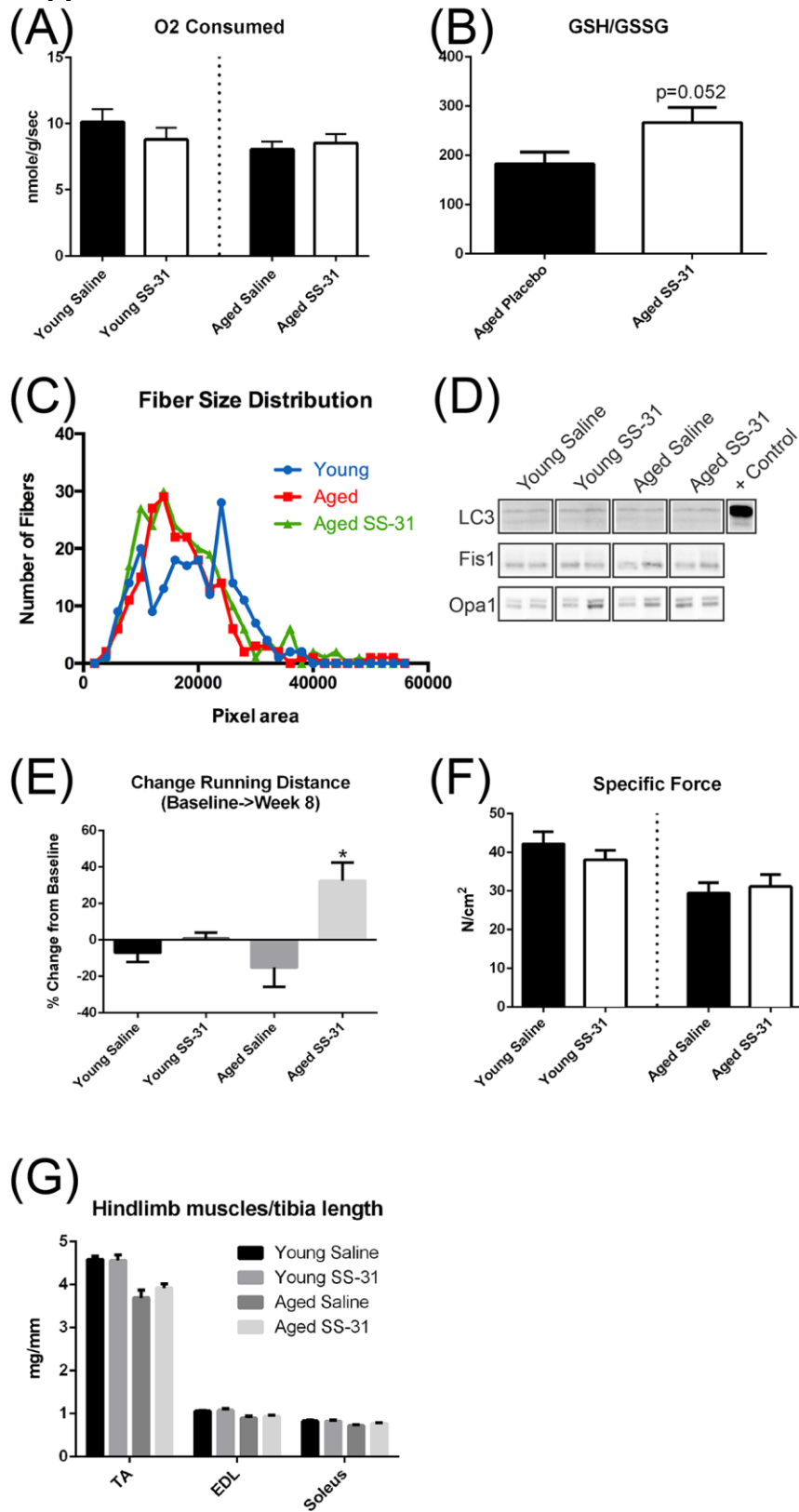


## Supplemental Materials



**Supplemental Figure 1. (A)** Hindlimb oxygen consumption measured using optical spectroscopy. **(B)** Ratio of reduced to oxidized glutathione in gastrocnemius. **(C)** Tibialis anterior fiber size distribution. **(D)** Representative western blot lanes showing no change in autophagy (LC3), mitochondrial fission (Fis1), or fusion (Opa1) **(E)** Treadmill performance change from baseline **(F)** Specific force as a function of cross-sectional area (CSA). **(G)** hindlimb muscle mass normalized to tibia length.

Isoform (s)	Young	Aged Saline		Aged SS-31	
	% of total	% of total	p-value (vs. Young)	% of total	p-value (vs. Aged)
18:2-18:2-16:1-16:1	1.0 ± 0	1.0 ± 0.0	n/a	0.8 ± 0.20	0.3466
18:1-18:2-16:1-16:1	1.0 ± 0.32	1.0 ± 0.0	>0.9999	0.8 ± 0.20	0.3466
18:1-18:1-16:1-16:1	0.60 ± 0.25	0.20 ± 0.20	0.2415	0.2 ± 0.20	>0.9999
18:1-18:1-16:0-16:1	0.40 ± 0.25	0.20 ± 0.20	0.5447	0.2 ± 0.20	>0.9999
18:1-18:1-16:0 16:0; 18:2-18:0-16:0-16:0; 18:1-18:0-16:0-16:1	0.40 ± 0.25	0.20 ± 0.20	0.5447	0.2 ± 0.20	>0.9999
20:4-18:2-16:1-16:1	0.0 ± 0.0	0.0 ± 0.0	n/a	0.0 ± 0.0	n/a
18:2-18:2-18:2-16:1	4.2 ± 0.20	4.2 ± 0.20	>0.9999	3.6 ± 0.51	0.3052
18:2-18:2-18:2-16:0	4.8 ± 0.73	3.4 ± 0.24	0.1083	3.6 ± 0.40	0.6811
18:2-18:1-18:1-16:1 18:2-18:2-18:1-16:0	3.2 ± 0.49	2.4 ± 0.24	0.1823	2.2 ± 0.37	0.6666
16:1-18:1-18:1-18:1	1.4 ± 0.40	1.2 ± 0.20	0.6666	1.2 ± 0.37	>0.9999
18:3-18:3-18:2-18:2; 16:1-20:4-20:4-16:1	0.40 ± 0.24	0.40 ± 0.24	>0.9999	0.2 ± 0.20	0.5447
18:3-18:2-18:2-18:2; 16:1-20:4-20:4-16:0	1.0 ± 0.0	1.0 ± 0.0	n/a	1.0 ± 0.0	n/a
18:2-18:2-18:2-18:2	18.8 ± 3.4	24.0 ± 1.3	0.1893	20.8 ± 1.9	0.2035
18:2-18:2-18:2-18:1	15.4 ± 0.93	16.2 ± 0.66	0.5028	16.0 ± 0.32	0.7924
18:2-18:2-18:1-18:1	7.6 ± 0.93	6.8 ± 0.58	0.4860	7.8 ± 0.37	0.1869
18:2-18:2-18:1-18:0; 18:2-18:1-18:1-18:1	0.80 ± 0.37	1.0 ± 0.32	0.6983	1.0 ± 0.32	>0.9999
18:2-18:2-18:2-20:5	2.4 ± 0.24	2.2 ± 0.20	0.5447	2.0 ± 0.32	0.6075
18:2-18:2-18:2-20:4	3.4 ± 0.51	2.8 ± 0.20	0.3052	3.2 ± 0.20	0.1950
18:2-18:2-18:2-20:3	3.6 ± 0.25	3.2 ± 0.20	0.2415	4.0 ± 0.0	0.0039
18:2-18:2-18:2-20:2	3.2 ± 0.20	3.0 ± 0.32	0.6075	3.0 ± 0.0	>0.9999
18:1-18:2-18:2-20:2	2.0 ± 0.32	1.8 ± 0.20	0.6075	1.8 ± 0.20	>0.9999
18:1-18:2-18:2-20:1; 18:1-18:1-18:2-20:2	0.0 ± 0.0	0.0 ± 0.0	n/a	0.0 ± 0.0	n/a
18:2-18:2-18:2-22:6	9.6 ± 0.68	9.8 ± 0.37	0.8028	10.4 ±	0.3706

				0.51	
18:2-18:2-18:2-22:5; 18:1-18:2-18:2-22:6	8.4 ± 0.68	7.0 ± 0.0	0.0729	8.4 ± 0.40	0.0081
18:2-18:2-18:2-22:4; 18:1-18:1-18:2-22:6	1.4 ± 0.40	1.0 ± 0.0	0.3466	1.2 ± 0.20	0.3466
18:2-18:2-20:4-22:6	0.0 ± 0.0	0.20 ± 0.20	0.3466	0.20 ± 0.20	>0.9999
18:2-18:2-20:3-22:6	0.40 ± 0.24	0.60 ± 0.24	0.5796	0.80 ± 0.20	0.5447
18:2-18:2-20:2-22:6; 18:1-18:2-20:3-22:6	0.60 ± 0.24	1.0 ± 0.0	0.1411	1.0 ± 0.0	n/a
18:2-18:2-22:6-22:6	1.4 ± 0.24	1.2 ± 0.20	0.5447	1.4 ± 0.24	0.5447
18:2-18:1-22:6-22:6	0.20 ± 0.20	0.40 ± 0.24	0.5447	0.80 ± 0.20	0.2415

**Supplemental Table 1 Cardiolipin isoform distribution.** Data are normalized as percentage of total cardiolipin and represented as means ± SE

Top Canonical Pathways	p-value	Overlap
LXR/RXR Activation	6.30x10 <sup>-5</sup>	20.0% 6/30
FXR/RXR Activation	1.11x10 <sup>-4</sup>	18.2% 6/33
Complement System	4.71x10 <sup>-4</sup>	42.9% 3/7
Acute Phase Response Signaling	5.78x10 <sup>-4</sup>	13.6% 6/44
Systemic Lupus Erythematosus Signaling	6.44x10 <sup>-3</sup>	18.8% 3/16
Top Diseases and Bio Functions	p-value	# of Molecules
Connective Tissue Disorders	2.41x10 <sup>-2</sup> - 1.73x10 <sup>-6</sup>	17
Organismal Injury and Abnormalities	2.49x10 <sup>-2</sup> - 1.73x10 <sup>-6</sup>	40
Ophthalmic Disease	2.49x10 <sup>-2</sup> - 1.4x10 <sup>-5</sup>	9
Renal and Urological Disease	1.60x10 <sup>-2</sup> - 1.73x10 <sup>-5</sup>	17
Inflammatory Response	2.49x10 <sup>-2</sup> - 1.88x10 <sup>-5</sup>	23
Molecular and Cellular Functions	p-value	# of Molecules
Cell-To-Cell Signaling and Interaction	2.41x10 <sup>-2</sup> - 1.06x10 <sup>-4</sup>	16
Cellular Movement	2.41x10 <sup>-2</sup> - 1.06x10 <sup>-4</sup>	17
Protein Trafficking	2.93x10 <sup>-4</sup> - 1.63x10 <sup>-4</sup>	8
Post-Translational Modification	2.33x10 <sup>-3</sup> - 2.93x10 <sup>-4</sup>	12
Protein Synthesis	1.76x10 <sup>-2</sup> - 2.93x10 <sup>-4</sup>	19

**Supplemental Table 2 Ingenuity Pathway Analysis.** Relative protein intensity changes Aged vs Young. FDR<0.1