

Supplementary Table 1 – Morphometric analysis of white adipose tissue harvested from control and endothelial c-Myc mice

Parameters	Females		Males	
	CT	EC-Myc KO	CT	EC-Myc KO
Area (μm^2)	44.19 \pm 4.67	47.22 \pm 5.48	54.45 \pm 6.78	70.18 \pm 7.78
Diameter (μm)	7.17 \pm 0.40	7.28 \pm 0.48	7.88 \pm 0.50	9.04 \pm 0.49
Volume (pL)	0.25 \pm 0.03	0.28 \pm 0.04	0.34 \pm 0.06	0.49 \pm 0.08
Mass (μg) $\times 10^4$	2.3 \pm 0.3	2.6 \pm 0.4	3.1 \pm 0.5	4.5 \pm 0.7
Adipocyte number $\times 10^9$	3.8 \pm 0.4	5.93 \pm 0.8*	6.2 \pm 3.3	6.9 \pm 3.5
Adipocyte Size Frequency	CT	EC-Myc KO	CT	EC-Myc KO
Small	16.59 \pm 4.34	20.34 \pm 6.37	22.51 \pm 4.89	10.81 \pm 2.43
Medium	21.59 \pm 3.23	17.65 \pm 2.57	23.66 \pm 3.42	15.00 \pm 2.20
Large	27.61 \pm 2.25	24.81 \pm 2.82	24.47 \pm 1.97	29.66 \pm 4.07
Very Large	34.21 \pm 6.82	37.18 \pm 6.95	29.36 \pm 7.62	44.45 \pm 7.91^{##}

Results represent mean \pm standard error. Significant findings are labeled in bold. **CT**, Control (n = 10-12); **EC-Myc KO**, Endothelial c-Myc knockout (n = 5-8). *p<0.05 EC-Myc KO vs CT (females), *p<0.01 very large vs medium size particles, #p<0.005 very large vs small size particles in EC-Myc KO (males).

Supplementary Table 2 – Metabolic assessment of control and endothelial c-Myc knockout mice

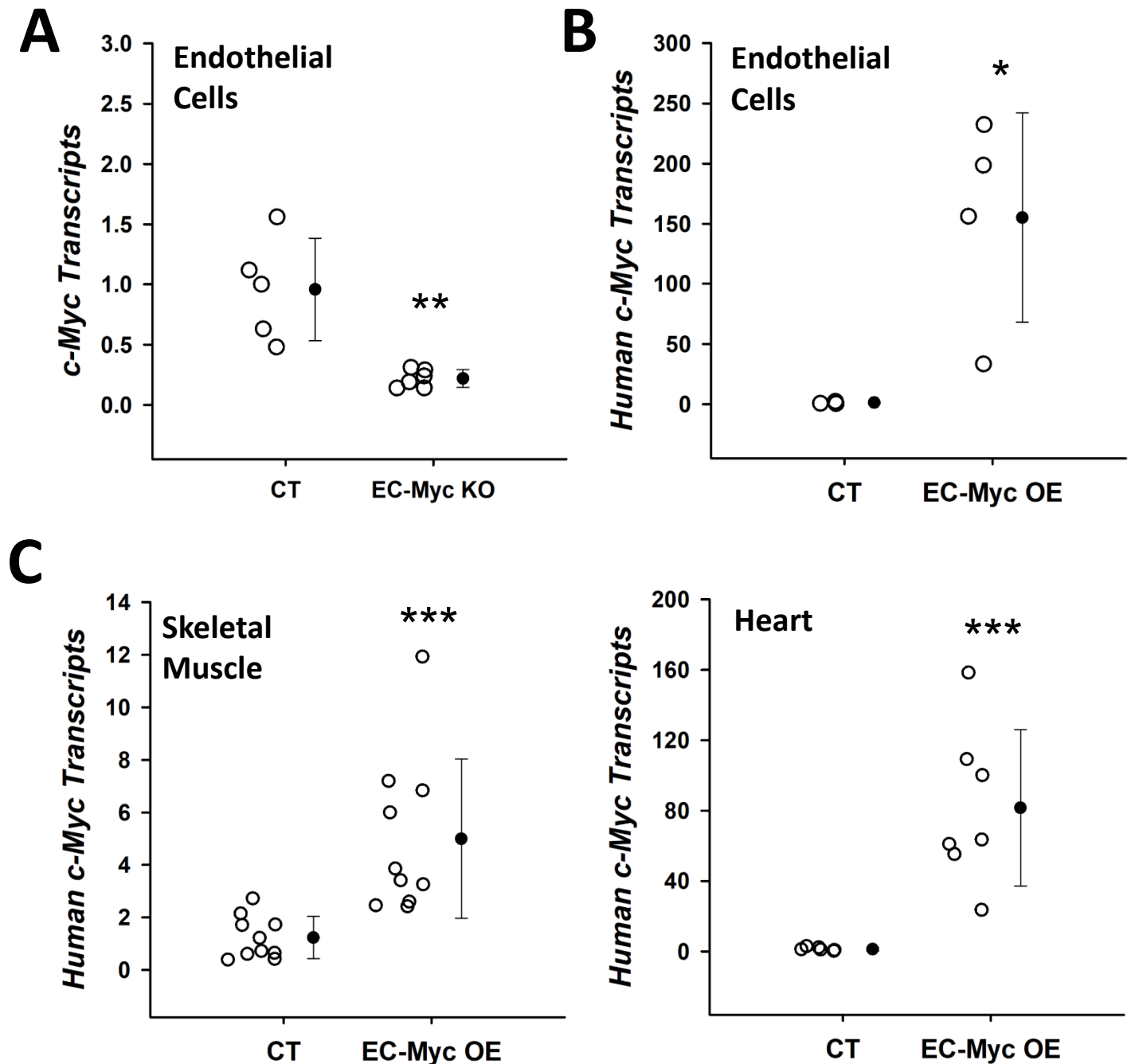
	Females		Males	
	CT	EC-Myc KO	CT	EC-Myc KO
VO ₂ (ml/kg/h) Dark	3687 ± 187	3203 ± 61*	3170 ± 232	2871 ± 139
VO ₂ (ml/kg/h) Light	3035 ± 163	2551 ± 84*	2450 ± 187	2235 ± 129
VCO ₂ (ml/kg/h) Dark	3240.8 ± 199	2791 ± 62*	2750 ± 235	2576 ± 151
VCO ₂ (ml/kg/h) Light	2557 ± 157	2146 ± 94*	2063 ± 182	1952 ± 124
Heat (Kcal/Kg/h) Dark	0.44 ± 0.02	0.38 ± 0.01*	0.51 ± 0.02	0.48 ± 0.02
Heat (Kcal/Kg/h) Light	0.36 ± 0.02	0.30 ± 0.01*	0.39 ± 0.02	0.38 ± 0.02
RER (VCO ₂ /VO ₂) Dark	0.87 ± 0.01	0.87 ± 0.005	0.86 ± 0.02	0.91 ± 0.01#
RER (VCO ₂ /VO ₂) Light	0.83 ± 0.01	0.83 ± 0.01	0.84 ± 0.02	0.88 ± 0.01#
EE Dark	18059 ± 444	15658 ± 196**	14084 ± 502	14126 ± 665
EE light	14704 ± 722	12352 ± 410*	12049 ± 929	11543 ± 595

Results represent mean ± standard error. Significant findings are labeled in bold. **CT**, Control (n = 5-7); **EC-Myc KO**, Endothelial c-Myc knockout (n = 8-11). VO₂, Volume of oxygen consumed; VCO₂, Volume of carbon dioxide produced; RER, Respiratory Exchange Ratio; EE, Energy expenditure. *p < 0.05 vs. CT female, **p < 0.01 vs. CT female, #p < 0.05 vs. CT male.

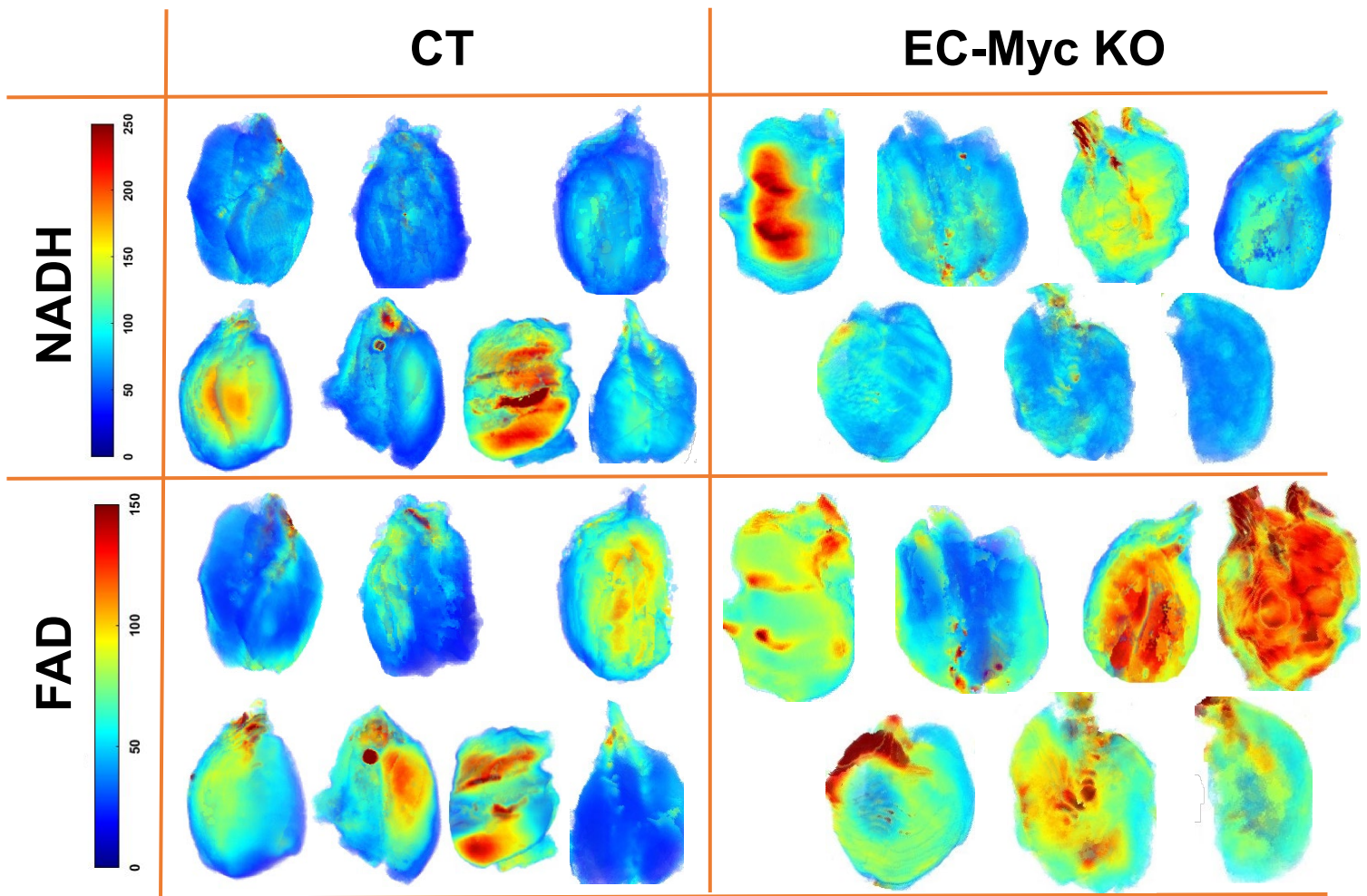
Supplementary Table 3 – Echocardiography analysis of control and endothelial c-Myc overexpression mice under control and western diet

MV FLOW	CT-CTD	CT-WD	OE-CTD	OE-WD
A' (mm/s)	-34.32 ± 8.55	-27.16 ± 3.07	-34.69 ± 6.17	-29.75 ± 6.05
E' (mm/s)	-30.45 ± 2.58	-20.57 ± 5.53	-28.02 ± 7.48	-27.44 ± 1.35
MV AET (ms)	51.94 ± 5.28	48.89 ± 3.78	49.72 ± 6.91	52.15 ± 3.88
IVCT (ms)	6.25 ± 1.10	10.56 ± 1.73*	8.43 ± 1.70	7.10 ± 1.42#
IVRT (ms)	14.34 ± 0.94	15.83 ± 3.31	13.70 ± 1.12	12.78 ± 1.88
MV A (mm/s)	511.11 ± 56.83	209.88 ± 68.19*	382.80 ± 34.31	427.28 ± 162.99#
MV E (mm/s)	666.01 ± 85.67	784.93 ± 22.25	804.09 ± 137.85	823.61 ± 75.14
LV MPI	0.39 ± 0.04	0.54 ± 0.08*	0.45 ± 0.06	0.38 ± 0.04#
MV E/A	1.31 ± 0.13	3.99 ± 1.15*	2.10 ± 0.35	2.18 ± 0.92#
MV E/E'	-22.03 ± 3.74	-40.22 ± 11.77	-30.39 ± 11.34	-29.85 ± 2.38
A'/E'	1.11 ± 0.19	1.36 ± 0.22	1.32 ± 0.48	1.08 ± 0.17
E'/A'	0.91 ± 0.16	0.75 ± 0.13	0.84 ± 0.36	0.94 ± 0.17
LAX (Long Axis)	CT-CTD	CT-WD	OE-CTD	OE-WD
Heart Rate (bpm)	479.04 ± 45.07	473.65 ± 21.14	469.01 ± 67.06	435.85 ± 18.10
Area;s (mm ²)	11.32 ± 2.78	11.12 ± 1.03	11.47 ± 1.45	10.73 ± 2.12
Area;d (mm ²)	18.39 ± 2.62	18.51 ± 0.25	19.13 ± 1.51	18.88 ± 2.10
Volume;s (uL)	18.33 ± 6.83	17.35 ± 2.44	17.89 ± 3.23	16.94 ± 5.91
Volume;d (uL)	42.95 ± 7.92	44.38 ± 1.82	44.87 ± 5.49	44.54 ± 9.72
Stroke Volume (uL)	24.62 ± 4.43	27.04 ± 4.14	26.98 ± 5.41	27.60 ± 4.13
Ejection Fraction (%)	60.51 ± 9.89	60.71 ± 6.82	59.97 ± 7.31	62.70 ± 5.74
Cardiac Output (mL/min)	15.85 ± 5.52	12.82 ± 2.16	12.44 ± 1.62	12.05 ± 1.81
SAX (Short Axis)	CT-CTD	CT-WD	OE-CTD	OE-WD
Diameter; s (mm)	2.56 ± 0.39	2.34 ± 0.18	1.94 ± 0.15*	2.24 ± 0.32
Diameter; d (mm)	3.79 ± 0.39	3.65 ± 0.24	3.33 ± 0.17	3.57 ± 0.29
Fractional shortening (%)	32.64 ± 4.16	35.86 ± 1.00	41.82 ± 1.78*	37.38 ± 4.23
LV mass corrected (mg)	114.12 ± 13.07	154.71 ± 12.50*	121.57 ± 5.12	122.27 ± 7.92#
LVAW;s (mm)	1.44 ± 0.07	1.76 ± 0.13*	1.52 ± 0.05	1.62 ± 0.07#
LVAW;d (mm)	1.05 ± 0.02	1.27 ± 0.06*	0.99 ± 0.10	1.19 ± 0.03*
LVPW;s (mm)	1.30 ± 0.28	1.56 ± 0.04	1.73 ± 0.18*	1.43 ± 0.13*
LVPW;d (mm)	0.91 ± 0.25	1.22 ± 0.09*	1.33 ± 0.12*	1.00 ± 0.12*

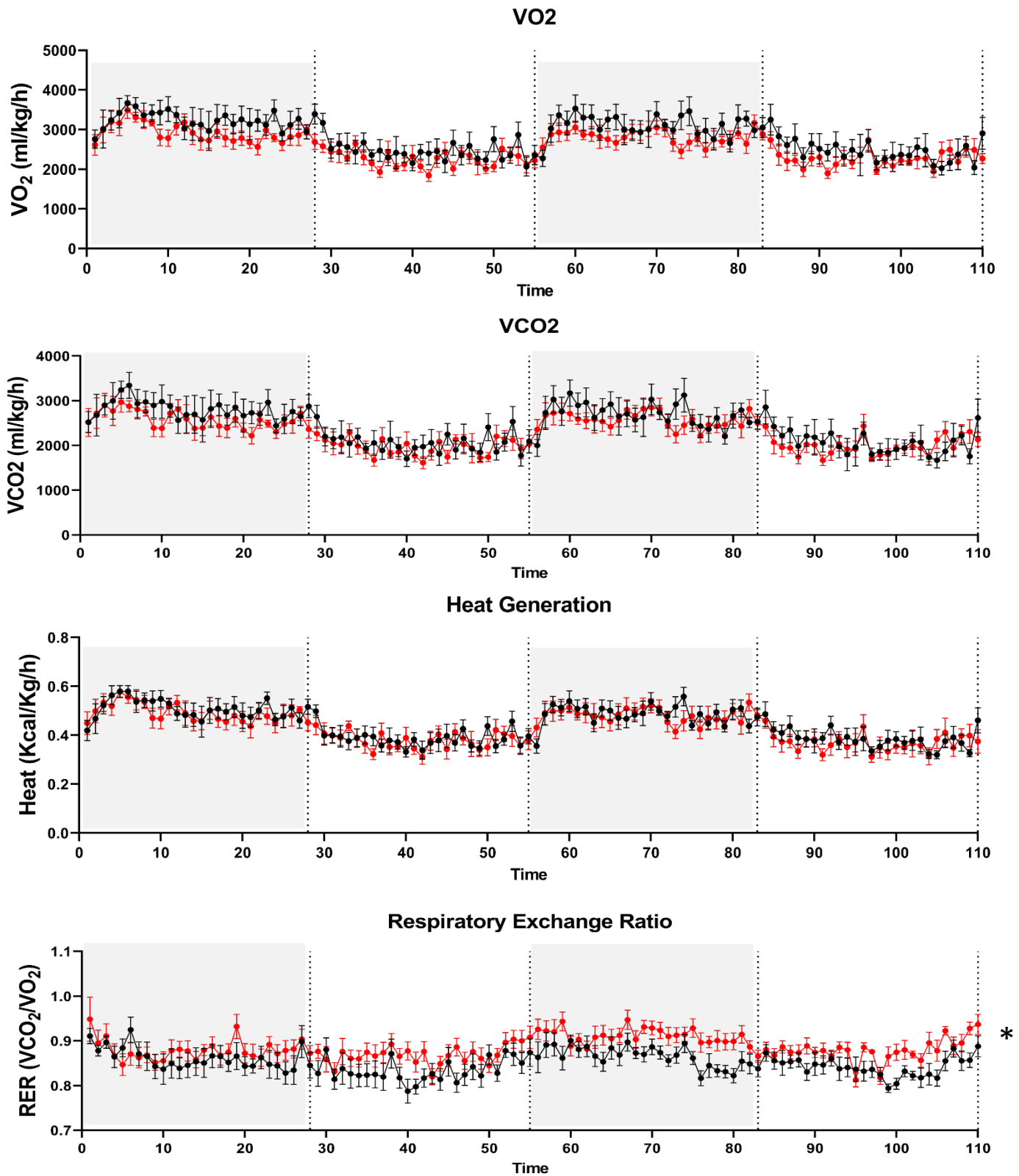
Results are expressed as mean ± standard deviation (n = 3-4). Significant findings are labeled in bold. **CT**, Control; **EC-Myc OE**, Endothelial c-Myc Overexpression; **CTD**, Control diet; **WD**, Western diet. **A'**, Velocity at A' Pulse Wave Tissue Doppler; **E'**, Velocity at E' Pulse Wave Tissue Doppler; **MV ET**, Mitral valve Ejection Time; **IVCT**, Isovolumetric Contraction Time; **IVRT**, Isovolumetric Relaxation Time; **MVA**, Pulse Wave Doppler mitral valve atrial peak; **MVE**, Pulse Wave Doppler Mitral valve early peak; **LV MPI**, Left Ventricular Myocardial Performance Index; **MV E/A**, Mitral valve E to A ratio; **MV E/E'**, Mitral valve E velocity to E' velocity ratio; **A'/E'**, Ratio of A' velocity to E' velocity (PW Tissue Doppler Mode); **E'/A'**, Ratio of E' velocity to A' velocity; **Area;s**, Systolic area; **Area;d**, Diastolic area; **Volume;s**, Systolic volume; **Volume;d**, Diastolic volume; **LVAW;S**, Left ventricular anterior wall (systole); **LVAW;d**, Left ventricular anterior wall (diastole); **LVPW;s**, Left ventricular posterior wall (systole); **LVPW;d**, Left ventricular posterior wall (diastole). *p≤0.05 vs CT-CTD; #p≤0.05 vs CT-WD; *p≤0.05 vs OE-CTD.



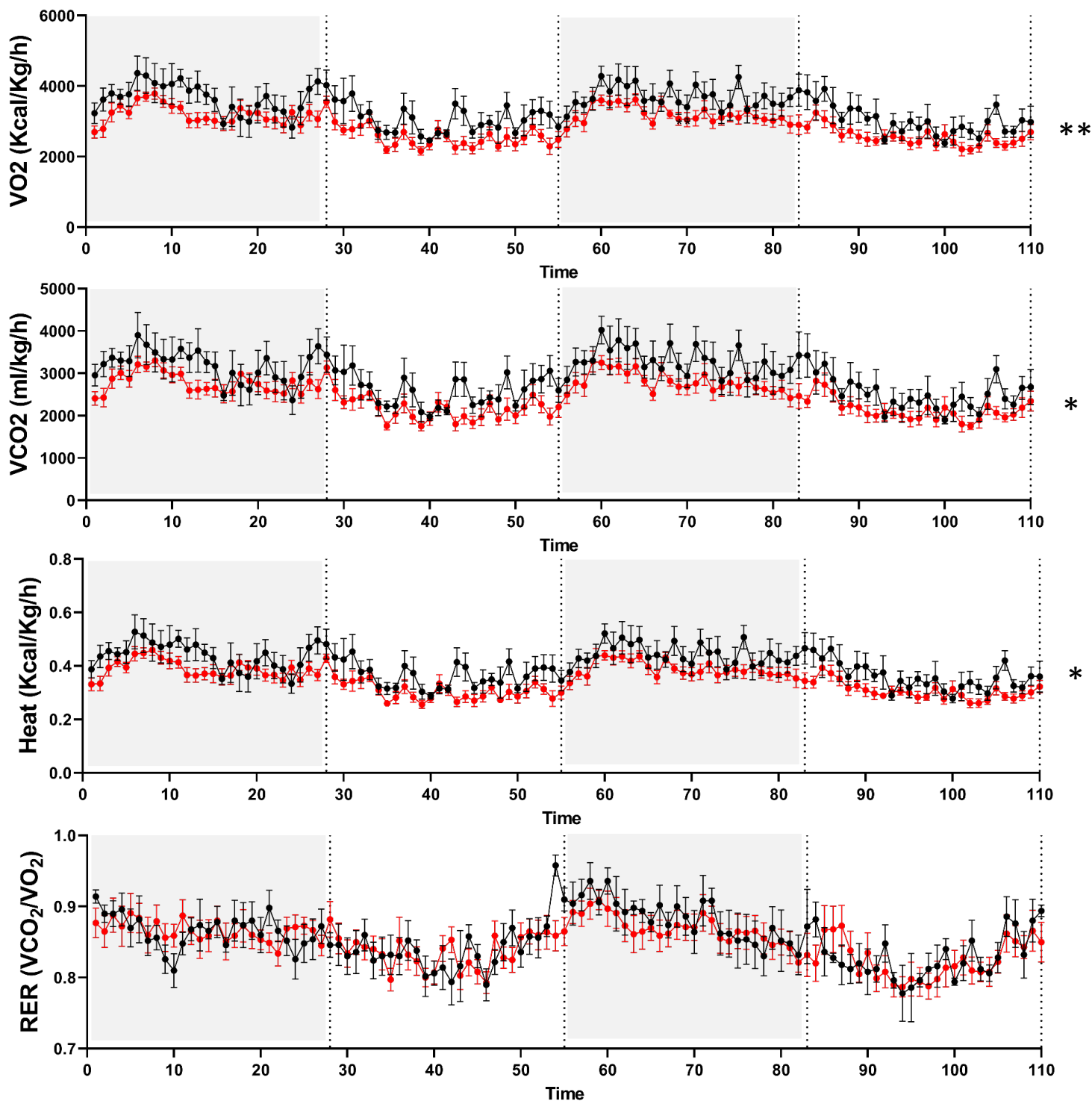
Supplementary Figure 1. Gene expression analysis of c-Myc in tissues and CD31+ sorted cells from endothelial c-Myc knockout and overexpression mice by qPCR. (A) Mouse c-Myc expression in endothelial cells sorted from knockout hearts (n = 5-6). (B) Human c-Myc overexpression in endothelial cells sorted from overexpression hearts (n = 4). (C) Human c-Myc overexpression in skeletal muscle (n = 10) and heart (n = 7) harvested from overexpression mice. Results are expressed as fold change relative to control. CT, control; EC-Myc KO, endothelial c-Myc knockout; EC-Myc OE, endothelial c-Myc overexpression. *p<0.03; **p<0.003; *p<0.001.**



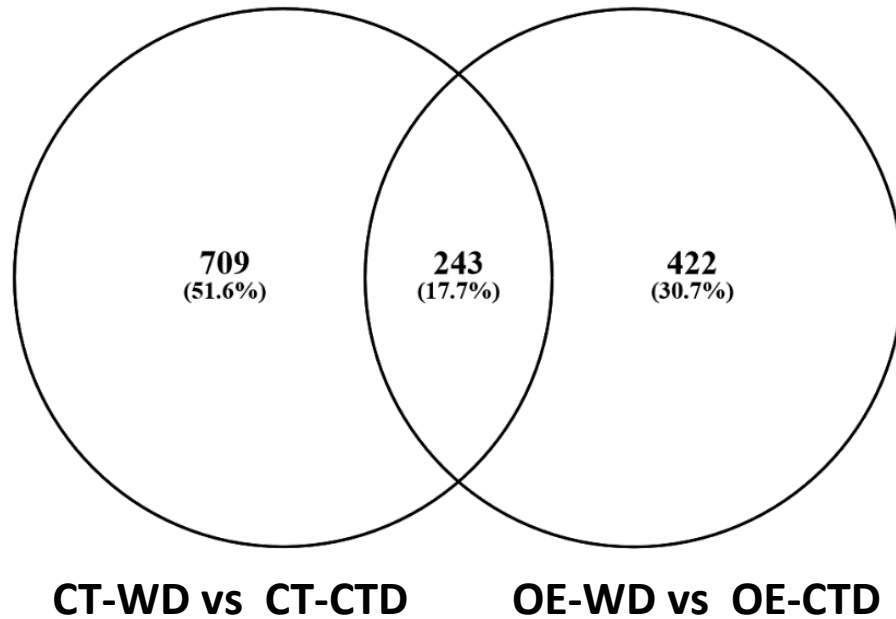
Supplementary Figure 2. Analysis of redox ratio in control and endothelial c-Myc knockout skeletal muscle. (A) Normalized intensities of NADH and FAD images are shown. For each group, seven representative muscle images are presented. CT, Control (n = 7); EC-Myc KO, Endothelial c-Myc knockout (n = 7).



Supplementary Figure 3A. Oxygen consumption (VO₂), Carbon dioxide release (VCO₂), Heat production (Heat) and Respiratory exchange ratio (RER) by indirect calorimetry using the Oxymax Comprehensive Lab Animal Monitoring System (CLAMS) in Control (CT) and Endothelial c-Myc knockout (EC-Myc KO) males. Black lines, CT (n = 7); Red lines, EC-Myc KO (n = 7). Grey, dark; White, light. *p<0.05, **p<0.01.

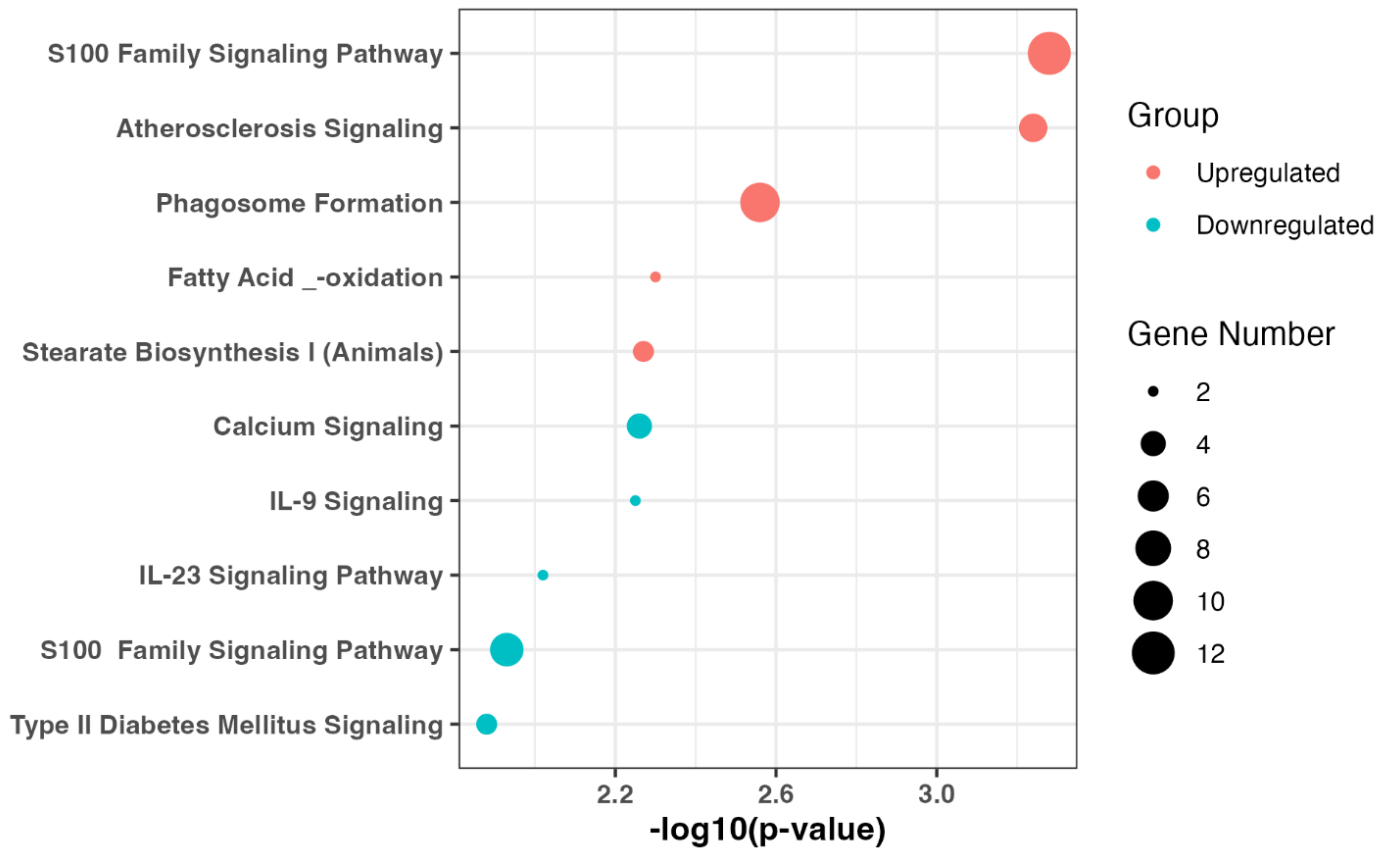


Supplementary Figure 3B. Oxygen consumption (VO_2), Carbon dioxide release (VCO_2), Heat production (Heat) and Respiratory exchange ratio (RER) by indirect calorimetry using the Oxymax Comprehensive Lab Animal Monitoring System (CLAMS) in Control (CT) and Endothelial c-Myc knockout (EC-Myc KO) females. Black lines, CT (n = 5); Red lines, EC-Myc KO (n = 11). Grey, dark; White, light. * $p < 0.05$, ** $p < 0.01$.



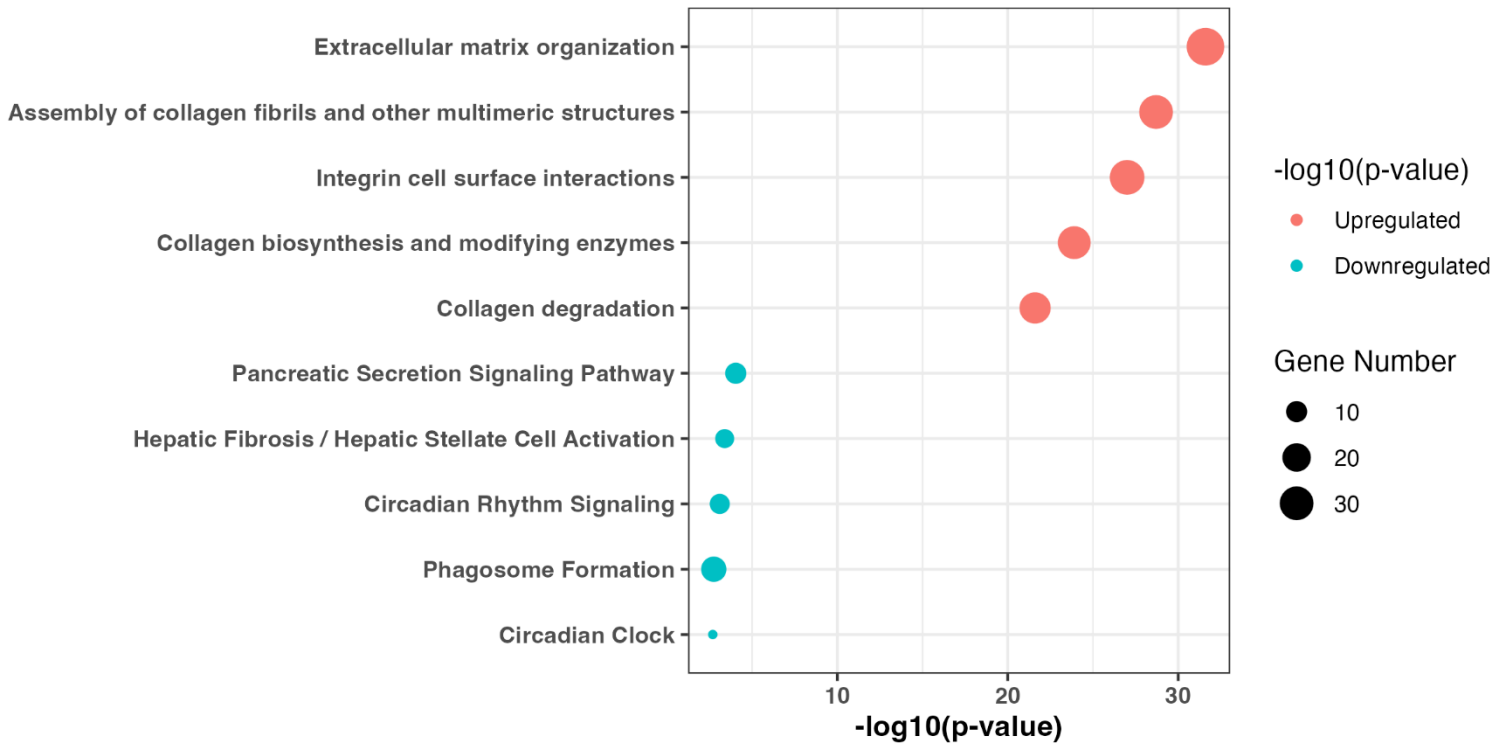
Supplementary Figure 4. Venn diagrams indicating the number of genes significantly altered by western diet exposure in skeletal muscle from control and endothelial c-Myc overexpression mice (n = 3-4). CT, control; OE, endothelial c-Myc overexpression; CTD, Control diet; WD, Western Diet.

OE-WD vs CT-WD

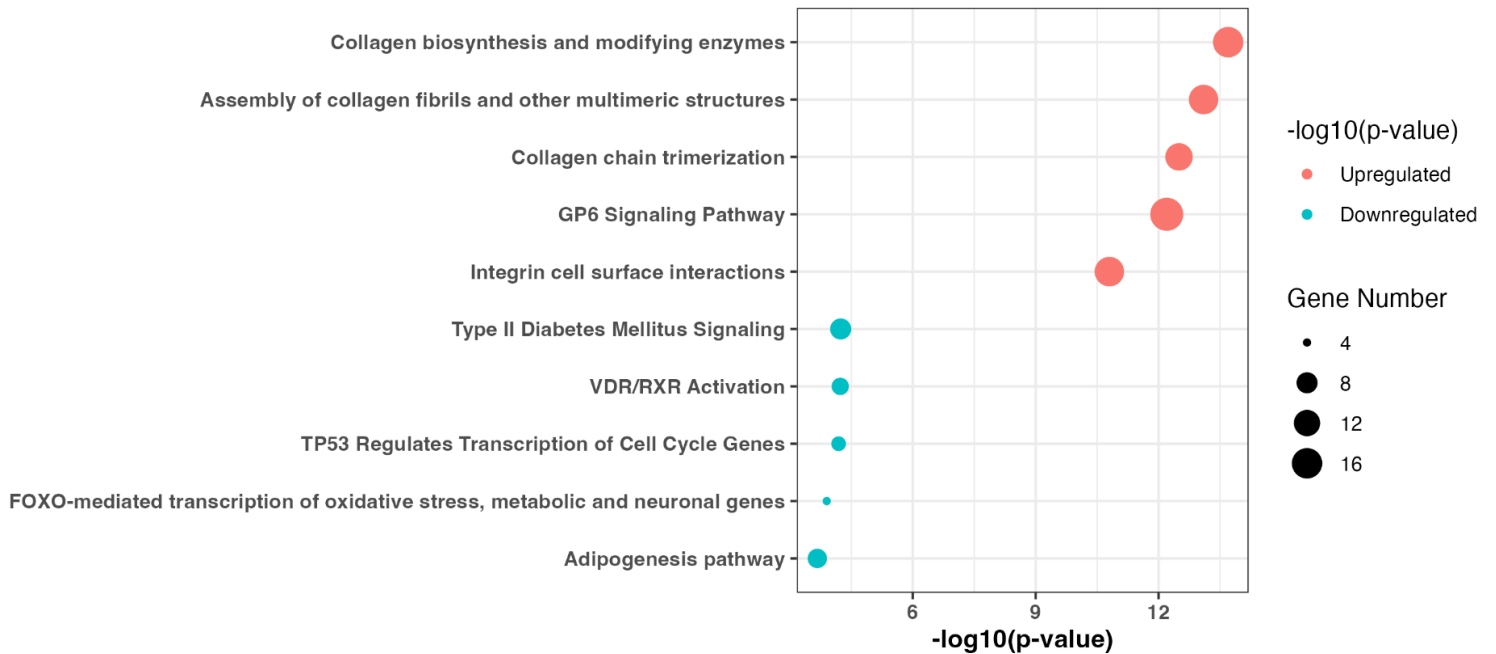


Supplementary Figure 5. Top canonical pathways identified by Ingenuity Pathway Analysis comparing up- and down-regulated genes in endothelial c-Myc OE skeletal muscle relative to CT under western diet. CT, Control; OE, endothelial c-Myc overexpression; WD, western diet. (n = 4).

CT-WD vs CT-CTD



OE-WD vs OE-CTD



Supplementary Figure 6. Top canonical pathways identified by Ingenuity Pathway Analysis comparing up- and downregulated genes in endothelial c-Myc OE and control skeletal muscle under western diet relative to control diet. CT, Control; OE, endothelial c-Myc overexpression; CTD, control diet; WD, western diet. (n = 3-4).