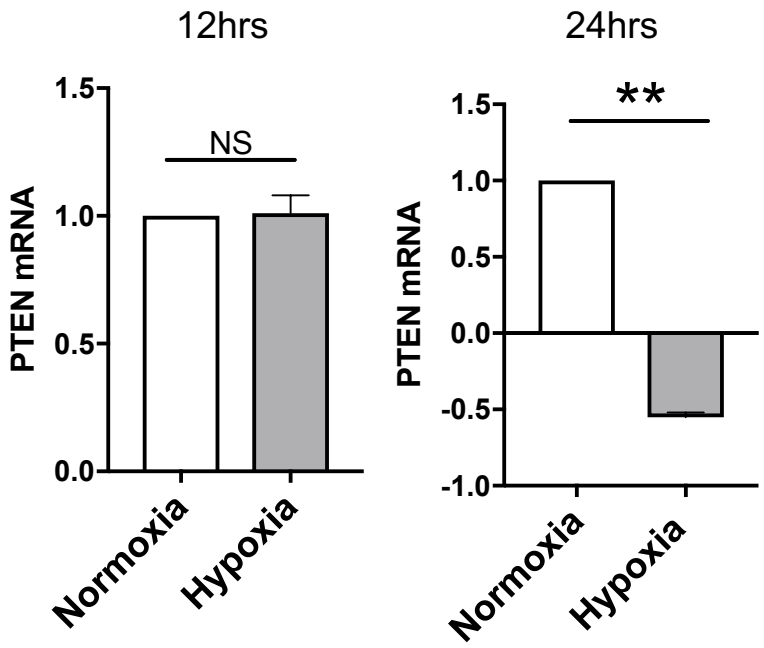
Supplementary Figure 1

A



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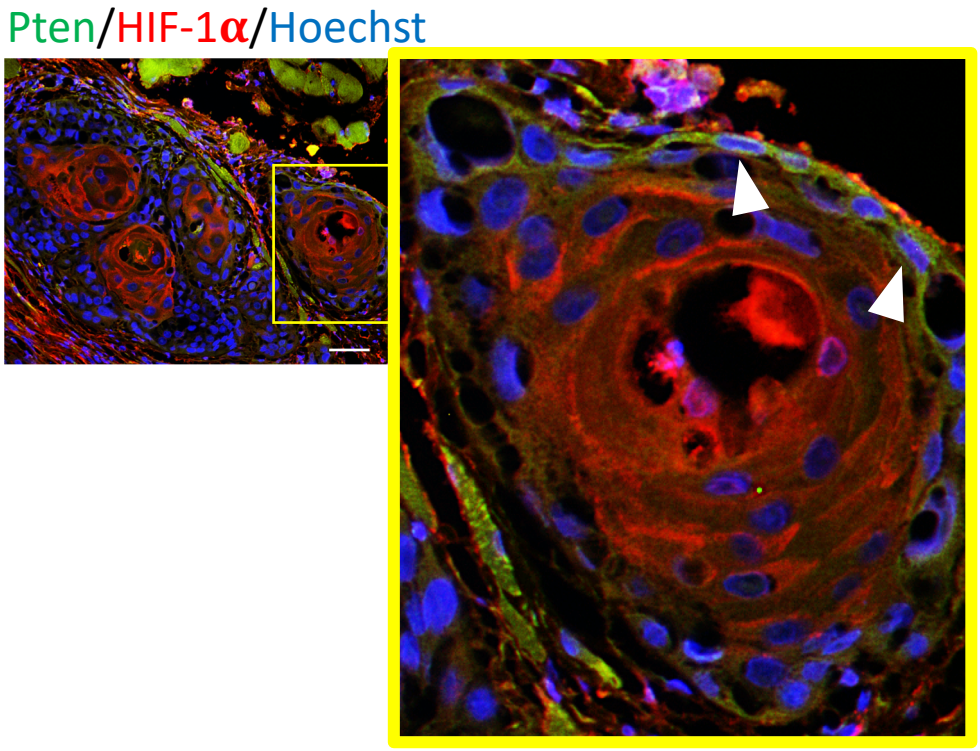
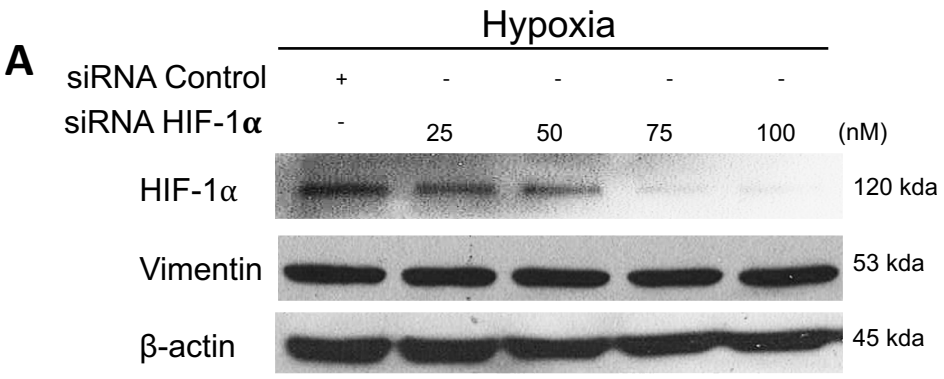
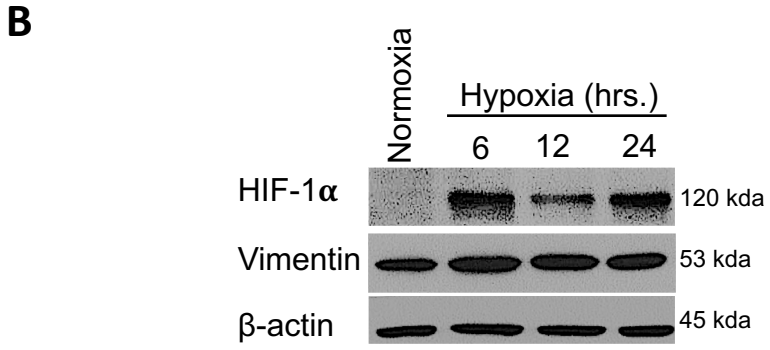
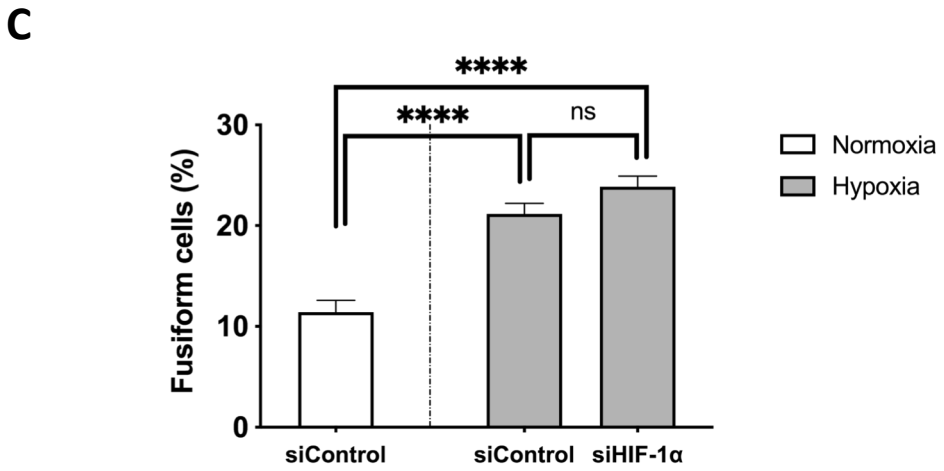
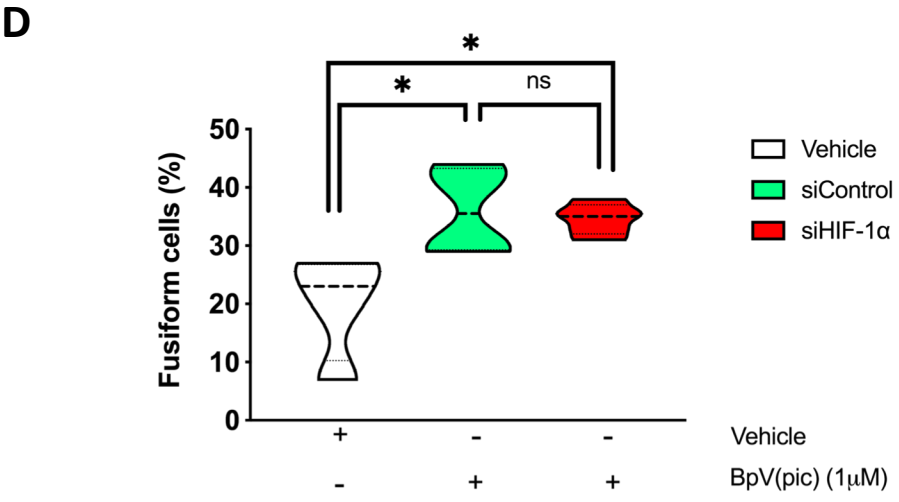


Supplementary Figure 2

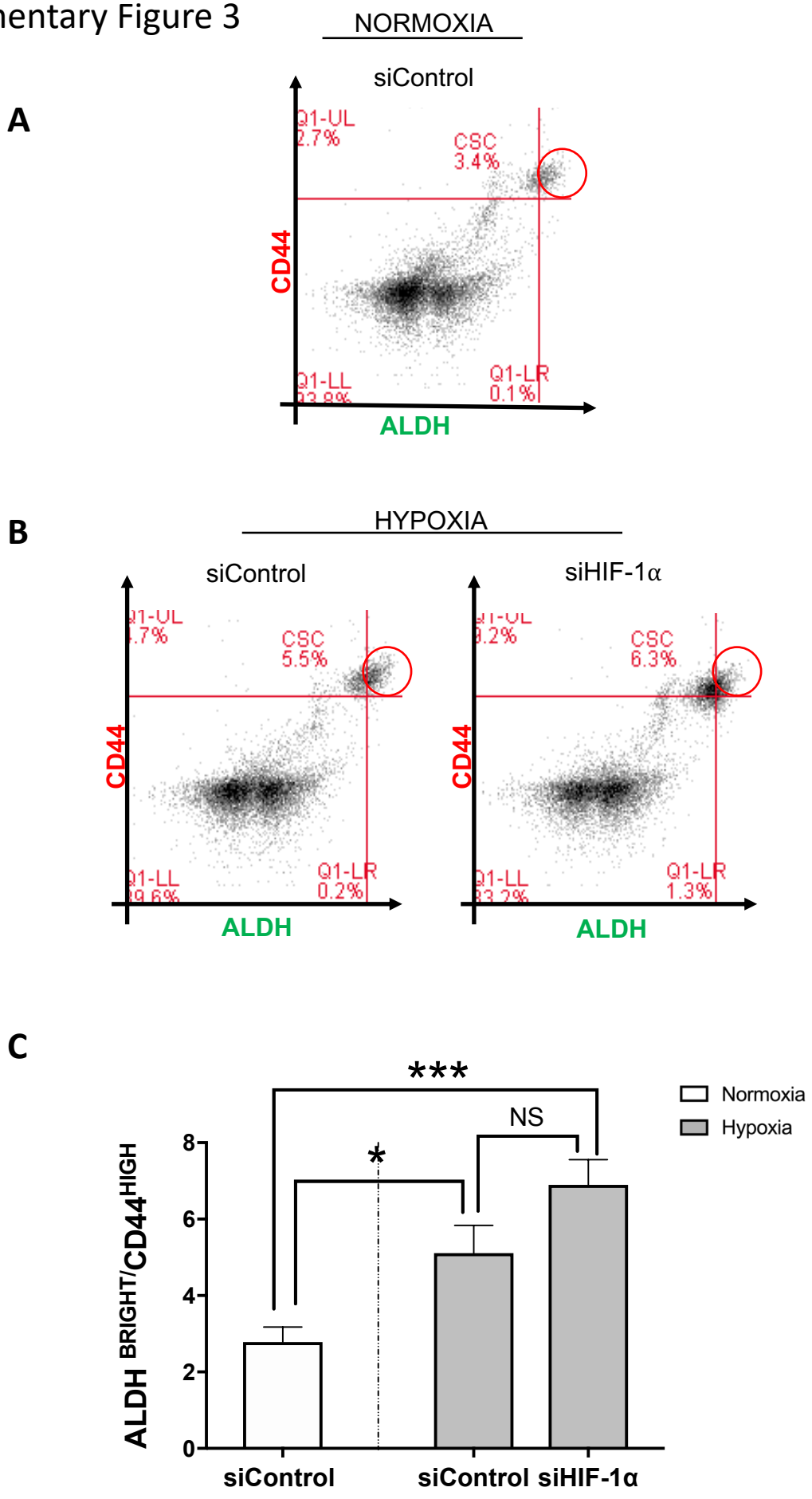




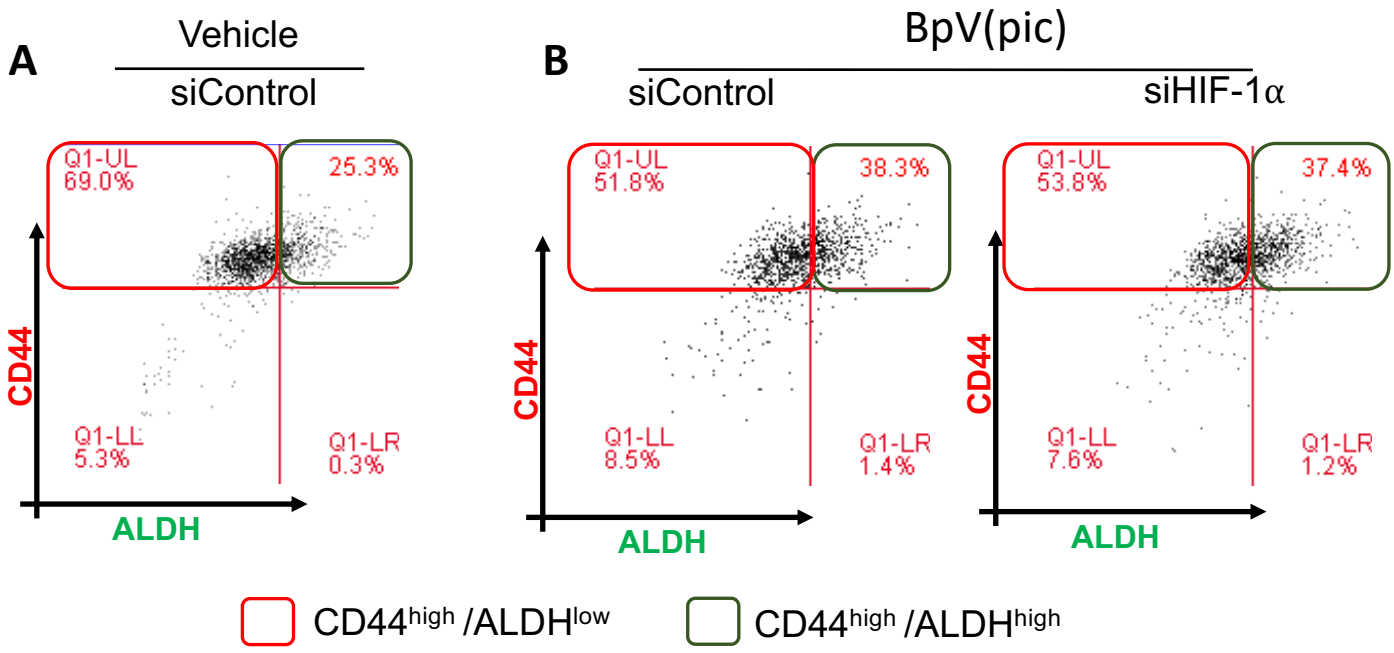


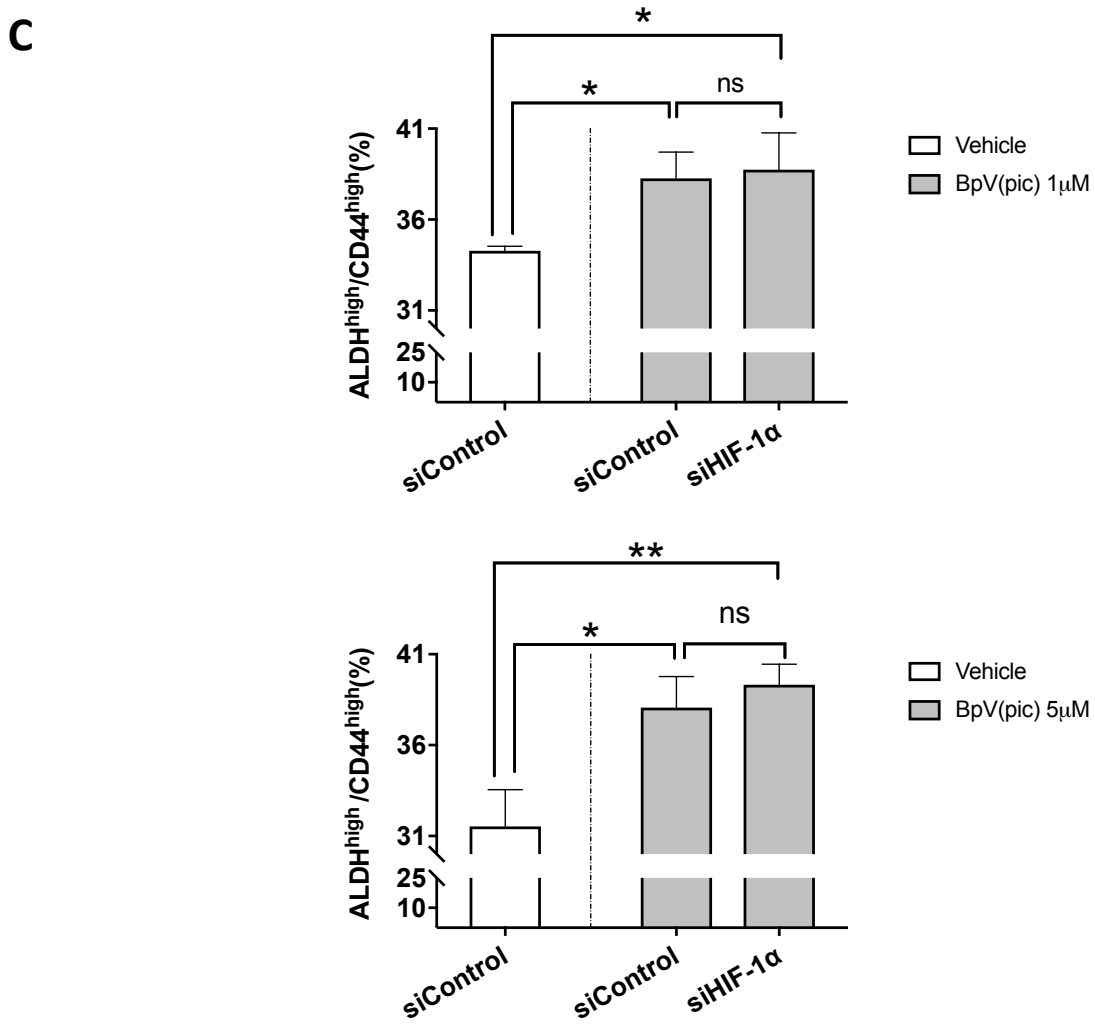


Supplementary Figure 3



Supplementary Figure 4





Supplementary Figure Legends

Supplementary figure 1. A. Reduced levels of Pten mRNA upon the culture of tumor cells under hypoxic conditions (lower than 2% of O_2 concentration) for 24 hrs (ns $p<0.05$; ** $p<0.01$). **B**. Immunofluorescence staining of squamous cell carcinoma xenografts displaying the merged image of HIF-1α staining (Alexa 568_red), PTEN staining (Alexa 488_green), and DNA staining (Hoechst 33342_blue). Cells positive for PTEN surrounding the hypoxic niche are characterized by a fusiform shape. Scale bar: 100μm.

Supplementary figure 2. A. Immunoblot of tumor cells receiving different concentrations of siRNA targeting HIF-1α (25nM tot 100nM). Note reduced protein levels of HIF-1α starting at 25nM of siRNA and achieving complete depletion at 100nM. Vimentin levels do not alter upon reduction of HIF-1α protein levels. β-actin was used as a loading control. **B.** immunoblot of tumor cells cultured under hypoxic conditions. Note the accumulation of HIF-1α after 6 hours of hypoxia. Protein levels of Vimentin are upregulated upon exposure of tumor cells to hypoxia. β-actin was used as a loading control. **C.** Quantification of tumor cells undergoing EMT upon downregulation of HIF-1α. Note that hypoxic conditions increase the percentage of tumor cells undergoing EMT. Depletion of HIF-1α does not influence the total number of tumor cells undergoing EMT (ns $p>0.05$; **** $p<0.0001$). **D.** Chemical inhibition of Pten using BpV(pic) triggers EMT on tumor cells. Depletion of HIF-1α does not enhance the number of tumor cells undergoing EMT (ns $p>0.05$; * $p<0.05$).

Supplementary figure 3. A and B. Scatter plots depicting the percentage of $ALDH^{bright}/CD44^{+}$ tumor cells under normoxia, and hypoxia. **C.** quantification of $ALDH^{bright}/CD44^{+}$ cells depicts the accumulation of CSC during hypoxic condition compared to normoxia. Note that loss of HIF-1α does not result in changes on the levels of CSC during hypoxic conditions.

Supplementary figure 4. A-B. Scatter plots depicting the percentage of $ALDH^{bright}/CD44^{+}$ tumor cells upon pharmacological administration of the Pten inhibitor

BpV(pic). **C**. Quantification of $ALDH^{bright}/CD44^{+}$ tumor cells receiving vehicle or BpV(pic) at the concentration of 1μM and 5μM. Note that tumors cells transduced with siRNA for HIF-1α present a similar number of CSC as cells receiving siRNA control (ns $p>0.05$; * $p<0.05$; ** $p<0.01$).