Figure S1: Stabilization of Hif-α and PEPCK-cre mediated inactivation of *Hif1a* in renal tubular epithelial cells in UUO kidneys. (A) Western analysis for Hif-2α in nuclear fractions from CTL and UUO kidneys 1 day (1), 4 days (4), and 8 days (8) post-ligation, + indicates positive control for Hif-2α (Vhlh-deficient liver tissue). Ponceau staining is shown as loading control. Graph shows densitometric analysis for HIF-2α protein normalized for protein loading and compared to sham operated (S) kidney level, which was arbitrarily set to 1 (a.u.: arbitrary units). **(B)** Hif-1α immunostaining in normal non-hypoxic kidney (nl. ki.), CTL and UUO kidneys 1 day post ligation (same animal processed identically). Arrows highlight epithelial cells with positive nuclear staining, magnification x400. **(C)** The extent of *PEPCK*-cre mediated recombination in 8 day CTL and UUO murine kidneys was detected using the ROSA26RlacZ reporter transgene. Approximately 50-70% of proximal tubular epithelial cells stained positive for β-gal (blue staining) confirming presence of active cre-recombinase, magnification x200. **(D)** *Hif1a exon 2* mRNA levels in $Hif1a^{+/+}$ and $Hif1a^{-/-}$ contralateral (CTL) and obstructed (UUO) kidneys. Exon 2 is flanked by loxP sites and is deleted upon cre-mediated recombination. Note, *PEPCK*-cre activity reduced *Hif1a* mRNA levels by approximately 25%, this reduction was not detected in UUO kidneys possibly due to infiltrating cells which express wild type *Hif1a*. $*P<0.05$.

Figure S2: HIF-1α staining in IgA nephropathy. Shown is a Masson Trichrome (MT) stain and immunohistochemical staining for HIF-1α in adjacent tissue sections of renal

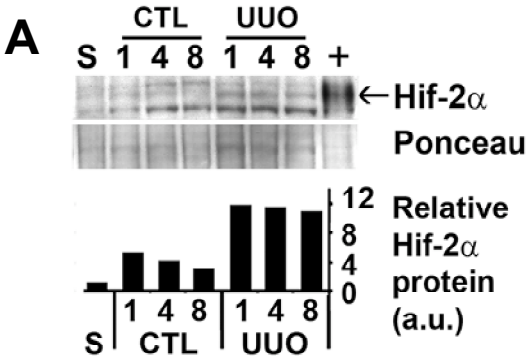
tissue from a patient with IgA nephropathy, magnification x200. Arrows depict HIF-1α expressing cells.

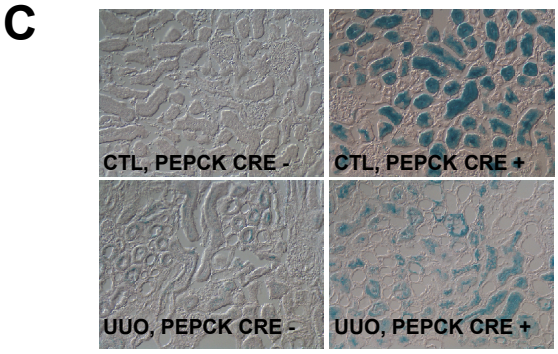
Figure S3: Hierarchical cluster analysis of HIF-1 regulated gene expression in diabetic nephropathy. Micro-dissected tubulointerstitial compartments of renal biopsies from 13 patients with an initial histological diagnosis of diabetic nephropathy (DN) and 7 control patients (4 patients with minimal change disease and normal renal function (MCD1-4) and 3 pre-transplant biopsies from related living donors (LD1-3)) were analyzed as previously described using an Affymetrix based microarray platform (64). The total number of differentially regulated genes between DN and control was 1,349. Shown are relative expression values of published (*) (59) or putative HIF-1 regulated genes, that we have identified as potentially HIF-1 regulated in *Hif1a*$^{+/+}$ PTECs, VHL and VHL/HIF deficient kidney or liver tissue using microarray analysis (28, 56). Serum creatinine mg/dl (bottom) and urine protein concentrations in g/dl (top) for each individual patient are shown in brackets. Although the expression levels of certain HIF-targets such as *VEGF* are expected to be increased in an hypoxic environment, *VEGF* was found to be down regulated in patients with DN (58), suggesting that *VEGF* regulation by HIF may be context-dependent. Clinical follow-up of patients revealed that DN14 had light chain deposit disease and DN15 had unclassified nodular glomerulosclerosis with mesangial matrix expansion.

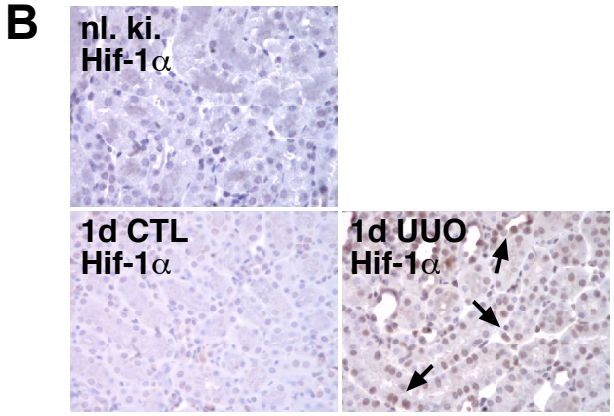
Figure S4: Hypoxia decreases *E-cadherin* mRNA levels in PTECs. Quantitative real time PCR analysis of *E-cadherin* (*E-cad*), *Cadherin 16* (*Cad16*), *hepatocyte nuclear*

factor-1β, (HNF-1β), Notch target *Hey-1* and transcriptional repressors *TCF3*, *ZFHX1A*, *ZFHX1B*, *Snail*, and *Twist-1* mRNA levels in *Hif1a*$^{+/+}$ (+/+) or *Hif1a*$^{-/-}$ (-/-) PTECs exposed to normoxia (Nx) or short term hypoxia (Hx, 1% O_2, 6h). Shown are relative gene expression levels normalized to *18S* rRNA.

Figure S1


A
CTL
UUO
S 1 4 8 1 4 8 +
Hif-2α
Ponceau
12
8
4
0
Relative
Hif-2α
protein
(a.u.)
S
1 4 8
CTL
1 4 8
UUO


C
CTL, PEPCK CRE -
CTL, PEPCK CRE +
UUO, PEPCK CRE -
UUO, PEPCK CRE +


B
nl. ki.
Hif-1α
1d CTL
Hif-1α
1d UUO
Hif-1α

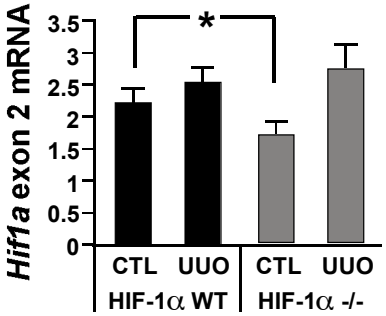

D
Hif1a exon 2 mRNA
3.5
3
2.5
2
1.5
1
0.5
0
*
CTL
UUO
CTL
UUO
HIF-1α WT
HIF-1α -/-

Figure S2

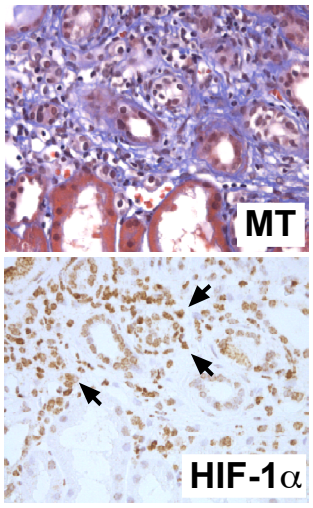


Figure S3

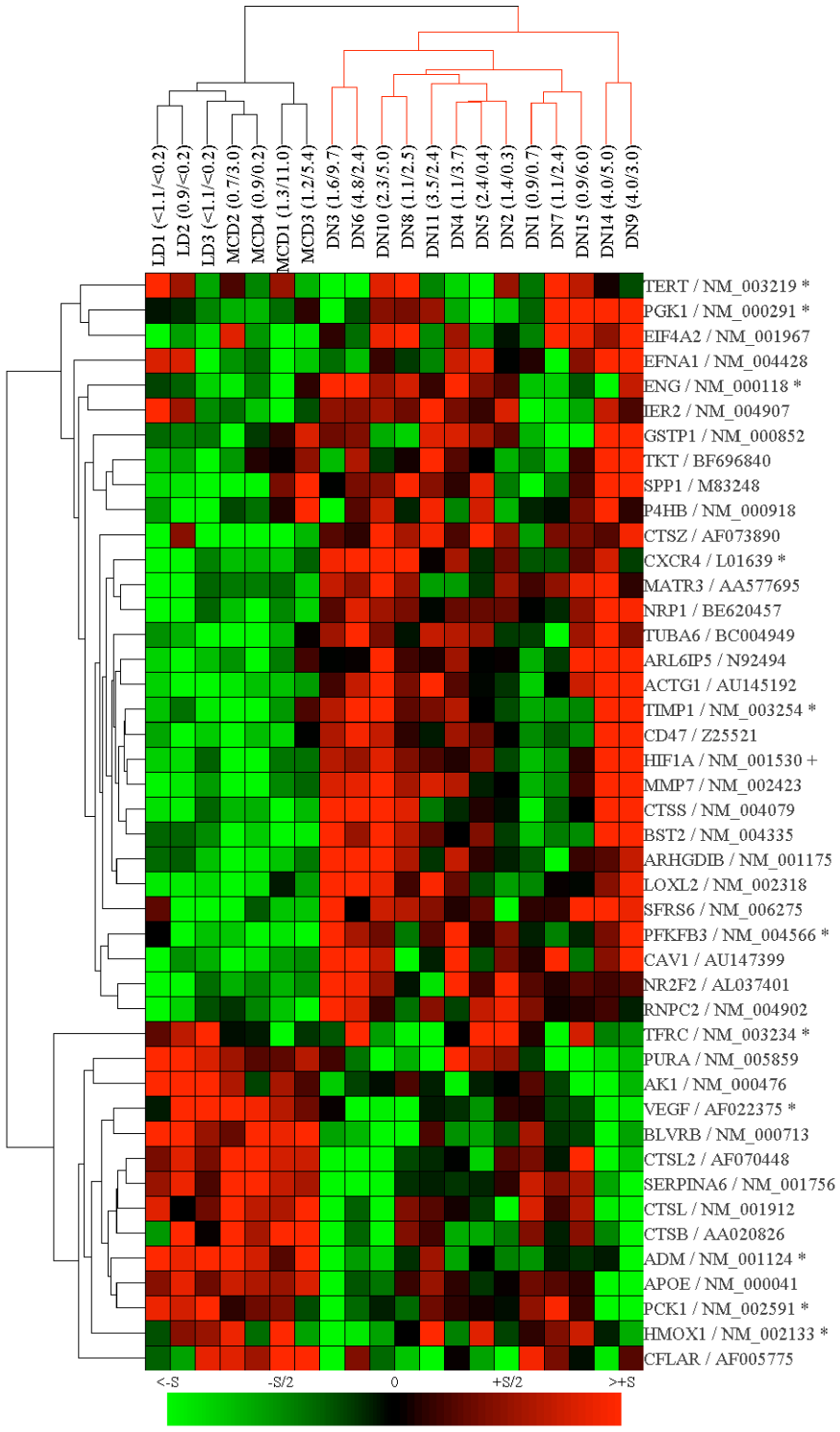
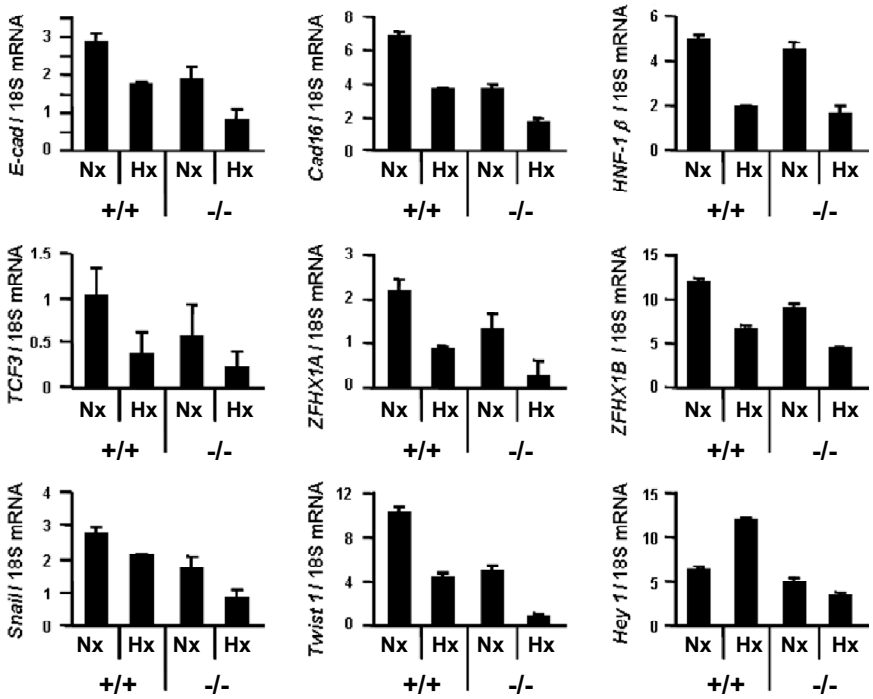

LD1 (<1.1/<0.2)
LD2 (0.9/<0.2)
LD3 (<1.1/<0.2)
MCD2 (0.7/3.0)
MCD4 (0.9/0.2)
MCD1 (1.3/11.0)
MCD3 (1.2/5.4)
DN3 (1.6/9.7)
DN6 (4.8/2.4)
DN10 (2.3/5.0)
DN8 (1.1/2.5)
DN11 (3.5/2.4)
DN4 (1.1/3.7)
DN5 (2.4/0.4)
DN2 (1.4/0.3)
DN1 (0.9/0.7)
DN7 (1.1/2.4)
DN15 (0.9/6.0)
DN14 (4.0/5.0)
DN9 (4.0/3.0)
TERT / NM_003219 *
PGK1 / NM_000291 *
EIF4A2 / NM_001967
EFNA1 / NM_004428
ENG / NM_000118 *
IER2 / NM_004907
GSTP1 / NM_000852
TKT / BF696840
SPP1 / M83248
P4HB / NM_000918
CTSZ / AF073890
CXCR4 / L01639 *
MATR3 / AA577695
NRP1 / BE620457
TUBA6 / BC004949
ARL6IP5 / N92494
ACTG1 / AU145192
TIMP1 / NM_003254 *
CD47 / Z25521
HIF1A / NM_001530 +
MMP7 / NM_002423
CTSS / NM_004079
BST2 / NM_004335
ARHGDIB / NM_001175
LOXL2 / NM_002318
SFRS6 / NM_006275
PFKFB3 / NM_004566 *
CAV1 / AU147399
NR2F2 / AL037401
RNPC2 / NM_004902
TFRC / NM_003234 *
PURA / NM_005859
AK1 / NM_000476
VEGF / AF022375 *
BLVRB / NM_000713
CTSL2 / AF070448
SERPINA6 / NM_001756
CTSL / NM_001912
CTSB / AA020826
ADM / NM_001124 *
APOE / NM_000041
PCK1 / NM_002591 *
HMOX1 / NM_002133 *
CFLAR / AF005775
<-S
-S/2
0
+S/2
>+S

Figure S4


E-cad / 18S mRNA
Cad16 / 18S mRNA
HNF-1 β / 18S mRNA
TCF3 / 18S mRNA
ZFHX1A / 18S mRNA
ZFHX1B / 18S mRNA
Snail / 18S mRNA
Twist 1 / 18S mRNA
Hey 1 / 18S mRNA
Nx
Hx
Nx
Hx
+/+
-/-