  
Myod1.EXP010557.C2C12.None.bed  
Pparg.EXP032349.immortalized\_brown\_preadipocytes..bed  
Cebpb.EXP010962.C2C12.None.bed  
Cebpa.EXP030545.Haematopoietic\_progenitor\_cells..bed  
anti-KLF4.EXP033032.3T3-L1..bed  
Cebpb.EXP030682.mouse\_brown\_preadipocytes\_WT\_CEBPbeta\_GFP\_CEBPbeta\_Ch  
Arntl.EXP000095.Liver\_ZT02.NULL.bed  
Anti-HA.EXP031688.differentiating\_murine\_hematopoietic\_cells..bed  
Myod1.EXP032275.C2C12\_myoblasts\_of\_C3H\_strain..bed  
Esr1.EXP030622.Uterus..bed  
Vdr.EXP032800.MC3T3-E1\_differentiated\_for\_15\_days.100nM\_125OH2D3.bed  
GRIP1.EXP030428.primary\_bone\_marrow-derived\_macrophages.LPS-stimulated\_macr  
Cebpa.EXP032898.BV2..bed  
Jund.EXP033005.3T3-L1..bed  
GRIP1.EXP030429.primary\_bone\_marrow-derived\_macrophages.Dexamethasone\_trea  
Spi1.EXP032897.BV2.mutant\_human\_Htt\_overexpression.bed  
Atf3.EXP032927.C57BL6.LPS.bed  
Jun.EXP030427.primary\_bone\_marrow-derived\_macrophages.Dexamethasone\_treated  
rabbit\_anti-Runx1\_EXP031986.BMiFLT315-3.bed  
sc-7208.EXP031853.mammary\_gland.17-estradiol\_for\_24\_hours\_and\_then\_17-estradiol  
runx1.EXP000340.Early\_haematopoietic\_cell\_line\_derived\_from\_ES\_cells.NULL.bed  
anti-NFATc1.EXP032431.Telogen\_quiescent\_hair\_follicle\_stem\_cells..bed  
Tcf12.EXP010142.C2C12.EqS\_2\_0pct\_60hr.bed  
Spi1.EXP032206.3T3-L1.adeno-PU1.bed  
Myod1.EXP032276.C2C12\_myoblasts\_of\_C3H\_strain..bed  
Tal1.EXP031694.differentiating\_murine\_hematopoietic\_cells.dox.bed  
Pparg.EXP000042.3T3-L1\_adipocytes.NULL.bed  
Cdx2.EXP032550.endoderm\_cells..bed  
Stat5a.EXP000715.mouse\_embryonic\_fibroblasts\_MEFs.Stat5\_KO\_Growth\_hormone.b  
Rxra.EXP001011.F9.NULL.bed  
Myog.EXP032277.C2C12\_myoblasts\_of\_C3H\_strain..bed

Nkx3-1.EXP031260.Recombinant\_inbred\_B6\_x\_129\_Nkx3-1\_--..bed  
Kmt2b.EXP032315.immortalized\_brown\_preadipocytes.D0\_of\_adipogenesis.bed  
Cebpb.EXP031692.differentiating\_murine\_hematopoietic\_cells..bed  
Vdr.EXP032799.MC3T3-E1\_differentiated\_for\_15\_days.ethanol\_vehicle.bed  
Cebpb.EXP030546.myeloid\_progenitor\_cells..bed  
Ncor2.EXP030955.wild-type\_primary\_bone\_marrow-derived\_macrophages..bed  
Pou5f1.EXP032982.embryonic\_stem\_cells\_ESC.Dox.bed  
Stat5a.EXP032238.mammary\_gland.L1.bed  
gata4.EXP030894.HL-1\_cardiac\_muscle\_cell\_line..bed  
Cebpb.EXP031960.Primary\_dermal\_fibroblasts.Thapsigargin\_treatment\_for\_3\_hrs.bed  
Spi1.EXP032896.BV2.wt\_human\_Htt\_overexpression.bed  
anti-NCOR.EXP030956.wild-type\_primary\_bone\_marrow-derived\_macrophages..bed  
Cebpa.EXP030544.Hematopoietic\_Stem\_Cells..bed  
Sox3\_T\_\_Edlund.EXP000015.ES-derived\_neural\_progenitor\_cells.NULL.bed  
Atf3.EXP032923.C57BL6.LPS.bed  
Smad3.EXP000842.V6\_5\_embryonic\_stem\_cells.NULL.bed  
AF2018.EXP000020.ESC.NULL.bed  
Pparg.EXP030713.3T3-L1\_cells\_ATCC\_CL-173..bed  
Sox2\_raised\_by\_ourselves.EXP032398.EGFP-TS3\_5\_TS\_cells..bed  
Mef2d.EXP031871.C2C12..bed  
Ascl1\_ab74065.EXP030565.C57BL6\_embryonic\_fibroblasts..bed  
Vdr.EXP033036.3T3-L1..bed  
Cdx2.EXP031623.Ainv15\_ATCC\_SCRC-1029\_with\_Dox-inducible\_Cdx2-V5\_construct.  
Cebpa.EXP000638.3T3-L1\_preadipocyte\_cell\_line.4\_hours\_of\_differentiation.bed  
Pparg.EXP000496.3T3L1\_cells.Day\_6\_of\_differentiation.bed  
Lhx3.EXP031090.Ainv15\_ATCC\_SCRC-1029\_with\_Dox-inducible\_Ngn2Isl1\_Lhx3-V5  
Rxa.EXP001010.F9.NULL.bed  
Foxa1.EXP032165.prostate.castratedplusvehicle.bed  
Thra.EXP031500.C17\_2a\_neural\_progenitor\_cells..bed  
Cebpb.EXP000045.3T3-L1.NULL.bed  
Cdx4.EXP001008.Ainv15\_ATCC\_SCRC-1029\_with\_inducible\_Flag-tagged\_Hoxc9.plus  
Pou3f2.EXP031249.ES-derived\_neural\_progenitor\_cells\_NPCs..bed  
Cebpb.EXP000635.3T3-L1\_preadipocyte\_cell\_line.4\_hours\_of\_differentiation.bed  
Cebpa.EXP033002.3T3-L1.none.bed  
Stat5a.EXP032419.mammary.none.bed  
Stat5a.EXP030766.Mammary\_tissues..bed  
Nfkb1.EXP032915.C57BL6..bed  
Stat5a.EXP032239.mammary\_gland..bed  
Cebpb.EXP033003.3T3-L1..bed  
Cebpa.EXP030673.primary\_B\_cells.Estradiol\_for\_18h.bed  
Pax7.EXP030937.primary\_myoblasts..bed  
Ebf1.EXP033046.3T3L1..bed  
Ptf1a.EXP030973.266\_6\_Pancreatic\_Cells..bed  
Pparg.EXP000534.3T3-L1.NULL.bed  
Myod1.EXP010522.C2C12.EqS\_2\_0pct\_7d.bed  
Stat5a.EXP000640.3T3-L1\_preadipocyte\_cell\_line.4\_hours\_of\_differentiation.bed  
Rela.EXP032921.C57BL6.LPS.bed  
Cdx2.EXP032547.ESC\_Ainv15\_ATCC\_SCRC-1029.plusDox\_plusFGF.bed  
Cebpb.EXP000633.3T3-L1\_preadipocyte\_cell\_line.day\_0\_of\_differentiation.bed  
Myod1.EXP030921.fibroblasts..bed

Msx1.EXP000382.C2C12.NULL.bed  
Cebpb.EXP000634.3T3-L1\_preadipocyte\_cell\_line.2\_hours\_of\_differentiation.bed  
Foxa2.EXP030514.ES-derived\_definitive\_endoderm\_cells..bed  
Pparg.EXP000643.3T3-L1\_preadipocyte\_cell\_line.day\_6\_of\_differentiation.bed  
Pou3f2.EXP030571.C57BL6\_neural\_progenitor..bed  
Pparg.EXP000495.3T3L1\_cells.Day\_4\_of\_differentiation.bed  
Stat5b.EXP030767.Mammary\_tissues..bed  
Pparg.EXP000642.3T3-L1\_preadipocyte\_cell\_line.day\_2\_of\_differentiation.bed  
Nanog.EXP000475.Embryonic\_stem\_cells.NULL.bed  
anti-NCOR.EXP030958.Bcl6\_knockout\_primary\_bone\_marrow-derived\_macrophages..b  
Smad1.EXP000419.Erthyroid\_Progenitor\_G1E.NULL.bed  
Pparg.EXP000493.3T3L1\_cells.Day\_2\_of\_differentiation.bed  
Tead2.EXP032944.Py2T\_breast\_cancer\_cells..bed  
Cebpb.EXP000636.3T3-L1\_preadipocyte\_cell\_line.day\_2\_of\_differentiation.bed  
Tal1.EXP010942.Megakaryo.NULL.bed  
Foxa1.EXP032177.prostate.castratedplustestosterone.bed  
Cebpb.EXP031959.Primary\_dermal\_fibroblasts.No\_treatment.bed  
Pparg.EXP031774.epididymal\_white\_adipose\_tissue-derived\_adipocytes.none.bed  
sc-8635.EXP000022.ESC.NULL.bed  
Ptf1a.EXP030598.Pancreas..bed  
Cebpb.EXP000046.3T3-L1\_6hr\_of\_differentiation.NULL.bed  
Pou5f1.EXP032980.embryonic\_stem\_cells\_ESC..bed  
Mef2d.EXP031872.C2C12..bed  
Pax3.EXP030938.primary\_myoblasts..bed  
Cdx4.EXP001007.Ainv15\_ATCC\_SCRC-1029\_with\_inducible\_V5-tagged\_Hoxc9.plusDr  
Esr1.EXP032050.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a  
Smad3.EXP000843.V6\_5\_embryonic\_stem\_cells.Activin.bed  
Sox2\_produced\_in-house.EXP030984.ZHBTc4.control.bed  
Glucocorticoid\_Receptor.EXP030424.primary\_bone\_marrow-derived\_macrophages.De  
Pparg.EXP000902.Cultured\_Adipocytes.NULL.bed  
Bcl6.EXP000035.primary\_bone\_marrow-derived\_macrophages..bed  
Pparg.EXP031775.inguinal\_white\_adipous\_tissue-derived\_adipocytes.none.bed  
Smad2.EXP000846.V6\_5\_embryonic\_stem\_cells.Activin.bed  
RD\_Systems\_MAB2018.EXP030813.Embryonic\_stem\_cells..bed  
Cdx2.EXP032397.ZHBTc4-TS\_cells..bed  
Pparg.EXP032205.3T3-L1.adeno-PU1.bed  
Nr1i2.EXP033037.3T3-L1..bed  
Esr1.EXP032051.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a  
Pparg.EXP031776.brown\_adipous\_tissue-derived\_adipocytes.none.bed  
Etv6.EXP031753.ES-derived\_neural\_progenitor\_like\_cells..bed  
Nanog.EXP000021.ESC.NULL.bed  
Ncor2.EXP030957.Bcl6\_knockout\_primary\_bone\_marrow-derived\_macrophages..bed  
Esr1.EXP032054.bed  
Zfp57.EXP000268.embryonic\_stem\_ES\_cells.NULL.bed  
Glucocorticoid\_Receptor.EXP030423.primary\_bone\_marrow-derived\_macrophages.De  
Esr1.EXP032052.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a  
Sox6.EXP000148.myotubes\_induced\_from\_wild\_type\_mouse\_fetal\_E18\_5\_primary\_my  
Zfp57.EXP000269.embryonic\_stem\_ES\_cells\_expressing\_HAZFP57.NULL.bed  
GR.EXP032048.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a\_1  
Esr1.EXP032055.bed

Myb.EXP000216.Conditional\_Myb\_transformed\_myeloid\_cell\_line.inactivated\_MYB.bed  
Sox2\_produced\_in-house.EXP030986.ZHBTc4.Tet.bed  
Rela.EXP030451.3T3-L1.differentiated\_TNF.bed  
GR.EXP000639.3T3-L1\_preadipocyte\_cell\_line.4\_hours\_of\_differentiation.bed  
Esr1.EXP032053.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a  
Myod1.EXP030918.myoblasts..bed  
GR.EXP032047.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a\_1  
GR.EXP032049.mouse\_mammary\_cells\_express\_GFP-GR\_and\_Cherry-ER\_under\_a\_1

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lult\_neural\_progenitor\_cell.LY.bed



## RED CLUSTER

Gabpa.EXP011066.CH12.None.bed  
Creb1.EXP030715.3T3-L1\_cells\_ATCC\_CL-173.DMSO.bed  
Creb1.EXP030716.3T3-L1\_cells\_ATCC\_CL-173.lactacystin.bed  
Jun.EXP032880.CD8plus\_T\_cells..bed  
E2f4.EXP010412.C2C12.EqS\_2\_0pct\_60hr.bed  
Myc.EXP032616.Pancreatic\_carcinoma\_cells\_derived\_from\_KrasG12Dplus\_p53R172H  
Mxi1.EXP010444.CH12.None.bed  
Stat6.EXP000055.in\_vitro\_polarized\_T\_helper2\_cells\_for\_7\_days.STAT6\_KO.bed  
sc-592\_Santa\_Cruz\_Biotechnology.EXP030516.primary\_CD4plus\_T\_cells\_from\_spleer  
Max.EXP010263.CH12.None.bed  
Jun.EXP031656.Th17\_Cells..bed  
Batf.EXP031648.CD4plus\_T\_Cells.IRF4KO.bed  
Irf4.EXP031651.CD4plus\_T\_Cells.BATFKO.bed  
Batf.EXP031649.CD4plus\_T\_Cells.IL21\_IRF4KO.bed  
Max.EXP010133.C2C12.EqS\_2\_0pct\_60hr.bed  
Fos.EXP032703.primary\_mast\_cells..bed  
Stat3.EXP031658.Th17\_Cells..bed  
Myc.EXP010764.CH12.None.bed  
Ddit3.EXP031252.Mouse\_embryonic\_fibroblast.Tunicamycin.bed  
Gabpa.EXP011012.MEL.None.bed  
Irf4.EXP031654.Th17\_Cells..bed  
Myc.EXP032618.MEFs\_derived\_from\_Miz1flox\_flox\_CreER-mice..bed  
Stat6.EXP000054.in\_vitro\_polarized\_T\_helper2\_cells\_for\_7\_days.NULL.bed  
Jund.EXP031657.Th17\_Cells..bed  
Stat3.EXP000348.CD4plus\_T\_cells.IL-6\_IL-23.bed  
Max.EXP011026.C2C12.None.bed  
Tbx21.EXP000710.in\_vitro\_polarized\_T\_helper1\_cells\_for\_7\_days.NULL.bed  
Stat3.EXP000323.WT-Th17\_polarized\_T\_cells\_from\_naive.NULL.bed  
Stat6.EXP031762.Th9.Th9\_conditions\_72\_hours.bed  
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Klf3.EXP031948.Klf3--\_murine\_embryonic\_fibroblasts\_rescued\_with\_Klf3-V5..bed  
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Irf4.EXP030759.Th17\_polarized\_cells..bed  
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Usf1.EXP010748.C2C12.EqS\_2\_0pct\_60hr.bed  
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Rela.EXP032252.Macrophage.Kdo2\_Lipid\_A\_KLA\_1h.bed  
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Stat5b.EXP000387.BalbC\_Th1.2\_rounds\_priming.bed  
Pknox1.EXP032892.Embryonic\_fibroblast..bed

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Bach2.EXP032019.in\_vitro\_polarized\_inducible\_regulatory\_cells\_for\_3\_days..bed  
Atf4.EXP031254.Mouse\_embryonic\_fibroblast.Tunicamycin.bed  
Rela.EXP032090.Peritoneal\_macrophages\_of\_C57BL6J.100\_ngml\_Kdo2-LipidA\_1\_hr.t  
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Irf4.EXP031638.CD4plus\_T\_Cells.IL21.bed  
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Rela.EXP032091.Peritoneal\_macrophages\_of\_BALBcJ.100\_ngml\_Kdo2-LipidA\_1\_hr.be  
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Stat5b.EXP030970.Dendritic\_Cell.IL21.bed  
Rela.EXP032261.Macrophage.DMSO\_2h\_Kdo2\_Lipid\_A\_KLA\_1h.bed  
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Foxp3.EXP032970.iTreg\_cells..bed  
Jun.EXP031647.CD4plus\_T\_Cells.IL21\_IRF4KO.bed  
Stat3.EXP030967.Dendritic\_Cell.IL21.bed  
Rela.EXP030646.Macrophage.Kdo2\_Lipid\_A\_KLA\_1h.bed  
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Cebpa.EXP032254.Macrophage.Kdo2\_Lipid\_A\_KLA\_1h.bed  
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Mafk.EXP010956.ES-E14.None.bed  
Rela.EXP032262.Macrophage.IBET\_2h\_Kdo2\_Lipid\_A\_KLA\_1h.bed  
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Jun.EXP010079.CH12.None.bed  
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Cebpb.EXP032592.MC3T3-E1\_differentiated\_for\_15\_days.ethanol\_vehicle.bed  
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Jund.EXP031904.STHdhQ111..bed  
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Jun.EXP030426.primary\_bone\_marrow-derived\_macrophages.LPS-stimulated.bed  
Jund.EXP010561.MEL.None.bed  
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Fosl2.EXP031902.STHdhQ111..bed  
Maf.EXP032675.Activated\_CD4plus\_T\_cells\_skewed\_towards\_a\_Th17\_subset\_mir15f  
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Junb.EXP033031.3T3-L1..bed  
Jun.EXP033030.3T3-L1..bed  
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tet\_regulated\_promoter.Dexamethasone\_plus\_Estradiol\_for\_30\_minutes.bed



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P..bed

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our.bed

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\_6\_hour.bed

our.bed  
bed

r.bed

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ta\_ChIP..bed

5\_KO.bed

tet\_regulated\_promoter.untreated.bed



### **Table EV3**

#### ***LIVER-ID genes***

LIVER-ID genes defining the GSEA Core Enrichment from Fig.3D, i.e. LIVER-ID genes showing lower repress

#### ***GO terms***

GO terms defining additional pathways and liver functions less repressed by ERS in NFIL3 KO compared to BubbleGUM analyses were performed using the “MousePath\_GO\_gmt.gmt” set of genes from the Gene S  
GO terms identified as repressed by ERS in both WT and NFIL3 KO mice were retrieved (FDR<0.25). Then a  
Genes defining the different GO terms are also provided.

tion upon ERS in NFIL3 KO mice.

WT mice.

Set Knowledgebase (GSKB) (Lai et al., 2016)

A comparison between gene expression levels in treated WT and NFIL KO mice was used to define GO term

is enriched for genes showing lower repression in NFIL3 KO compared to WT livers.

**Table EV4**

This table provides the list of MUSCLE-ID and UBQ genes used in Appendix Fig.S26

**Table EV5**

List of primers used in this study for real-time PCR analyses.

