**Supplemental Figure Legends**

**Figure S1: Representative HAF, HIF-2α and HIF-1α stained cores from the ccRCC tumor microarray.** Images shown for immunohistochemistry (IHC) of HAF (A), HIF-2α (B), and HIF-1α (C) in representative cores of stage 1 and stage 4 tumors with enlargements shown inset.

**Figure S2: Staining controls used for tissue sets 1-3 comprising formalin-fixed paraffin embedded pellets of ACHN cells exposed to normoxia or hypoxia (1%O2) for 24 hours.** Cell pellets were used to optimize staining conditions for HIF-1α, HIF-2α or HAF antibodies, which were then used to stain the indicated tissue.

**Figure S3: Representative images for segmentation of low and high HIF-1α expressing cells in tissue set 1 using InForm software.** Tumor cells typically showed low intensity HIF-1α expression (yellow) whereas HIF-1α staining in the stroma were typically of high intensity (red). Blue indicates negative stained nuclei. A) core showing mainly tumor cell-specific HIF-1α expression; B-C) cores showing low tumor cell specific HIF-1α expression but high expression in stromal cells; B) core with low stromal cell positivity; B) core with high stromal cell positivity.

**Figure S4:** **Kaplan Meier plots showing associations of HIF-1α (stroma), (A), HIF-2α, (B), and HAF, (C) with progression-free survival.**

**Figure S5: Representative images for segmentation of uninvolved and tumor region within large ccRCC tissue sections using Aperio digital imaging software.** Quantitation of percent nuclear positivity in ccRCC tissue and uninvolved tissue (normal) from tissue set 2 using Aperio digital imaging software for each marker is shown in the table.

**Figure S6-S8: Representative images of tumor and uninvolved tissue from tissue set 2 stained with HIF-1α, HIF-2α and HAF respectively**. Images on the left are bright field images, whereas images on the right are bright field images overlaid with the Aperio quantitation macro. Blue indicates negative nuclei, orange indicates low staining nuclei, red indicates high staining nuclei.

**Figure S9: Additional HIF-2α antibodies used for tissue sets 4 and 5.** A) Staining controls for HIF-2α MAB3472 antibody using ACHN cell pellets as in Figure S1. These conditions were used to stain tissue set 4, together with the pre-optimized HAF and HIF-1α conditions in S1. B) Table showing quantitation of percent nuclear positivity in ccRCC tissue and uninvolved (normal) from tissue set 4 using Aperio digital imaging software for each marker. C) Staining controls for HIF-2α ab109616 using ACHN cell pellets as in Figure S1. These conditions were used to stain tissue set 5, together with the pre-optimized HAF and HIF-1α conditions in S1.

**Figure S10: Identification of cell type clusters and HIF expressing cell types in ccRCC using single cell sequencing**. A) Heatmap showing average transcript expression levels of genes used to determine cluster identities. B-C) T-SNE plots showing *NDUFA4L2* and *CAIX* (B), or *HIF1A* and *EPAS1,* (C) transcript expression distribution within ccRCC tissue. Black dotted lines indicate Tumor A (TuA), Tumor B (TuB) and vasculature (V) clusters. Red dotted lines indicate the three macrophage clusters, MA, MB and MC with high *HIF1A* transcript expression.

**Figure S11: Expression of HIF target genes within ccRCC-associated cell types.** Heatmap showing average transcript expression levels of classical HIF target genes within each cell type cluster.

**Figure S12: Representative images of baseline HIF-1α levels in ccRCC tumors prior to treatment with sunitinib.** A) Clinical characteristics of patients used in the analysis. B-C) Representative images with multiple enlargements inset showing, (B) strong stromal/macrophage-specific HIF-1α staining with negative staining in ccRCC tumor cells (observed in >90% of tumor cores), and (C) strong stromal/macrophage-specific HIF-1α staining together with weaker nuclear staining in ccRCC tumor cells (observed in <10% of tumor cores). D-E) Kaplan Meier plots showing survival curves of patients with advanced/metastatic ccRCC who received clinical benefit (CB) defined as stable disease (SD), partial response (PR) or complete response (CR) to sunitinib, or no CB defined as progressive disease (PD) in response to sunitinib.

**Figure S13: Principal component analysis of single cell sequencing data**. A) Elbow plot for 30 principal components. B) Plot of PC1 and PC2 for all patients. C) Heatmaps of the first 15 principal components included in downstream analysis.

**Figure S14:** **Supporting data for single cell sequencing quality control and analysis.** A) Table indicating numbers of cells, genes and other parameters for ccRCC and uninvolved tissue from each patients post quality control. B) Cell type markers used for cluster identification and associated references.