

**Supplemental Table 1 for Henneicke H *et al.* Differentially-regulated canonical pathways in bones from wild-type and HSD2<sup>OB</sup>-tg mice at 3, 6, 12 and 18 months of age.** Canonical pathways with only one gene differentially expressed were excluded from analysis. z-scores indicate directionality of change, with positive being overexpressed in HSD2<sup>OB</sup>-tg mice, negative being down-regulated in HSD2<sup>OB</sup>-tg mice. *p*-values relate to the degree of overlap between all of the genes in the pathway and the number of genes identified as differentially expressed, assessed by a one-sided Fischer's exact test. Only canonical pathways with a *p*<0.05 were considered.

Timepoint	Pathway	Genes, with direction of change indicated	z-score	Overlap (%)	<i>p</i> -value
3 months	Triacylglycerol Biosynthesis	↓DGAT2L6, ↑GPAT3, ↓PLPPR3, ↑PLPPR4, ↑TAZ	0.447	5/44 (11%)	0.0144
	Ceramide Biosynthesis	↑KDSR, ↓SPTSSB	N/A	2/7 (29%)	0.0204
	Mineralocorticoid Biosynthesis	↓CYP11B1, ↑Hsd3b4 (includes others)	N/A	2/8 (25%)	0.0266
	Glucocorticoid Biosynthesis	↓CYP11B1, ↑Hsd3b4 (includes others)	N/A	2/9 (22%)	0.0334
	Neuropathic Pain Signaling In Dorsal Horn Neurons	↑ELK1, ↑FRS2, ↑GPR37, ↑GRIN2A, ↑GRM1, ↓PLCH1, ↓PTPN11, ↓TACR1	0.707	8/115 (7%)	0.0363
	Ketogenesis	↓BDH1, ↑HMGCS1	N/A	2/10 (20%)	0.0409
	6 months	Coenzyme A Biosynthesis	↑COASY, ↓PPCS	N/A	2/3 (67%)
Inflammasome pathway		↑IL1B, ↑NLRP1, ↑NOD2	N/A	3/19 (16%)	0.0356
Maturity Onset Diabetes of Young Signaling		↑INS, ↑INSR, ↓PDX1	N/A	3/21 (14%)	0.0461
12 months	LPS/IL-1 mediated inhibition of RXR function	↓ABCG8, ↑ACSBG1, ↓ALDH18A1, ↑CD14, ↑CYP2C8, ↑Cyp4a14, ↑FABP6, ↓HMGCS1, ↓HS6ST2, ↑IL1RN, ↑LBP, ↑MYD88, ↑PPARA, ↑SULT2A1, ↓SULT2B1, ↑TNFRSF1B	0.707	16/204 (8%)	0.0065
	Nucleotide Excision Repair Pathway	↓GTF2H1, ↓GTF2H4, ↓POLR2L, ↓RAD23B, ↓RPA1	N/A	5/33 (15%)	0.0086

	DNA Double-Strand Break Repair by Homologous Recombination	↓MRE11, ↓RAD50, ↓RPA1	N/A	3/14 (21%)	0.0157
	Communication between Innate and Adaptive Immune Cells	↑Ccl9, ↓HLA-A, ↑IGHG1, ↑Ighg2b, ↑IL1RN, ↓Tlr11, ↑Tlr13	N/A	7/74 (9%)	0.0253
	TNFR2 Signaling	↓BIRC2, ↓Naip1 (includes others), ↓TBK1, ↑TNFRSF1B	1.000	4/30 (13%)	0.0282
	Sucrose Degradation V (Mammalian)	↑ALDOB, ↑GALM	N/A	2/8 (25%)	0.0365
	Assembly of RNA Polymerase II Complex	↓GTF2E1, ↓GTF2H1, ↓GTF2H4, ↓POLR2L, ↓TAF1	N/A	5/48 (10%)	0.0385
	Citrulline Biosynthesis	↓ALDH18A1, ↑ARG1	N/A	2/9 (22%)	0.0457
18 months	Galactose degradation I (Leloir pathway)	↑GALK2, ↑GALM	N/A	2/5 (40%)	0.0140
	SPINK1 pancreatic cancer pathway	↓CPM, ↓ELANE, ↓F2RL1, ↓KLK3, ↓KLK8, ↓Prss (includes others)	1.633	6/54 (11%)	0.0180
	MSP/RON signalling pathway	↑ACTG1, ↑ITGAM, ↓KLK3, ↓KLK8, ↓PIK3C2B, ↓PIK3R1	N/A	6/56 (11%)	0.0212
	B cell development	↓CD19, ↓CD79A, ↓CD79B, ↓HLA-DMB	N/A	4/28 (0.14)	0.0221
	Chondroitin Sulfate Degradation (Metazoa)	↑Chi3/Chi4, ↑GALNS, ↑HEXD	N/A	3/16 (19%)	0.0225
	LXR/RXR activation	↑ABCG8, ↑APOA4, ↑ARG2, ↓C4A/C4B, ↑IL1B, ↑IL1RL2, ↑MSR1, ↓NFKB2, ↓NR1H3	-0.378	9/110 (8%)	0.0277
	IL-23 Signaling Pathway	↑IL1B, ↓IL23R, ↓NFKB2, ↓PIK3C2B, ↓PIK3R1	-1.342	5/45 (11%)	0.0298
	Sucrose Degradation V (Mammalian)	↑GALM, ↑KHK	N/A	2/8 (25%)	0.0362
	Hepatic cholestasis	↑ABCG8, ↓FABP6, ↑IL1B, ↑IL1RL2, ↑IL31, ↑IRAK3, ↑IRAK4, ↓NFKB2, ↓NR1H3, ↓PRKCE, ↓SLC22A6, ↓TNFSF8		12/173 (7%)	

B cell receptor signaling

↓ABL1, ↓CD19, ↓CD79A, ↓CD79B, ↓FOXO1, ↑INPP5J,  
↓MAP3K6, ↑MAPK13, ↓NFKB2, ↓PAX5, ↓PIK3C2B,  
↓PIK3R1

-2.111

12/176 (7%)

0.0426

**Supplemental Table 2. Upstream regulators of differential gene (DE) expression at 3, 6, 12 and 18 months.** DE genes were analysed using IPA to determine potential upstream regulators of gene expression at each timepoint. The table lists all potential upstream regulators with a z-score either greater than +2 (indicating activation) and less than -2 (indicating inhibition). *p*-values are calculated based upon overlap between the number of DE genes and the total number of genes in the pathway, significance is calculated using a one-sided Fisher's exact test.

Timepoint	Factor	Function	Genes regulated by the factor, and their direction	z-score	p-value
3 months	AGO2	translation regulator	↓let-7, ↓mir-130, ↓mir-154, ↓mir-467, ↓mir-489	-2.194	0.19
	NR1H3	ligand-dependent nuclear receptor	↑ATF3, ↓CYP7A1, ↓CYTH1, ↑DIO2, ↑MFGE8, ↑PTGS2	-2.172	1
	ZBTB16	transcription regulator	↑CD200R1, ↓DTX1, ↑PTGS2, ↓RARG	-2	0.472
	TLR4	transmembrane receptor	↑ATF3, ↑CD200R1, ↓NAA80, ↓ORMDL3, ↑PTGS2, ↓SCARB1	2.164	1
6 months	SRF	transcription regulator	↓GATA4, ↑GFI1, ↑MGST2, ↓mir-133, ↑MOGAT2, ↑MS4A3, ↓MYOCD, ↑Ngp	-2.8	0.265
	MRTFB	transcription regulator	↑GFI1, ↑MGST2, ↑MOGAT2, ↑MS4A3, ↑Ngp	-2.236	0.198
	MRTFA	transcription regulator	↑GFI1, ↑MGST2, ↑MOGAT2, ↑MS4A3, ↑Ngp	-2.236	0.275
	Creb	group	↓IFI16, ↑mir-124, ↓mir-9, ↑PLIN3, ↑SYNPO	-2.219	1
	GATA1	transcription regulator	↑HPSE, ↓IKZF4, ↓PECAM1, ↓POU4F1, ↓ZNF496	-2	1
	P2RY14	G-protein coupled receptor	↑MAFA, ↑PDE1C, ↓RASL10B, ↑SSTR1	2	0.0201

12 months	MYD88	other	↑ACPP, ↓AK3, ↑CCL4, ↑CEBPD, ↑IFNA4, ↑IL1B, ↑INHBA, ↑NOD2	2.116	1
	PTPRJ	phosphatase	↑ACPP, ↑CCL4, ↑CEBPD, ↑FGL2, ↑INHBA	2.236	0.0267
	SASH1	other	↑ACPP, ↑CCL4, ↑FGL2, ↑HHEX, ↑INHBA	2.236	0.13
	NOS2	enzyme	↑CCL4, ↑GSPT2, ↑IL1B, ↑KRT13, ↑Orm1 (includes others), ↑PLSCR1	2.236	0.547
	STAT1	transcription regulator	↑ARG1, ↓BATF2, ↓Cxcl11, ↑CYP2C8, ↓IFIT3, ↓PSMB10, ↓TAPBPL	-2.401	0.47
	EGFR	kinase	↑ARG1, ↓HNRNPD, ↓KPNB1, ↓TIMM10, ↓XRN2	-2.233	0.433
	MRTFB	transcription regulator	↑DMKN, ↑GFI1, ↓HLA-A, ↑PRG3, ↑SLPI	-2	0.208
	MRTFA	transcription regulator	↑DMKN, ↑GFI1, ↓HLA-A, ↑PRG3, ↑SLPI	-2	0.288
	LHX1	transcription regulator	↑ALDOB, ↑CLTRN, ↓HHEX, ↑SLC22A24, ↑SLC34A1, ↑SOSTDC1, ↑SPP2, ↑UGT2B28	2	0.0474
	mir-223	microRNA	↑C5AR1, ↑IL1RN, ↓MLKL, ↑Tlr13	2	1
	IKZF1	transcription regulator	↓Grifin, ↓PPP1R9A, ↓PRRT3, ↑SLPI	2	0.556
	TCF7L2	transcription regulator	↑BACE1, ↑CREB5, ↑CYP2C8, ↓EPS15, ↓Gcg, ↑MOG, ↑PIM3, ↑PLEKHH1, ↑SMCO3	2.121	1
	PTTG1	transcription regulator	↓MBD4, ↓RAD50, ↓SUMO1, ↓TLK1, ↓XRN2	2.219	0.0899
	PRDM1	transcription regulator	↓CABP5, ↑Gm14685 (includes others), ↑IGHG1, ↑JCHAIN, ↑TRIM65	2.236	0.251

18 months	MRTFA	transcription regulator	↑CTSG, ↑DMKN, ↑ELANE, ↑FABP3, ↑GFI1, ↑LILRB4, ↑MAPK13, ↑MS4A3, ↑Ngp, ↑PGLYRP1, ↑PRSS57, ↑PRTN3	-3.317	0.000214
	MRTFB	transcription regulator	↑CTSG, ↑DMKN, ↑ELANE, ↑GFI1, ↑LILRB4, ↑MAPK13, ↑MS4A3, ↑Ngp, ↑PGLYRP1, ↑PRSS57, ↑PRTN3	-3.162	0.000276
	SRF	transcription regulator	↑ACTG1, ↓CD19, ↑CTSG, ↑DMKN, ↑ELANE, ↑GFI1, ↑ITGAM, ↑MAPK13, ↑MS4A3, ↑Ngp, ↑PGLYRP1, ↑PRSS57, ↑PRTN3, ↑TBXT	-3.051	0.00353
	ZEB2	transcription regulator	↑CTSG, ↑ELANE, ↑GATM, ↑LTA4H, ↑MPO, ↑MS4A3, ↑PRTN3	-2.646	0.000364
	IL10RA	transmembrane receptor	↑ARG2, ↑CLEC12A, ↑CLEC4E, ↑CLEC5A, ↑CST7, ↑ERO1A, ↑F13A1, ↑IL1B, ↓KLK3, ↓Nnt, ↓NR1H3, ↑OLR1, ↓SLC7A11, ↓Speer4a (includes others), ↑TARM1, ↓TTLL6	-2.523	0.101
	ADAMTS12	peptidase	↑CHI3L1, ↑Chil3/Chil4, ↑CLEC4E, ↑HDC, ↑S100A6	-2.219	0.00225
	NCSTN	peptidase	↑CD84, ↑CTSG, ↑ELANE, ↑MPO	-2	0.0358
	INSIG1	other	↑ALOX5AP, ↑CLEC4E, ↑OLR1, ↑RAB27A	-2	0.477
	LTB4R	G-protein coupled receptor	↑CLEC10A, ↓mir-10, ↓mir-146, ↓NR1H3	-2	0.0141
	Hbb-b2	other	↑CALCB, ↑CD44, ↑IL1B, ↑ITGAM	2	0.0977
	CREB1	transcription regulator	↑Chil3/Chil4, ↓CYP46A1, ↑ENTPD1, ↑NFIL3, ↑PDXK, ↑SPTY2D1	2.2	0.0891

HOXA10	transcription regulator	↓ADIPOQ, ↑G6pd2, ↑GFI1, ↓Gstt1, ↓PIK3R1	2.236	0.305
Hbb-b1	transporter	↑CALCB, ↑CD44, ↑IL1B, ↑ITGAM, ↑SURF1	2.236	0.282
TCF7L2	transcription regulator	↑CERS2, ↑DEGS1, ↑GJC2, ↓Gm11237 (includes others), ↑KLHL2, ↑LTV1, ↑RHOG, ↑SMIM15, ↑STRN	2.333	1
CCR2	G-protein coupled receptor	↓ADIPOQ, ↑Ccl6, ↑Chi3/Chi4, ↑F13A1, ↑IL1B, ↑THBS1, ↑VCAN	2.377	0.0916
IL4	cytokine	↑ACTG1, ↑ANXA2, ↓CD2, ↑CD44, ↑Chi3/Chi4, ↑CLEC10A, ↑CLTC, ↑CST7, ↓EPHX1, ↓GATA3, ↑GATM, ↑IL1B, ↑NFIL3, ↑PLSCR1, ↑RIN1, ↑TYRO3, ↑UGGT1	2.51	0.345