Supplementary data

PGC-1α plays a pivotal role in simvastatin-induced exercise impairment in mice

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Running title: PGC-1α and statin-induced myotoxicity

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Suppl. Figure 1. Skeletal muscle mRNA expression of lactate carriers. Expression of mRNA was determined by real time PCR as described in Methods. Physical capacity was determined as running distance and vertical power using a treadmill. Results were normalized to *18s* expression and were determined in white gastrocnemius for **(A)** *Mct1* and **(B)** *Mct2*. Data are presented as mean ± SEM of 10 animals per group. *p <0.05 between simvastatin-treated and respective control mice. #p <0.05 between control groups of KO or OE mice and WT mice. Abbreviations: WT, wild type; KO, PGC-1α knock-out mice; OE, PGC-1α overexpressing mice; Ctl: control; Simv, simvastatin; MCT, monocarboxylate transporter.

Suppl. Figure 2. Number of electrical shocks during the treadmill exercise test. Physical capacity was determined as running distance and vertical power using a treadmill. Mice received non-harmful electrical shocks from a grid at the basis of the treadmill to motivate them to run. Total number of shocks received for individual mice are shown for **(A)** WT mice, **(B)** KO mice and **(C)** OE mice. The average time to reach 40 shocks is shown in **(D)**. Data are presented as individual curves (**A** – **C**) or mean ± SEM of 10 animals per group. *p <0.05 between simvastatin-treated and respective control mice. #p <0.05 between control groups of KO or OE mice and WT mice. Abbreviations: WT, wild type; KO, PGC-1α knock-out mice; OE, PGC-1α overexpressing mice; Ctl: control; Simv, simvastatin.

Suppl. Figure 3. Respiratory control ratio (RER) during the treadmill exercise. Physical capacity was determined as running distance and vertical power using a treadmill. Consumption of oxygen (VO_2) and production of CO_2 (VCO_2) was determined during the entire exercise time, allowing us to calculate the RER as VCO_2/VO_2. **(A)** Oxygen consumption (VO_2), **(B)** CO_2 production (VCO_2) and **(C)** RER (VCO_2/VO_2). The average time to reach 40 shocks is shown in **(D)**. Data are presented as individual curves (**A** – **C**) or mean ± SEM of 10 animals per group. *p <0.05 between simvastatin-treated and respective control mice. #p <0.05 between control groups of KO or OE mice and WT mice. Abbreviations: WT,

wild type; KO, PGC-1α knock-out mice; OE, PGC-1α overexpressing mice; Ctl: control; Simv, simvastatin.

Suppl. Figure 4. Number of mitochondria in white and red quadriceps muscle per area. The number of mitochondria was determined morphometrically in muscle sections analyzed by electron microscopy in 64 μm^2. Number of mitochondria per 64 μm^2 in white quadriceps **(A)** and in red quadriceps **(B)**. Data are presented as mean ± SEM of 6 separate micrographs per group. *p <0.05 between simvastatin-treated and respective control mice. $^{\#}$p <0.05 between control groups of KO or OE mice and WT mice. Abbreviations: WT, wild type; KO, PGC-1α knock-out mice; OE, PGC-1α overexpressing mice; Ctl: control; Simv, simvastatin.

Suppl. Table 1 - Treadmill data of control (Ctl) and simvastatin-treated (Simv) mice.

Mouse model	**WT**		**KO**		**OE**	
Treatment	**Ctl**	**Simv**	**Ctl**	**Simv**	**Ctl**	**Simv**
			Shock number until exhaustion			
Shocks number	205±26	198±28	80±11	82±13	251±23	285±35
			RER			
Speed (cm x s^{-1})						
17	0.89±0.03	0.93±0.03	0.97±0.01#	0.93±0.02	0.85±0.02	0.87±0.02
20	0.89±0.03	0.90±0.02	0.97±0.01	0.93±0.02	0.84±0.02	0.87±0.02
23	0.90±0.04	0.90±0.03	0.97±0.01	0.94±0.02	0.85±0.02	0.86±0.02
26	0.92±0.06	0.93±0.04	1.01±0.02	0.96±0.02	0.85±0.02	0.88±0.02
29	0.91±0.04	0.94±0.04	1.03±0.02#	1.00±0.02	0.86±0.03	0.88±0.02
32	0.94±0.06	0.94±0.03	1.04±0.02	1.02±0.03	0.85±0.02	0.90±0.02
35	0.94±0.05	0.94±0.03	1.05±0.03	1.04±0.03	0.88±0.03	0.90±0.02
38	0.95±0.04	0.96±0.03	1.10±0.04#	1.03±0.01	0.87±0.02	0.90±0.02
41	1.00±0.06	0.96±0.03			0.87±0.03#	0.90±0.02
44	1.04±0.08	0.96±0.02			0.87±0.03#	0.91±0.01
47	1.01±0.06	0.96±0.02			0.87±0.02#	0.91±0.02
50	1.07±0.04	0.99±0.02			0.87±0.02#	0.92±0.02
53					0.88±0.02	0.92±0.02
56					0.88±0.02	0.93±0.02

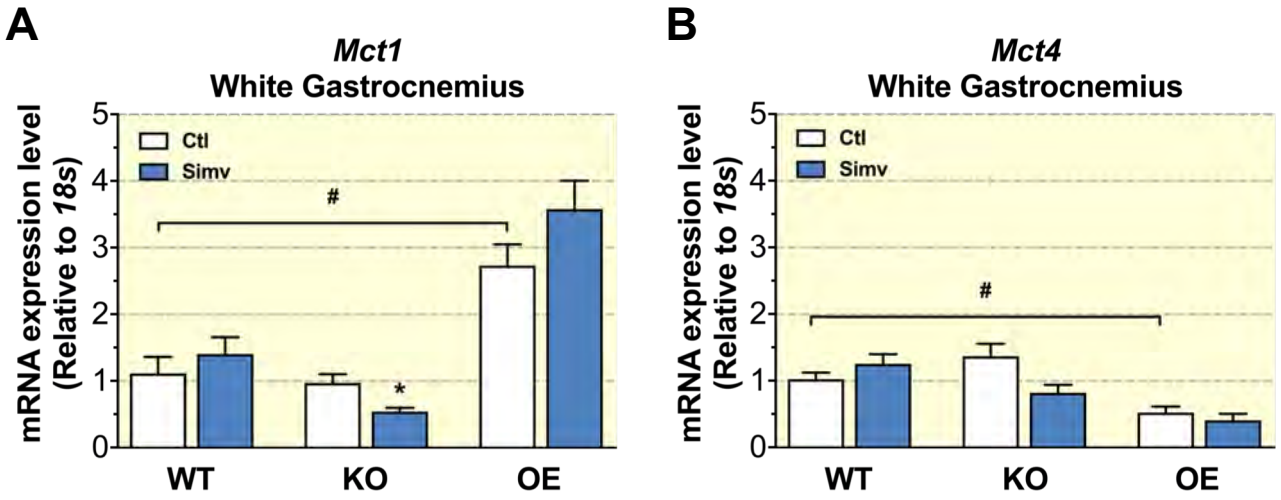
WT, wild-type mice; KO, muscle PGC-1α knockout mice; OE, muscle PGC-1α overexpression mice. All values are expressed as mean±SEM with n=10 per group. #p<0.05 between the control groups of KO or OE mice and WT mice for the same speed.

Suppl. Table 2: Primer list for quantitative real-time PCR amplification

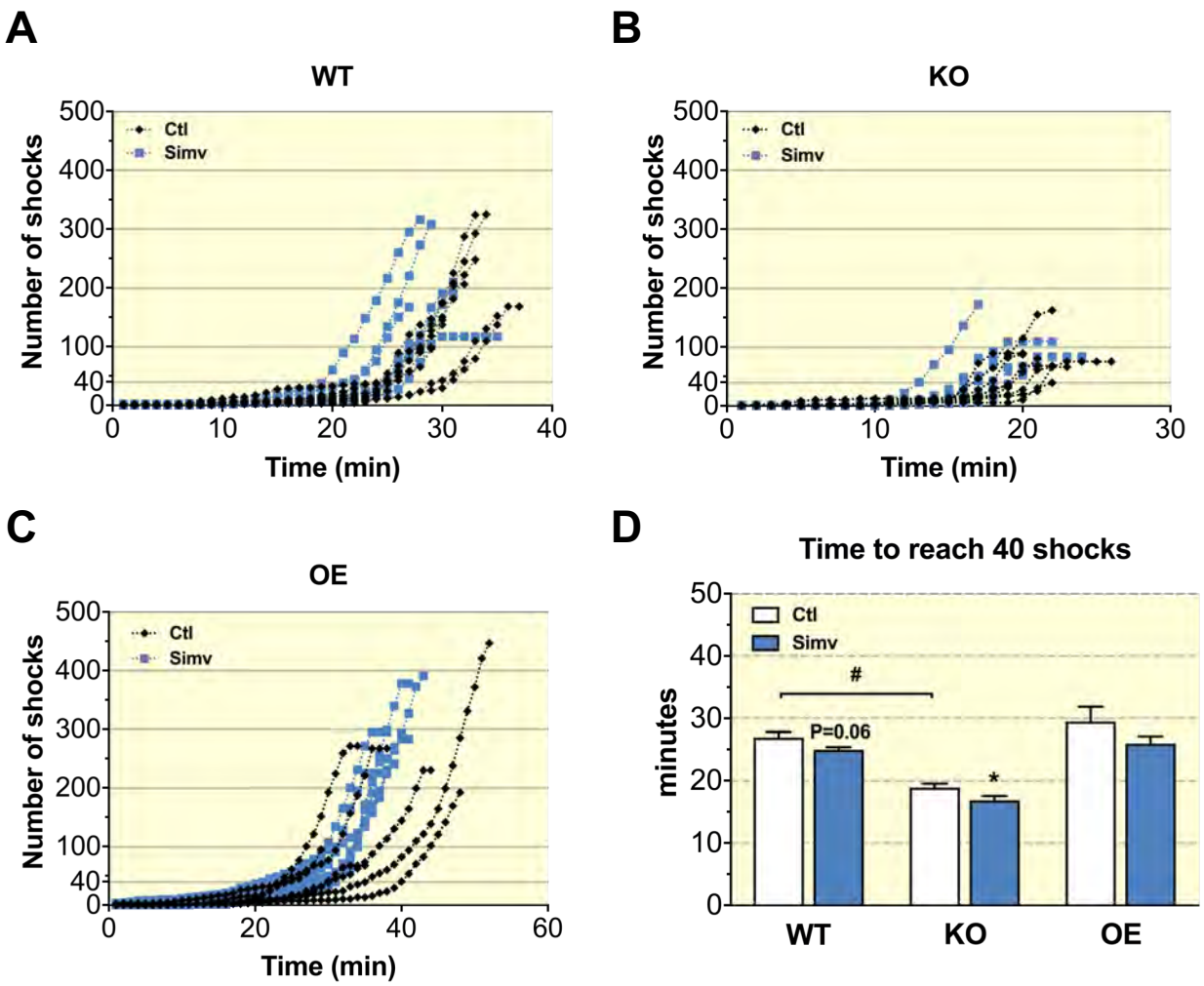
Gene	Species	Forward primer	Reverse primer
Cox2	Mouse	GTT GAT AAC CGA GTC GTT CTG C	CCT GGG ATG GCA TCA GTT TT
Hk2	Mouse	GCC AGC CTC TCC TGA TTT TAG TGT	GGG AAC ACA AAA GAC CTC TTC TGG
Sod1	Mouse	GGC AAA GGT GGA AAT GAA GA	GTT TAC TGC GCA ATC CCA AT
Sod2	Mouse	TCA ATG GTG GGG GAC ATA TT	GCT TGA TAG CCT CCA GCA AC
Mct1	Mouse	TGC AAC GAC CAG TGA AGT ATC A	ACA ACC ACC AGC GAT CAT TAC T
Mct4	Mouse	AGA GCA CTT AAA GTC GCC CCC	GGG CTG CTT TCA CCT GTT ACC
18s	Mouse	AGT CCC TGC CCT TTG TAC ACA	CGA TCC GAG GGC CTC ACT A

Cox2, cytochrome oxidase 2; *Hk2*, hexokinase 2; *Sod1*, superoxide dismutase 1; *Sod2*, superoxide dismutase 2; *Mct1*, monocarboxylate transporter 1; *Mct4*, monocarboxylate transporter 4; *18s*, 18s ribosome RNA.

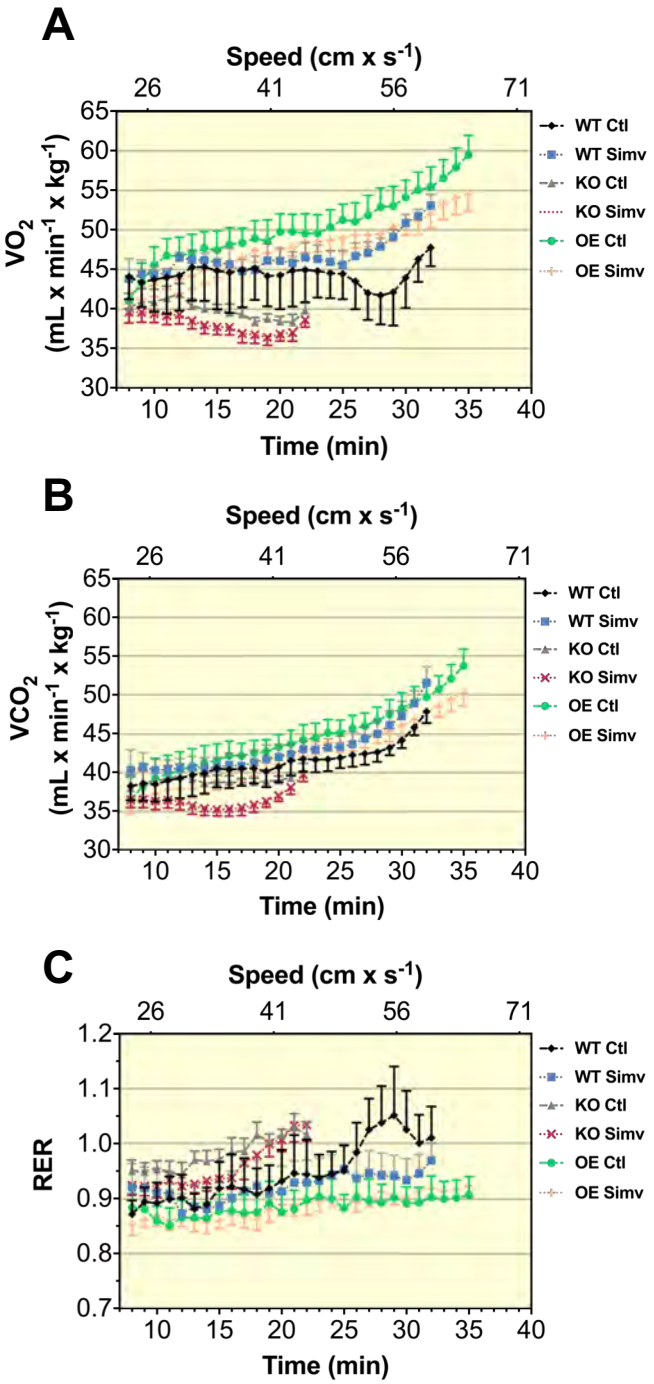
Suppl. Figure 1



Suppl. Figure 2



Suppl. Figure 3



Suppl. Figure 4