

Figure S1. Upregulation of NRF2 target genes in response to autophagy inhibition. Male *Alb-Cre* mice were crossed with female *Atg7^{F/F}* mice to generate liver-specific *Atg7* knockout (*Atg7^{LKO}*) mice as well as control littermate *Atg7^{F/F}* mice. (a) Hepatomegaly was confirmed in *Atg7^{LKO}* mice. (b) Hepatic expression levels of *Atg7* gene were determined in *Atg7^{F/F}* and *Atg7^{LKO}* mice by qPCR analysis. $n = 3$ per group, $**p < 0.01$ vs *Atg7^{LKO}* mice. Data represent mean \pm s.e.m. and are plotted as fold change. (c-d) Hepatic ATG7 and p62 protein levels were assessed in *Atg7^{F/F}* and *Atg7^{LKO}* mice by immunoblot analysis. β -actin is a loading control. Each lane indicates individual mouse. (e) Hepatic expression levels of *Nqo1*, an NRF2 target gene were determined in *Atg7^{F/F}* and *Atg7^{LKO}* mice shown in Figure 1a by qPCR analysis. $n = 4$ per group, $**p < 0.01$ vs *Atg7^{F/F}* mice treated with vehicle. $^{##}p < 0.01$. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual mouse. (f,g) Expression levels of NRF2 target genes *Nqo1* and *Hmox1* were determined in AML12 cells shown in Figure 1c by qPCR analysis. $n = 3$ per group, $**p < 0.01$ vs AML12 cells treated with vehicle. $^{##}p < 0.01$ vs AML12 cells treated with GW7647. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual sample. Statistics by a two-tailed, unpaired Student *t*-test.

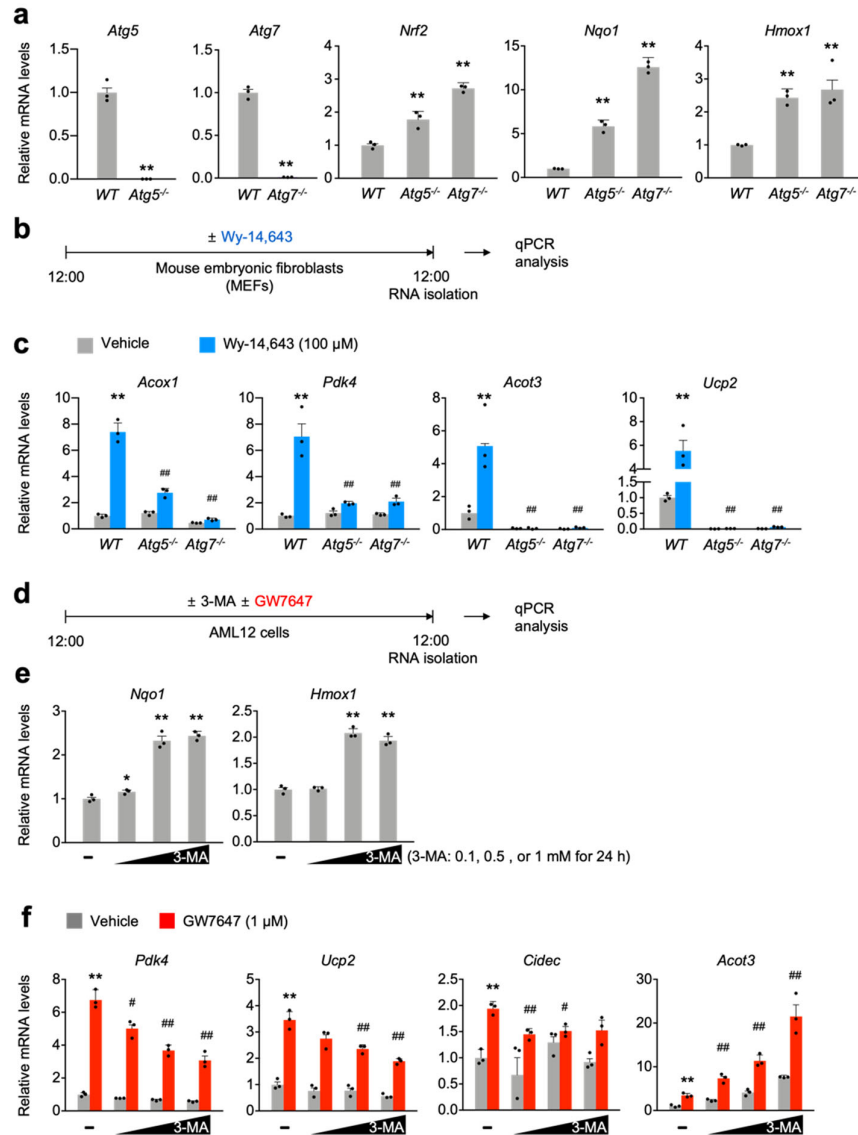


Figure S2. Both genetic and pharmacological inhibitions of autophagy suppress the pharmacological PPAR α activation. (a) Expression levels of core-autophagy genes *Atg5* and *Atg7*, and NRF2 target genes *Nrf2*, *Nqo1*, and *Hmox1* were determined in wild-type, *Atg5*^{-/-}, or *Atg7*^{-/-} mouse embryonic fibroblasts (MEFs) by qPCR analysis. n = 3 per group, **p < 0.01 vs WT MEFs. (b) A schematic diagram of an experimental procedure in MEFs. These cells treated with either vehicle or Wy-14,643 (100 μM), the synthetic PPAR α agonist for 24 h. Vehicle is 0.1% DMSO. Total RNAs from these cells were prepared to perform qPCR analysis. (c) Expression levels of PPAR α target genes *Acox1*, *Pdk4*, *Acot3*, and *Ucp2* were determined in MEFs shown in panel a by qPCR analysis. n = 3 per group. **p < 0.01 vs. WT MEFs treated with vehicle. ##P < 0.01 vs. WT MEFs treated with Wy-14,643. (d) A schematic diagram of an experimental procedure in AML12 cells. AML12 cells were treated with 3-methyladenine (3-MA, 0.1, 0.5, or 1 mM), an autophagy inhibitor in a dose-dependent manner in the absence or presence of GW7647 (1 μM) for 24 hr. Vehicle is 0.1% DMSO. Total RNAs from these cells were prepared to perform qPCR analysis. (e) Expression levels of NRF2 target genes *Nqo1*, and *Hmox1* were determined in AML12 cells shown in panel d by qPCR analysis. n = 3 per group, **p < 0.01 vs AML12 cells treated with vehicle (denoted by "-"). (f) Expression levels of PPAR α target genes *Pdk4*, *Ucp2*, *Cidec*, and *Acot3* were determined in AML12 cells shown in panel d by qPCR analysis. n = 3 per group. **p < 0.01 vs. AML12 cells treated with vehicle. ##P < 0.01 vs. AML12 cells treated with GW7647. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual well. Statistics by a two-tailed, unpaired Student *t*-test. WT, wild-type.

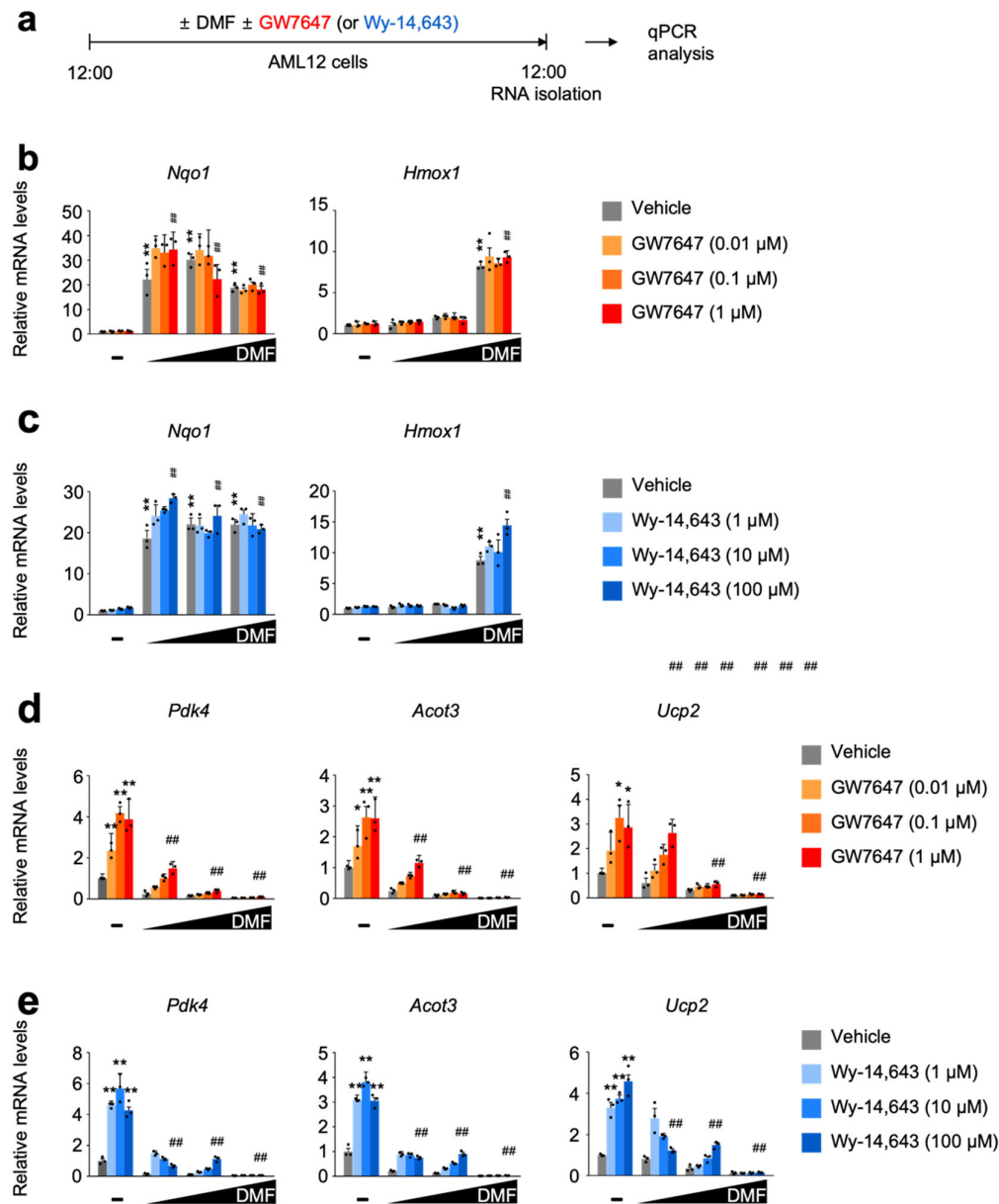


Figure S3. DMF-mediated NRF2 activation in a dose-dependent manner impairs a pharmacologic PPAR α transactivation. **(a)** A schematic diagram of an experimental procedure in AML12 cells. AML12 cells were treated with dimethylfumarate (DMF, 50, 75, or 100 μ M), a known NRF2 activator in a dose-dependent manner in the absence or presence of synthetic PPAR α agonists (GW7647: 0.01, 0.1 or 1 μ M; Wy-14,643: 1, 10 or 100 μ M) for 24 hr. Vehicle is 0.1% DMSO. Total RNAs from these cells were prepared to perform qPCR analysis. **(b,c)** Expression levels of NRF2 target genes *Nqo1* and *Hmox1* were determined in AML12 cells shown in panel **a** by qPCR analysis. $n = 3$ per group. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual well. $**p < 0.01$ vs. AML12 cells treated with vehicle. $^{##}p < 0.01$ vs. AML12 cells treated with 1 μ M GW7647. **(d,e)**, Expression levels of PPAR α target genes *Pdk4*, *Acot3*, and *Ucp2* were determined in AML12 cells shown in panel **a** by qPCR analysis. $n = 3$ per group, $*p < 0.05$, $**p < 0.01$ vs. AML12 cells treated with vehicle. $^{##}p < 0.01$ vs. AML12 cells treated with either 1 μ M GW7647 or 100 μ M Wy-14,643. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual sample. Statistics by a two-tailed, unpaired Student t -test (**d,e**).

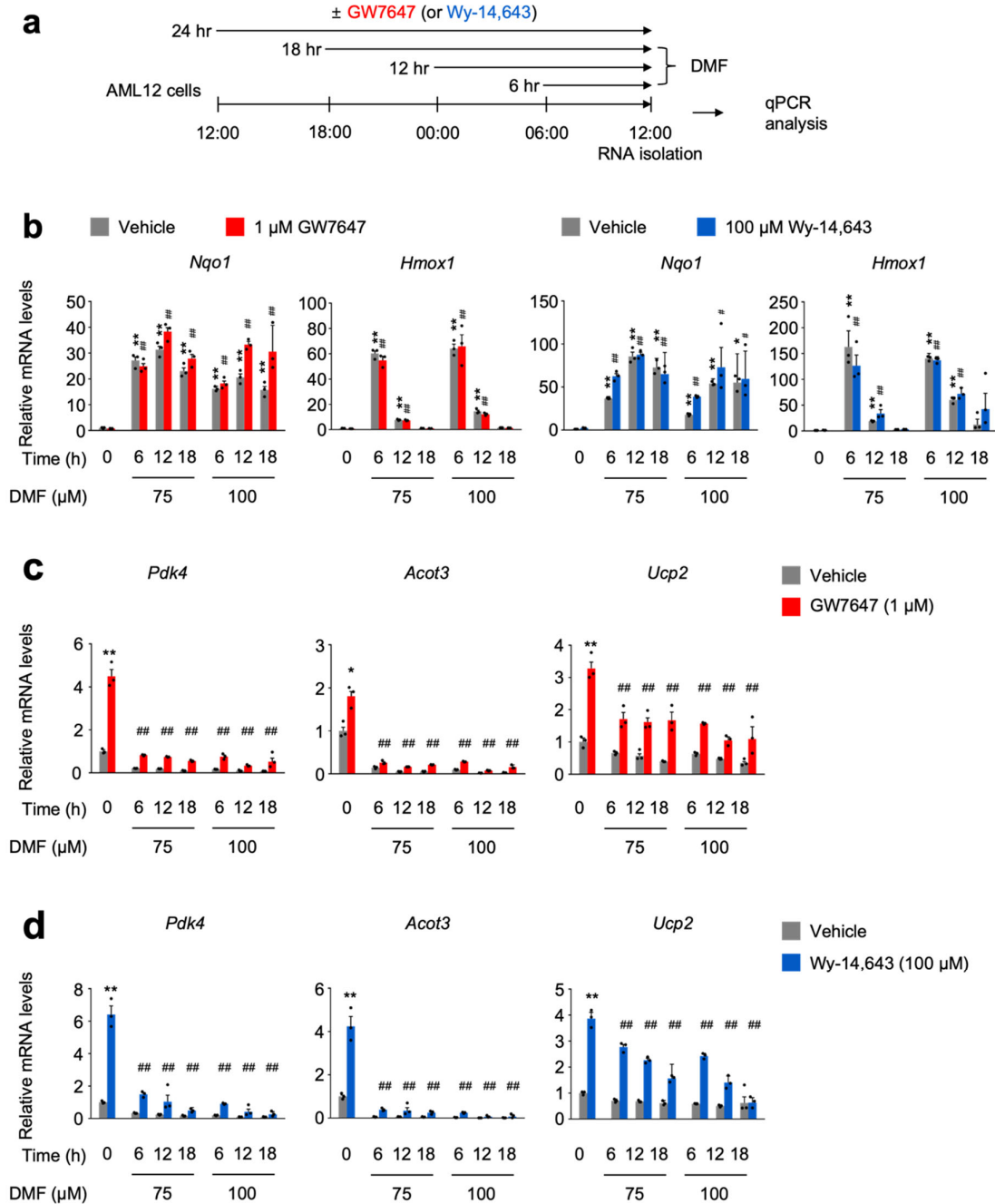


Figure S4. DMF-mediated NRF2 activation in a time-dependent manner impairs a pharmacologic PPAR α transactivation. (a) A schematic diagram of an experimental procedure in AML12 cells. AML12 cells were treated with either 75 μ M or 100 μ M of dimethylfumarate (DMF), a known NRF2 activator in a time-dependent manner (6 h, 12 h or 18 h) in the absence or presence of synthetic PPAR α agonists (1 μ M of GW7647; 100 μ M of Wy-14,643) for 24 h. Vehicle is 0.1% DMSO. Total RNAs from these cells were prepared to perform qPCR analysis. (b) Expression levels of NRF2 target genes *Nqo1* and *Hmox1* were determined in AML12 cells shown in panel a by qPCR analysis. * p < 0.05, ** p < 0.01 vs. AML12 cells treated with vehicle. ## p < 0.01 vs. AML12 cells treated with either GW7647 or Wy-14,643. (c,d) Expression levels of PPAR α target genes *Pdk4*, *Acot3*, and *Ucp2* were determined in AML12 cells shown in panel a by qPCR analysis. n = 3 per group, * p < 0.05, ** p < 0.01 vs. AML12 cells treated with vehicle. ## p < 0.01 vs. AML12 cells treated with either GW7647 or Wy-14,643. Data represent mean \pm s.e.m. and are plotted as fold change. Each dot indicates individual sample. Statistics by a two-tailed, unpaired Student t -test.

Table S1. Mouse primer sequences for qPCR analysis

Gene	Sequences
Atg7 exon 14-15 Fwd	CTAATGGACACCAGGGAGAG
Atg7 exon 14-15 Rvs	CATGTCTCATGACAACAAAGGT
Pdk4 Fwd	GTCGAGCATCAAGAAAACCGTCC
Pdk4 Rvs	TGTGATGCCCTTCAGGAAGGAG
Acot3 Fwd	ACTACGAGGACCTCCCTAAGGA
Acot3 Rvs	CATGGCAAAGCCAAGTTCACCC
Ucp2 Fwd	TAAAGGTCCGCTTCAGGCTCA
Ucp2 Rvs	ACGGGCAACATTGGGAGAAGTC
Acot2 Fwd	AAGAAGCCGTGAACTACCTGCG
Acot2 Rvs	TGTGATGCCCTTCAGGAAGGAG
Cidec Fwd	TCGGAAGGTTGCAAAAGGCATC
Cidec Rvs	CTCCACGATTGTGCCATCTTCC
Acox1 Fwd	GCCATTGATACAGTGCTGTGAG
Acox1 Rvs	CCGAGAAAGTGGAAGGCATAGG
Fgf21 Fwd	ATCAGGGAGGATGGAACAGTGG
Fgf21 Rvs	AGCTCCATCTGGCTGTTGGCAA
Nrf2 exon 4-5 Fwd	TTAAGCAGCATAGAGCAGGA
Nrf2 exon 4-5 Rvs	TTCTGTCACTGTGGCTTCTG
Nqo1 Fwd	GCCGAACACAAGAAGCTGGAAG
Nqo1 Rvs	GGCAAATCCTGCTACGAGCACT
Hmox-1 Fwd	CACTCTGGAGATGACACCTGAG
Hmox-1 Rvs	GTGTTCTCTGTGTCAGCATCACC
Gstp1 Fwd	TGGAAGGAGGAGGTGGTTACCA
Gstp1 Rvs	GGTAAAGGTGAGGTCTCCATC
36B4 Fwd	CAACCCAGCTCTGGAGAAAC
36B4 Rvs	CCAACAGCATATCCCGAATC
Keap1 exon 4-5 Fwd	ATCCAGAGAGGAATGAGTGGCG
Keap1 exon 4-5 Rvs	TCAACTGGTCCTGCCCATCGTA
Gsta1 Fwd	GTGCCTTGGCAAAAGATAGGACC
Gsta1 Rvs	CTTCCAGTAGGTGGATGTCCAC