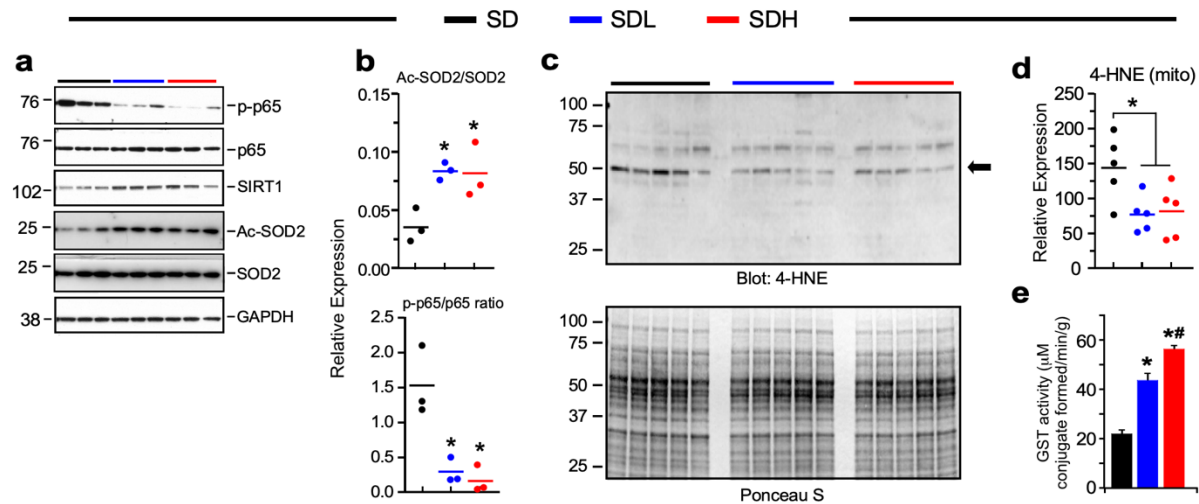
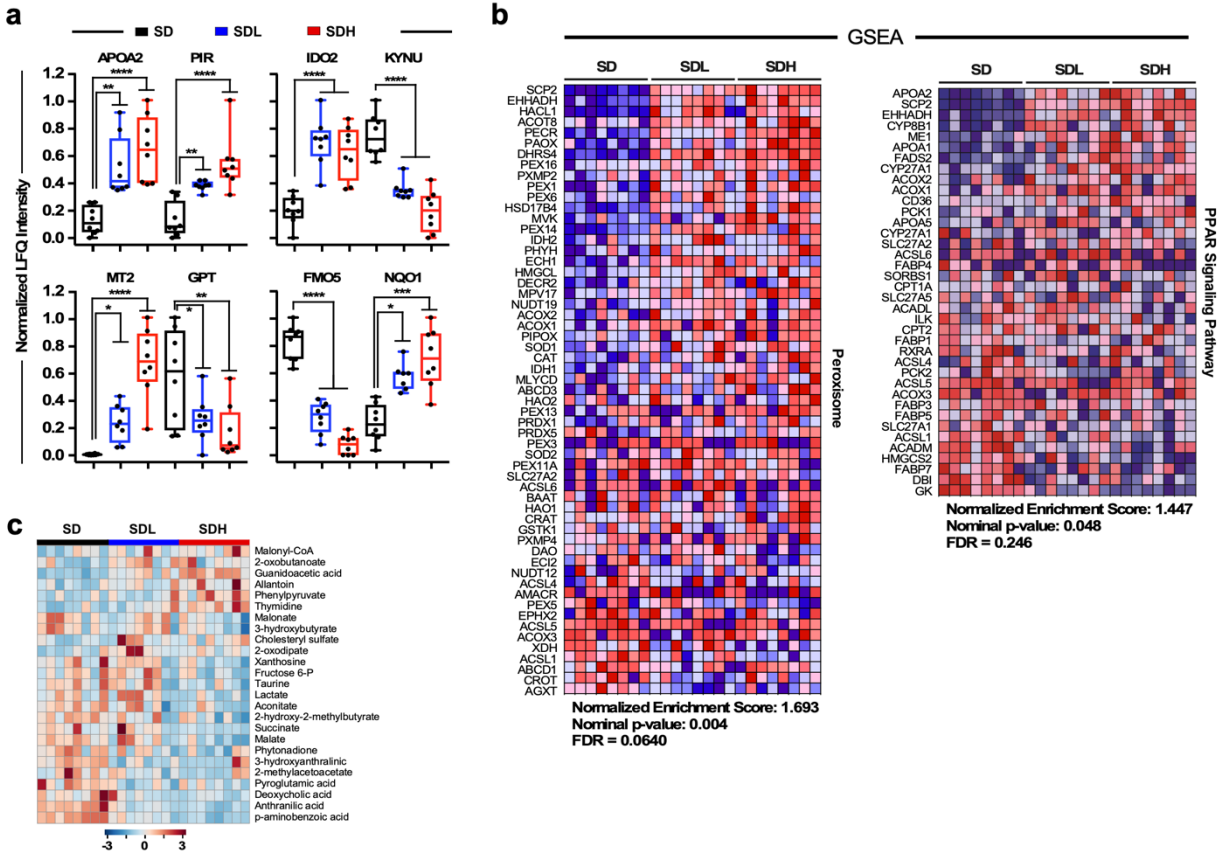


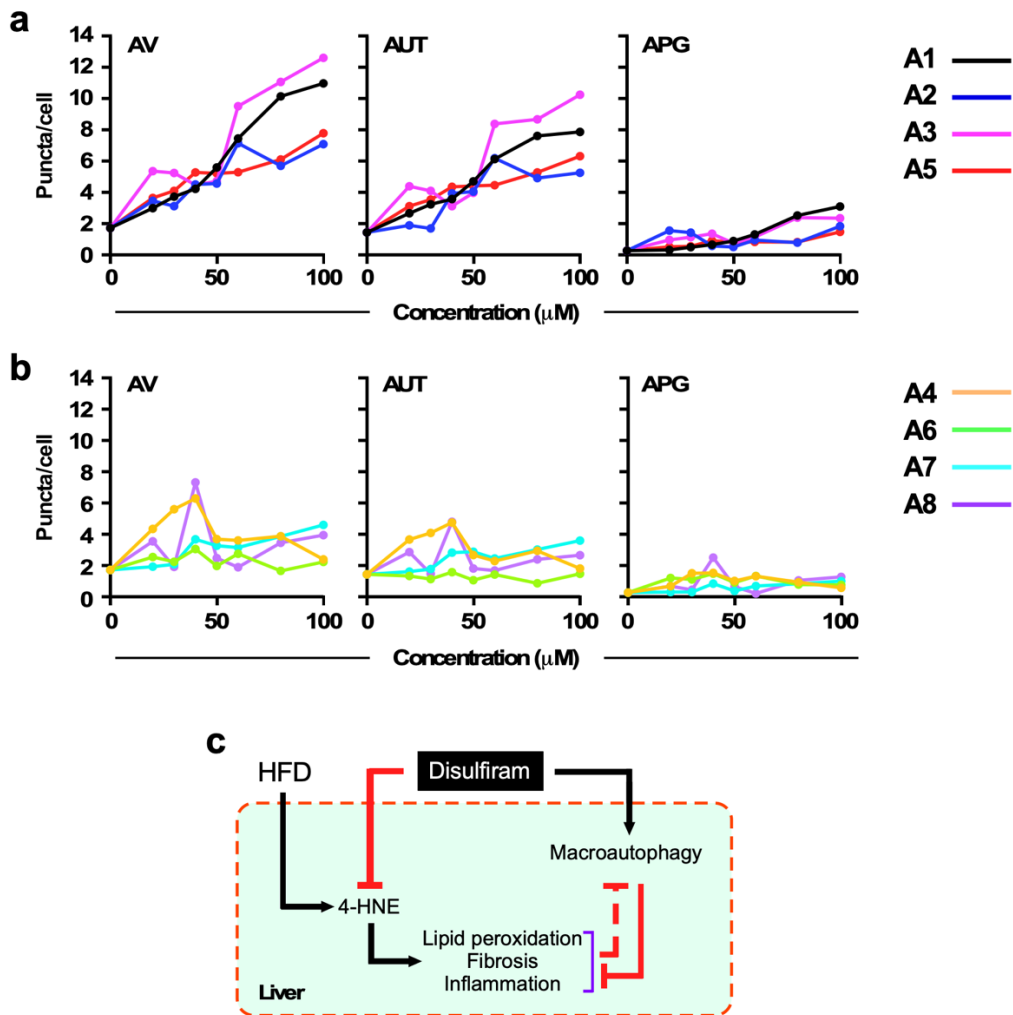
**Supplementary Fig. 1. Molecular alterations in the liver of standard diet-fed mice supplemented with DSF.** **a** Venn diagrams depicting genes significantly upregulated (red) and downregulated (green) in SD livers in response to low and high doses of DSF. **b** Venn diagrams depicting GO terms and canonical pathways significantly upregulated (red) or downregulated (green) in the SDH\_SD and SDL\_SD pairwise comparisons. **c** Enrichment of select pathways shared between the SDH\_SD and SDL\_SD pairwise comparisons. **d** Validation of microarray data by quantitative real-time PCR.  $n = 5$  per group. Values were normalized to SD controls. **e** Liver extracts were prepared from mice after 40 weeks on the indicated dietary intervention and immunoblotted for IGFBP2 (upper panel). Relative IGFBP2 protein expression after data normalization using Ponceau S staining of the membrane is depicted in the lower panel.  $n = 3$  per group. \*,  $P \leq 0.05$ . Related to Fig. 1



**Supplementary Fig. 2. Molecular and biochemical alterations in the liver of SD-fed mice supplemented with DSF.** **a** Immunoblotting of liver lysates for total and phosphorylated forms of p65Rel A, total and acetylated forms of SOD2, and SIRT1. **b** Relative acetylated/total ratio for p65Rel A and SOD2 after data normalization using GAPDH as loading control. **c** Detection of 4-HNE-conjugated proteins in liver homogenates. Ponceau S staining of the membrane confirmed equal protein load. Molecular mass markers (in kDa) are depicted on the left of immunoblots. **d** Densitometric analysis of 4-HNE signals shown in **c**. **e** GST activity measured in liver microsomal fractions. \*  $P \leq 0.05$  versus SD; #,  $P \leq 0.05$  versus SD + low DSF. Related to Fig. 2.



**Supplementary Fig. 3. Treatment with DSF for 12 weeks alters liver proteome and serum metabolome in chow-fed rats.** **a** Abundance of a select group of proteins significantly impacted by DSF treatment. Normalized LFQ intensity values are represented in box and whisker plot format ( $n = 8$  per group). Statistics for the effects of DSF intervention represent the p-value from a one-way ANOVA with Dunnett's post-hoc tests. \*, \*\*, \*\*\*, \*\*\*\*,  $P < 0.05, 0.01, 0.001, \text{ and } 0.0001$ . **b** Gene Set Enrichment Analysis (GSEA) depicting two sets of proteins whose expression was significantly impacted by DSF supplementation. These sets of proteins were grouped together based on their involvement in peroxisome (*left panel*) and PPAR signaling pathway (*right panel*). **c** Heatmap of the 25 metabolites in the rat serum metabolome that contributed to the separation between control and DSF-treated groups. Related to Fig. 3.



**Supplementary Fig. 4. Structure-activity of DSF derivatives on autophagy.** **a,b** NIH3T3 cells expressing the mCherry-GFP-LC3 reporter were exposed to the indicated concentrations of DSF (A1) and dithiocarbamate analogs (A2-A8) for 24 h and the changes in the number of autophagic vacuoles (AV), autolysosomes (AUT) or autophagosomes (APG) was quantified using high-content microscopy. Compounds with potent stimulatory effect on autophagy are shown in **a** and those with a more discrete effect in **b**. All values are mean of 4 individual wells and quantifications were done in at least 2500 cells per condition in three different experiments using high-content microscopy. Abbreviations: A1, bis(diethylthiocarbamate) disulfide aka disulfiram; A2, ammonium pyrrolidinedithiocarbamate; A3,  $\text{Mn}^{2+}$ - $\text{Zn}^{2+}$  ethylenebis(dithiocarbamate); A4,  $\text{Mn}^{2+}$  ethylenebis(dithiocarbamate) aka pestanal; A5,  $\text{Na}^+$  diethyldithiocarbamate trihydrate; A6, triethylammonium *N*-(3,4-dichlorophenyl) dithiocarbamate; A7, *S*-cyanomethyl-*N*-methyl-*N*-(pyridin-4-yl) dithiocarbamate; A8,  $\text{Zn}^{2+}$  dimethyldithiocarbamate. **c** Schematic model of the proposed dual mechanism of action of DSF in its protective effect against high-fat diet (HFD). The cellular processes inhibited through the effect of DSF on 4-HNE levels and autophagy are indicated. Related to Fig. 4.

**Supplementary Table 1.** Partial list of genes reciprocally affected in response to DSF supplementation in male C57BL/6 mice fed either an HFD or SD diet. Related to Fig. 1.

Gene name	Definition/Function	zratio		
		HFD-SD	HFDH-HFD	HFDL-HFD
Cyp2b9	Oxidoreductase activity toward steroids, FA and xenobiotics	<b>17.65</b>	<b>-9.00</b>	-7.82
Upp2	Liver-specific uridine phosphorylase 2	<b>5.76</b>	<b>-4.01</b>	-0.89
Gstm2	GST-class Mu - detoxification of electrophilic compounds	<b>5.10</b>	<b>-2.57</b>	-3.36
Jak3	Cytokine receptor-mediated intracellular signal transduction	<b>3.27</b>	<b>-1.64</b>	-0.85
Cyp2b13	Oxidoreductase activity	<b>17.92</b>	<b>-16.03</b>	<b>-14.29</b>
Cidec	Binds to lipid droplets and regulates their enlargement	<b>6.47</b>	<b>-7.36</b>	<b>-9.56</b>
Hk2	Hexokinase 2 - involved in the increased rate of glycolysis	<b>6.18</b>	<b>-6.36</b>	<b>-7.33</b>
Tceal8	Transcription elongation factor A-like 8	<b>5.13</b>	<b>-7.18</b>	<b>-8.22</b>
Raetib	Retinoic acid early transcript beta – macrophage activation	<b>4.52</b>	<b>-12.08</b>	<b>-11.58</b>
Vldr	Very low-density lipoprotein receptor – triglyceride metab.	<b>3.93</b>	<b>-6.08</b>	<b>-6.50</b>
Spp1	Osteopontin – acts as a cytokine by reducing IL-10 production	<b>3.60</b>	<b>-3.85</b>	<b>-6.90</b>
Hsd3b5	3 $\beta$ -HSD - Biosynthesis of hormonal steroids	<b>-20.04</b>	<b>15.81</b>	<b>20.75</b>
Igfbp2	IGF binding protein 2 – prolongs IGFs' half-life	<b>-4.27</b>	<b>8.13</b>	<b>9.14</b>
Cyp7b1	Homeostasis of cholesterol, bile acids and oxysterols	<b>-3.99</b>	<b>5.85</b>	<b>6.27</b>
Cdh1	E-cadherin – mechanisms regulating cell-cell adhesion	<b>-3.58</b>	<b>5.70</b>	<b>4.43</b>
Elov13	Elongation of very long chain fatty acids, e.g. C18-acylCoA	<b>-6.58</b>	<b>2.43</b>	-0.12
C6	Key role in the innate and adaptive immune response	<b>-4.73</b>	<b>5.75</b>	4.37
Mup21	Major urinary protein 21 – pheromone ligand	<b>-3.98</b>	<b>4.75</b>	3.91
Gstp1	GST-class Pi – conjugation of reduced glutathione to electrophiles.	<b>-3.61</b>	<b>6.06</b>	3.59

Gene name	Definition/Function	SDH-SD	SDL-SD
Cyp2b20	aka Cyp2b6. Steroid, ketone and xenobiotic metabolism	<b>18.41</b>	<b>24.34</b>
Tff3	trefoil factor 3 promotes the mobility of epithelial cells in healing proc.	<b>12.99</b>	<b>12.41</b>
Mt2	Melatonin Receptor 1B	<b>12.41</b>	<b>9.23</b>
Lpl	lipoprotein lipase	<b>11.04</b>	<b>6.09</b>
Cxcl1	Chemokine (C-X-C Motif) Ligand 1	<b>9.37</b>	<b>9.09</b>

Hsd17b9	retinol dehydrogenase 5	<b>9.37</b>	<b>9.71</b>
Gsta2	glutathione S-transferase alpha 2	<b>9.04</b>	<b>5.50</b>
Slc39a4	solute carrier family 39 (zinc transporter). Zinc uptake	<b>8.60</b>	<b>12.54</b>
Rbp1	retinol binding protein 1, cellular	<b>8.51</b>	<b>6.97</b>
Socs3	suppressor of cytokine signaling 3. JAK2 inhibitor	<b>8.48</b>	<b>7.14</b>
Cyp2c29	Has aldehyde oxygenase activity. Xenobiotic metabolism	<b>7.96</b>	<b>9.76</b>
Cfd	complement factor D (adipsin), serine protease	<b>-15.23</b>	<b>-17.91</b>
Cidea	cell death-inducing DFFA-like effector a	<b>-14.49</b>	<b>-19.49</b>
Per2	period circadian clock 2	<b>-9.12</b>	<b>-5.72</b>
Raet1b	retinoic acid early transcript beta	<b>-8.29</b>	<b>-12.69</b>
Apoa4	apolipoprotein A-IV has a role in chylomicrons and VLDL	<b>-8.25</b>	<b>-9.43</b>
Ntrk2	catabolism	<b>-7.65</b>	<b>-7.41</b>
Clstn3	neurotrophic tyrosine kinase, receptor, type 2	<b>-7.24</b>	<b>-7.50</b>
Tgfbli4	calsyntenin 3 stabilizes APP metabolism	<b>-6.85</b>	<b>-7.94</b>
	TGFβ-1-induced transcript 4 acts as a transcriptional repressor		

HFD, high-fat diet; HFDH, HFD+high DSF; HFDL, HFD+low DSF. SD, standard diet; SDH, SD+high DSF; SDL, SD+low DSF. **Boldface**: significant expression; *italic*, non-significant.

**Supplementary Table 2.** Partial list of GO Terms and pathways significantly affected in response to DSF supplementation in male C57BL/6 mice fed either a HFD or SD diet. Related to Fig. 1.

GO Term	Zscore		
	HFD-SD	HFDH-HFD	HFDL-HFD
02504-Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	<b>4.737</b>	<b>-4.336</b>	0
19886-Antigen processing and presentation of exogenous peptide antigen via MHC class II	<b>4.582</b>	<b>-3.971</b>	0
42613-MHC Class II protein complex	<b>4.352</b>	<b>-3.973</b>	0
05764-Lysosome	<b>4.037</b>	<b>-3.471</b>	<b>-3.591</b>
08152-Metabolic process	<b>3.131</b>	<b>-6.379</b>	<b>-5.577</b>
04029-Aldehyde dehydrogenase (NAD) activity	<b>2.896</b>	<b>-5.226</b>	0
06631-Fatty acid metabolic process	<b>2.774</b>	<b>-4.688</b>	<b>-2.794</b>
05634-Nucleus	<b>-5.452</b>	<b>2.042</b>	<b>2.494</b>
03676-Nucleic acid binding	<b>-5.097</b>	<b>1.991</b>	<b>3.556</b>
06355-Regulation of transcription DNA-dependent	<b>-4.066</b>	<b>2.662</b>	<b>3.336</b>
06350-Transcription	<b>-3.927</b>	<b>1.892</b>	<b>2.881</b>
45449-Regulation of transcription	<b>-3.218</b>	<b>3.073</b>	<b>1.785</b>
05667-Transcription factor complex	<b>-3.077</b>	<b>2.576</b>	<b>2.230</b>
Pathway	HFD-SD	HFDH-HFD	HFDL-HFD
Reactome metabolism of amino acids	<b>4.736</b>	<b>-2.213</b>	0
KEGG valine leucine and isoleucine degradation	<b>4.581</b>	<b>-4.658</b>	<b>-3.876</b>
Reactome regulation of insulin secretion	<b>3.950</b>	0	<b>-4.021</b>
KEGG oxidative phosphorylation	<b>3.487</b>	0	<b>-1.994</b>
Reactome electron transport chain	<b>3.377</b>	0	<b>-3.005</b>
KEGG propanoate metabolism	<b>3.167</b>	<b>-5.246</b>	<b>-5.352</b>
KEGG peroxisome	<b>2.849</b>	<b>-3.338</b>	<b>-2.287</b>
KEGG butanoate metabolism	<b>2.555</b>	<b>-4.475</b>	<b>-4.517</b>
Reactome mitochondrial FFA $\beta$ -oxidation	<b>2.506</b>	<b>-2.631</b>	0
KEGG lysosome	<b>2.368</b>	0	<b>-3.134</b>

GO Term		SDH-SD	SDL-SD
04364-Glutathione transferase activity		<b>9.188</b>	<b>7.311</b>
05830-Cytosolic ribosome		<b>7.805</b>	<b>7.711</b>
06953-Acute phase response		<b>7.334</b>	<b>7.250</b>
16712-Oxidoreductase activity acting on paired donors		<b>7.202</b>	0
50381-Unspecific monooxygenase activity		<b>6.305</b>	0
06695-Cholesterol biosynthetic process		<b>4.970</b>	0
02504-Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II		<b>-3.320</b>	0
42613-MHC Class II protein complex		<b>-3.232</b>	0

32259-Methylation		<b>-2.768</b>	0
06886-Intracellular protein transport		<b>-3.565</b>	<b>-2.463</b>
05739-Mitochondrion		<b>-3.564</b>	<b>-6.141</b>
09374-Biotin binding		<b>-3.274</b>	<b>-3.017</b>
16573-Histone acetylation		<b>-2.169</b>	<b>-2.411</b>
Pathway		SDH-SD	SDL-SD
Reactome Glutathione conjugation		<b>11.700</b>	<b>8.850</b>
Reactome peptide chain elongation		<b>10.530</b>	<b>10.617</b>
KEGG ribosome		<b>10.365</b>	<b>10.457</b>
KEGG metabolism of xenobiotics by cytochrome p450		<b>10.060</b>	<b>7.968</b>
Reactome cholesterol biosynthesis		<b>8.515</b>	0
KEGG steroid biosynthesis		<b>5.490</b>	0
KEGG Snare interactions in vesicular transport		<b>-2.092</b>	0
Reactome hormone-sensitive lipase HSL-mediated TG		<b>-2.865</b>	<b>-2.552</b>
Reactome platelet activation triggers		<b>-2.767</b>	<b>-2.827</b>
KEGG cytosolic DNA sensing pathway		<b>-2.163</b>	<b>-3.761</b>

HFD, high-fat diet; HFDH, HFD+high DSF; HFDL, HFD+low DSF. SD, standard diet; SDH, SD+high DSF; SDL, SD+low DSF. **Boldface**: significant expression; The entry '0' indicates no significant difference.



**Supplementary Table 3.** Partial list of genes whose expression levels in response to DSF supplementation were shared in male C57BL/6 mice fed both SD and HFD diets. Related to Fig. 1.

Gene name	Zratio				
	HFD-SD	HFDH-HFD	HFDL-HFD	SDH-SD	SDL-SD
Raet1b	<b>4.52</b>	<b>-12.08</b>	<b>-11.58</b>	<b>-8.29</b>	<b>-12.69</b>
Raet1b	<b>4.00</b>	<b>-10.52</b>	<b>-10.84</b>	<b>-6.93</b>	<b>-10.66</b>
Lgals1	<b>3.16</b>	<b>-10.33</b>	<b>-11.17</b>	<b>-4.85</b>	<b>-5.80</b>
1600023A02R	<b>3.06</b>	<b>-10.44</b>	<b>-9.45</b>	<b>-8.55</b>	<b>-5.26</b>
LOC268782	<b>1.51</b>	<b>-2.89</b>	<b>-2.60</b>	<b>-2.01</b>	<b>-3.03</b>
Igfbp2	<b>-4.27</b>	<b>8.13</b>	<b>9.14</b>	<b>5.39</b>	<b>6.46</b>
Cdh1	<b>-3.58</b>	<b>5.70</b>	<b>4.43</b>	<b>4.88</b>	<b>4.89</b>
Avpr1a	<b>-3.20</b>	<b>6.14</b>	<b>5.89</b>	<b>4.04</b>	<b>3.61</b>
Avpr1a	<b>-3.04</b>	<b>9.33</b>	<b>8.35</b>	<b>6.30</b>	<b>5.08</b>
Csad	<b>-2.96</b>	<b>3.85</b>	<b>3.78</b>	<b>5.87</b>	<b>7.23</b>
Abca8a	<b>-2.77</b>	<b>3.60</b>	<b>3.11</b>	<b>2.22</b>	<b>2.78</b>
Cyp2b20	<i>6.15</i>	<b>15.99</b>	<b>17.87</b>	<b>18.41</b>	<b>24.34</b>
Igfbp2	<i>-3.20</i>	<b>8.80</b>	<b>10.16</b>	<b>6.12</b>	<b>6.83</b>
Socs2	<i>3.24</i>	<b>8.32</b>	<b>5.38</b>	<b>7.46</b>	<b>7.72</b>
Slco2a1	<i>-1.36</i>	<b>5.73</b>	<b>5.45</b>	<b>6.42</b>	<b>7.79</b>
Cyp2c29	<i>2.01</i>	<b>4.95</b>	<b>4.73</b>	<b>7.96</b>	<b>9.76</b>
Cyp1a2	<i>-0.59</i>	<b>4.92</b>	<b>5.83</b>	<b>2.85</b>	<b>3.62</b>
3110082I17Rik	<i>1.31</i>	<b>4.71</b>	<b>3.79</b>	<b>4.41</b>	<b>3.92</b>
Cyp1a2	<i>-0.50</i>	<b>4.61</b>	<b>5.76</b>	<b>2.25</b>	<b>2.62</b>
Apom	<i>0.01</i>	<b>4.43</b>	<b>3.40</b>	<b>4.16</b>	<b>3.92</b>
Ptpre	<i>0.61</i>	<b>4.03</b>	<b>3.15</b>	<b>2.61</b>	<b>2.09</b>
Cyp2c37	<i>1.45</i>	<b>4.01</b>	<b>3.65</b>	<b>2.90</b>	<b>2.36</b>
Iap	<i>-0.83</i>	<b>3.93</b>	<b>3.60</b>	<b>2.75</b>	<b>1.91</b>
Pnp	<i>0.61</i>	<b>3.85</b>	<b>2.07</b>	<b>2.47</b>	<b>2.06</b>
Foxq1	<i>1.02</i>	<b>3.50</b>	<b>2.91</b>	<b>4.01</b>	<b>6.22</b>
H13	<i>-0.68</i>	<b>3.43</b>	<b>1.74</b>	<b>1.57</b>	<b>1.73</b>
Rpl12	<i>0.22</i>	<b>3.42</b>	<b>2.36</b>	<b>3.33</b>	<b>3.41</b>
Cyp4f13	<i>-0.20</i>	<b>3.34</b>	<b>2.68</b>	<b>1.74</b>	<b>2.24</b>
Zfp259	<i>-0.08</i>	<b>3.26</b>	<b>2.73</b>	<b>2.95</b>	<b>1.96</b>
Cyp2c50	<i>1.46</i>	<b>3.17</b>	<b>3.44</b>	<b>2.96</b>	<b>2.42</b>
Rps10	<i>-0.03</i>	<b>3.11</b>	<b>1.68</b>	<b>1.62</b>	<b>1.68</b>
Cidea	<i>1.64</i>	<b>-16.66</b>	<b>-19.16</b>	<b>-14.49</b>	<b>-19.49</b>
Cfd	<i>-0.79</i>	<b>-12.72</b>	<b>-15.73</b>	<b>-15.23</b>	<b>-17.91</b>
Mmd2	<i>3.94</i>	<b>-12.28</b>	<b>-12.47</b>	<b>-6.24</b>	<b>-6.88</b>
Clstn3	<i>-0.25</i>	<b>-10.35</b>	<b>-10.57</b>	<b>-7.24</b>	<b>-7.50</b>
Robo1	<i>2.53</i>	<b>-8.49</b>	<b>-8.50</b>	<b>-2.86</b>	<b>-4.58</b>
Ntrk2	<i>-1.65</i>	<b>-8.06</b>	<b>-9.01</b>	<b>-7.65</b>	<b>-7.41</b>
Bhmt	<i>-0.17</i>	<b>-7.58</b>	<b>-6.42</b>	<b>-2.90</b>	<b>-5.23</b>

Slc17a8	-2.38	<b>-7.57</b>	<b>-3.09</b>	<b>-4.22</b>	<b>-4.25</b>
Anxa2	<i>3.07</i>	<b>-6.86</b>	<b>-8.69</b>	<b>-3.88</b>	<b>-5.15</b>
Lyplal1	<i>0.18</i>	<b>-5.55</b>	<b>-4.47</b>	<b>-1.98</b>	<b>-2.71</b>
Acot11	<i>-1.52</i>	<b>-5.45</b>	<b>-4.01</b>	<b>-5.87</b>	<b>-5.79</b>
1110028A07R	<i>1.38</i>	<b>-4.99</b>	<b>-5.10</b>	<b>-3.05</b>	<b>-2.42</b>
Rgs5	<i>0.96</i>	<b>-4.56</b>	<b>-3.25</b>	<b>-2.06</b>	<b>-1.94</b>
S100a11	<i>1.90</i>	<b>-4.19</b>	<b>-4.87</b>	<b>-2.34</b>	<b>-3.30</b>
Cd59b	<i>-0.29</i>	<b>-4.16</b>	<b>-3.98</b>	<b>-2.62</b>	<b>-2.12</b>
BC026585	<i>1.26</i>	<b>-4.07</b>	<b>-5.32</b>	<b>-2.13</b>	<b>-2.80</b>
Slc44a1	<i>-0.12</i>	<b>-3.98</b>	<b>-3.33</b>	<b>-1.81</b>	<b>-2.04</b>
1300018L09Rik	<i>-1.39</i>	<b>-3.95</b>	<b>-1.83</b>	<b>-1.59</b>	<b>-1.61</b>
1300013J15Rik	<i>0.39</i>	<b>-3.94</b>	<b>-2.54</b>	<b>-5.08</b>	<b>-6.14</b>
1300013J15Rik	<i>0.96</i>	<b>-3.90</b>	<b>-2.90</b>	<b>-5.45</b>	<b>-5.74</b>

HFD, high-fat diet; HFDH, HFD+high DSF; HFDL, HFD+low DSF; SD, standard diet; SDH, SD+high DSF; SDL, SD+low DSF. **Boldface**, significant expression; *italic*, non-significant.

**Supplementary Table 4.** List of the top 20 significantly changed proteins in the livers of rat treated with low (L-DSF) and high (H-DSF) doses of DSF vs. control chow (ctrl). FC, fold change. Related to Fig. 3.

Protein_IDs	Protein_names	Gene_names	Global_Log10P_BH	Log10P_BH		Log2FC	
				H-DSF-ctrl	L-DSF-ctrl	H-DSF-ctrl	L-DSF-ctrl
P46418;A0A0G2JB1;A0A0G2K8O5	Glutathione S-transferase alpha-5	Gsta5	5.91	6.58	3.22	<b>4.00</b>	<b>3.33</b>
B2GV28;A0A140UHW7;P00176f;1LMN1;	Cytochrome P450 2B1	Cyp2b1	2.64	3.16	1.53	<b>2.91</b>	<b>2.63</b>
P38918	Aflatoxin B1 aldehyde reductase member 3	Akr7a3	3.49	4.03	2.06	<b>2.45</b>	<b>1.70</b>
G6T5E9;Q63662	UDP-glucuronosyltransferase 2B1	Ugt1a1;Ugt1a6	4.08	4.53	2.68	<b>2.29</b>	<b>1.86</b>
P09875;A0A0G2JUD3	UDP-glucuronosyltransferase 2B1	Ugt2b1	4.11	4.68	2.40	<b>2.07</b>	<b>1.75</b>
G6T5E8;G6T5E7	Lambda-crystallin homolog	Ugt1a1	2.72	3.19	1.62	<b>1.88</b>	<b>1.54</b>
O811X6	Glutathione S-transferase alpha-2;Glutathione S-transferase	Cyt1	2.43	2.89	1.56	<b>1.85</b>	<b>1.50</b>
P04903;Q4FZZ3	Pirin	Gsta2;Gsta5	6.11	6.68	3.19	<b>1.58</b>	<b>1.03</b>
O5M827	Carboxylic ester hydrolase	Pir	3.03	3.59	1.63	<b>1.38</b>	<b>1.11</b>
Q32Q55	Metalloreductase STEAP3	Ces2h	6.92	7.29	5.19	<b>1.30</b>	<b>0.96</b>
A0A0H2U126;Q5RKL5	Beta-glucuronidase	Steap3	5.26	5.31	4.42	<b>-1.07</b>	<b>-0.95</b>
F1LQO8;P06760;Q77P13	Dimethylamine monoxygenase [N-oxide-forming] 5	Gusb	9.62	9.45	8.98	<b>-1.13</b>	<b>-1.04</b>
Q8K4C0	Arylacetamide deacetylase	Fmos	7.92	8.38	5.99	<b>-1.14</b>	<b>-0.72</b>
Q5I0ND;Q9QZH8	Trifunctional enzyme subunit beta, mitochondrial;3-ketoacyl	Aadac	4.35	4.91	2.67	<b>-1.18</b>	<b>-0.60</b>
G60587;A0A0G2K330	Trifunctional enzyme subunit alpha, mitochondrial;long-ch	Hadhb	8.76	9.16	6.95	<b>-1.19</b>	<b>-0.83</b>
G64428	PHD finger protein 11	Phf11b;Phf11	9.12	9.45	7.37	<b>-1.22</b>	<b>-0.86</b>
MORB46;Q5I0E2;F1LQ59	Acyl-coenzyme A amino acid N-acyltransferase 2	Achna2	2.56	2.46	2.33	<b>-1.28</b>	<b>-1.68</b>
Q5FVR5;A0A0G2IV92;A0A0G2K2H6	Cytochrome P450 3A2	Cyp3a2	3.86	4.15	2.83	<b>-1.38</b>	<b>-0.97</b>
P05183	Acetyl-CoA acetyltransferase, mitochondrial	Acat1	4.68	4.81	4.06	<b>-1.50</b>	<b>-1.34</b>
P17764			8.47	8.60	7.08	<b>-1.75</b>	<b>-1.31</b>

**Supplementary Table 5.** Enrichment of KEGG pathways (from STRING) and GSEA report establishing a number of KEGG pathways statistically significant in livers of DSF-treated rats vs. controls. Related to Fig. 3.

# term ID	Term description	# Genes	Fdr
mmu01100	Matabolic pathways	31	6.94E-17
mmu00983	Drug metabolism – other enzymes	12	2.51E-14
mmu00980	Metabolism of xenobiotics by cytochrome P450	10	2.12E-12
mmu05204	Chemical carcinogenesis	10	3.80E-11
mmu00982	Drug metabolism – cytochrome P450	9	7.27E-11
mmu00380	Tryptophan metabolism	6	2.40E-07
mmu00071	Fatty acid degradation	6	3.73E-07
mmu01212	Fatty acid metabolism	6	3.73E-07
mmu00280	Valine, leucine and isoleucine degradation	6	5.04E-07
mmu00480	Glutathione metabolism	6	8.11E-07

KEGG pathway	# Genes	ES	NES	NOM <i>P</i> -val	Q-value
Drug_Metabolism_CYP450	35	0.747	1.689	0.000	0.055
Peroxisome	57	0.600	1.693	0.004	0.064
Snare_Interactions_in_Vesicular_Transport	19	0.571	1.696	0.004	0.077
Metabolism_of_Xenobiotics_by_CYP450	30	0.824	1.715	0.000	0.084
Retinol_Metabolism	16	0.783	1.617	0.006	0.094
Proteasome	37	0.642	1.785	0.018	0.117
Glutathione_Metabolism	34	0.686	1.718	0.000	0.124
PPAR_Signaling_Pathway	38	0.497	1.447	0.048	0.246
Tyrosine_Metabolism	17	0.586	1.463	0.082	0.249

# Gene, number of genes in Geneset; ES, enrichment score; NES, normalized ES; NOM *P*-val, normalized *P* value; Q-value, false discovery rate with cut-off value of 0.25.

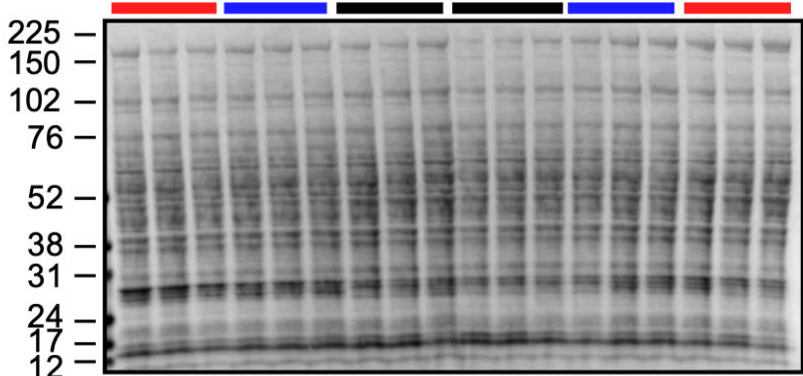
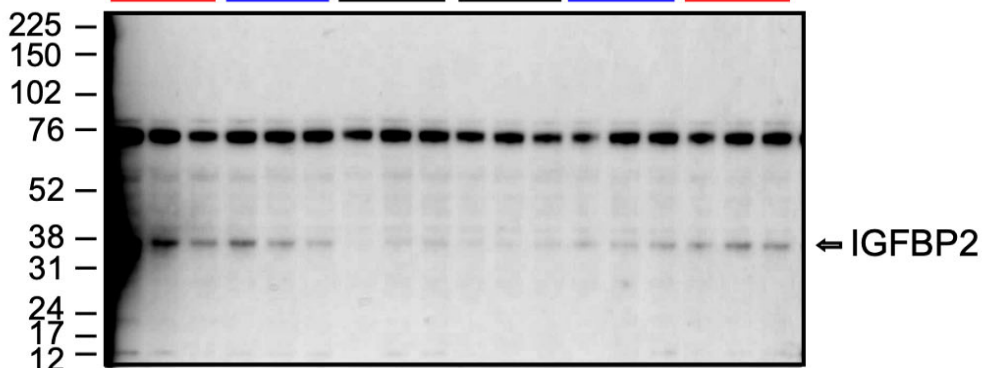
**Supplementary Table 6.** List of murine oligonucleotide primers used for validation of microarray analysis. Related to Fig. 1.

Target mRNA	Primer	Sequence (5' → 3')
Igfbp2	For Rev	CAGACGCTACGCTGCTATCC CCCTCAGAGTGGTCGTCATCA
Avpr1A	For Rev	GCTGGCGGTGATTTTCGTG GCAAACACCTGCAAGTGCT
Cyp2c29	For Rev	CATCGACCTCCTCCCCACTAGC GGTTGGGAAACTCCTTGCTGTCA
Socs2	For Rev	AGTTCGCATTCAGACTACCTACT TGGTACTCAATCCGCAGGTTAG
Raet1b	For Rev	TGGACACTCACAAGACCAATG CCCAGGTGGCACTAGGAG
Acot11	For Rev	TGGGGAGCTGAGCATTGGA GGCCGACACTAATGGTATGGT
Cidea	For Rev	ATCACAACCTGGCCTGGTTACG TACTACCCGGTGTCCATTTCT
Hprt	For Rev	TGGGAGGCCATCACATTGT GCTTTTCCAGTTTCACTAATGACA
18S	For Rev	GTAACCCGTTGAACCCATT CCATCCAATCGGTAGTAGCG

Figure S1e

Figure 1i

SDH SDL SD HFD HF DL HFDH



Ponceau S staining

SDH SDL SD HFD HF DL HFDH

