Supplementary material for

Clinically approved HIF-PHIs modulate redox metabolism, cell growth, and angiogenesis independent of HIF-1α/HIF-2α

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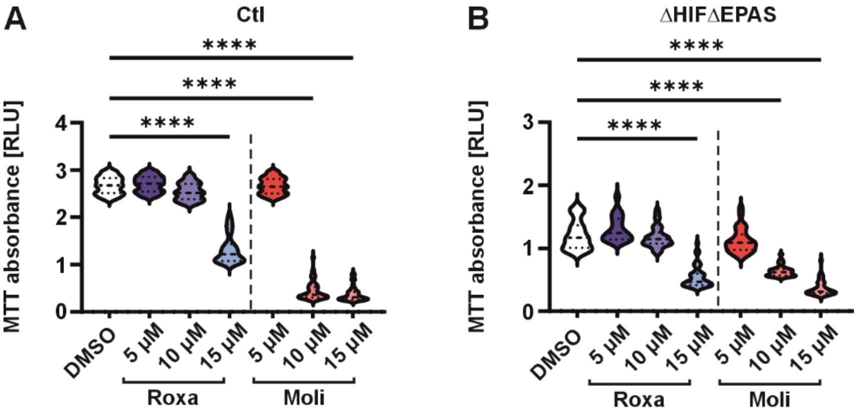


Figure S1. High concentrations of roxadustat and molidustat inhibit cell viability.

(A,B) PC-3 control (Ctl) and ΔHIF1ΔEPAS1 cells were cultured for 24 h, then treated with roxadustat (Roxa) or molidustat (Moli) at different concentrations and further cultured for 24 h. Thereafter, an MTT assay was performed.

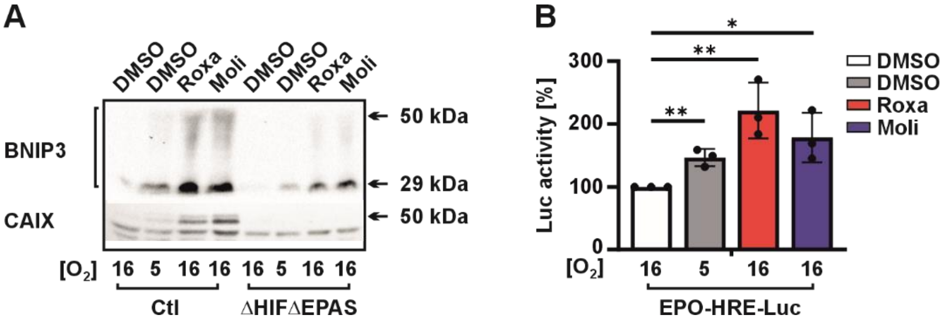


Figure S2. Roxadustat and molidustat induce HIF-target gene expression as well as HRE-Luc activity.

(A) PC-3 control (Ctl and ΔHIF1ΔEPAS1 cells were cultured for 24 h, then treated with either roxadustat (Roxa) or molidustat (Moli) and further cultured under normoxia or hypoxia (5%O_2) for 16 h. Total protein levels were measured by Western blot with antibodies against BNIP3, CAIX and α-tubulin. **(B)** HEK 293 cells were transfected with an EPO-HRE-Luc expression plasmid for 5 h. After a medium change, cells were treated with roxadustat (Roxa) or molidustat (Moli) and further cultured under normoxic or hypoxic (5%O_2) conditions for 24 h.

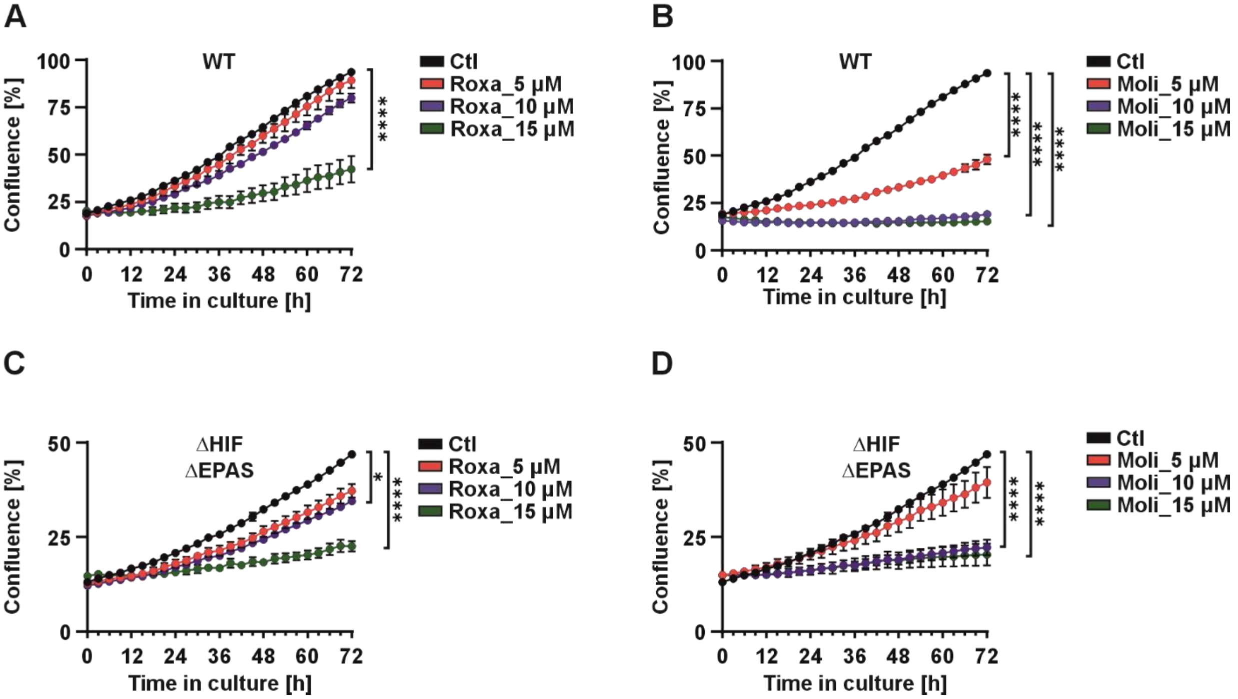


Figure S3. High concentrations of roxadustat and molidustat inhibit cell proliferation.

(A - D) PC-3 control (Ctl) and ΔHIF1ΔEPAS1 cells were cultured for 16 h, after which they were treated with roxadustat (Roxa) or molidustat (Moli) at different concentrations. The live cell proliferation rate was measured with the InCucyte®ZOOM every 3 h for 72 h.

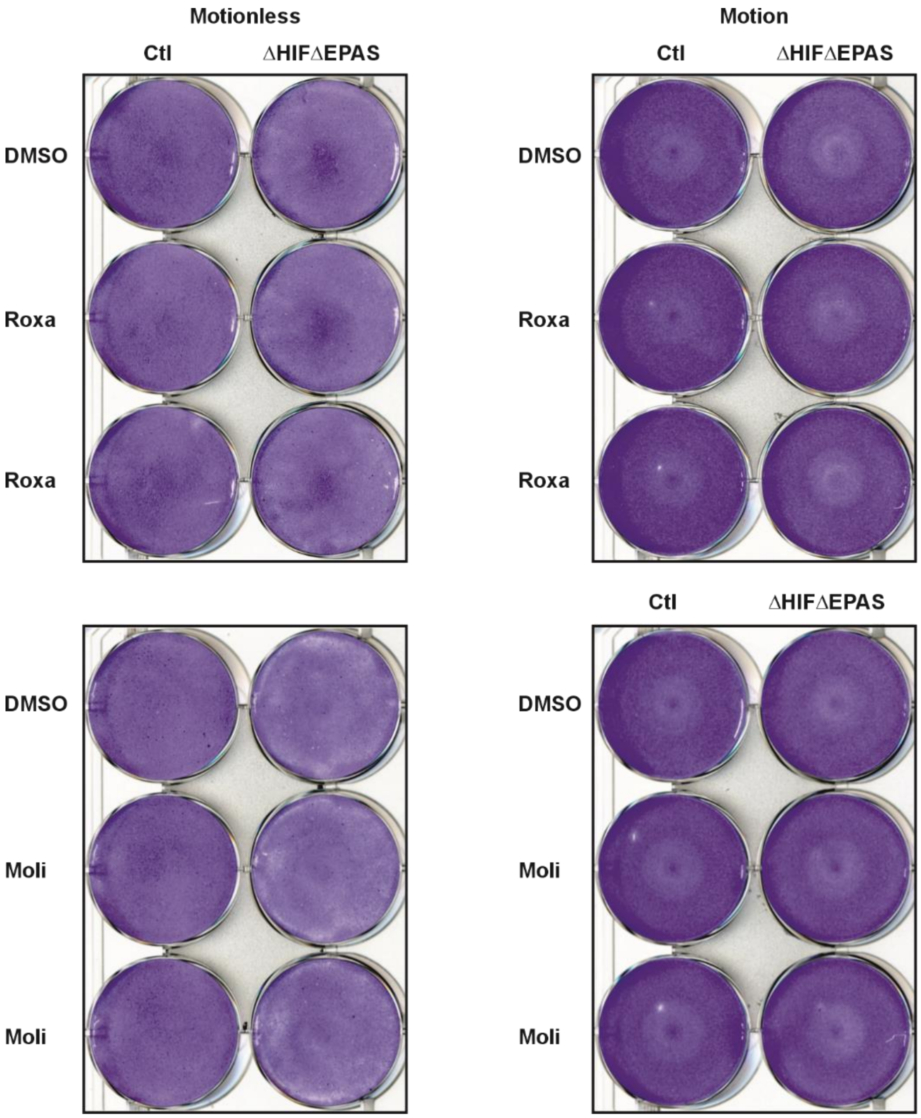


Figure S4. Roxadustat and molidustat do not affect cell adhesion.

PC-3 control (Ctl) and ΔHIF1ΔEPAS1 cells were plated on 6-well plates and grown until confluence was reached. The cells were then treated with roxadustat (Roxa; 10 µM) or molidustat (Moli; 5 µM) and further cultured for 24 h. Thereafter, the plates were transferred to an orbital shaker for an additional 8 h. Control plates remained in the cell incubator.

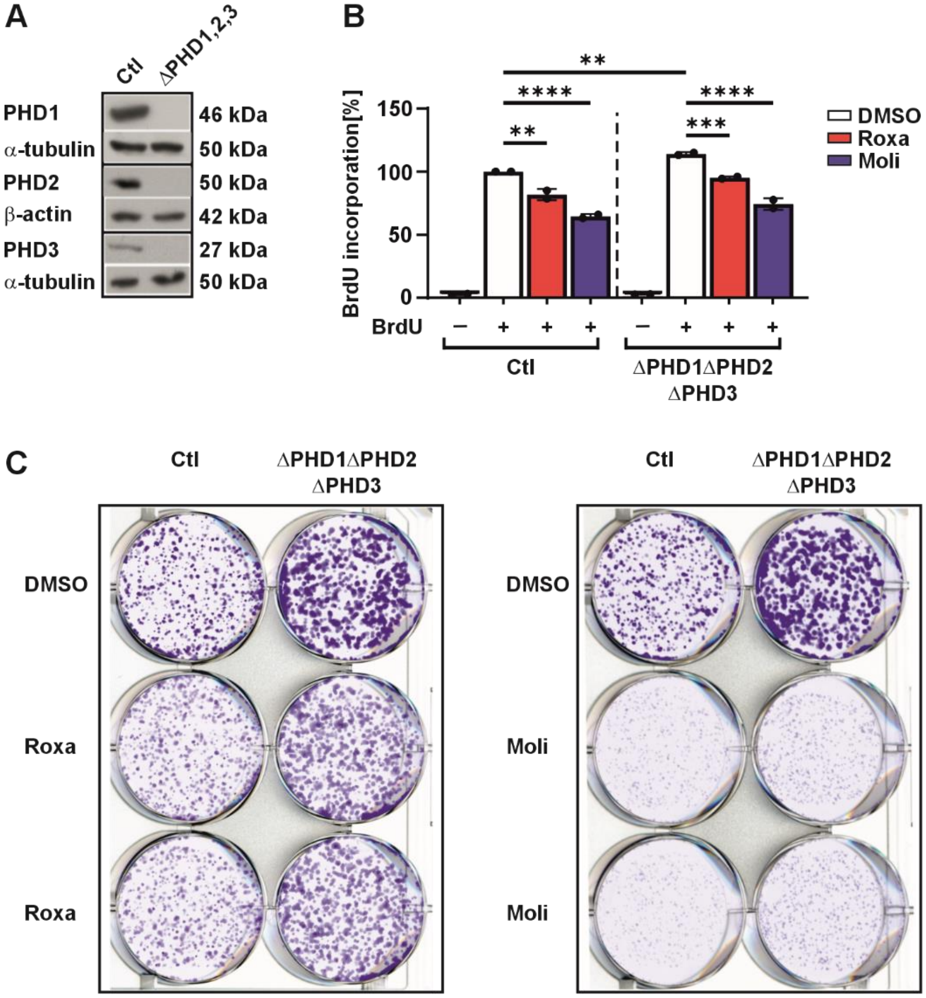


Figure S5. Roxadustat and molidustat inhibit proliferation and colony formation in the absence of HIF-PHD1-3.

(A) Representative Western blot analysis. 100 µg of total protein lysate from control B16-F10 mouse melanoma cells and ΔPHD1,2,3 cells was analyzed with antibodies against PHD1, PHD2, PHD3 and α-tubulin. **(B)** BrdU incorporation. Cells were treated with roxadustat (Roxa; 10 µM) or molidustat (Moli; 5 µM) for 24 h and then further analyed. Statistics: Ordinary one-way ANOVA. *$p<0.05$, **$p<0.01$, ***$p<0.001$ ****$p<0.0001$. **(C)** Colony formation. Representative images of stained colonies fromcontrol (Ctl) and ΔPHD1,2,3 cells. Cells were seeded onto 6-well plates at a density of 2,000 cells/well, allowed to settle for 24 h, and then treated with roxadustat (Roxa; 10 µM) or molidustat (Moli; 5 µM). The cells were cultured for an additional 8 days. Every second day, medium was replaced with fresh inhibitors. Afterwards, cells were fixed with 4% paraformaldehyde and stained with crystal violet.

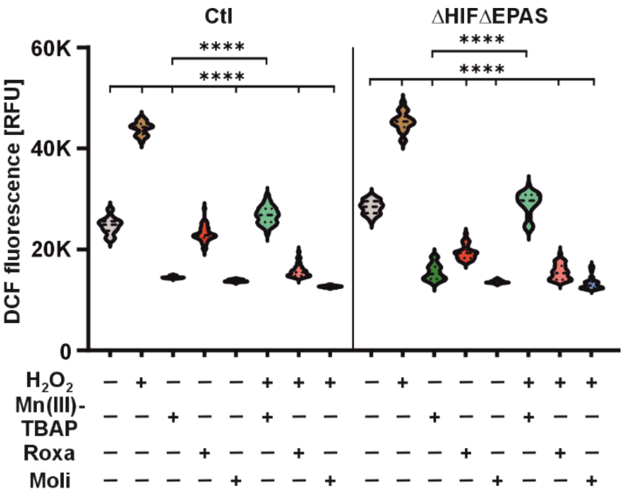


Figure S6. Roxadustat and molidustat do not increase reactive oxygen species.

PC-3 control cells (Ctl) and ΔHIF1ΔEPAS1 cells were treated with roxadustat (10 µM), molidustat (5 µM) or Mn(III)TBAP (20 µM) for 24 h and then stimulated with H_2O_2 (500 µM) for additional 30 min.

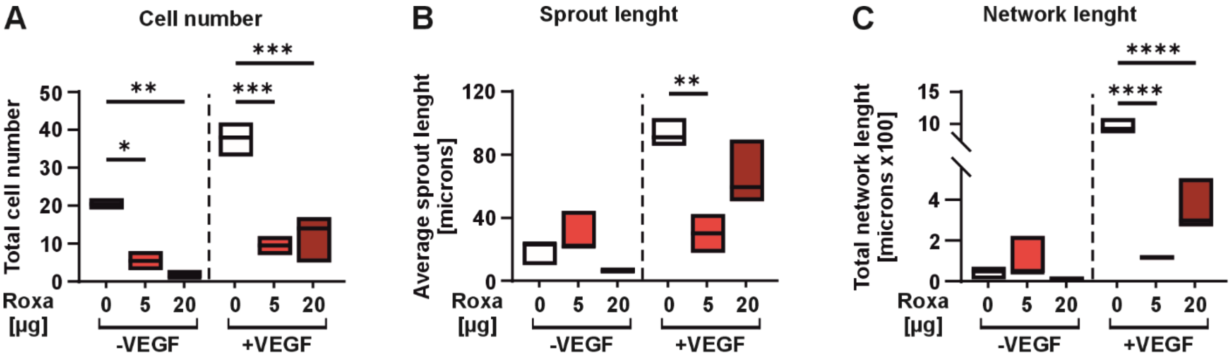


Figure S7. Roxadustat affects angiogenesis in HUVEC cells.

Quantification of the angiogenesis assay in HUVEC cells after 3 days of roxadustat (Roxa) treatment for 3 days: **(A)** cell number, **(B)** sprout length, and **(C)** network length.

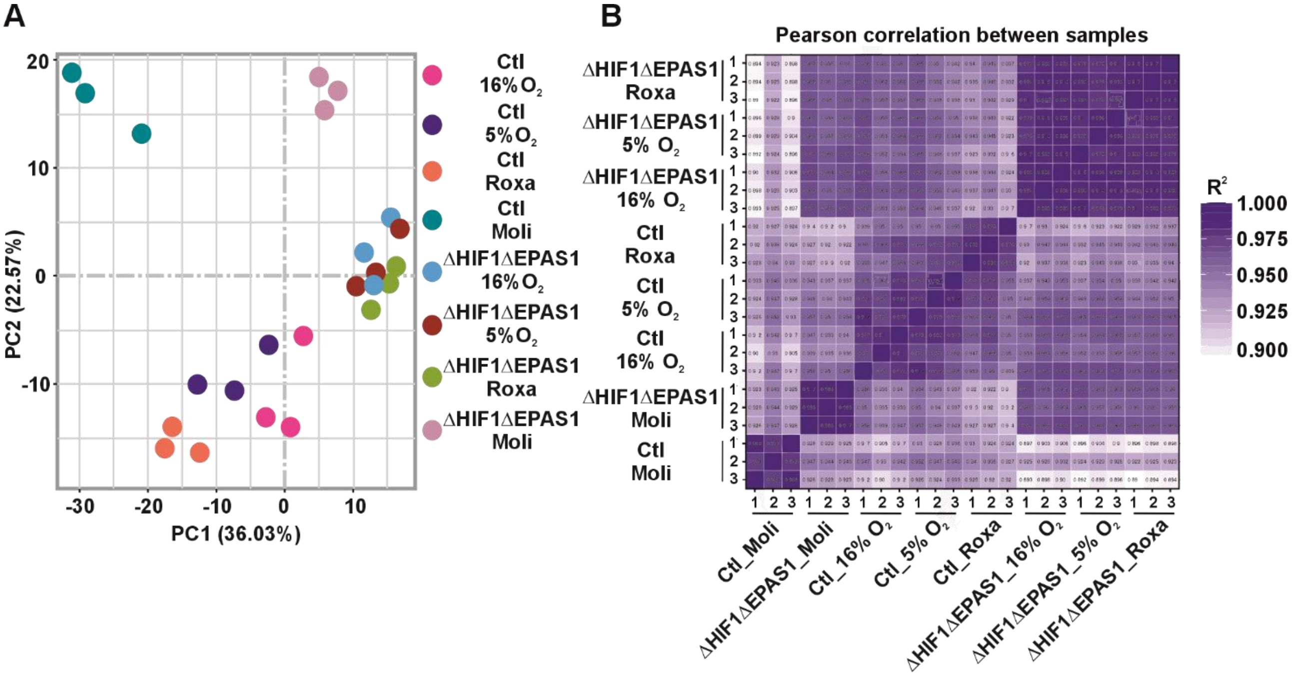


Figure S8. Correlation of the RNA-seq samples.

(A) Principal component analysis (PCA) was performed on normalized gene expression data from all samples. Each point represents an individual sample and is colored by experimental group. **(B)** Pearson correlation between the samples.

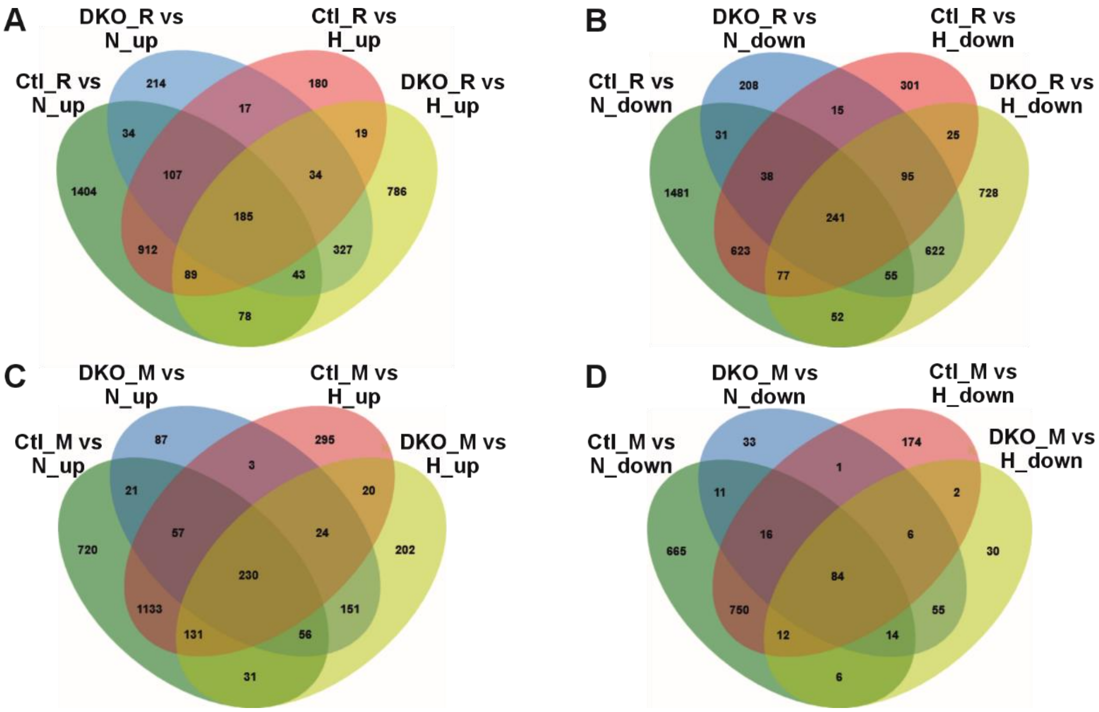
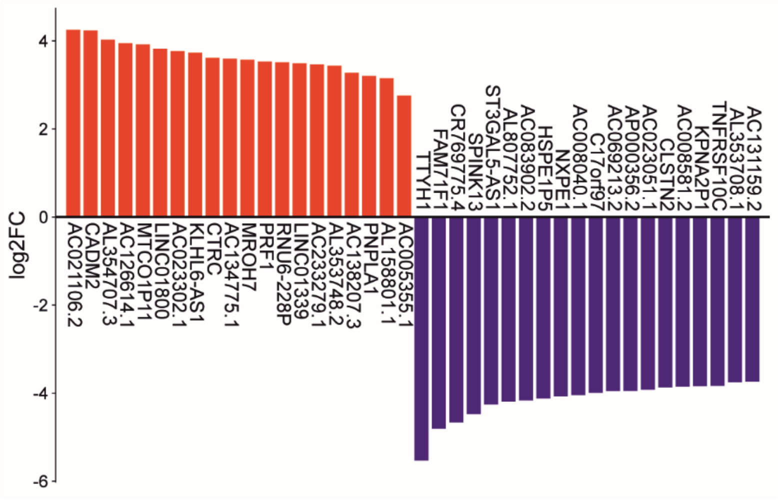


Figure S9. Venn diagrams of all different treatment groups.

Venn diagrams of differentially expressed unique and shared genes. **(A)** Upregulated genes in control (Ctl) or ΔHIF1ΔEPAS1 (DKO) cells upon roxadustat (R) treatment. **(B)** Down-regulated genes in control (Ctl) or ΔHIF1ΔEPAS1 (DKO) cells upon roxadustat (R) treatment. **(C)** Upregulated genes in control (Ctl) or ΔHIF1ΔEPAS1 (DKO) cells upon molidustat (M) treatment. **(D)** Down-regulated genes in control (Ctl) or ΔHIF1ΔEPAS1 (DKO) cells upon molidustat (M) treatment.

A ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_Normoxia



B ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_Hypoxia

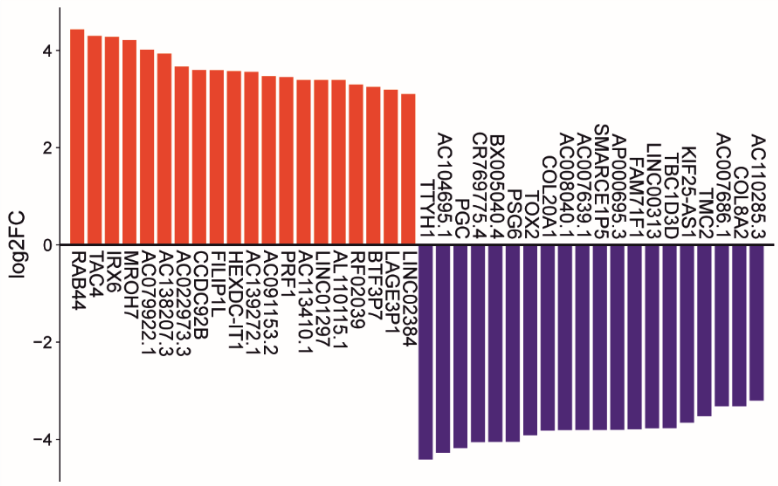


Figure S10. The 20 most significant up- and downregulated genes in ΔHIF1ΔEPAS1 cells treated with roxadustat.

(**A**) Most up- and downregulated genes in ΔHIF1ΔEPAS1 cells upon roxadustat (Roxa) treatment compared to normoxia. **(B)** Most up- and downregulated genes in ΔHIF1ΔEPAS1 cells upon roxadustat (Roxa) treatment compared to hypoxic conditions.

Table S1: List of the 20 most significant up- and downregulated genes in ΔHIF1ΔEPAS1 cells treated with roxadustat.

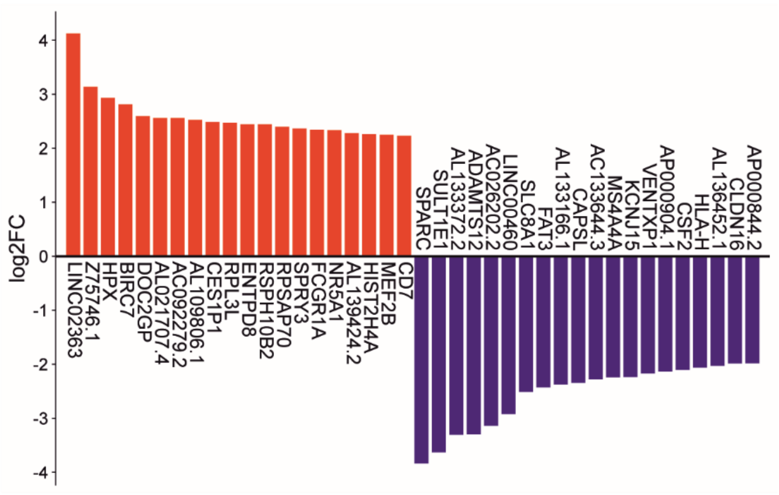
ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_16%_up			
gene_name	**gene description**	**log2FoldChange**	**pvalue**
AC021106.2	–	4.25110381425737	0.016369509169116
CADM2	cell adhesion molecule 2	4.23204212257094	0.0162207699951032
AL354707.3	–	4.02697442966771	0.0327610238484835
AC126614.1	–	3.94489010475098	0.04011068455859
MTCO1P11	mitochondrially encoded cytochrome c oxidase I pseudogene 11	3.91983939809433	0.0389054231138303
LINC01800	long intergenic non-protein coding RNA 1800	3.82175636674758	0.0251366658568029
AC023302.1	–	3.76782241215689	0.0187779865741235
KLHL6-AS1	KLHL6 antisense RNA 1	3.72842647184467	0.0339741141919712
CTRC	chymotrypsin C	3.61412422484737	0.0313237266541947
AC134775.1	–	3.59698787836515	0.0295978126506214
MROH7	maestro heat like repeat family member 7	3.57010332518439	0.0495947775303425
ANGPTL4	angiopoietin like 4	3.54327893702169	5.53857948504564e-21
PRF1	perforin 1	3.52801224352852	0.03762723941479
RNU6-228P	RNA, U6 small nuclear 228	3.51016794047536	0.0345519966594117
LINC01339	long intergenic non-protein coding RNA 1339	3.49162869214271	0.0407609520573268
AC233279.1	–	3.46175590753035	0.0179148842845204
AL353748.2	–	3.43719869634609	0.0189052802875152
AC138207.3	–	3.275161739182	0.0352898234156878
PNPLA1	patatin like phospholipase domain containing 1	3.20274554041267	0.036139677790327
AL158801.1	–	3.15041182047568	0.0351164590093427

ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_16%_down			
gene_name	**gene_description**	**log2FoldChange**	**pvalue**
TTYH1	tweety family member 1	-5.5305139472315	0.0049239409759158
FAM71F1	family with sequence similarity 71 member F1	-4.8069104981950	0.0021845410308173
CR769775.4	–	-4.6653508918063	0.0031762556817239
SPINK13	serine peptidase inhibitor, Kazal type 13	-4.4733064495421	0.0094344366116633
AC019077.1	–	-4.3299906874013	0.0088265931160631
ST3GAL5-AS1	ST3GAL5 antisense RNA 1	-4.2563241566824	0.0134075878812257
AL807752.1	–	-4.1927824416610	0.0131840341460607
AC083902.2	Homo sapiens uncharacterized mRNA	-4.1653022604615	0.0213993916612154
HSPE1P5	heat shock protein family E (Hsp10) member 1 pseudogene 5	-4.1214163951244	0.0198136221176007
NXPE1	neurexophilin and PC-esterase domain family member 1	-4.0758021942240	0.0180843190710995
AC008040.1	–	-4.0418256716972	0.025958513992419
C17orf97	chromosome 17 open reading frame 97	-3.9915530511858	0.0204534260081648
AC069213.2	–	-3.9531828569857	0.0384724111688657
AP000356.2	–	-3.9511222552957	0.0280603656973256
AC023051.1	–	-3.9200152035844	0.0414828260136305
CLSTN2	calsyntenin 2	-3.8671399077646	0.0420715238656027
AC008581.2	–	-3.8532508240544	0.0318125121477224
KPNA2P1	karyopherin subunit alpha 2 pseudogene 1	-3.8427555520414	0.0440306296725191
TNFRSF10C	TNF receptor superfamily member 10c	-3.8320078421588	0.0439753497998583
AL353708.1	–	-3.7509962485701	0.0402384190778598
ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_5%_up			

gene_name	**gene_description**	**log2FoldChange**	**pvalue**
RAB44	RAB44, member RAS oncogene family	4.43147383744201	0.0114963841488993
TAC4	tachykinin 4	4.29938255809375	0.0136549191575972
IRX6	iroquois homeobox 6	4.27643954676251	0.0138934300971196
MROH7	maestro heat like repeat family member 7	4.21526253730117	0.0338495626905336
ANGPTL4	angiopoietin like 4	4.03481050968723	8.7978057190112e-106
AC079922.1	–	4.01700823596797	0.0290375212828793
AC138207.3	–	3.93205967413021	0.0127971923169908
AC022973.3	–	3.67003050933242	0.0226605857692435
CCDC92B	coiled-coil domain containing 92B	3.59482485457105	0.0289835915516324
FILIP1L	filamin A interacting protein 1 like	3.59258359875987	0.0150228861967677
HEXDC-IT1	HEXDC intronic transcript 1	3.57379801879588	0.0283933931025906
AC139272.1	–	3.55956040713841	0.0116073804931782
AC091153.2	–	3.47263615474527	0.0419881329404442
PRF1	perforin 1	3.44958590785904	0.0422929551287605
AC113410.1	–	3.38954799504244	0.0486557703079607
LINC01297	long intergenic non-protein coding RNA 1297	3.38952780669328	0.0489270591555231
AL110115.1	–	3.3895225030957	0.0489986831912477
RF02039	–	3.29589677754106	0.0278447926629382
BTF3P7	basic transcription factor 3 pseudogene 7	3.24802877444933	0.0274020121604096
LAGE3P1	L antigen family member 3 pseudogene 1	3.18983379718521	0.0379555522735144
ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_5%_down			
gene_name	**gene_description**	**log2FoldChange**	**pvalue**

TTYH1	tweety family member 1	-4.4159484708801	0.0086207622653908
AC104695.1	–	-4.275846128436	0.0104336866473935
PGC	progastricsin	-4.1776015872331	0.0213086207899371
CR769775.4	–	-4.0567850197357	0.0210786856157868
BX005040.4	–	-4.0518257952064	0.0199828658191368
PSG6	pregnancy specific beta-1-glycoprotein 6	-4.0477241794998	0.0303406359236037
TOX2	TOX high mobility group box family member 2	-3.9180357442009	0.0090516702520155
COL20A1	collagen type XX alpha 1 chain	-3.8196453336853	0.0388662412960011
AC008040.1	–	-3.8077097064386	0.0360396855758217
AC007639.1	–	-3.8064980457902	0.0361216733561968
SMARCE1P5	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1 pseudogene 5	-3.8050650136367	0.0399143601181898
AP000695.3	–	-3.8028237767676	0.0333543551421014
FAM71F1	family with sequence similarity 71 member F1	-3.7917496697098	0.0371352706123496
LINC00313	–	-3.7719392771629	0.0206392229118594
TBC1D3D	TBC1 domain family member 3D	-3.7684892953517	0.0220164344125558
LINC00173	–	-3.6684646428677	0.0059135484461750
KIF25-AS1	KIF25 antisense RNA 1	-3.656968249634	0.0492041317456691
TMC2	transmembrane channel like 2	-3.5252098227442	0.0248166128694425
AC007686.1	–	-3.3198660350859	0.0380191760948364
COL8A2	collagen type VIII alpha 2 chain	-3.3183744561146	0.0391185827558056

A ΔHIF1ΔEPAS1_Moli vs ΔHIF1ΔEPAS1_Normoxia



B ΔHIF1ΔEPAS1_Moli vs ΔHIF1ΔEPAS1_Hypoxia

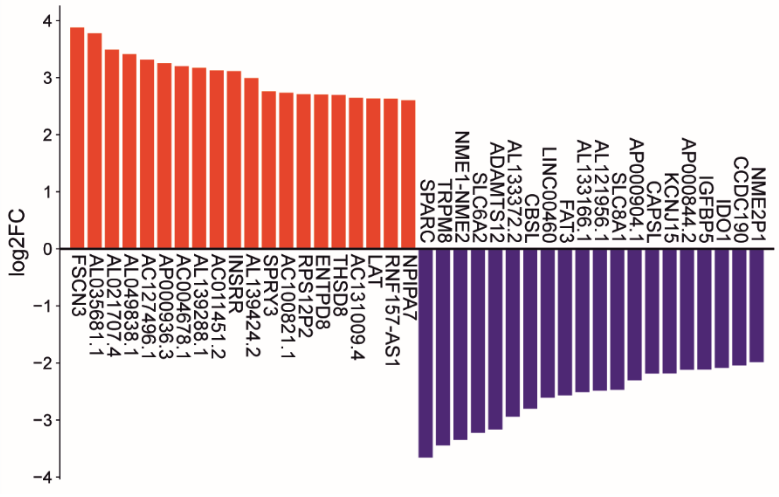


Figure S10. The 20 most significant up- and downregulated genes in ΔHIF1ΔEPAS1 cells treated with molidustat.

(A) Most up- and downregulated genes in ΔHIF1ΔEPAS1 cells upon molidustat (Moli) treatment compared to normoxia. **(B)** Most up- and downregulated genes in ΔHIF1ΔEPAS1 cells upon molidustat (Moli) treatment compared to hypoxic conditions.

Table S2: List of the 20 most significant up- and downregulated genes in ΔHIF1ΔEPAS1 cells treated with molidustat.

ΔHIF1ΔEPAS1_Moli% vs ΔHIF1ΔEPAS1_16%_up			
gene_name	**gene description**	**log2FoldChange**	**pvalue**
LINC02363	long intergenic non-protein coding RNA 2363	4.125191639166	0.00111694839126803
RN7SL5P	RNA, 7SL, cytoplasmic 5, pseudogene	3.83247004621268	2.24434576558843e-12
LGI4	leucine rich repeat LGI family member 4	3.39309231109637	0.000146535129200782
MTND1P23	MT-ND1 pseudogene 23	3.2187088806798	0.00188739351070372
Z75746.1	zinc finger protein 770 (ZNF770) pseudogene	3.13848037835054	0.00251901795116945
FTH1P10	ferritin heavy chain 1 pseudogene 10	2.99299591511548	0.0020820008867955
HPX	hemopexin	2.93096466163835	1.20741462622584e-05
BIRC7	baculoviral IAP repeat containing 7	2.81441480532244	0.00375300046973752
ASPDH	aspartate dehydrogenase domain containing	2.81333130087414	1.4597319433785e-07
AC105118.1	novel transcript	2.71862813259455	0.00804908241493532
DLX5	distal-less homeobox 5	2.63815707790216	1.95859006628022e-08
DOC2GP	double C2 domain gamma pseudogene	2.59668386975338	0.000189122459722773
AL021707.4	novel transcript	2.56120764252375	0.00536148332430468
AC092279.2	–	2.56045241726826	0.00688952597684355
RTN1	reticulon 1	2.52805086639081	5.14334581574025e-09
AL109806.1	–	2.52565068951881	0.00504066326704339
CES1P1	carboxylesterase 1 pseudogene 1	2.48433117198925	0.00748627916156018
AC025165.1	–	2.47661838241036	8.76339746228076e-07
RPL3L	ribosomal protein L3 like	2.47217387533416	0.00083921254639391
DNM1P35	dynamin 1 pseudogene 35	2.45180760345262	0.00487633606619009
ΔHIF1ΔEPAS1_Moli% vs ΔHIF1ΔEPAS1_16%_down			
gene_name	**gene description**	**log2FoldChange**	**pvalue**
SPARC	secreted protein acidic and cysteine rich	-3.8369246857312	0.000141175381471456
AL355032.1	ribosomal protein L26-like 1 (RPL26L1) pseudogene	-3.7609805803694	1.45390554295429e-71

SULT1E1	sulfotransferase family 1E member 1	-3.6318218643488	0.000226978768731904
SLC6A2	solute carrier family 6 member 2	-3.4839005071521	0.000771267068747036
AC078817.1	ribosomal protein L26 (RPL26) pseudogene	-3.3666906907108	5.69285781168308e-07
AL133372.2	novel transcript	-3.3042155588911	0.000270849241932067
ADAMTS12	ADAM metallopeptidase with thrombospondin type 1 motif 12	-3.2966800253899	3.07322860387379e-07
AC026202.2	novel transcript, antisense to ARL8B	-3.1400248994270	0.0029449039126687
CEACAM6	carcinoembryonic antigen related cell adhesion molecule 6	-3.0392018691646	8.92161198667905e-11
LINC00460	long intergenic non-protein coding RNA 460	-2.9231351609495	0.000285340227467184
AC091804.1	ezrin (EZR) pseudogene	-2.7862149754643	5.129743715994e-07
SERPINB4	serpin family B member 4	-2.7770337919236	7.84088682202909e-19
KCNU1	potassium calcium-activated channel subfamily U member 1	-2.7188025288494	3.79517164576709e-05
AC245595.1	–	-2.5837797619900	0.000839945229497557
SLC8A1	solute carrier family 8 member A1	-2.5108555561112	0.000509263919470933
LINC02432	long intergenic non-protein coding RNA 2432	-2.4705489114297	0.000682620275337847
FAT3	FAT atypical cadherin 3	-2.4290303764695	0.00123572570975092
AC005912.1	ribosomal protein S27 (RPS27) pseudogene	-2.4105031460297	1.4982872230834e-135
AL133166.1	novel transcript	-2.3739838996334	0.0174892238426419
LINC01111	long intergenic non-protein coding RNA 1111	-2.3586488142204	7.13957720685815e-12
ΔHIF1ΔEPAS1_Moli% vs ΔHIF1ΔEPAS1_5%_up			
gene_name	**gene description**	**log2FoldChange**	**pvalue**
FSCN3	fascin actin-bundling protein 3	3.87952780294271	0.00283976315212858
AL035681.1	novel transcript, antisense to L3MBTL2	3.7759759604687	0.00431176889058696
AL021707.4	novel transcript	3.48989915676668	0.00268739461748927
AL049838.1	novel transcript, overlapping C14orf37	3.41235716913338	0.00272233527603503
CADM2	cell adhesion molecule 2	3.38825940973766	0.000235097515792054
AC127496.1	novel transcript, antisense to RPTOR	3.31324451391683	0.00572491917285015
CA8	carbonic anhydrase 8	3.30615675473237	0.000237500627846509

SSC5D	scavenger receptor cysteine rich family member with 5 domains	3.27725785345986	0.00510234583541764
AP000936.3	ribosomal protein S27 (metallopanstimulin 1) (RPS27) pseudogene	3.25486469941206	0.00524102680183323
AC004678.1	novel pseudogene	3.20198082985856	0.00687171875566619
AL139288.1	novel transcript	3.1726056168871	0.00682659559961707
AL136295.6	novel transcript	3.15019461480246	0.00271481955814129
AC011451.2	UBX domain protein 2A (UBXN2A) pseudogene	3.12598039865234	0.00904861859961816
INSRR	insulin receptor related receptor	3.11258506385599	0.00911828949676872
AL139424.2	novel transcript	2.99296069047	0.00715073725152314
AC243772.2	novel transcript, antisense to FCGR1A	2.84722920060711	6.47611340525519e-07
AC233723.2	–	2.80726706196701	9.76096338058895e-07
SPRY3	sprouty RTK signaling antagonist 3	2.75821996013914	0.00437595603537586
AC100821.1	ESF1, nucleolar pre-rRNA processing protein, homolog	2.73362718377227	0.00618958536275403
LINC02363	long intergenic non-protein coding RNA 2363	2.72322349520283	0.00748352115913129
ΔHIF1ΔEPAS1_Moli% vs ΔHIF1ΔEPAS1_5%_down			
gene_name	**gene description**	**log2FoldChange**	**pvalue**
AC078817.1	ribosomal protein L26 (RPL26) pseudogene	-3.7210911618622	1.06871796823022e-08
SPARC	secreted protein acidic and cysteine rich	-3.6574743572470	0.000784690384454086
AL355032.1	ribosomal protein L26-like 1 (RPL26L1) pseudogene	-3.6121404543259	2.49849978020154e-61
TRPM8	transient receptor potential cation channel subfamily M member 8	-3.4462676291313	0.00329710871686214
NME1-NME2	NME1-NME2 readthrough	-3.3477050857833	0.00100043456624711
SLC6A2	solute carrier family 6 member 2 [	-3.222618485797	0.00396796302031868
ADAMTS12	ADAM metallopeptidase with thrombospondin type 1 motif 12	-3.1653874889211	9.507643083536e-07
CEACAM6	carcinoembryonic antigen related cell adhesion molecule 6	-3.1385768718485	2.03305997951004e-09
AL133372.2	novel transcript	-2.9437133556175	0.00123086887778334
CBSL	cystathionine-beta-synthase like	-2.8000447132517	0.00170769208732752
AC091804.1	ezrin (EZR) pseudogene	-2.6908695393494	1.97561484648598e-06

LINC00460	long intergenic non-protein coding RNA 460	-2.6080415797804	0.00342339018576234
FAT3	FAT atypical cadherin 3	-2.5681300927589	0.000208419855603779
SERPINB4	serpin family B member 4	-2.5238995154585	9.15004517448924e-15
AL133166.1	novel transcript	-2.5101699939773	0.00795073988591321
AL121956.1	uncharacterized LOC101929297	-2.4853259103739	0.00632766798632879
SLC8A1	solute carrier family 8 member A1	-2.4694516580972	0.00129768678253616
KCNU1	potassium calcium-activated channel subfamily U member 1	-2.3999706844395	0.000414273880826074
TCN1	transcobalamin 1	-2.3996811640443	5.31286561989932e-11
LINC01111	long intergenic non-protein coding RNA 1111	-2.3567798376163	2.20542340901587e-12

Table S3: Overlap between our Top-20 lists and GSE77789 (Egln1/PHD2 KO) Top-250 (GEO2R)

Gene	Egln1/PHD2 KO (GSE77789)	Our Top-20 direction (context)	Concordance
IGFBP3	Up	**Up** (multiple contrasts incl. roxadustat in control cells)	**Concordant**
HMCN1	Up	**Up** (ΔHIF1ΔEPAS1_16% vs Ctl_16%)	**Concordant**
CDH11	Up	**Down** (Ctl_Roxa vs Ctl_16%; Ctl_Roxa vs Ctl_5%; ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_5%)	**Discordant**
PCDH18	Up	**Down** (Ctl_Roxa vs Ctl_5%)	**Discordant**
TTC5	Up	**Down** (Ctl_5% vs Ctl_16%)	**Discordant**
PHLDA3	Down	**Up** (ΔHIF1ΔEPAS1_Roxa vs ΔHIF1ΔEPAS1_16%)	**Discordant**
STC1	Down	**Up** (Ctl_5% vs Ctl_16%; Ctl_Moli vs Ctl_16%; Ctl_Moli vs Ctl_5%)	**Discordant**

Table S4: Nucleotide sequences used for CRISPR-Cas9 gene editing.

Gene	**Nucleotide sequence (5' to 3')**
HIF1A (guide)	CCATCAGCTATTTGCGTGTG
EPAS1 (guide)	CAAGGCCTCCATCATGCGAC
Egln1 (guide)	CACCGCGGGCAGCAGATCGGCGATG
Egln2 (guide)	CACCGAGGTTCCCGCGAATGTTGCG
Egln3 (guide)	CACCGCGTGCGCCGGCGTCTCCAAG
Genotyping/ Sequencing	**Nucleotide sequence (5' to 3')**
HIF1A	Forward: GAAAAGTCTCGAGATGCAGCCA
	Reverse: GGGAAAAGCCAGTATCTTATTCCTG
EPAS1	Forward: CCCATGTGAAGCCCTGTTCT
	Reverse: CCCATGTTCTTCCCTGGTCC
Egln1	Forward:ACTTACTTTCGTTCGGCCGT Reverse:TCCGAGGATCCTCCGCTTAG
Egln2	Forward:CCAGTAGGCTTCCTCCCGTA Reverse:AGCGACGATGCAAGTGGAAA
Egln3	Forward:TGGATCTGGAGAAGATCGCC Reverse:ATCCACGTGATCTGGTCGC
CBFA2T3 (off-target *HIF1A*)	Forward: GAGGAGCTCAACCACTGGG
	Reverse: CTCGGACAAGGTCTGGCTC
ALDH1L1 (off-target *EPAS1*)	Forward: TGATCTCTCAGTGTCACAGCCA
	Reverse: GCCCCTTCACACCCTTATCC

Table S5: List of antibodies used in the study.

Primary Antibodies	**Origin**	**Clonality**	**Dilution factor**	**Company**	**Catalog nr.**
HIF-1α	Mouse	monoclonal	1:1.000	BD Bioscience	#610959
HIF-2α (D9E3)	Rabbit	monoclonal	1:1.000	Cell signaling	#7096
CA IX (H-11)	Mouse	monoclonal	1:1.000	Santa Cruz	#sc-365900
BNIP3 (D7U1T)	Rabbit	monoclonal	1:1.000	Cell signaling	#44060
PHD1	Rabbit	monoclonal	1:1000	Cell signaling	#33985
PHD2	Rabbit	polyclonal	1:1000	Cell signaling	#3293
PHD3	Rabbit	monoclonal	1:500	Abcam	#ab184714
α-Tubulin (clone B-5-1-2)	Mouse	monoclonal	1:10.000	Sigma-Aldich	#T5168
Secondary Antibodies	**Origin**		**Dilution factor**	**Company**	**Catalog nr.**
Mouse-HRP	Goat		1:5.000	Bio-Rad	#1706516
Rabbit-HRP	Goat		1:5.000	Bio-Rad	#1706515