SUPPLEMENTAL MATERIAL

Supplemental Methods.

Cell culture. HUVECs were obtained from ATCC and grown on gelatin-coated dishes in Vascular Cell Basal Medium (PCS-100-030; ATCC) supplemented with microvascular endothelial growth factors (PCS-100-041; ATCC). HUVECs were transfected with control, *HIF2a*, or *ARNT* small interfering RNA (siRNA) oligonucleotides using the HiPerFect (Qiagen Inc.) transfection reagents according to the manufacturer's protocols (Qiagen Inc). The following siRNA oligonucleotides were purchased through Qiagen's pre-validated siRNA database: siRNA target sequence for *HIF2a*; CTCGGCGTCTGAACGTCTCAA and *ARNT*; ACGGAACAAGATGACAGCCTA.

Hypoxia experiments were conducted 48 hours after transfection. Hypoxic conditions were achieved by exposing cells to 0.5% O_2, 5% CO_2 and 95% humidity in an Invivo2 200 hypoxia chamber (Ruskinn Technologies).

miRNA Expression analysis. Starting with 10ng of total RNA, mature miRNAs were reverse transcribed to cDNA (TaqMan Advanced miRNA cDNA Synthesis Kit, Applied Biosystems), which was amplified via fluorescently labeled Taqman probe and primer sets. For normalization, *miR-16* was used as endogenous reference control given prior reports of its consistent expression in hypoxia and models of pulmonary hypertension. (Parikh et al, Circulation 2012;125: 1520-1532).

Supplemental Table 1. Primer sequences. Shown are sequences of primer sets used for the expression analysis of the indicated genes by RT-PCR.

Gene	**Forward Primer** **Reverse Primer**
Pgk1	5′-CAAACAACCAAAGGATCAAGG-3′ 5′-CCCAAGATAGCCAGGAAGG-3′
Ldha	5′- CGTCTCCCTGAAGTCTCTTAACC-3′ 5′- CCCACACCATCTCAACACC-3′
Glut1	5′- GTCCTATCTGAGCATCGTGGC-3′ 5′- TAATACGACTCACTATAGGGCT-3′
Edn1	5′- ACTTCTGCCACCTGGACATC -3′ 5′- TCTGTGGCCTTATTGGGAAG -3′
Apln	5′- GCTGCTCTGGCTCTCCTTGA -3′ 5′- CCATCTGGAGGCAACATCAGT -3′
Aplnr	5′- AGGCACCACAGGCAATGG -3′ 5′- TCTCTTTTCGCGGCTGGTT -3′

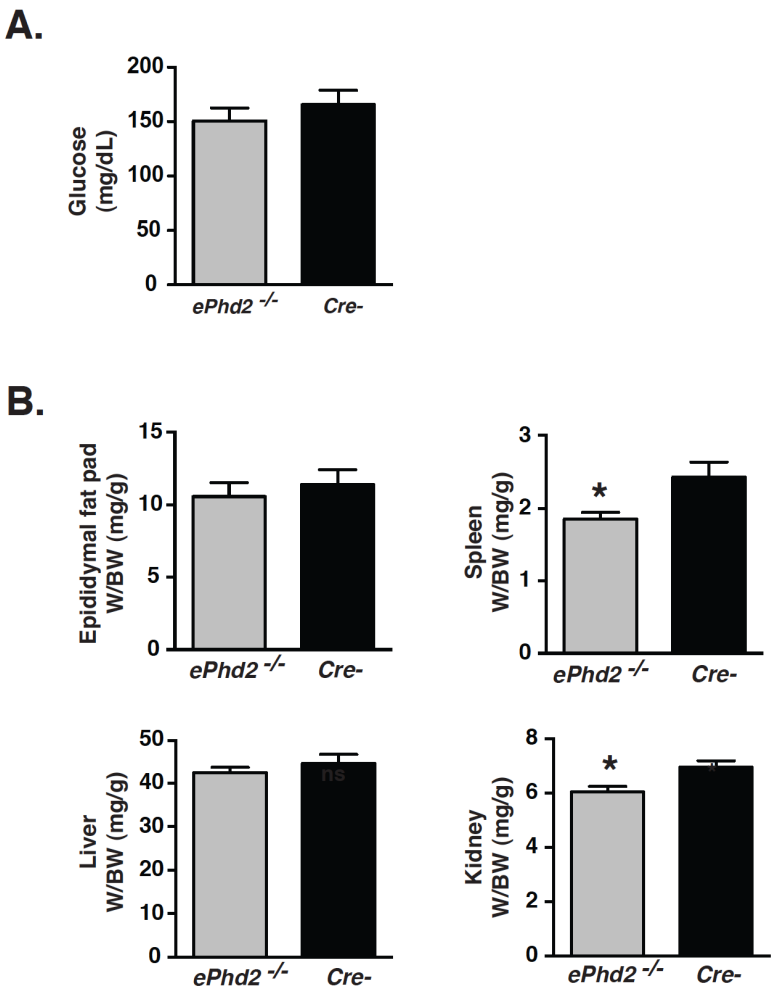

Figure S1. Phenotypic characterization of mice with endothelial *Phd2* inactivation. (A) Blood glucose levels for *ePhd2*$^{-/-}$ mice and *Cre-* controls. **(B)** Shown are ratios of epididymal fat pad, spleen, liver or kidney weight (W) to body weight (BW) for the mice with the indicated genotypes. Bars represent mean values ± SEM; *, P<0.05.

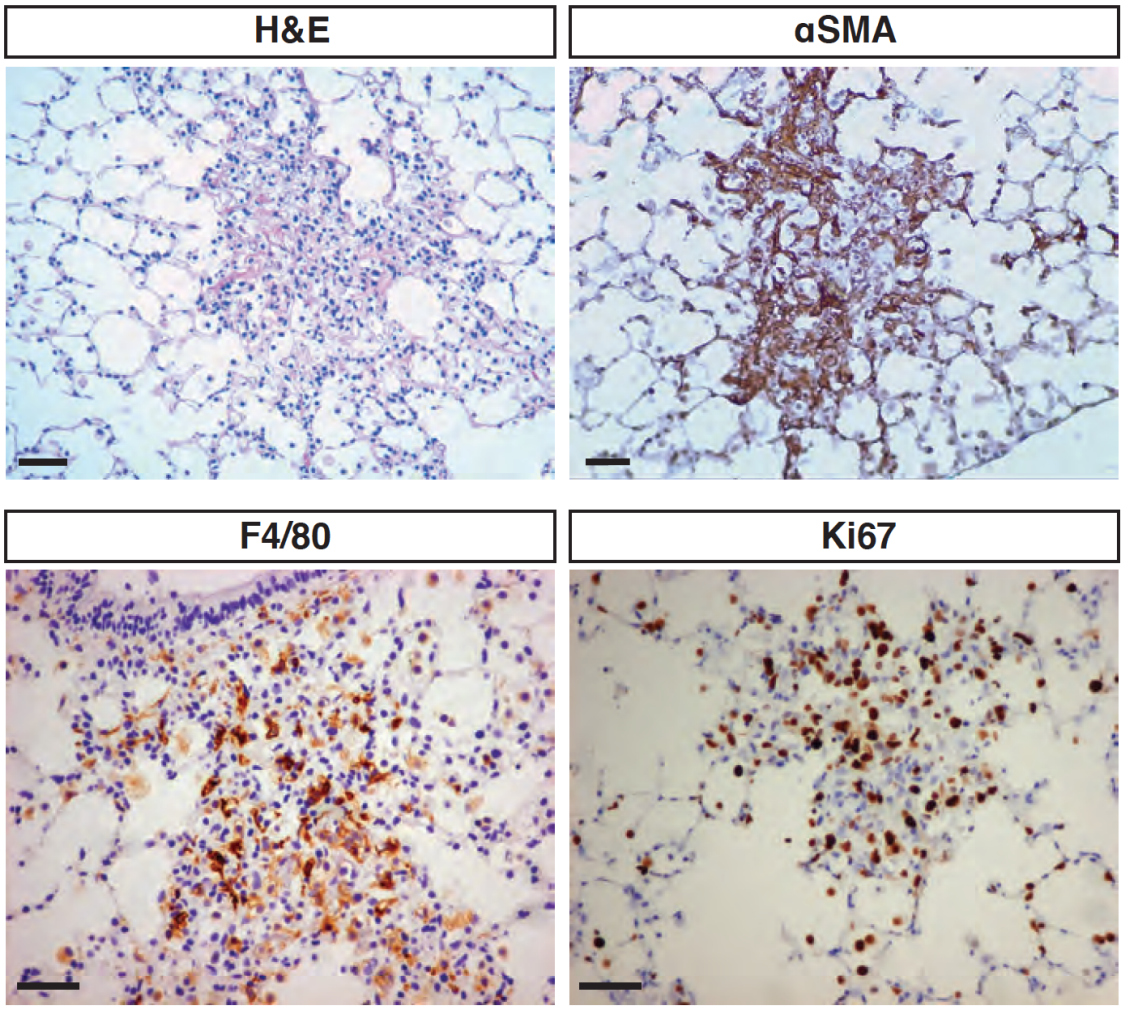

Figure S2. Alveolar injury is present in a subset of *ePhd2*$^{-/-}$ mutants. Representative images from areas of alveolar injury in H&E, αSMA-, F4/80- and Ki67-stained lung sections of *ePhd2*$^{-/-}$ mutants. Scale bars indicate 50 μm.

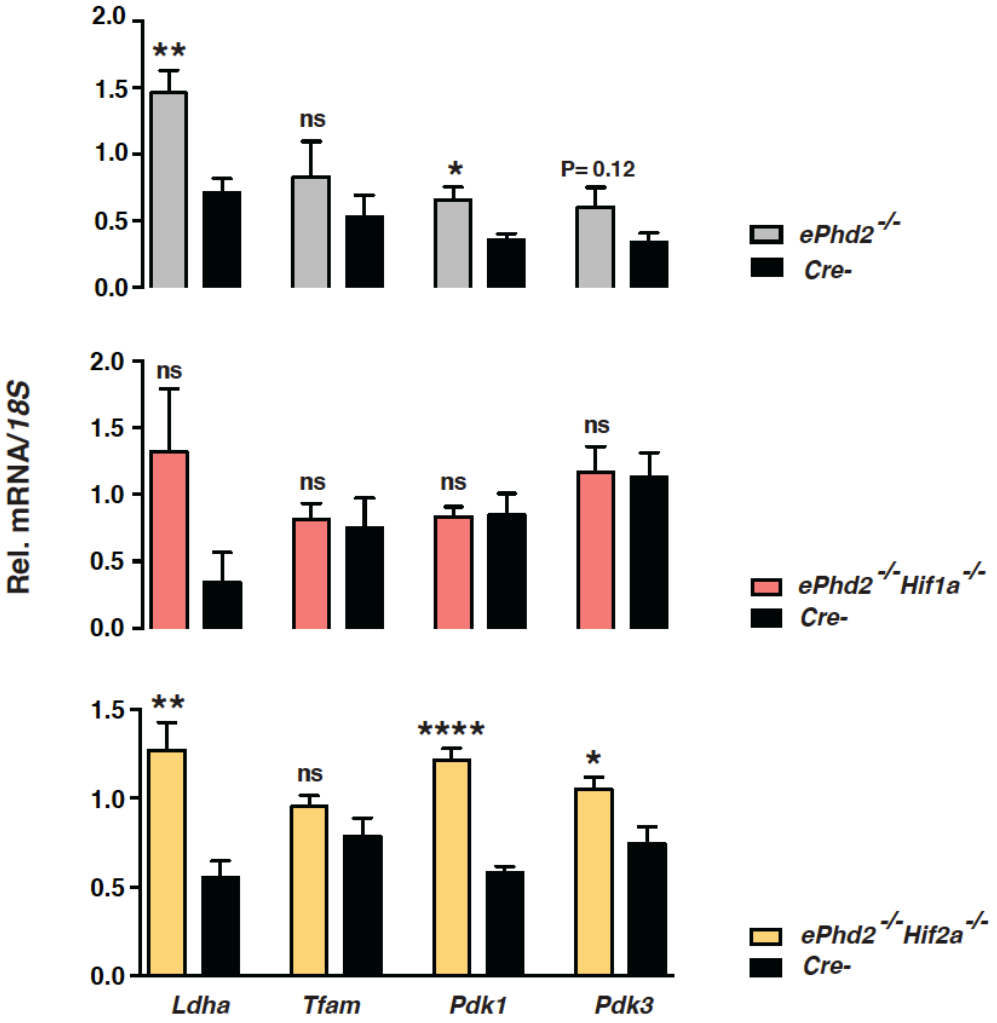

Figure S3. Endothelial HIF-1 regulates pulmonary expression of glycolytic genes. *Ldha*, *Tfam, Pdk1* and *Pdk3* mRNA levels in *ePhd2*$^{-/-}$ (n=8), *ePhd2*$^{-/-}$ *Hif1a*$^{-/-}$ (n=5), *ePhd2*$^{-/-}$ *Hif2a*$^{-/-}$ (n=6) and their corresponding *Cre*$^{-}$ littermate controls. *18S* was used for normalization. Bars represent mean values ± SEM; *, P<0.05; **, P<0.01; ****, P<0.0001.

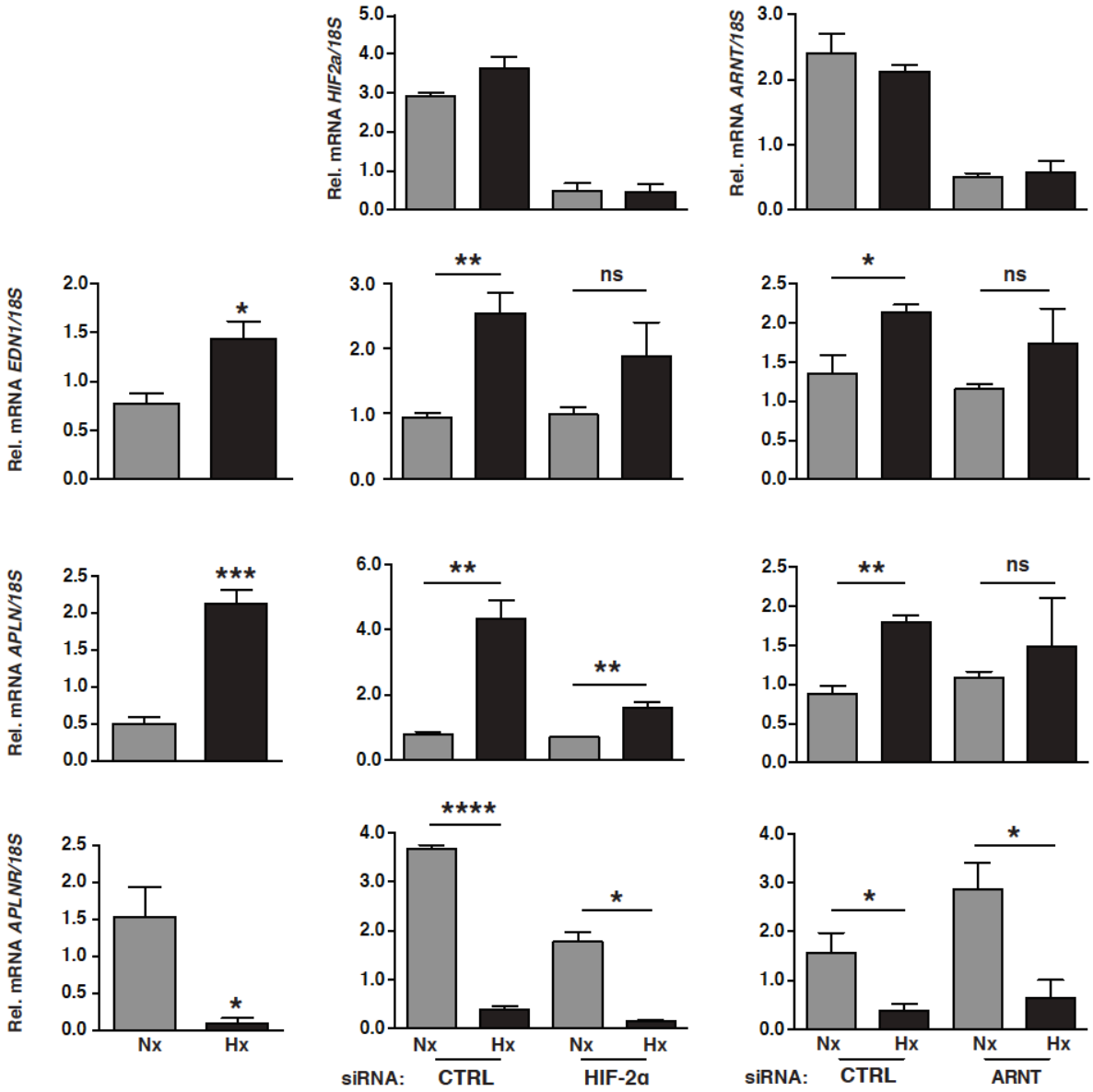

Figure S4. The hypoxic suppression of *APLNR* in HUVEC is independent of HIF. Relative levels of *EDN1*, *APLN* and *APLNR* in normoxic (Nx) and hypoxic (Hx; 0.5%, O_2, for 24hrs) HUVEC under baseline conditions and treatment with control, *HIF2a* or *ARNT* siRNA (n=3-4). Top panels: Transfection efficiency assessed by qPCR analysis of *HIF2a* and *ARNT*. *18S* was used for normalization. Bars represent mean values ± SEM; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.

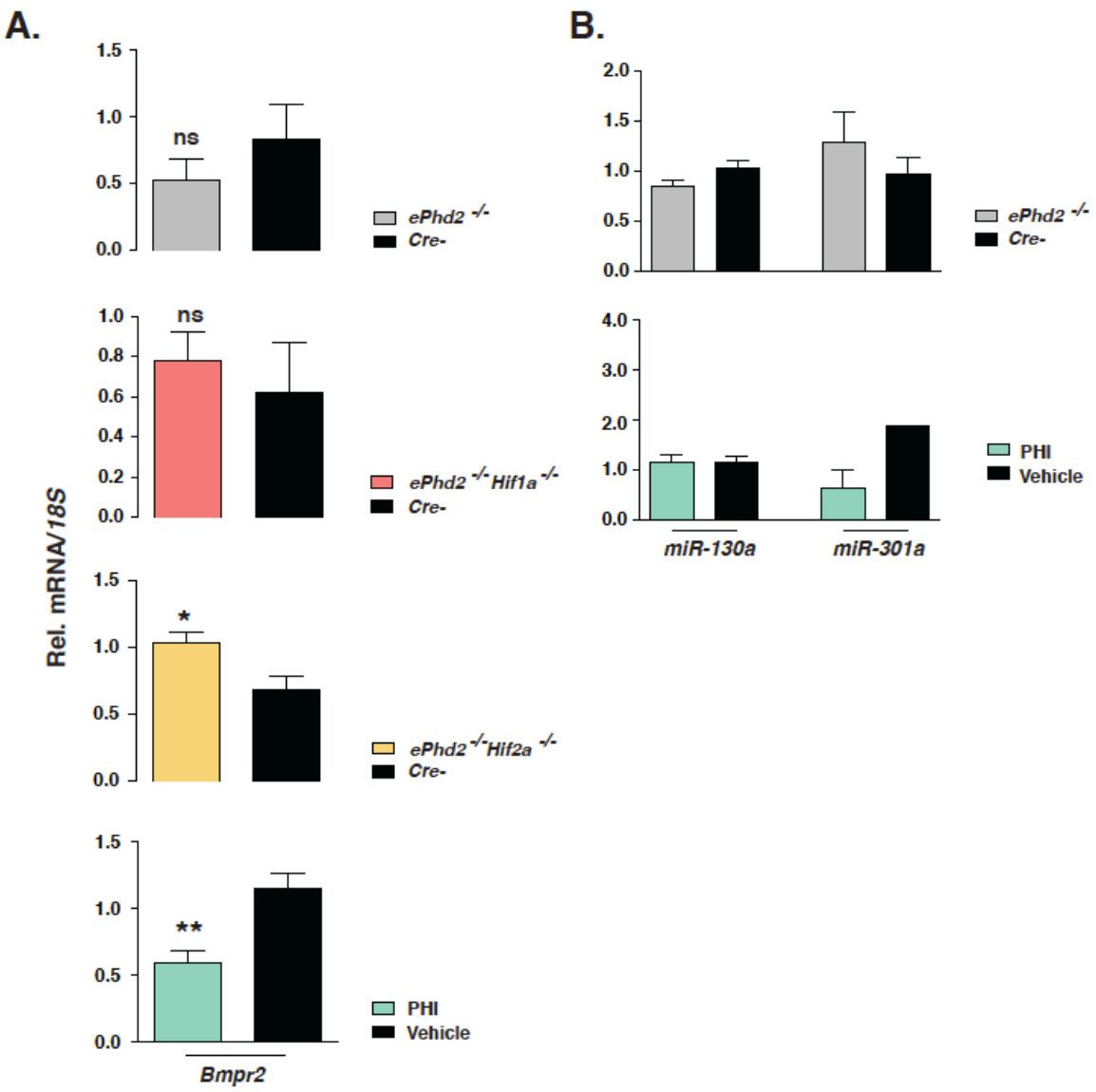

Figure S5. HIF-2 alters the expression of pulmonary *Bmpr2* but not *miR-130/301*. (A) Relative *Bmpr2* mRNA expression in lungs of *ePhd2*$^{-/-}$ (n=8), *ePhd2*$^{-/-}$ *Hif1a*$^{-/-}$ (n=5), *ePhd2*$^{-/-}$ *Hif2a*$^{-/-}$ (n=6) and their corresponding *Cre*$^{-}$ littermate controls. Bottom panel shows the relative levels of *Bmpr2* in PHI-or vehicle-treated mice (n=4-5). **(B)** Expression analysis of *miR-130a* and *miR-301a* in lungs of *ePhd2*$^{-/-}$ and their *Cre*$^{-}$ controls (n=4-5), as well as PHI- and vehicle-treated mice (n=4-5). *18S* was used for normalization. Bars represent mean values ± SEM; *, P<0.05; **, P<0.01.