Supplementary Figure 1. Breeding schemes to generate the transgenic mice used in the study. A) Breeding scheme to generate *Hif1α$^{fl/fl}$;UBC-creER$^{+/-}$ and Hif1α$^{fl/fl}$;UBC-creER$^{-/-}$* mice. **B)** Breeding scheme to generate *Hif2α$^{fl/fl}$;UBC-creER$^{+/-}$ and Hif2α$^{fl/fl}$;UBC-creER$^{-/-}$* mice. **C)** Breeding scheme to generate *Hif2α$^{fl/wt}$;UBC-creER$^{+/-}$ and Hif2α$^{fl/wt}$;UBC-creER$^{-/-}$* mice **D.**) Breeding scheme to generate *Hif2α$^{fl/fl}$;Ve-cadherin-cre$^{+/-}$* and *Hif2α$^{fl/fl}$;Ve-cadherin-cre$^{-/-}$* mice.

Supplementary Figure 2. Hif2 ASO reduces cardiac function of mice under hypoxia. Mice were treated Control or HIF2a ASO as described in Fig. 3. At the end of the experiment, cardiac expression of Hif2a mRNA was determined by qRT-PCR (A). Levels of catecholamines in blood plasma as determined by HPLC (B). C-E: Parameters of cardiac function, Millar catheter measurements. Statistical significance determined by t-test (B) or by 2-way ANOVA (other panels).

Supplementary Figure 3. **HIF2 inhibitor PT2567 significantly normalizes the levels of some mis-expressed genes in lungs of rats exposed to hypoxia for 4 weeks**. A-C: levels of HIF target genes and PH related genes in the lungs from rats under normoxia or hypoxia, treated with control reagent or HIF2 inhibitor PT2567 (N=6 for each group). **A**) Classical HIF target genes; **B**) Genes involved in inflammation; **C**) Genes involved in signaling and proliferation. Statistical significance determined by t-test.

Supplementary Figure 4. **HIF inhibitor PT2567 significantly normalizes the levels of some mis-expressed genes in lungs of the rats exposed to hypoxia for four days**. A-C: levels of HIF target genes and PH related genes in the lungs of rats under normoxia or hypoxia, treated with control or HIF2 inhibitor PT2567 (N=6 for each group). **A**) Classical HIF target genes. **B**) Genes involved in inflammation. **C**) Genes involved in signaling and proliferation. Statistical significance determined by t-test.

Supplementary Figure 5. Hif2α, not Hif1α siRNA significantly prevents gene expression changes observed in normal pulmonary artery endothelial cells in response to acute hypoxia. To determine if HIF2 or HIF1 activity is responsible for hypoxia-mediated gene expression changes in EC, normal human pulmonary artery EC cells (N=3) were transfected with control or siRNAs targeting Hif1α or Hif2α mRNAs. Post-transfection of 16 hours, cells were exposed to normoxia or hypoxia (1.5% O2) for additional 16 hours, and then cells were collected for RNA preparation and qRT-PCR. **A**) Hif1α and Hif2α mRNA levels, to monitor the knockdown efficiency; **B**) Select classical HIF target genes; **C**) Genes involved in inflammation that are significantly induced by hypoxia in EC (Fig 6B); **D**) Genes involved in signaling and proliferation that are significantly altered by hypoxia in EC (Fig 6C). Statistical significance determined by t-test.

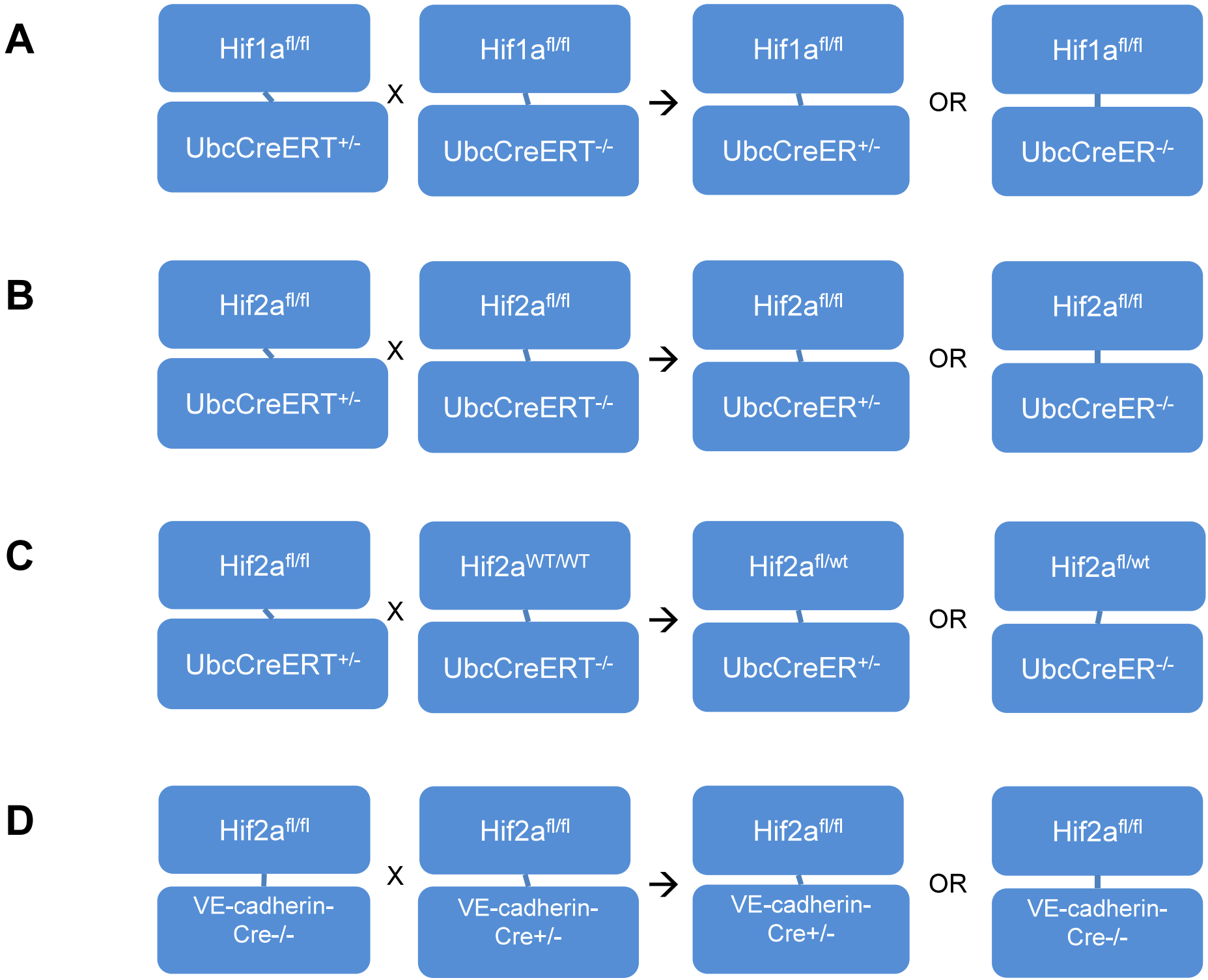
Supplementary Figure 6. Signals generated from normal pulmonary vascular EC under hypoxia, in a HIF2 activity dependent manner, significantly activate normal pulmonary vascular SMCs. Conditional medium prepared from normal pulmonary vascular ECs (N=3), cultured under normoxia or hypoxia (1.5% O2 for 24 hours), in the presence of DMSO or HIF2 inhibitor PT2567 (1 μM), were added to culture

medium of normal pulmonary vascular SMCs (N=3) that were cultured under normaxia. After 24 hours, SMC cells were collected for RNAs that were used to examine the mRNA levels of the indicated genes involved in cell proliferation (CCNE1 and CCNE2), pro-inflammation (CCL2) and anti-apoptosis (BCL2, BCL2L1 and BIRC5). Statistical significance determined by t-test.

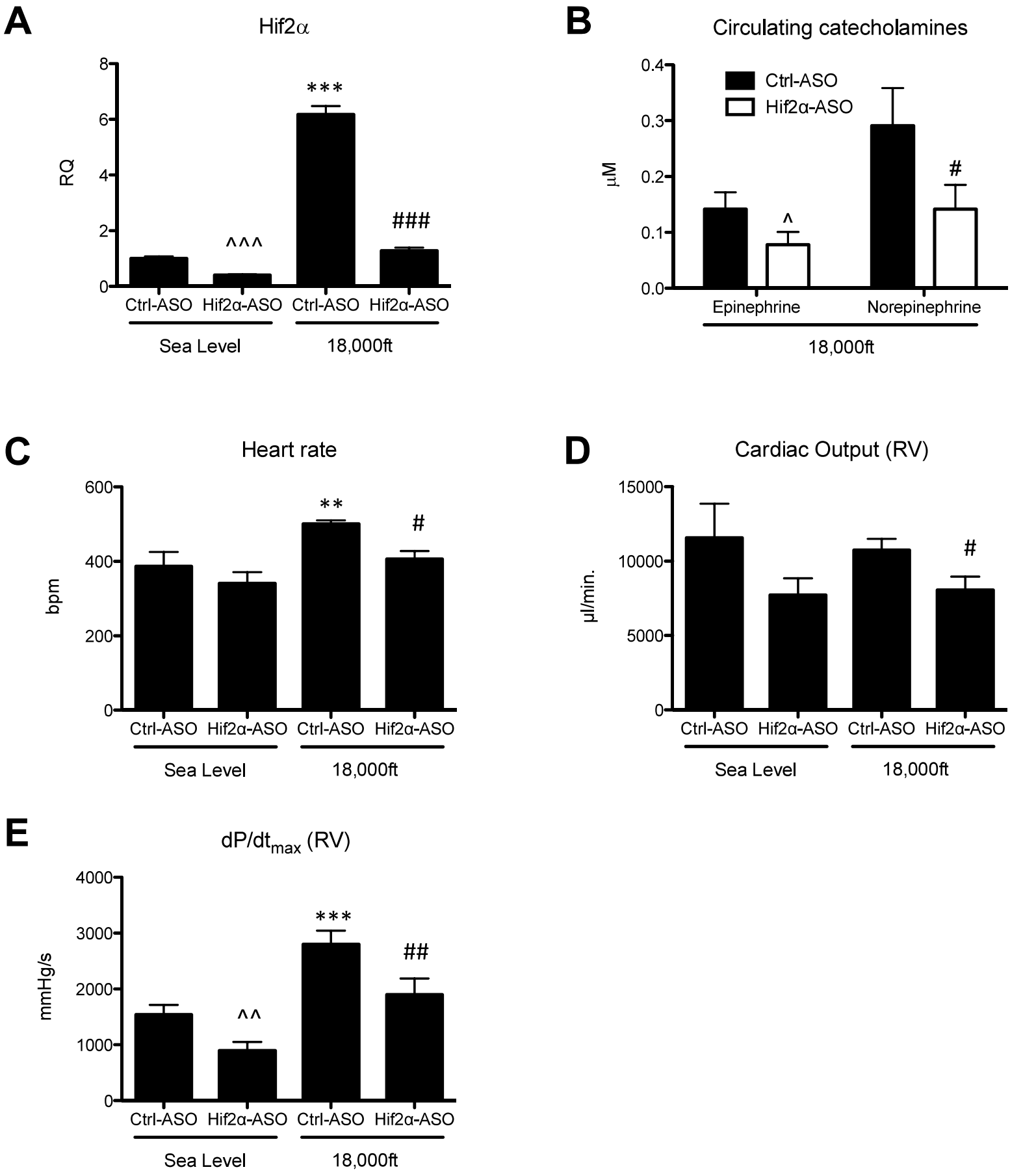
Supplementary Figure 7. **Endothelial deletion of Hif2α markedly attenuates some pathologic gene expression in the lungs of chronically (5 weeks) hypoxic mice. A-C**: levels of HIF target genes and PH related genes in the lungs of normoxic or hypoxic mice, with or without EC deletion of Hif2α gene. **A**) Classical HIF target genes. **B**) Genes involved in inflammation. **C**) Genes involved in signaling and proliferation. Statistical significance determined by t-test.

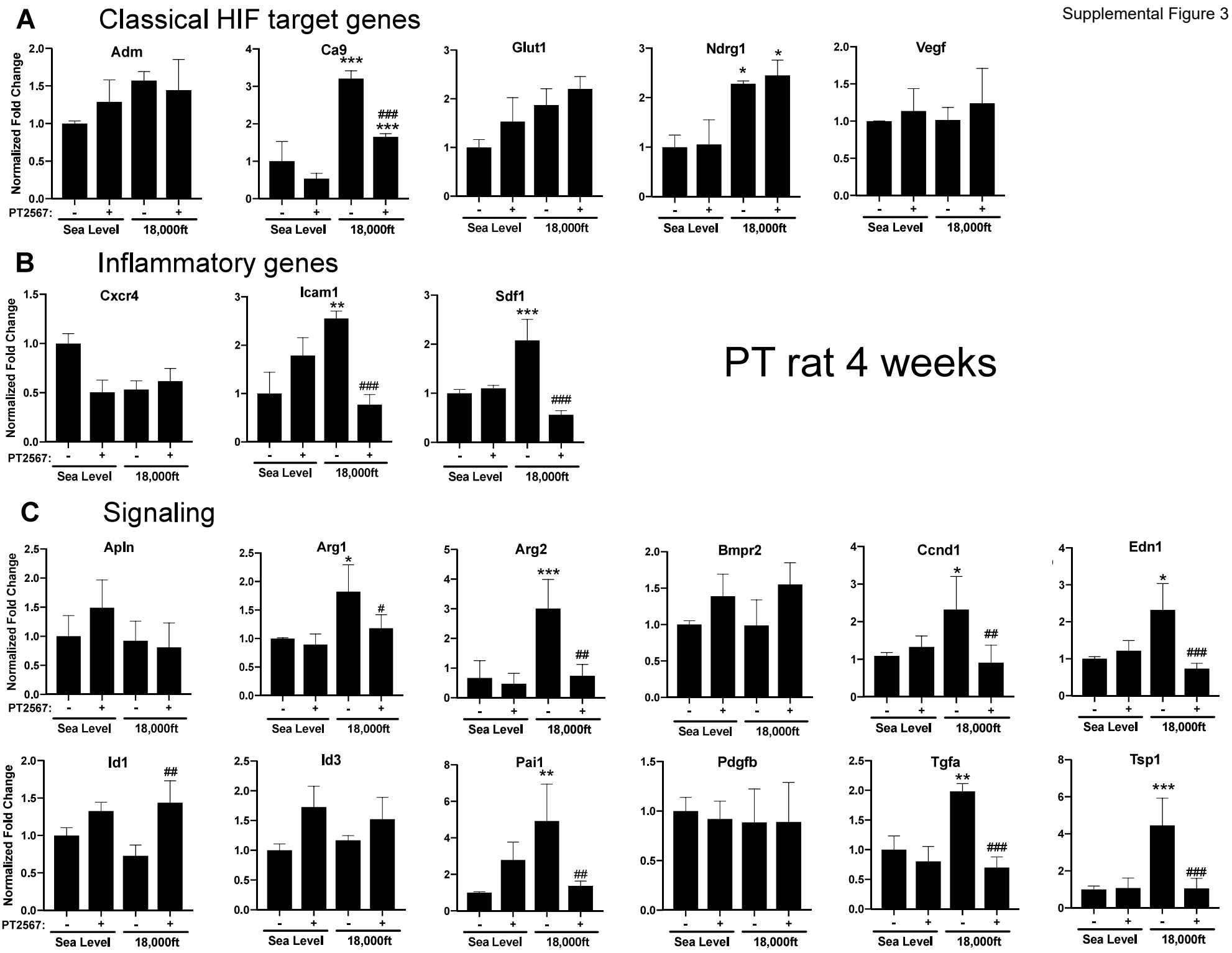
Supplementary Figure 8. **Endothelial deletion of Hif2α markedly attenuates pathologic gene expression in the RVs of chronically hypoxic mice.** In the hypertrophic heart, cardiac myocytes display an altered gene signature, such as isoform switching from α-myosin heavy chain (α-MHC, Myh6) to β-MHC (Myh7) and re-expression of skeletal muscle α-actin (Acta1). **A**) Increased expression of Acta1 was attenuated in hypoxic EC-Hif2α KO mice. **B**) Myh6 expression was reduced in hypoxia-exposed mice, but was not reversed in hypoxic EC-Hif2α KO mice. **C**) Increased expression of Myh7 was attenuated in hypoxic EC-Hif2α KO mice. Statistical significance determined by t-test.

Supplemental Figure 1

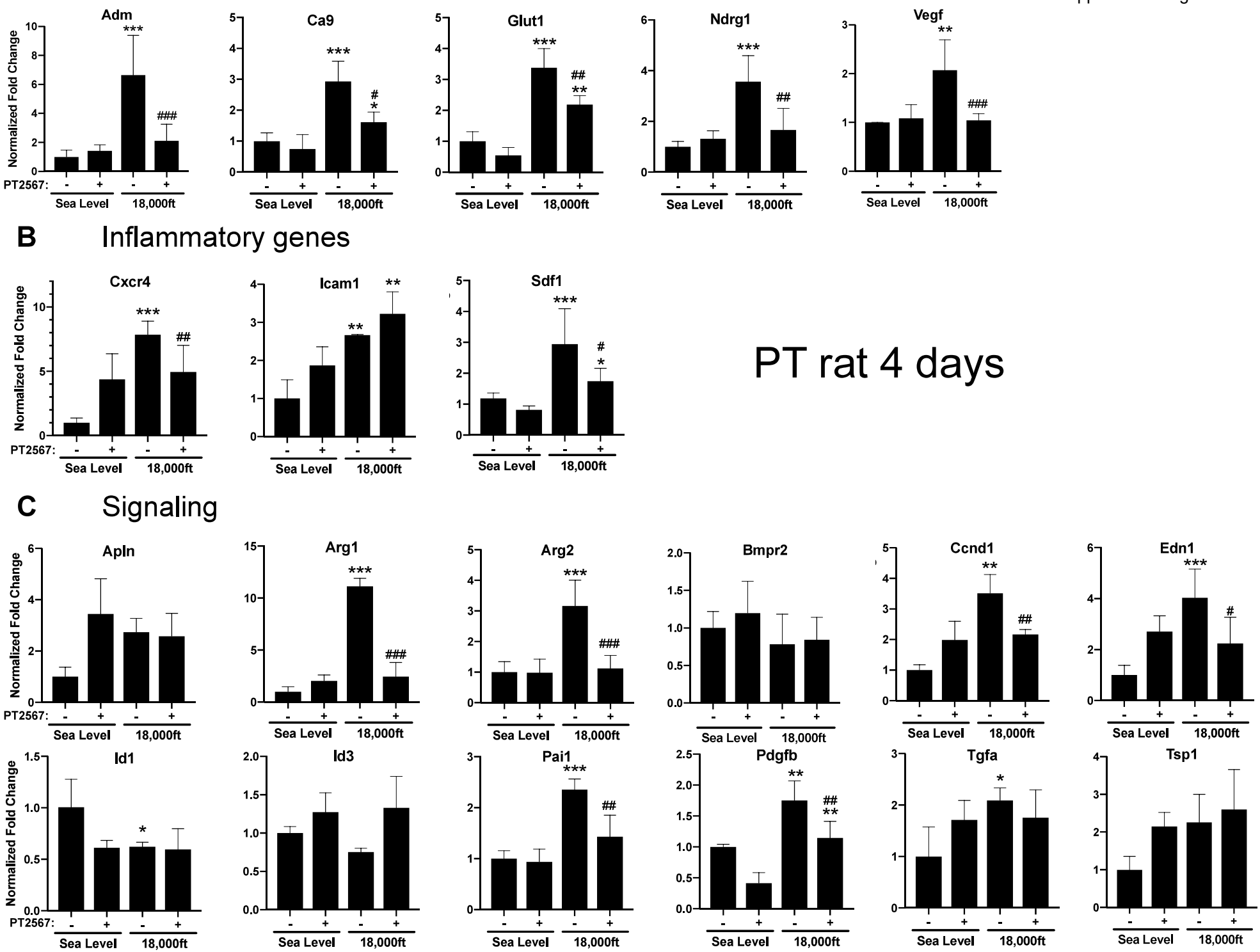


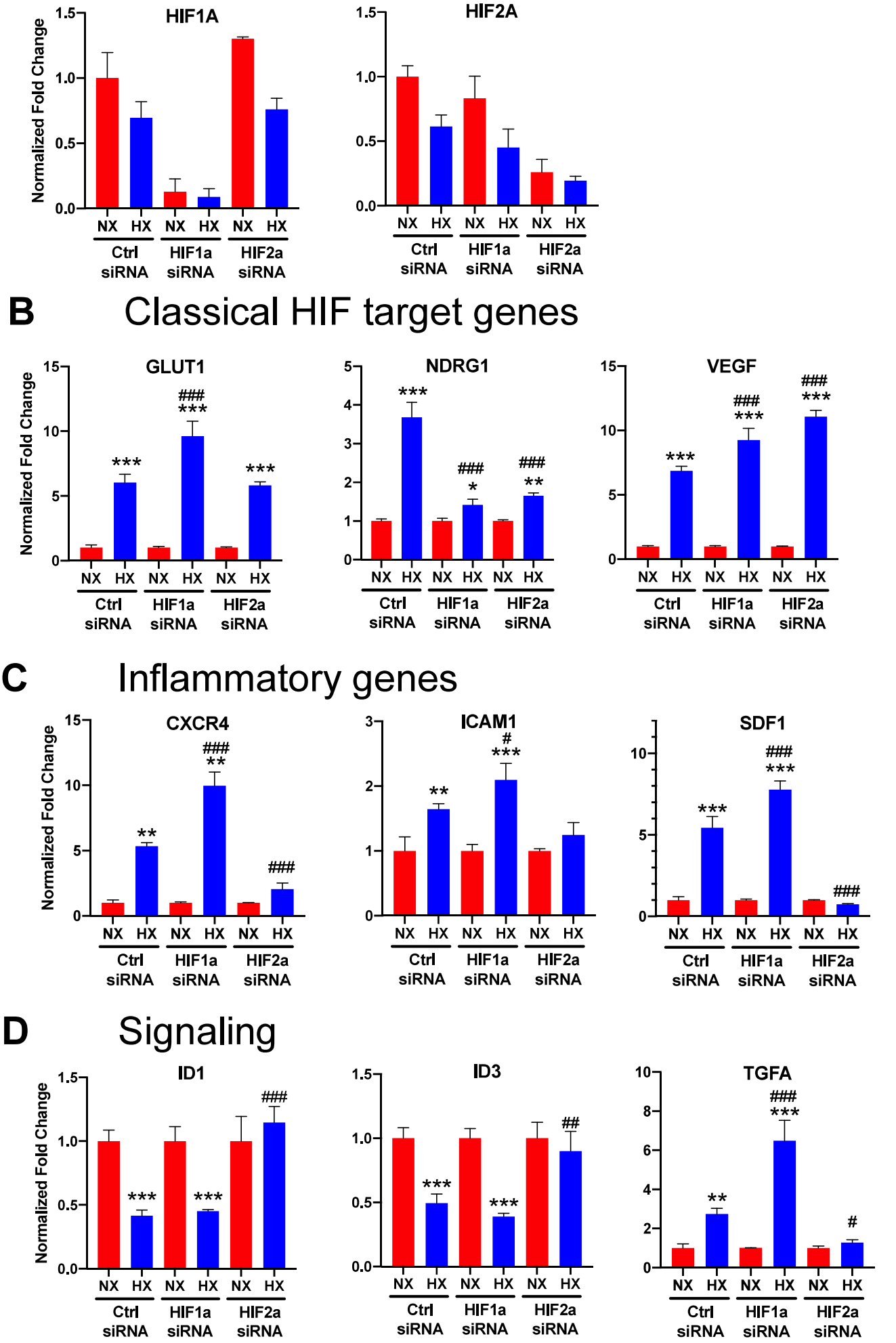
Supplemental Figure 2

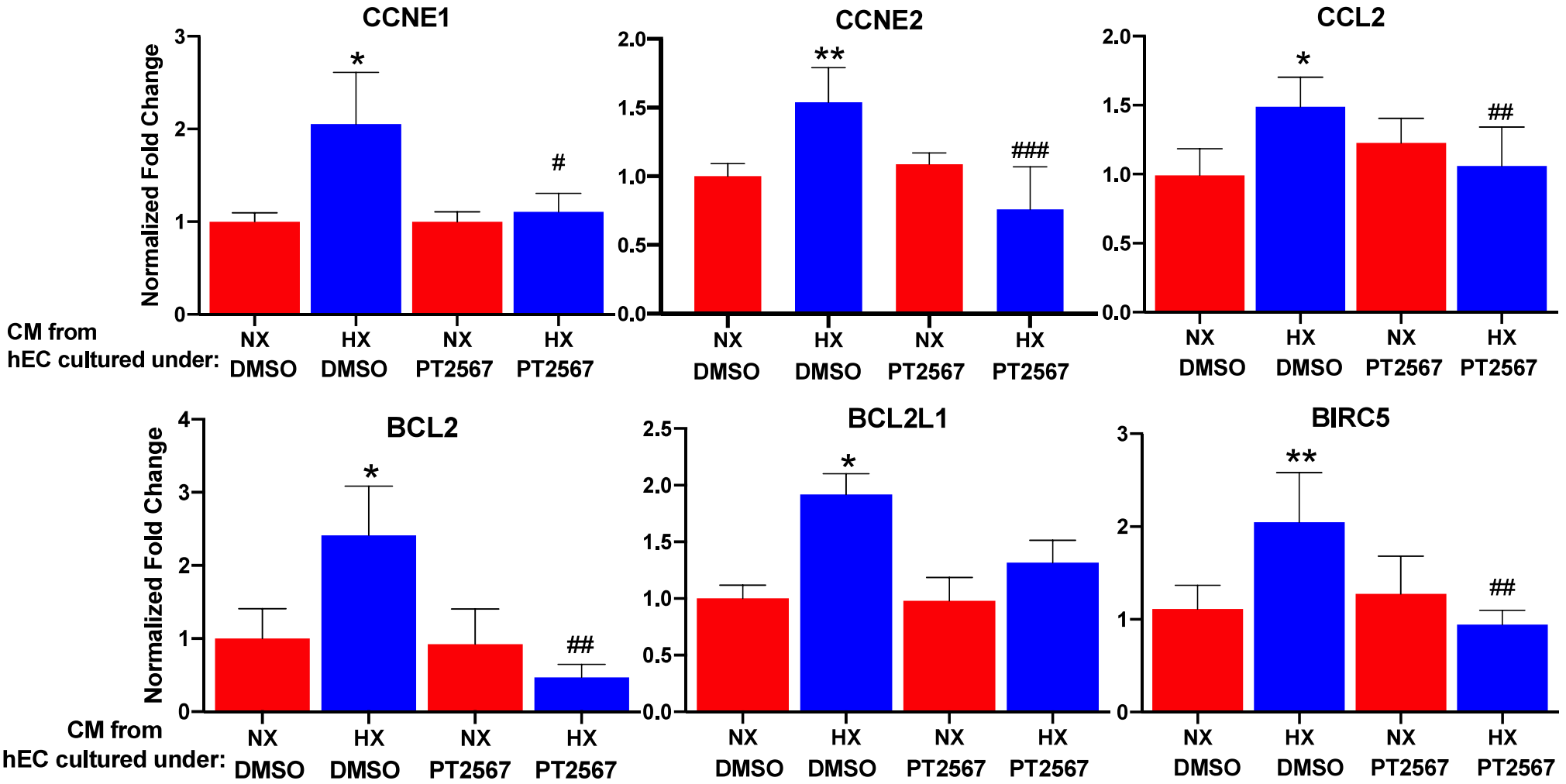



A
Classical HIF target genes
Adm
Ca9
Glut1
Ndrg1
Vegf
B
Inflammatory genes
Cxcr4
Icam1
Sdf1
PT rat 4 weeks
C
Signaling
Apln
Arg1
Arg2
Bmpr2
Ccnd1
Edn1
Id1
Id3
Pai1
Pdgfb
Tgfa
Tsp1
Normalized Fold Change
PT2567:
Sea Level
18,000ft

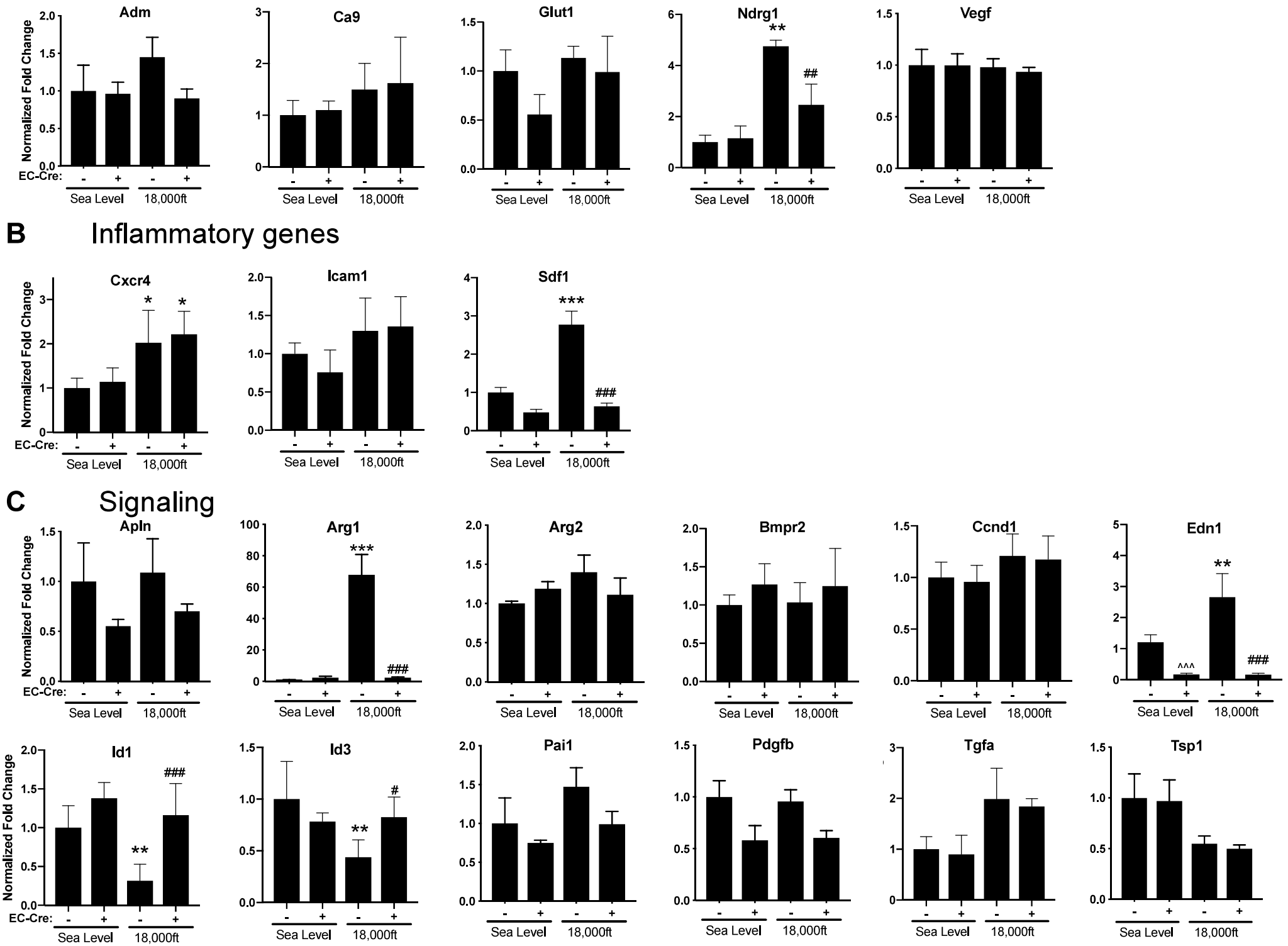
Supplemental Figure 4




A
HIF-a
HIF1A
HIF2A
Normalized Fold Change
NX HX NX HX NX HX
Ctrl siRNA
HIF1a siRNA
HIF2a siRNA
B
Classical HIF target genes
GLUT1
NDRG1
VEGF
C
Inflammatory genes
CXCR4
ICAM1
SDF1
D
Signaling
ID1
ID3
TGFA


CCNE1
CCNE2
CCL2
BCL2
BCL2L1
BIRC5
Normalized Fold Change
CM from
hEC cultured under:
NX DMSO
HX DMSO
NX PT2567
HX PT2567
*
**
#
##
###

Supplemental Figure 7



Supplemental Figure 8