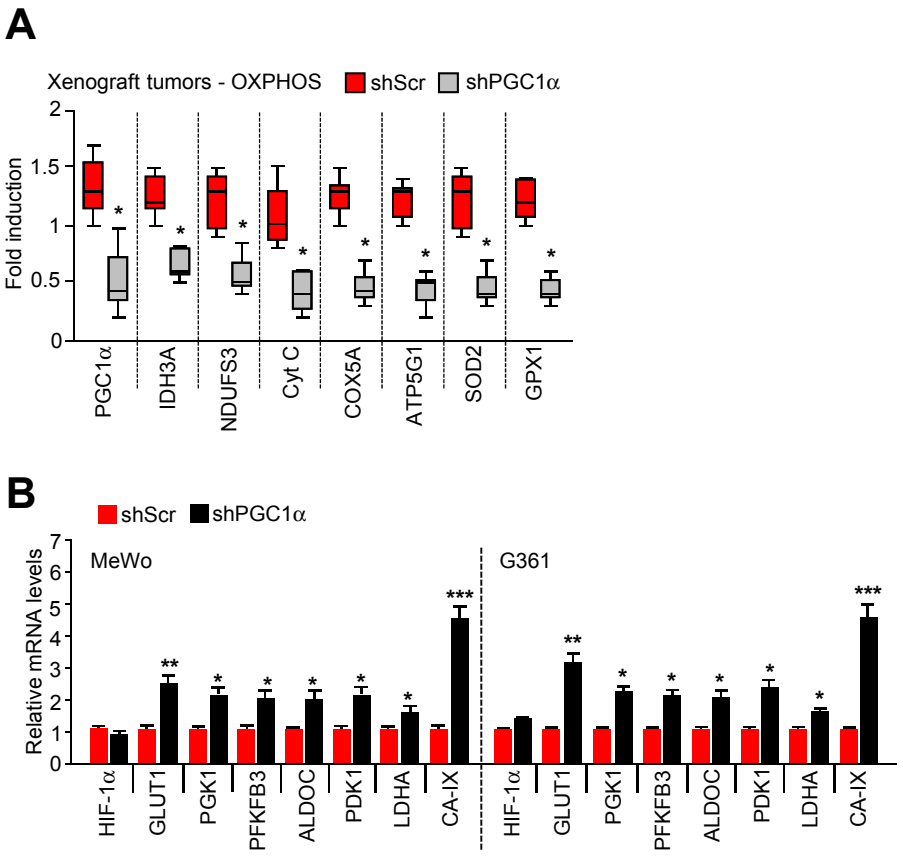
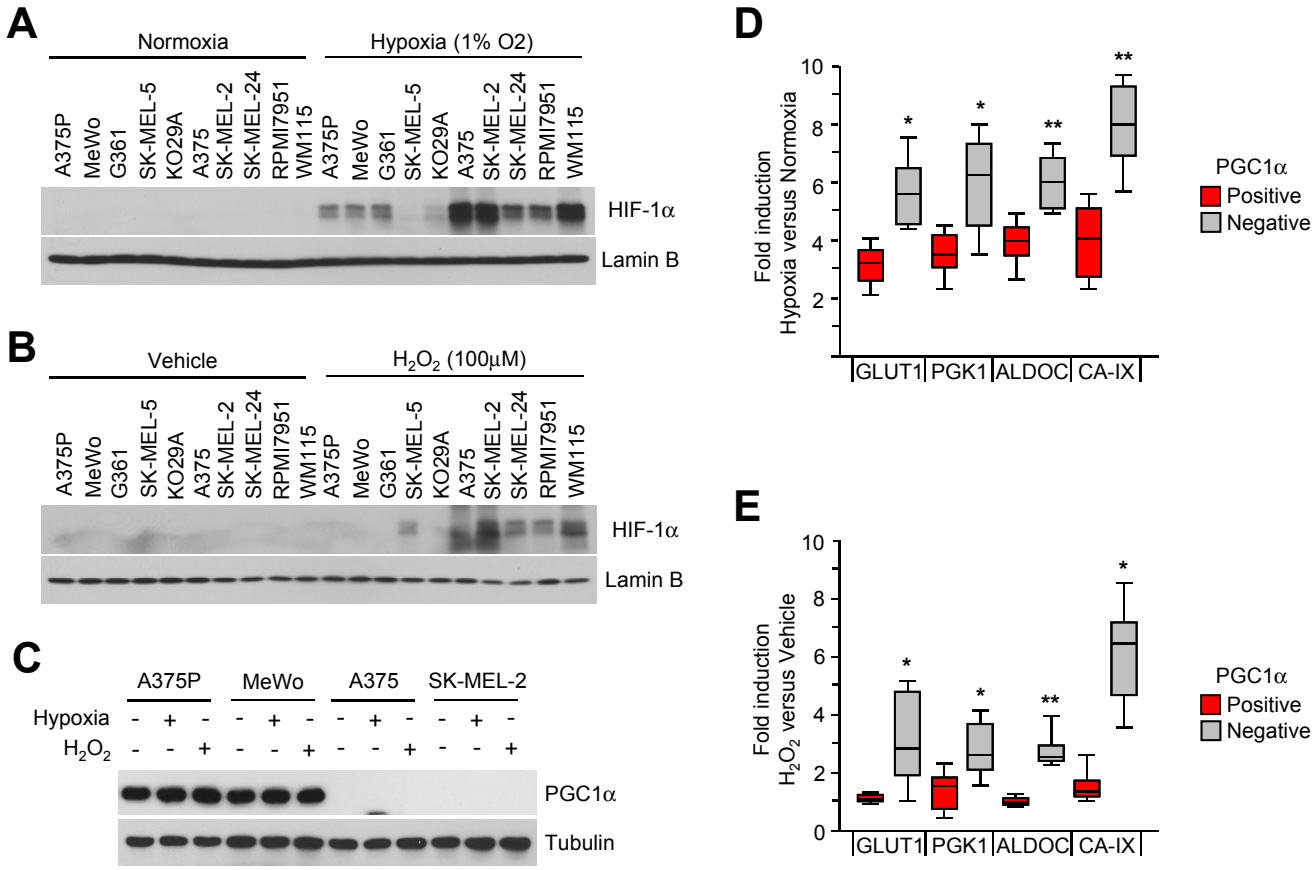
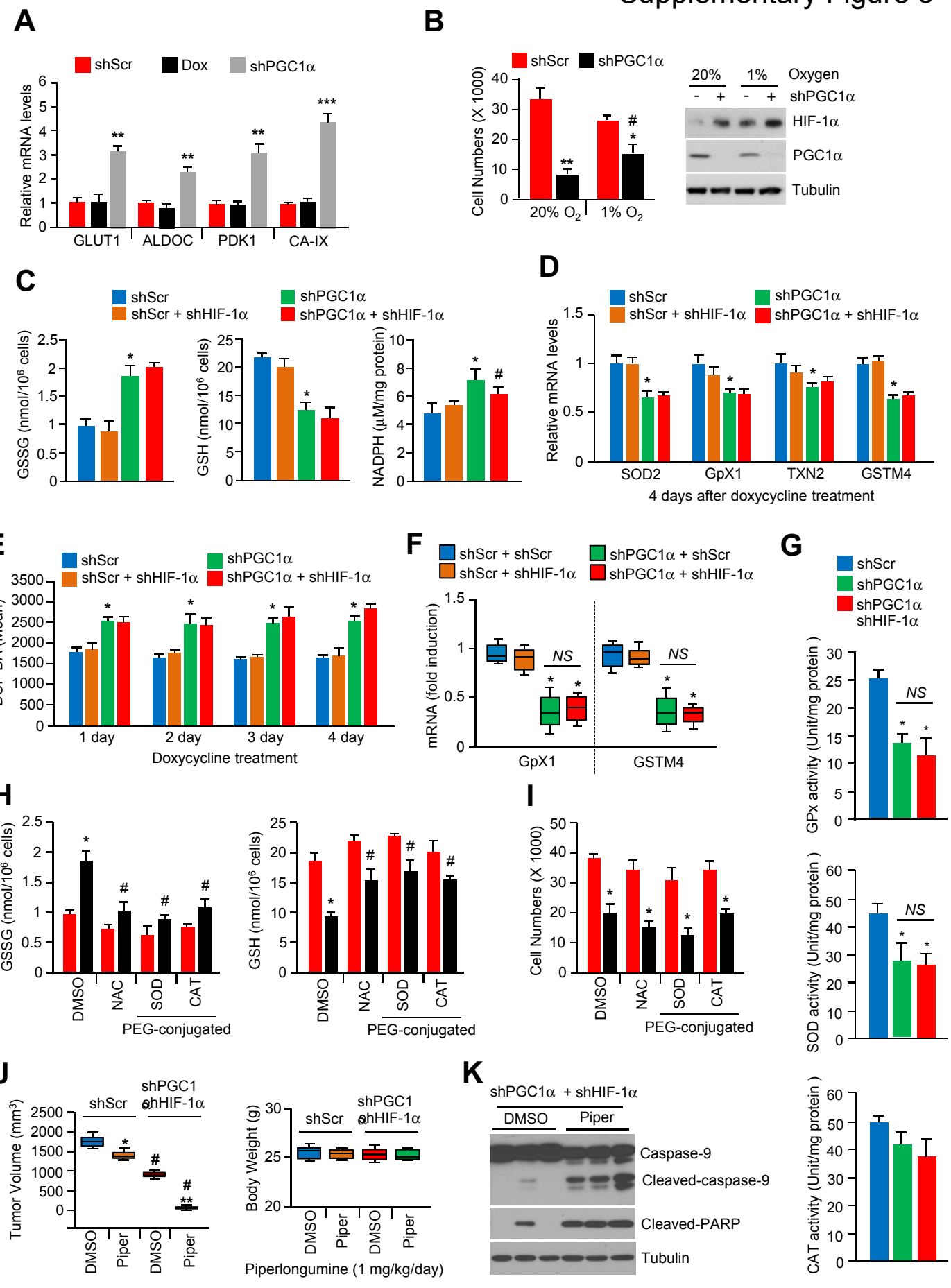


Supplementary Figure 1. A, Levels of PGC1α target genes in PGC1α-suppressed tumors. Values of three independent experiments performed in duplicate (n=5) were averaged; *p < 0.05 versus control shRNA. The whiskers in the box plots represent the maximum and the minimum value. **B,** HIF-1α glycolytic target gene expression after PGC1α knockdown. Glycolytic gene expression was measured by qPCR in PGC1α-suppressed cells. Values represent mean ± SD of three independent experiments performed in triplicate; *p < 0.05, **p < 0.01 and ***p < 0.001 versus control shRNA.



Supplementary Figure 2. HIF-1α protein levels and glycolytic target genes in PGC1α negative and positive melanoma cells after exposure to hypoxia or oxidative stress. A, B and C, Cells were incubated under hypoxia or 100μM H_2O_2 for 12 h, nuclear or total protein extracts were used to measure HIF-1α or PGC1α levels and **D and E**, total RNA was used to measure glycolytic gene expression. PGC1α positive cells: A375P, MeWo, G361, SK-MEL-5, and KO29A; PGC1α negative cells: A375, SK-MEL-2, SK-MEL-24, RPMI7951 and WM115. Values of three independent experiments performed in triplicate were averaged; *$p < 0.05$ and **$p < 0.01$ versus PGC1α positive melanoma cells. The whiskers in the box plots represent the maximum and the minimum value.

Supplementary Figure 3



Supplementary Figure 3. A, Effects of doxycycline treatment on the expression of HIF-1α target glycolytic genes. **B,** Effect of hypoxia on apoptosis induced by PGC1α suppression. Infected cells were cultured in puromycin containing medium for 2 days, and then cells were further incubated under normoxic (20% O_2) or hypoxic (1% O_2) conditions for 2 days. **C,** Effects of PGC1α and HIF-1α suppression on redox state. **D and E,** Effects of HIF-1α suppression on antioxidant genes expression (D) and intracellular ROS levels (E). **F,** Levels of antioxidant gene expression in PGC1α and HIF-1α depleted tumors. **G,** ROS detoxification enzymatic activity in PGC1α and HIF-1α suppressed A375P cells. **H,** Effects of ROS detoxification enzymes on redox state in PGC1α and HIF-1α depleted A375P cells. **I,** Effects of ROS detoxification enzymes on cell growth in PGC1α and HIF-1α suppressed A375P cells. Cells were incubated with 100 units/ml of PEG-SOD (superoxide dismutase-polyethylene glycol) or 50 units/ml of PEG-catalase (catalase-polyethylene glycol) as indicated. **J,** Effect of piperlongumine on tumor growth and body weight in PGC1α and HIF-1α suppressed tumors described in Fig 3I. **K,** Apoptosis after piperlongumine treatment in the tumors described in Fig 3I. Values represent mean ± SD of three independent experiments performed in triplicate; $^{**}p < 0.01$ and $^{***}p < 0.001$. The whiskers in the box plots represent the maximum and the minimum value**.**

Supplementary Table 1: Gene sets of genes induced under hypoxia (from MsigDB) listed in the table were tested for enrichment in PGC1α suppressed A375P cells using GSEA with the default parameters. 11 out of the 13 genesets scored as being enriched in the PGC1α depleted samples with a q<0.25.

NAME	NES	NOM p-val	FDR q-val
ELVIDGE_HYPOXIA_UP	2.53	0.00	0.00
ELVIDGE_HYPOXIA_BY_DMOG_UP	2.47	0.00	0.00
MANALO_HYPOXIA_UP	2.36	0.00	0.00
FARDIN_HYPOXIA_11	2.14	0.00	0.00
LEONARD_HYPOXIA	2.06	0.00	0.00
WINTER_HYPOXIA_UP	2.04	0.00	0.00
WINTER_HYPOXIA_METAGENE	2.00	0.00	0.00
MENSE_HYPOXIA_UP	2.00	0.00	0.00
QI_HYPOXIA	1.99	0.00	0.00
KIM_HYPOXIA	1.87	0.00	0.00
JIANG_HYPOXIA_NORMAL	1.61	0.00	0.01
JIANG_HYPOXIA_CANCER	0.88	0.67	0.68
WEINMANN_ADAPTATION_TO_HYPOXIA_UP	-1.60	0.01	0.01

Supplementary Table 2: shRNA sequences

Vector Name	Sequence	Related figures
pLKO-shPGC1α #1-puro	CCTAAGGTTAAGTCGCCCTCG	Fig.1A, 1C, 1D, 1E, 1G, 1H, 1I, 1J, 2 and S1A
pLKO-shScr #1-puro	GCAGAGTATGACGATGGTATT	
pLKO-shScr #1-blast	CCTAAGGTTAAGTCGCCCTCG	Fig.1B
pLKO-shScr #2-blast	CAACAAGATGAAGAGCACCAA	
pLKO-shPGC1α #1-blast	GCAGAGTATGACGATGGTATT	
pLKO-shPGC1α #2-blast	CCGTTATACCTGTGATGCTTT	
pLKO-shPGC1α #3-blast	TGCTGCTCTTGAAAATGGATA	
pLKO-shPGC1α #4-blast	CACTTTGCGCAGGTCAAACGA	
pLKO-shScr #1-blast	CCTAAGGTTAAGTCGCCCTCG	Fig.3, 4 and S3
pLKO-shScr #2-puro-tet-on	CAACAAGATGAAGAGCACCAA	
pLKO-shPGC1α #1-blast	GCAGAGTATGACGATGGTATT	
pLKO-shHIF1α #1-puro-tet-on	GTGATGAAAGAATTACCGAAT	

Supplementary Table 3: Sequence of primers for quantitative RT-PCR

Gene	Forward	Reverse
HIF-1α	*TATTGCACTGCACAGGCCACATTC*	*TGATGGGTGAGGAATGGGTTCACA*
GLUT1 *F*	*GGCATTGATGACTCCAGTGTT*	*ATGGAGCCCAGCAGCAA*
PGK1	*CTTGGGACAGCAGCCTTAAT*	*CAAGCTGGACGTTAAAGGGA*
PFKFB3	*GGGGAGTTGGTCAGCTTTG*	*AAGATGCCGTTGGAACTGAC*
ALDOC	*CAGGGCAATGTCAGACAACT*	*GGCTGCGGCTGCTAACT*
PDK1	*ATGATGTCATTCCCACAATGGCCC*	*TGAACATTCTGGCTGGTGACAGGA*
LDHA	*ACCCAGTTTCCACCATGATT*	*CCCAAAATGCAAGGAACACT*
CA-IX	*GCGACGCAGCCTTTGAAT*	*CCACTCCAGCAGGGAAGGA*
VEGF	*AGCTGCGCTGATAGACATCC*	*CTACCTCCACCATGCCAAGT*
ANGPTL4	*TCTCCGTACCCTTCTCCACT*	*AGTACTGGCCGTTGAGGTTG*
SOD2	TGACCACCACCATTGAACTT	CGTCACCGAGGAGAAGTACC
GpX1	AAGAGCATGAAGTTGGGCTC	CAACCAGTTTGGGCATCAG
TXN2	*TCAAGACCGAGTGGTCAACA*	*AATATCCACCTTGGCCATCA*
GSTM4	*TTGGAGAACCAGGCTATGGAC*	*TTCCCCAGGAACTGTGAGAAGT*
PGC1α	*GTAAATCTGCGGGATGATGG*	*AATTGCTTGCGTCCACAAA*
IDH3A	*CTGCTCAGTGCCGTGATG*	*TCCTCTGTGAAGTCTGAGCATTT*
NDUFS3	GCTGACGCCCATTGAGTCTG	GGAACTCTTGGGCCAACTCC
COX5A	CGAGCATCAAACTCCTCAT	GAGGCCTCCTGCACTCC
ATP5G1	GCCTGATTAGACCCCTGGTA	GGCTAAAGCTGGGAGACTGA