SUPPLEMENTARY MATERIALS

Identification of bona fide DREs and calculation of MS scores

Bona fide DREs were identified DREs from previous computational analysis of genome wide DREs (Dere *et al.*, 2011; Sun *et al.*, 2004) and through literature searching. Newly identified DREs were considered *bona fide* if (1) Direct AhR binding was confirmed, (2) AhR binding to the DRE was shown to elicit changes in gene expression (e.g. reporter assay), and (3) removal of the DRE ablated the transcriptional response. Consequently, four new functional DREs reported for human *Bach2* (De Abrew *et al.*, 2011) and *Cyp1b1* (Shehin *et al.*, 2000) were added. *Bona fide* DRE sequences are provided in Table S7. The new position weight matrix (PWM) was calculated as previously described (Dere *et al.*, 2011). To update matrix similarity scores, the mouse genome (mm10; GRCm38) was downloaded from the UCSC genome database and the UCSC tool findMotif was used to extract all DREs. The UCSC tool twoBitToFA was used to extract DRE sequences and 5' and 3' flanking regions. Matrix similarity scores (MSS) were calculated for the 19bp sequences as previously described (Dere *et al.*, 2011)

Targeted metabolomics LC gradients

For analysis of hepatic extracts, the LC parameters were as follows: autosampler temperature, 10 ºC; injection volume, 10 µl; column temperature, room temperature; and flow rate, 200 µl·min^{-1}. The LC solvents were Solvent A: 10 mM tributylamine and 15 mM acetic acid in 97:3 water:methanol (pH 4.95); and Solvent B: methanol. Elution from the column was performed over 50 min with the following gradient: t = 0, 0% B; t = 5, 0% B; t = 10, 20% B; t = 20, 20% B; t = 35, 65% B; t = 38, 95% B; t = 42, 95% B, t = 43, 0% B; t = 50, 0% B. ESI spray voltage was 3,000 V. Nitrogen was used as the sheath gas at 30 psi and as the auxiliary gas at 10 psi, and argon as the collision gas at 1.5 mTorr, with the capillary temperature at 325 ºC. Scan time for each MRM transition was 0.1 s with a scan width of 1 m/z. The LC runs were divided into time segments, with the MRM scans within each time segment containing compounds eluting during that time interval. For compounds eluting near boundaries between time segments, the MRM scan corresponding to the compound was conducted in both time segments. Instrument control, chromatographic control, and data acquisition were performed by the Xcalibar software (Thermo Scientific).

For analysis of serum extracts, the LC parameters were as follows: autosampler temperature, 10 ºC; injection volume, 10 µl; column temperature, 50ºC and flow rate, 150 µl·min^{-1}. The LC solvents were Solvent A: 10 mM tributylamine and 15 mM acetic acid in 97:3

water:methanol (pH 4.95); and Solvent B: methanol. Elution from the column was performed over 11 min with the following gradient: t = 0, 0% B; t = 3, 20% B; t = 7.5, 55% B; t = 9, 95% B; t = 10, 95% B; t = 10.5, 0% B. The LC runs were divided into time segments, with the MRM scans within each time segment containing compounds eluting during that time interval. For compounds eluting near boundaries between time segments, the MRM scan corresponding to the compound was conducted in both time segments. Instrument control, chromatographic control, and data acquisition were performed by the MassLynx software (Waters).

Hepatic glutathione levels

Total hepatic glutathione levels were determined according to manufacturer's instructions (Sigma-Aldrich; CS0260) using a Tecan Infinite 200 microplate reader (Männedorf, Switzerland).

cDNA and QRTPCR

cDNA synthesis from total RNA (Nault *et al.*, 2015) was performed as described Briefly, total RNA (2 µg) was reverse transcribed by SuperScript II reverse transcriptase (Invitrogen) and anchored oligo-dT primer (Invitrogen) according to manufacturer's instructions. QRTPCR was performed using iQ SYBR Green Supermix (Bio-Rad) on a Bio-Rad CFX96 detection system. Primers were designed and verified using the NCBI Primer-BLAST (http://www.ncbi.nlm.nih.gov/tools/primer-blast/) and UCSC genome browser in-silico PCR (https://genome.ucsc.edu/) tools (Table S7). Melt-curve analysis confirmed the uniformity of PCR products. Relative expression was determined using the $2^{-\Delta\Delta CT}$ method and the geometric mean of reference genes *ActB*, *Gapdh*, and *Hprt*.

References

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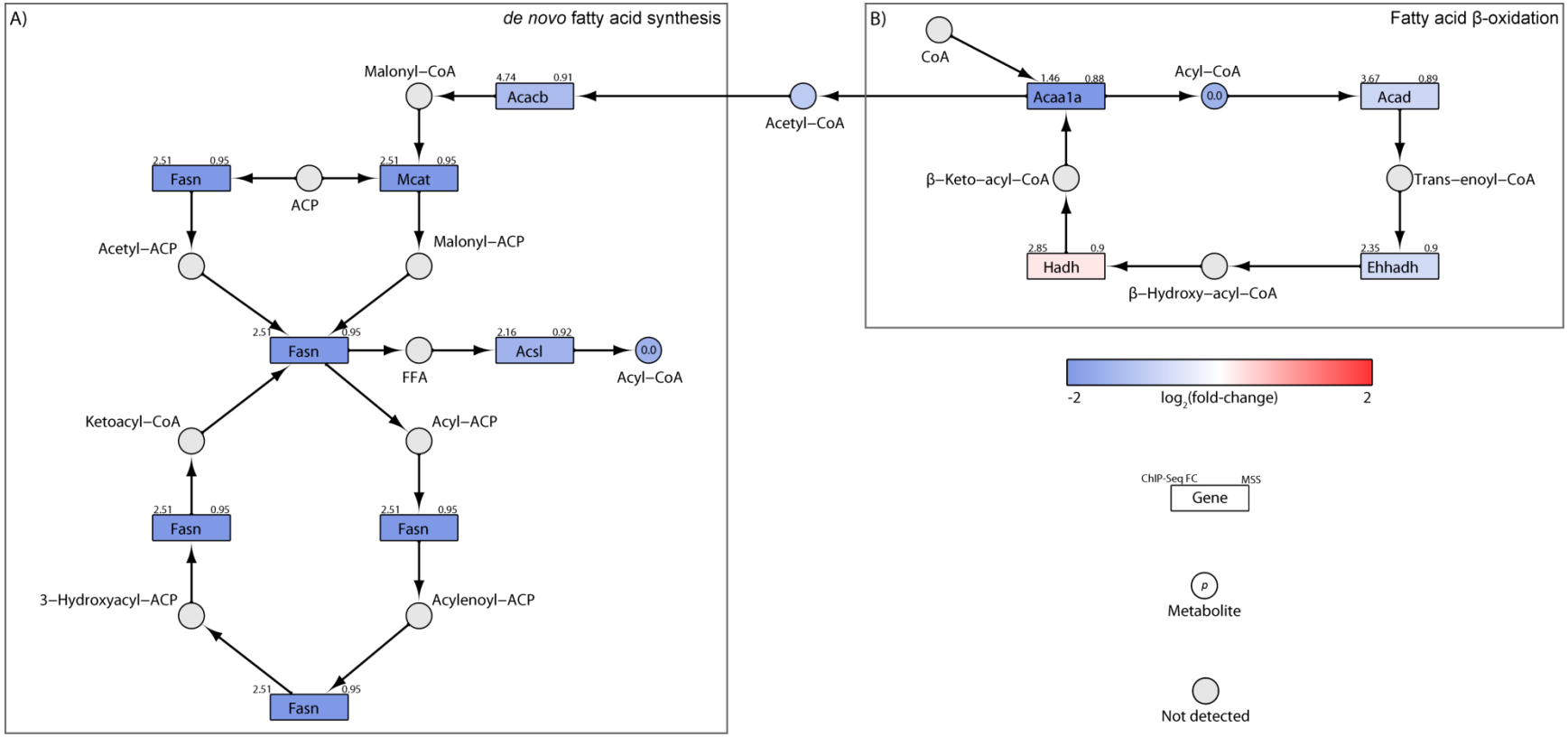

Figure S1. Inhibition of de novo fatty acid synthesis and β-oxidation

(A-B) Integration of transcriptomic, metabolomic, and KEGG pathway data for (A) de novo fatty acid synthesis and (B) β-oxidation. Color scale represents the $\log_2$(fold-change) for genes and metabolites. Gray indicates metabolites were not measured or detected. Genes are identified as rectangles and metabolites as circles. The upper left corner describes the maximum AhR enrichment fold-change and upper right corner indicates the highest scoring pDRE MSS for genes. Circles contain the *p*-value for detected metabolites. An expandable and more interactive version of this figure that provides additional complementary information can be viewed at http://dbzach.fst.msu.edu/index.php/supplementarydata.html.

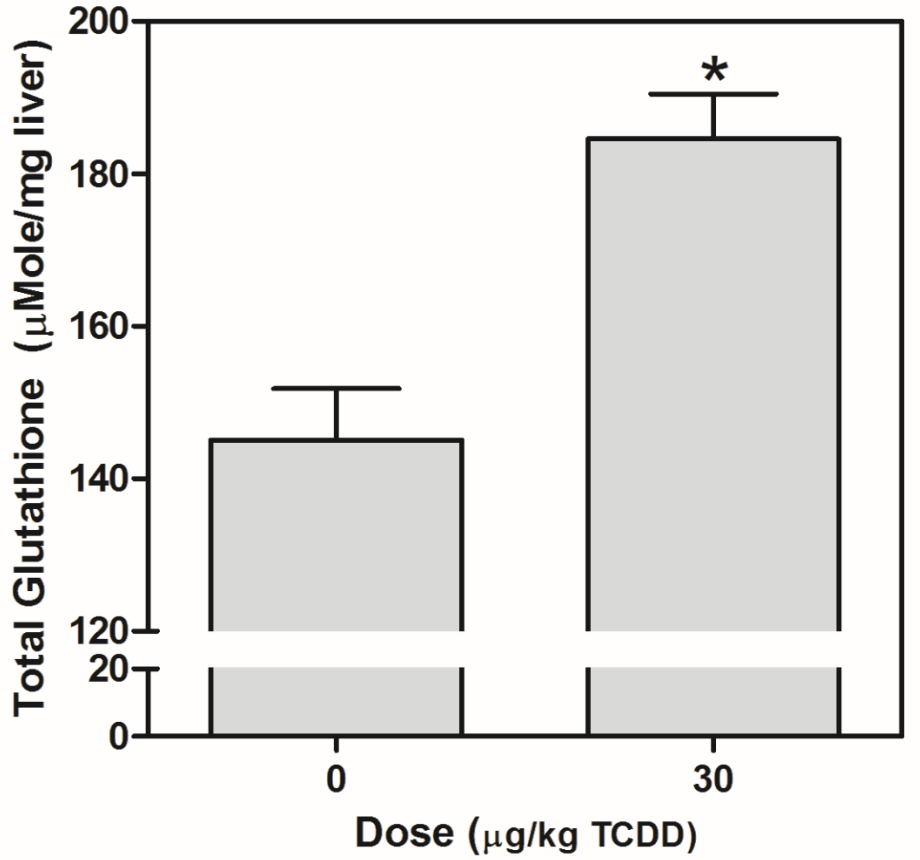

Figure S2. Total glutathione levels

Total hepatic glutathione levels in livers of mice gavaged with sesame oil vehicle or 30 µg/kg TCDD every 4 days for 28 days. Bars represent mean ± SEM for n=4-5. Asterisks (*) indicates a significant difference ($p \leq 0.05$) determined by student's t-test.