**Supplementary Figure S1. IGF-2R is not involved in regulation of *HIF2A*.** (A-B) *IGF2R* mRNA expression in a clinical neuroblastoma material (A) and in SK-N-BE(2)c and KCN-69n cells cultured at 21% or 1% O2 for 72 hours (B). Expression of *HIF2A* mRNA after downregulation of *IGF2R* in SK-N-BE(2)c cells using siRNAs at normoxia (21% O2) (C) or hypoxia (1% O2) (D). Expression is normalized against siC within each experiment and statistical significance is calculated compared to siC. Relative mRNA was measured by qRT-PCR and data are presented as mean±SEM from at least three independent experiments. Statistical significance was calculated using Student’s t test: \*p<0.05, \*\*p<0.01, \*\*\*p<0.001. No asterisk (\*) indicates no significance.

**Supplementary Figure S2. PI3K/Akt signaling is enhanced in hypoxic neuroblastoma cells.** (A) Six neuroblastoma cell lines (four *MYCN* amplified: SK-N-BE(2)c, KCN-69n, IMR-32 and LA-N-5, and two *MYCN* non-amplified: SHSY-5Y and SH-EP) were investigated for PTEN protein expression by western blotting. (B) pAkt(S473) expression in SK-N-BE(2)c and KCN-69n neuroblastoma cells cultured at 21%, 5% or 1% O2 for 1, 4, 48, or 72 hours, as detected by western blot analysis. Actin was used as loading control.

**Supplementary Figure S3. All Akt isoforms are expressed in neuroblastoma cells.** (A-C) *AKT* mRNA expression in cells cultured at 21%, 5%, or 1% O2 for 48 hours. (D) *AKT* mRNA expression after combined knockdown of all three *AKT* isoforms for 4 or 48 hours at 5% O2. Expression is normalized against control within each setting. (E) SK-N-BE(2)c cells were treated with Akt inhibitor GDC-0068 for 1 hour at normoxia (21% O2) or hypoxia (1% O2), and mRNA levels of *HIF2A* and *HIF1A* were determined. (F-G) PRAS40 (pT246) protein expression after short-term (1 hour, F) or long-term (48 hours, G) treatment with GDC-0068 at normoxia or hypoxia. SDHA was used as loading control. (H) Expression of pAkt (S473) in GDC-0068-treated cells at 4 or 48 hours of normoxia or hypoxia. Actin was used as loading control. (I) *HIF2A* expression after knockdown of mTORC1-specific component Raptor. Expression is normalized against siC within each experiment, and statistical significance is calculated compared to siC. Relative mRNA was measured by qRT-PCR and data are presented as mean±SEM from at least three independent experiments. Statistical significance was calculated using Student’s t test: \*p<0.05, \*\*p<0.01, \*\*\*p<0.001. No asterisk (\*) indicates no significance.

**Supplementary Figure S4. mTORC1 signaling is dispensable for HIF-2α activity.** (A-B) Cells were treated with mTORC1 inhibitor rapamycin for 4 or 48 hours at 21%, 5%, or 1% O2 and *SERPINB9* (A) and *DEC1* (B) mRNA levels were quantified using qRT-PCR. Data are presented as mean±SEM from three independent experiments. Statistical significance was calculated using Student’s t test. No asterisk (\*) indicates no significance.