

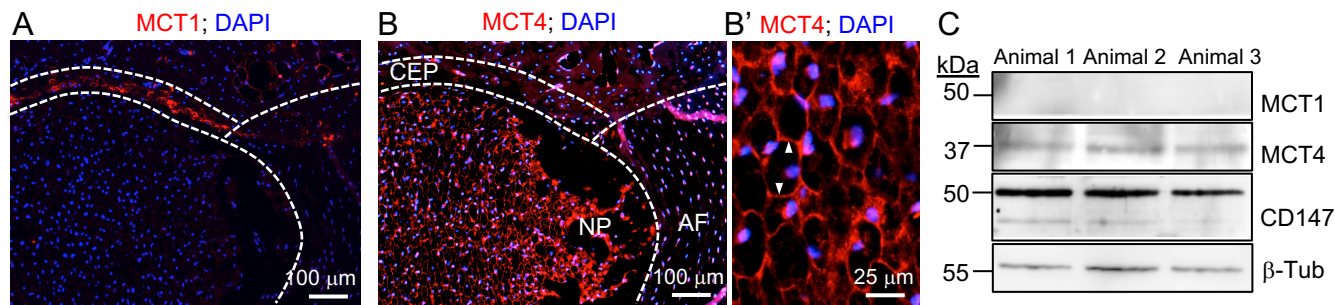
Supplemental Figure 1: Levels of *SLC16A1* (MCT1), *SLC16A3* (MCT4) and *BSG* (CD147) Expression in Human Disc Tissue

A-C) qRT-PCR expression levels of *SLC16A1*, *SLC16A3*, and *BSG* mRNA in healthy (4), moderately-degenerate (4.6-6.9), severely-degenerate (7), and immune cell-infiltrated (INF) human discs. Graphs display the percent of disc samples expressing mRNA in each group.

D-D'') Representative immunohistochemical images showing MCT1-positive cells and MCT1-negative cells in healthy (D), moderately-degenerate (D'), and severely-degenerate (D'') human samples.

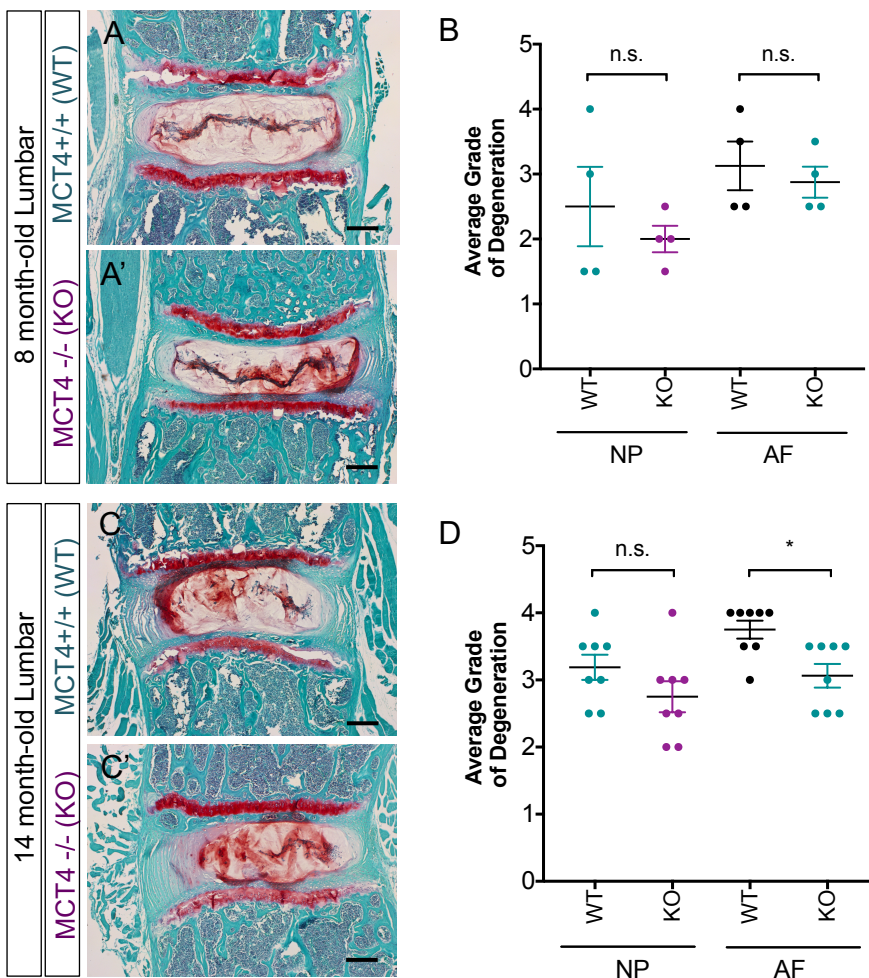
E) Percent MCT1 immunopositivity in healthy, moderately-, and severely-degenerate human discs. F-F'') Representative immunohistochemical images showing CD147-positive cells and CD147-negative cells in healthy (F), mid-degenerate (F'), and severe degenerate (F'') human samples.

G) Percent CD147 immunopositivity in healthy, moderately-, and severely-degenerate human discs. H-J) Negative control IHC for MCT1 (H) and MCT4 (I) with Rabbit IgG, and CD147 (J) with Goat IgG. Lack of HRP-positive staining indicates antibody specificity. Statistical analysis on non-parametric IHC quantification was performed by Kruskal Wallis and Conover Ingman post hoc test. n.s.= not significant.



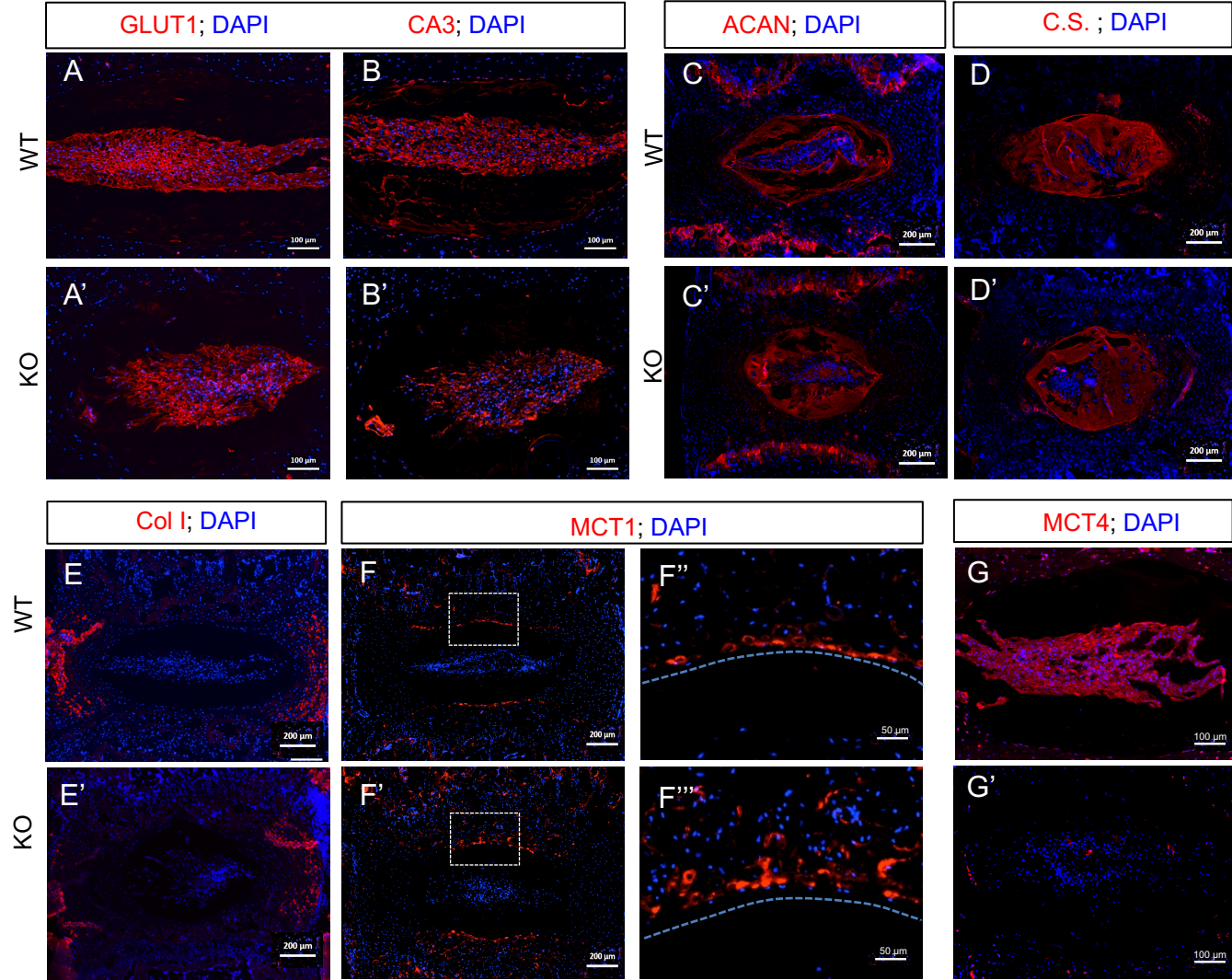
Supplemental Figure 2: Levels of MCT and CD147 Expression in Rodent Disc Tissue

A) Representative immunostaining showing MCT1 expression in the CEP. B, B') Representative immunostaining showing MCT4 expression in the NP compartment. C) Representative Western blot showing relative MCT1, MCT4, and CD147 expression in tissue protein lysate from rat NP.



Supplemental Figure 3: Histological Grades of Degeneration in WT and MCT4 KO Lumbar Spine

A, A') Safranin-O/Fast Green staining of the intervertebral disc in 8 mo WT and global MCT4 KO mice (Scale bar = 200  $\mu$ m). C) Average modified-Thompson grade of NP and AF degeneration. C, C') Safranin-O/Fast Green staining of the intervertebral disc in 14 mo WT and global MCT4 KO mice (Scale bar = 200  $\mu$ m). C) Average modified-Thompson grade of NP and AF degeneration. Statistical analysis: *t*-test, n.s.= not significant; \*, *p*-value  $\leq$  0.05.



Supplemental Figure 4: Characterization of NP phenotype and matrix composition in MCT4 KO mice.

Representative immunostaining in the intervertebral discs of 14 mo WT and MCT4 KO mice. NP phenotypic markers: A, A') GLUT1; B, B') CA3. (Scale bars= 100  $\mu$ m). Extracellular matrix molecules: C, C') ACAN; D-D') Chondroitin Sulfate, E-E) Collagen I. (Scale bars= 200  $\mu$ m). F-F''') Expression of MCT1 is not compensatory for loss of MCT4. G, G') MCT4 expression is lost in MCT4 KO animals. Imaged at 10X and 20X (Left scale bars= 200  $\mu$ m; Right scale bars= 50  $\mu$ m). Dotted lines were drawn to demarcate different tissue compartments within the disc. All staining was performed using at least 3 animals/genotype corresponding to Grade 2.

	Reference	Source	Age	IVD Level	Intact IVD?	Average Grade	Classification
HD	40	PM	74	L2/L3	Yes	11	SD
HD	65	Surgical	43	L4/L5	No	10	I
HD	71	Surgical	42	L5/S1	Yes	3	ND
HD	89	Surgical	21	L5/S1	No	4	ND
HD	98	Surgical	65	L3/L4	Yes	11	SD
HD	103	Surgical	45	C5/C6	No	9.5	SD
HD	145	Surgical	38	L4/L5	No	11	I
HD	154	Surgical	52	L4/L5	No	11	SD
HD	158	Surgical	38	L4/L5	No	7	I
HD	159	Surgical	39	L4/L5	No	9	I
HD	203	Surgical	45	L5/S1	Yes	4	ND
HD	219	Surgical	54	L5/S1	No	11	I
HD	229	Surgical	56	L5	Yes	6	MD
HD	233	Surgical	44	L5/S1	Yes	10	SD
HD	234	Surgical	54	L5/S1	Yes	9	SD
HD	254	Surgical	47	L4/L5	No	6	I
HD	257	Surgical	46	L5/S1	No	3	I
HD	264	Surgical	65	C3/C5	Yes	6	MD
HD	266	Surgical	27	L5/S1	No	4	ND
HD	270	Surgical	45	L5/S1	No	6	MD
HD	282	Surgical	21	L5/S1	No	4	ND
HD	310	Surgical	37	L4/L5	Yes	5	I
HD	319	Surgical	47	L5/S1	No	5	MD
HD	330	Surgical	32	L5/S1	Yes	5.5	MD
HD	346	Surgical	46	C5/C6	Yes	6	MD
HD	359	Surgical	40	L5/S1	No	4	ND
HD	360	Surgical	50	C6		5.5	MD
HD	370	Surgical	50	L5/S1	Yes	8	SD
HD	375	Surgical	41	L5/S1	No	6	MD
HD	380	PM	33	L2/L3	Yes	4	ND

Supplemental Table S1: Human Intervertebral disc sample information.

Samples were separated into different grades, 0-4 (Non-degenerate, ND), 4.1-6.9 (Moderately-degenerate, MD) and 7-12 (Severely-degenerate, SD).

Grade	Nucleus pulposus	Annulus Fibrosus
Grade 1	Aggrecan-rich, bulging tissue	Discrete fibrous lamellae
Grade 2	Peripheral fibrous tissue	Mucinous material between lamellae
Grade 3	Consolidated fibrous tissue	Extensive mucinous material between lamellae and loss of NP-AF demarcation
Grade 4	Horizontal clefts parallel to the endplate	Focal lamellar disruptions (clefts)
Grade 5	Clefts through NP and AF	Clefts through NP and AF

Supplemental Table S2: Modified Thompson scale used for histological grading.

Category	Term	Count	List Total	Fold Enrichment	Bonferroni	FDR (%)
GOTERM_CC_FAT	GO:0000786-nucleosome	29	274	11.48865113	3.89E-20	1.17E-19
GOTERM_CC_FAT	GO:0044815-DNA packaging complex	29	274	11.03515175	1.44E-19	4.31E-19
KEGG_PATHWAY	mmu05322:Systemic lupus erythematosus	28	145	9.244522043	1.36E-17	9.26E-17
GOTERM_CC_FAT	GO:0032993-protein-DNA complex	30	274	6.940729927	5.31E-14	1.55E-13
GOTERM_CC_FAT	GO:0000788-nuclear nucleosome	17	274	16.95293229	5.31E-14	1.55E-13
GOTERM_CC_FAT	GO:0000790-nuclear chromatin	41	274	4.705190592	5.31E-14	1.55E-13
KEGG_PATHWAY	mmu05034:Alcoholism	29	145	6.356302521	1.81E-13	1.23E-12
GOTERM_CC_FAT	GO:0000785-chromatin	45	274	3.526793662	1.00E-10	2.99E-10
GOTERM_BP_FAT	GO:0006334-nucleosome assembly	21	298	7.325542835	1.36E-08	6.48E-09
GOTERM_BP_FAT	GO:0031497-chromatin assembly	22	298	6.724970594	2.18E-08	1.04E-08
GOTERM_CC_FAT	GO:0044454-nuclear chromosome part	43	274	3.196780065	1.04E-08	3.12E-08
GOTERM_CC_FAT	GO:0000228-nuclear chromosome	44	274	3.111166634	1.40E-08	4.19E-08
GOTERM_BP_FAT	GO:0065004-protein-DNA complex assembly	23	298	5.455785235	5.10E-07	2.43E-07
GOTERM_BP_FAT	GO:0006333-chromatin assembly or disassembly	22	298	5.722124102	5.60E-07	2.67E-07
GOTERM_BP_FAT	GO:0006323-DNA packaging	22	298	5.575402971	9.31E-07	4.44E-07
GOTERM_BP_FAT	GO:0034728-nucleosome organization	21	298	5.874256047	9.94E-07	4.74E-07
GOTERM_BP_FAT	GO:0071103-DNA conformation change	24	298	4.907752835	1.67E-06	7.97E-07
GOTERM_BP_FAT	GO:0071824-protein-DNA complex subunit organization	23	298	4.671049002	1.10E-05	5.26E-06
GOTERM_CC_FAT	GO:0044427-chromosomal part	51	274	2.441895877	1.59E-06	4.76E-06
GOTERM_CC_FAT	GO:0005694-chromosome	53	274	2.254036067	1.11E-05	3.34E-05
GOTERM_BP_FAT	GO:0006325-chromatin organization	45	298	2.46179945	1.31E-04	6.25E-05
GOTERM_BP_FAT	GO:0006342-chromatin silencing	18	298	5.232530596	1.59E-04	7.59E-05
GOTERM_BP_FAT	GO:0002227-innate immune response in mucosa	8	298	18.24677336	2.53E-04	1.21E-04
GOTERM_BP_FAT	GO:0045814-negative regulation of gene expression, epigenetic	18	298	4.988019821	3.31E-04	1.58E-04
GOTERM_BP_FAT	GO:0002385-mucosal immune response	8	298	14.82550336	0.001547429	7.38E-04
GOTERM_BP_FAT	GO:0002251-organ or tissue specific immune response	8	298	14.82550336	0.001547429	7.38E-04
GOTERM_BP_FAT	GO:0051276-chromosome organization	53	298	2.073223424	0.001628717	7.77E-04
GOTERM_BP_FAT	GO:0019730-antimicrobial humoral response	8	298	13.95341492	0.002553995	0.001218542
GOTERM_BP_FAT	GO:0019731-antibacterial humoral response	8	298	13.95341492	0.002553995	0.001218542
GOTERM_BP_FAT	GO:0016458-gene silencing	19	298	3.456252316	0.032467809	0.015726583
GOTERM_BP_FAT	GO:0050830-defense response to Gram-positive bacterium	10	298	6.308724832	0.080063022	0.039756536
GOTERM_BP_FAT	GO:0008045-motor neuron axon guidance	7	298	10.9240551	0.095083142	0.04759739
GOTERM_BP_FAT	GO:0040029-regulation of gene expression, epigenetic	19	298	3.095434767	0.139043703	0.071312935
GOTERM_MF_FAT	GO:0031492-nucleosomal DNA binding	8	277	7.481046931	0.052682154	0.105860719
GOTERM_MF_FAT	GO:0031720-haptoglobin binding	4	277	29.92418773	0.105462586	0.21787281
GOTERM_CC_FAT	GO:0005833-hemoglobin complex	4	274	28.91970803	0.072617163	0.225427555
GOTERM_CC_FAT	GO:0031838-haptoglobin-hemoglobin complex	4	274	28.91970803	0.072617163	0.225427555
GOTERM_BP_FAT	GO:0006959-humoral immune response	10	298	4.941834452	0.460498993	0.293624708
GOTERM_BP_FAT	GO:0022008-neurogenesis	50	298	1.663917324	0.727773051	0.618072522
GOTERM_BP_FAT	GO:0007399-nervous system development	63	298	1.536195249	0.788150999	0.736752708
GOTERM_MF_FAT	GO:0031490-chromatin DNA binding	10	277	4.336838801	0.287792089	0.661993647
GOTERM_BP_FAT	GO:0030182-neuron differentiation	43	298	1.720638716	0.863779648	0.945407611
GOTERM_BP_FAT	GO:0098754-detoxification	6	298	8.471716203	0.87836997	0.99886609
GOTERM_MF_FAT	GO:0003677-DNA binding	64	277	1.50325898	0.364309242	0.882709431
GOTERM_BP_FAT	GO:0031175-neuron projection development	34	298	1.866915237	0.897664942	1.080317982
GOTERM_BP_FAT	GO:0045892-negative regulation of transcription, DNA-templated	42	298	1.710635003	0.925906245	1.232412284
GOTERM_BP_FAT	GO:0048666-neuron development	37	298	1.786787049	0.939239718	1.325739367
GOTERM_BP_FAT	GO:1903507-negative regulation of nucleic acid-templated transcription	42	298	1.703614613	0.940403494	1.334832098
GOTERM_MF_FAT	GO:0031491-nucleosome binding	8	277	5.093478762	0.483229381	1.283649355
GOTERM_BP_FAT	GO:0048812-neuron projection morphogenesis	23	298	2.171889027	0.96730562	1.616700812
GOTERM_BP_FAT	GO:1902679-negative regulation of RNA biosynthetic process	42	298	1.687455667	0.97593281	1.620843725
KEGG_PATHWAY	mmu05203:Viral carcinogenesis	16	145	2.592075391	0.167436844	1.240430365
GOTERM_BP_FAT	GO:0030030-cell projection organization	45	298	1.63717215	0.981725905	1.889034028
GOTERM_BP_FAT	GO:2000113-negative regulation of cellular macromolecule biosynthetic process	47	298	1.612959856	0.982647822	1.913232061
GOTERM_MF_FAT	GO:0005344-oxygen transporter activity	4	277	17.09953584	0.595593669	1.756183198
KEGG_PATHWAY	mmu05144:Malaria	6	145	7.113479624	0.189991897	1.425014745
GOTERM_BP_FAT	GO:0048699-generation of neurons	45	298	1.623230294	0.991097929	2.224687786
GOTERM_BP_FAT	GO:0006335-DNA replication-dependent nucleosome assembly	6	298	7.116241611	0.992760062	2.320929568
GOTERM_BP_FAT	GO:0034723-DNA replication-dependent nucleosome organization	6	298	7.116241611	0.992760062	2.320929568
GOTERM_BP_FAT	GO:0051253-negative regulation of RNA metabolic process	43	298	1.640918003	0.993940339	2.403724643
GOTERM_MF_FAT	GO:0043566-structure-specific DNA binding	11	277	3.393464587	0.66300335	2.106153885
GOTERM_BP_FAT	GO:0032776-DNA methylation on cytosine	6	298	6.84254001	0.997359314	2.789240242
GOTERM_BP_FAT	GO:0008285-negative regulation of cell proliferation	25	298	1.982019165	0.998865808	3.179924089
GOTERM_MF_FAT	GO:0005230-extracellular ligand-gated ion channel activity	4	277	14.96209386	0.756693103	2.728250104
GOTERM_BP_FAT	GO:0098542-defense response to other organism	19	298	2.25347651	0.999367138	3.448714516
GOTERM_CC_FAT	GO:0005887-integral component of plasma membrane	25	274	1.964654078	0.598711543	2.696339101
GOTERM_BP_FAT	GO:0010558-negative regulation of macromolecule biosynthetic process	47	298	1.560579301	0.999657298	3.73050617
GOTERM_BP_FAT	GO:0048468-cell development	59	298	1.462716886	0.99765405	3.904209281
GOTERM_BP_FAT	GO:0009605-response to external stimulus	53	298	1.499526103	0.99988074	4.2135072
GOTERM_MF_FAT	GO:0015276-ligand-gated ion channel activity	5	277	7.874786244	0.914425545	4.697250525
GOTERM_MF_FAT	GO:0022834-ligand-gated channel activity	5	277	7.874786244	0.914425545	4.697250525
KEGG_PATHWAY	mmu04080:Neuroactive ligand-receptor interaction	7	145	4.681520778	0.436956509	3.836983827
GOTERM_MF_FAT	GO:0020037-heme binding	8	277	4.05751698	0.922210935	4.874991139

Supplemental Table S3: Functional Annotation Analysis of DEGs from Microarray Data.

Gene Name	Primer Location		Primer Sequence	
	Start	End	Forward	Reverse
SLC16A3 Promoter	-1399	-1231	5'-ccccgtaagtggagaatgg-3'	5'-ggcgactttaagtgctctca-3'
SLC16A3 Intron	+775	+902	5'-cctactccaggcaatacgg-3'	5'-tggaagtagtgggccagtcg-3'
Car12	-172	-24	5'-gagtcgccacataaaaagca-3'	5'- ccgctggctctaagctgt-3'

Supplemental Table S4: Primer Sequences used for Chromatin Immunoprecipitations