Supplemental Figure 2. Hypoxic shRNA transduced RCC4 cells induce HIF and c-Myc target genes consistent with their HIF-α subunit expression. **A.** Expression of VEGF, PGK and Oct4 as described above. Results measured by QRT-PCR and averaged from 4 experiments, error bars ±1 SEM. **B.** Summary of cell cycle progression by % in S-phase in RCC4 cell lines measured by BrdU incorporation after 24 or 48 hrs. at 0.5% O_2. Results averaged from 3 experiments error bars ±1 SEM, ** $p < 0.01$. **C.** Proliferation in empty vector clones, measured by serial cell counts; data from one representative experiment. Error ±1 SD. **D.** Expression of p27 and Cyclin D2 mRNA as described above. Results measured by QRT-PCR and averaged from 4 experiments, error bars ±1 SEM. **E.** Expression of p27 and Cyclin D2 protein following 24 hrs. 0.5% O_2. Actin loading control is shown in Figure 2C.

Supplemental Figure 3. EC lines recapitulate HIF-α effects on c-Myc activity observed in HCT116 and WT8 cells. **A.** Characterization of HIF-α expression in EC lines following 4 hrs. DFX treatment. **B.** Altered expression of VEGF and PGK following 24 or 48 hrs. at 0.5% O_2 in EC lines consistent with transcriptional activity by both HIF-1α and HIF-2α. Results measured by QRT-PCR and averaged from 4 experiments, error bars ±1 SEM. **C.** Altered p27 and Cyclin D2 expression following 24 or 48 hrs. hypoxia in EC lines consistent with HIF-α expression. Results measured as above. **D.** Western blot analysis of Cyclin D2 and p27 expression in EC lines following 48 hrs. at 0.5% O_2.

Supplemental Figure 4. Direct HIF-α DNA binding is not required for altered c-Myc promoter occupancy. **A.** HCT116 cells were grown at 21% O_2 (N) or 0.5% O_2 (H) for 20 hrs., and then assayed for HIF-1α binding to c-Myc promoter sites by ChIP as above. The graphs show the fold difference between c-Myc IP and isotype control (background) with results from 4 experiments, ±1 SEM. **B.** WT8 cells were treated and analyzed as in A. **C.** Cis-control using primers directed at p53 binding site upstream of p21 promoter reveal specificity of ChIP in HCT116 and WT8 cells.

Supplemental Figure 5. c-Myc promoter binding is regulated by HIF-1α and HIF-2α in HEK293 cells. **A.** Induction of transgenes encoding stablized forms of HIF-1α and HIF-2α after 24 hrs. doxycycline treatment in Tet-regulatable HEK293 cells. **B.** c-Myc promoter binding after 24 hrs. induction of HIF-1α or HIF-2α in Tet-regulable HEK293 cells. **C.** HEK293 cells were treated and analyzed as above, with Myctag IP for Myctag-HIF-1α and Myctag-HIF-2α. **D.** Cis-control using primers directed at p53 binding site upstream of p21 promoter reveal specificity of ChIP in HEK293 cells.

Supplemental Figure 6. c-Myc/Max binding is unaltered under normoxia in HIF-1α and HIF-2α overexpressing WT8 cells. **A.** Sp1, Miz1, Max, c-Myc and Mad1 expression in HCT116 and WT8 cells grown at 0.5% O_2 for 4 and 20 hrs. **B.** Vector control (V1) and HIF-1α overexpressing cell lines were cultured at 21% O_2 and Max IP was performed and analyzed for co-precipitated c-Myc. IP control and whole cell lysates are also shown. **C.** Vector control (V1) and HIF-2α overexpressing cell lines were cultured at 21% O_2 and Max IP was performed and analyzed for co-precipitated c-Myc, with controls as above.