SUPPLEMENTAL MATERIAL

“Obesity and dyslipidemia are associated with partially reversible modifications to DNA hydroxymethylation of apoptosis- and senescence-related genes in swine adipose-derived mesenchymal stem/stromal cells”

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Supplemental Tables

Table S1. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes with a multiplicity* of at least 2 in the 95 gene sets with high 5hmC/high mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.†

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0060337~type I interferon signaling pathway	66	2.49	4.26E-53	3.33E-49	3.33E-49	3.06E-49
GO:0019221~cytokine-mediated signaling pathway	145	5.46	1.93E-45	1.51E-41	7.54E-42	6.94E-42
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	311	11.72	3.09E-36	2.41E-32	8.05E-33	7.41E-33
GO:0006954~inflammatory response	150	5.65	2.01E-35	1.57E-31	3.93E-32	3.62E-32
GO:0006915~apoptotic process	188	7.08	1.89E-34	1.48E-30	2.96E-31	2.73E-31
GO:0001666~response to hypoxia	88	3.32	1.17E-30	9.12E-27	1.38E-27	1.27E-27
GO:0043066~negative regulation of apoptotic process	170	6.41	1.23E-30	9.64E-27	1.38E-27	1.27E-27
GO:0010628~positive regulation of gene expression	163	6.14	7.33E-29	5.73E-25	7.16E-26	6.60E-26
GO:0043065~positive regulation of apoptotic process	131	4.94	1.61E-27	1.26E-23	1.40E-24	1.29E-24
GO:0043123~positive regulation of I-kappaB kinase/NF-kappaB signaling	85	3.20	1.73E-26	1.35E-22	1.35E-23	1.25E-23
GO:0006687~glycosphingolipid metabolic process	36	1.36	2.15E-26	1.68E-22	1.53E-23	1.41E-23
GO:0007165~signal transduction	285	10.74	4.74E-26	3.70E-22	3.09E-23	2.84E-23
GO:0043312~neutrophil degranulation	149	5.61	2.32E-25	1.81E-21	1.40E-22	1.29E-22
GO:0008285~negative regulation of cell proliferation	142	5.35	1.93E-24	1.51E-20	1.08E-21	9.94E-22
GO:0071260~cellular response to mechanical stimulus	51	1.92	4.09E-24	3.20E-20	2.13E-21	1.96E-21
GO:0042493~response to drug	104	3.92	8.02E-24	6.27E-20	3.92E-21	3.61E-21
GO:0000187~activation of MAPK activity	60	2.26	2.92E-22	2.28E-18	1.34E-19	1.24E-19

GO:0045893~positive regulation of transcription, DNA-templated	178	6.71	3.77E-22	2.94E-18	1.64E-19	1.51E-19
GO:0001934~positive regulation of protein phosphorylation	82	3.09	5.92E-22	4.63E-18	2.44E-19	2.24E-19
GO:0071222~cellular response to lipopolysaccharide	78	2.94	9.83E-22	7.68E-18	3.84E-19	3.54E-19
GO:0001525~angiogenesis	91	3.43	2.18E-21	1.70E-17	8.10E-19	7.46E-19
GO:0008284~positive regulation of cell proliferation	151	5.69	3.29E-21	2.57E-17	1.17E-18	1.08E-18
GO:0051607~defense response to virus	84	3.17	1.18E-20	9.24E-17	4.02E-18	3.70E-18
GO:0071456~cellular response to hypoxia	61	2.30	1.28E-20	1.00E-16	4.18E-18	3.85E-18
GO:0030335~positive regulation of cell migration	92	3.47	1.66E-20	1.30E-16	5.19E-18	4.78E-18

*This multiplicity requirement is invoked to adjust the size of a composite list of genes (from 95 gene-sets) to a number that is viable for the overlap analysis, while prioritizing the most important genes.

[†] Salient Gene Ontology (GO) terms with functions related to apoptotic process, cell proliferation, defense response, or cytokine-mediated signaling are highlighted.

Table S2. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes with a multiplicity of at least 3 in the 95 gene sets with high 5hmC/high mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0060337~type I interferon signaling pathway	56	5.31	1.62E-57	9.06E-54	9.06E-54	8.24E-54
GO:0019221~cytokine-mediated signaling pathway	99	9.39	1.25E-47	7.01E-44	3.50E-44	3.19E-44
GO:0006954~inflammatory response	92	8.73	5.37E-33	3.00E-29	1.00E-29	9.11E-30
GO:0006915~apoptotic process	108	10.25	2.84E-30	1.59E-26	3.97E-27	3.62E-27
GO:0061621~canonical glycolysis	24	2.28	9.06E-29	5.07E-25	1.01E-25	9.22E-26
GO:0043066~negative regulation of apoptotic process	100	9.49	1.54E-28	8.63E-25	1.44E-25	1.31E-25
GO:0001666~response to hypoxia	57	5.41	6.15E-28	3.44E-24	4.91E-25	4.47E-25
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	157	14.90	1.82E-26	1.02E-22	1.27E-23	1.16E-23
GO:0009615~response to virus	43	4.08	9.46E-25	5.29E-21	5.88E-22	5.35E-22
GO:0071222~cellular response to lipopolysaccharide	54	5.12	3.02E-24	1.69E-20	1.69E-21	1.53E-21
GO:0042493~response to drug	66	6.26	5.21E-24	2.91E-20	2.65E-21	2.41E-21
GO:0043065~positive regulation of apoptotic process	76	7.21	1.20E-23	6.74E-20	5.61E-21	5.11E-21
GO:0051607~defense response to virus	57	5.41	3.40E-23	1.90E-19	1.46E-20	1.33E-20
GO:0010628~positive regulation of gene expression	89	8.44	8.38E-23	4.69E-19	3.35E-20	3.05E-20
GO:0030335~positive regulation of cell migration	60	5.69	4.76E-22	2.66E-18	1.77E-19	1.61E-19
GO:0008285~negative regulation of cell proliferation	81	7.69	1.51E-21	8.46E-18	5.29E-19	4.81E-19
GO:0006096~glycolytic process	25	2.37	2.34E-21	1.31E-17	7.69E-19	7.00E-19
GO:0071260~cellular response to mechanical stimulus	34	3.23	5.93E-21	3.31E-17	1.84E-18	1.68E-18
GO:0006687~glycosphingolipid metabolic process	24	2.28	1.42E-19	7.95E-16	4.19E-17	3.81E-17
GO:0043312~neutrophil degranulation	80	7.59	1.65E-19	9.25E-16	4.62E-17	4.21E-17

GO:0008284~positive regulation of cell proliferation	84	7.97	7.97E-19	4.46E-15	2.12E-16	1.93E-16
GO:0007165~signal transduction	137	13.00	1.32E-17	7.35E-14	3.34E-15	3.04E-15
GO:0010832~negative regulation of myotube differentiation	15	1.42	1.92E-17	1.07E-13	4.66E-15	4.24E-15
GO:0045893~positive regulation of transcription, DNA-templated	92	8.73	5.80E-17	6.21E-13	1.35E-14	1.23E-14
GO:0071456~cellular response to hypoxia	37	3.51	8.49E-17	6.21E-13	1.86E-14	1.69E-14

Table S3. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes with a multiplicity of at least 4 in the 95 gene sets with high 5hmC/high mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0060337~type I interferon signaling pathway	32	6.81	4.21E-32	1.66E-28	1.66E-28	1.50E-28
GO:0019221~cytokine-mediated signaling pathway	53	11.28	5.14E-28	2.03E-24	1.01E-24	9.17E-25
GO:0061621~canonical glycolysis	20	4.26	4.71E-27	1.86E-23	6.19E-24	5.60E-24
GO:0006954~inflammatory response	54	11.49	3.19E-24	1.26E-20	3.15E-21	2.85E-21
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	92	19.57	3.05E-23	1.20E-19	2.38E-20	2.16E-20
GO:0006915~apoptotic process	63	13.40	3.63E-23	1.43E-19	2.38E-20	2.16E-20
GO:0010832~negative regulation of myotube differentiation	15	3.19	2.67E-22	1.05E-18	1.50E-19	1.36E-19
GO:0043066~negative regulation of apoptotic process	59	12.55	3.05E-22	1.20E-18	1.50E-19	1.36E-19
GO:0001666~response to hypoxia	36	7.66	8.47E-22	3.34E-18	3.71E-19	3.36E-19
GO:0009615~response to virus	29	6.17	1.04E-20	4.09E-17	4.09E-18	3.70E-18
GO:0008285~negative regulation of cell proliferation	52	11.06	3.93E-20	1.55E-16	1.41E-17	1.28E-17
GO:0006096~glycolytic process	19	4.04	2.05E-19	8.07E-16	6.72E-17	6.09E-17
GO:0043065~positive regulation of apoptotic process	46	9.79	5.67E-19	2.24E-15	1.72E-16	1.56E-16
GO:0071222~cellular response to lipopolysaccharide	33	7.02	3.06E-18	1.21E-14	8.61E-16	7.80E-16
GO:0010628~positive regulation of gene expression	52	11.06	7.30E-18	2.88E-14	1.92E-15	1.74E-15
GO:0030335~positive regulation of cell migration	36	7.66	8.90E-17	4.38E-13	2.19E-14	1.99E-14
GO:0045893~positive regulation of transcription, DNA-templated	57	12.13	3.56E-16	1.31E-12	8.27E-14	7.48E-14
GO:0071260~cellular response to mechanical stimulus	22	4.68	3.84E-16	1.31E-12	8.40E-14	7.61E-14
GO:0048661~positive regulation of smooth muscle cell proliferation	20	4.26	1.44E-15	5.69E-12	2.98E-13	2.70E-13

GO:0043312~neutrophil degranulation	47	10.00	1.56E-15	6.13E-12	3.07E-13	2.78E-13
GO:0042493~response to drug	36	7.66	2.66E-15	1.05E-11	4.79E-13	4.34E-13
GO:0051607~defense response to virus	32	6.81	2.68E-15	1.05E-11	4.79E-13	4.34E-13
GO:0060333~interferon-gamma-mediated signaling pathway	20	4.26	4.57E-15	1.79E-11	7.52E-13	6.81E-13
GO:0008284~positive regulation of cell proliferation	49	10.43	4.58E-15	1.79E-11	7.52E-13	6.81E-13
GO:0007165~signal transduction	77	16.38	8.08E-15	3.19E-11	1.27E-12	1.15E-12

Table S4. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes with a multiplicity of at least 5 in the 95 gene sets with high 5hmC/high mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0061621~canonical glycolysis	17	7.26	7.81E-26	2.30E-22	2.30E-22	2.06E-22
GO:0006954~inflammatory response	41	17.52	3.42E-25	1.01E-21	5.05E-22	4.51E-22
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	63	26.92	2.00E-23	5.92E-20	1.97E-20	1.76E-20
GO:0043066~negative regulation of apoptotic process	40	17.09	8.30E-20	2.45E-16	6.12E-17	5.47E-17
GO:0019221~cytokine-mediated signaling pathway	32	13.68	3.06E-19	9.04E-16	1.81E-16	1.62E-16
GO:0071222~cellular response to lipopolysaccharide	26	11.11	5.33E-19	1.57E-15	2.62E-16	2.34E-16
GO:0045893~positive regulation of transcription, DNA-templated	43	18.38	7.06E-19	2.08E-15	2.98E-16	2.66E-16
GO:0008285~negative regulation of cell proliferation	36	15.38	1.83E-18	5.40E-15	6.43E-16	5.75E-16
GO:0006915~apoptotic process	40	17.09	1.96E-18	5.78E-15	6.43E-16	5.75E-16
GO:0001666~response to hypoxia	25	10.68	2.64E-18	7.78E-15	7.78E-16	6.96E-16
GO:0060337~type I interferon signaling pathway	18	7.69	4.33E-18	1.28E-14	1.16E-15	1.04E-15
GO:0006096~glycolytic process	15	6.41	1.03E-17	3.05E-14	2.54E-15	2.27E-15
GO:0042493~response to drug	26	11.11	1.02E-14	3.02E-11	2.32E-12	2.07E-12
GO:0010628~positive regulation of gene expression	33	14.10	2.69E-14	7.93E-11	5.67E-12	5.07E-12
GO:1902895~positive regulation of pri-miRNA transcription from RNA polymerase II promoter	13	5.56	1.90E-13	5.60E-10	3.72E-11	3.33E-11
GO:0035994~response to muscle stretch	10	4.27	2.02E-13	5.96E-10	3.72E-11	3.33E-11
GO:0008284~positive regulation of cell proliferation	32	13.68	4.74E-13	1.40E-09	8.24E-11	7.36E-11
GO:0043312~neutrophil degranulation	30	12.82	1.03E-12	3.04E-09	1.63E-10	1.45E-10
GO:0000187~activation of MAPK activity	17	7.26	1.05E-12	3.09E-09	1.63E-10	1.45E-10

GO:0010832~negative regulation of myotube differentiation	9	3.85	2.35E-12	6.93E-09	3.46E-10	3.10E-10
GO:0030335~positive regulation of cell migration	22	9.40	6.05E-12	1.79E-08	8.51E-10	7.61E-10
GO:0009615~response to virus	16	6.84	7.50E-12	2.21E-08	1.01E-09	8.99E-10
GO:1903800~positive regulation of production of miRNAs involved in gene silencing by miRNA	8	3.42	2.52E-11	7.45E-08	3.24E-09	2.90E-09
GO:0051607~defense response to virus	20	8.55	2.67E-11	7.89E-08	3.29E-09	2.94E-09
GO:0001934~positive regulation of protein phosphorylation	19	8.12	5.93E-11	1.75E-07	7.01E-09	6.26E-09

Table S5. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes with a multiplicity of at least 6 in the 95 gene sets with high 5hmC/high mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0019221~cytokine-mediated signaling pathway	26	19.85	1.08E-19	2.36E-16	9.66E-17	8.69E-17
GO:0043066~negative regulation of apoptotic process	31	23.66	1.32E-19	2.89E-16	9.66E-17	8.69E-17
GO:0006954~inflammatory response	28	21.37	1.32E-19	2.90E-16	9.66E-17	8.69E-17
GO:0071222~cellular response to lipopolysaccharide	21	16.03	1.57E-18	3.45E-15	8.63E-16	7.76E-16
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	40	30.53	3.49E-17	7.66E-14	1.53E-14	1.38E-14
GO:0008285~negative regulation of cell proliferation	26	19.85	3.98E-16	9.74E-13	1.46E-13	1.31E-13
GO:0001666~response to hypoxia	17	12.98	9.22E-14	2.02E-10	2.89E-11	2.60E-11
GO:0035994~response to muscle stretch	9	6.87	1.38E-13	3.03E-10	3.79E-11	3.41E-11
GO:0030335~positive regulation of cell migration	18	13.74	1.67E-12	3.67E-09	4.07E-10	3.66E-10
GO:0061621~canonical glycolysis	9	6.87	2.24E-12	4.92E-09	4.48E-10	4.03E-10
GO:0045893~positive regulation of transcription, DNA-templated	26	19.85	2.25E-12	4.93E-09	4.48E-10	4.03E-10
GO:0060337~type I interferon signaling pathway	11	8.40	3.21E-11	7.04E-08	5.87E-09	5.28E-09
GO:0006915~apoptotic process	23	17.56	5.03E-11	1.10E-07	8.48E-09	7.63E-09
GO:0042493~response to drug	17	12.98	9.16E-11	2.01E-07	1.44E-08	1.29E-08
GO:0000187~activation of MAPK activity	12	9.16	4.68E-10	1.03E-06	6.84E-08	6.15E-08
GO:0008284~positive regulation of cell proliferation	21	16.03	5.09E-10	1.12E-06	6.98E-08	6.28E-08
GO:1902895~positive regulation of pri-miRNA transcription from RNA polymerase II promoter	9	6.87	7.04E-10	1.54E-06	9.07E-08	8.15E-08
GO:0048661~positive regulation of smooth muscle cell proliferation	10	7.63	7.44E-10	1.63E-06	9.07E-08	8.15E-08
GO:0010628~positive regulation of gene expression	20	15.27	1.74E-09	3.82E-06	2.01E-07	1.81E-07

GO:0071356~cellular response to tumor necrosis factor	12	9.16	2.88E-09	6.32E-06	3.16E-07	2.84E-07
GO:0051607~defense response to virus	14	10.69	3.37E-09	7.39E-06	3.52E-07	3.17E-07
GO:0071260~cellular response to mechanical stimulus	10	7.63	4.56E-09	1.00E-05	4.36E-07	3.92E-07
GO:0031663~lipopolysaccharide-mediated signaling pathway	8	6.11	4.57E-09	1.00E-05	4.36E-07	3.92E-07
GO:0009615~response to virus	11	8.40	4.98E-09	1.09E-05	4.55E-07	4.09E-07
GO:0006096~glycolytic process	8	6.11	6.75E-09	1.48E-05	5.93E-07	5.33E-07

Table S6. DAVID Functional Annotation Chart (GOTERM_BP_DIRECT) computed for genes from 7 gene sets with low 5hmC/low mRNA levels identified in an integrative analysis of swine Obese- versus Lean-MSCs.‡

Term	Count	%	P-Value	Bonferroni	Benjamini	FDR
GO:0045494~photoreceptor cell maintenance	44	8.19	2.61E-66	8.09E-63	8.09E-63	7.92E-63
GO:0001916~positive regulation of T cell mediated cytotoxicity	25	4.66	2.64E-36	8.18E-33	4.09E-33	4.00E-33
GO:0045954~positive regulation of natural killer cell mediated cytotoxicity	24	4.47	8.12E-34	2.52E-30	8.39E-31	8.20E-31
GO:0032729~positive regulation of interferon-gamma production	18	3.35	2.13E-11	6.60E-08	1.65E-08	1.61E-08
GO:0050776~regulation of immune response	25	4.66	3.15E-09	9.75E-06	1.95E-06	1.91E-06
GO:0002486~antigen processing and presentation of endogenous peptide antigen via MHC class I via ER pathway, TAP-independent	7	1.30	9.03E-09	2.80E-05	4.67E-06	4.56E-06
GO:0007268~chemical synaptic transmission	27	5.03	1.47E-08	4.56E-05	6.51E-06	6.37E-06
GO:0002480~antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent	7	1.30	2.65E-08	8.21E-05	9.12E-06	8.92E-06
GO:0050953~sensory perception of light stimulus	7	1.30	2.65E-08	8.21E-05	9.12E-06	8.92E-06
GO:0007601~visual perception	23	4.28	3.21E-08	9.96E-05	9.96E-06	9.74E-06

‡Salient Gene Ontology (GO) terms with functions related to leukocyte-mediated cytotoxicity are highlighted.

Table S7. Laboratory measures and demographic data of Lean and Obese patients (*n* = 5, each).

	Lean	**Obese**
Demographics:		
Age (years)	60.4 ± 7.2	56.6 ± 9.5
Sex (Male/Female)	2/3	2/3
Body Mass Index (kg/m^2)	24.8 (24.3-26.8)	45.9 (39.4-48.3)*
Relevant laboratory measures:		
Mean blood pressure (mmHg)	82.4 ± 12.6	91.5 ± 7.9
Total cholesterol (mg/dL)	198.3 ± 25.4	209.5 ± 7.8
Triglycerides (mg/dL)	73.6 ± 8.3	111.5 ± 10.6*
LDL (mg/dL)	128.3 ± 8.7	125.5 ± 4.9
Fasting glucose (mg/dL)	92.0 (83.0-118.5)	96.0 (89.0-137.5)

*LDL: low-density lipoprotein. Data displayed as mean ± standard deviation, or median (interquartile range). * $p \leq 0.05$ vs. Lean.*