

## Supplemental Materials and Methods.

**Apoptosis analysis.** APC-Annexin V (550474), 7-AAD (559925), and Annexin V binding buffer (556454) were purchased from BD Biosciences. The assays were carried out according to manufacturer's protocol.

**XTT assay.** Cell viability assays were performed using an "In Vitro Toxicology Assay Kit, XTT based" (Sigma-Aldrich) according to manufacturers' protocol.

**Chromatin immunoprecipitation.** The chromatin immunoprecipitation assay was performed using SimpleChIP Plus Enzymatic Chromatin IP Kit (Magnetic Beads) (#9005, CST) with HIF-1 $\alpha$  antibody (79233S, CST), KDM3A antibody (ab91252, Abcam), and dimethyl-Histone H3 antibody (#07-441, Merck) according to manufacturer's protocol. PCR primers are described in Supplemental Table S4.

**Xenograft mouse model.** U266 ( $1 \times 10^6$  each) were subcutaneously injected into the right or left side of the body of 6- to 8-week-old female NOD/Shi-scid IL-2 $\gamma$ nul (NOG) mice (Central Institute for Experimental Animals, Kawasaki, Japan). The protocols for animal experimentation described in this paper were previously approved by the Animal Committee, Akita University (approval number: b-1-2301).

**Co-culture with HS-5.** We purchased human stromal cell line HS-5 from ATCC. HS-5 were plated in 12-well plate at a density of  $0.5 \times 10^6$  cells per well and cultured for 48 hours with DMEM medium. After we co-cultured HS-5 and U266 for 24 hours with RPMI1640. U266 cells were separated from the HS-5 layer by carefully pipetting twice with PBS.

**Reagents.** Bromopyruvic acid (16490) was purchased from Sigma-Aldrich. (St. Louis, MO, USA). Recombinant human IL-6 (#8904SC) was purchased from CST. Z-VAD (G723B) was purchased from Promega (Madison, WI, USA).

**Supplemental Table S1. Sequence information of siHIF1A, siHIF2A, siKDM3A, siMALAT1, and shKDM3A.**

| siRNA     | siRNA ID# | probe                         | 5'-3'                  |
|-----------|-----------|-------------------------------|------------------------|
| siHIF1A   | s6539     | sense                         | CCAUAUAGAGAUACUCAAAtt  |
|           |           | antisense                     | UUUGAGUAUCUCUAUAUGGtg  |
| siHIF2A   | s4698     | sense                         | CACCUACUGUGAUGACAGAtt  |
|           |           | antisense                     | UCUGUCAUCACAGUAGGUGaa  |
| siKDM3A#1 | s224392   | sense                         | GAAGAUCGGAAAU AUGGAAtt |
|           |           | antisense                     | UCCAUUUUCCGAUCUUCag    |
| siKDM3A#2 | s224393   | sense                         | GACUCAAGAAUACACCAAAtt  |
|           |           | antisense                     | UUUGGUGUAUUCUUGAGUCca  |
| siMALAT1  | n511399   | sense                         | CCGCUGCUAUUAGAAUGCAtt  |
|           |           | antisense                     | UGCAUUCUAAUAGCAGCGGga  |
| shRNA     | tube IDs  | 5'-3'                         |                        |
| shKDM3A#A | TL303857A | CAAGTCAACTGTGAGGAGATTCCAGCACT |                        |
| shKDM3A#B | TL303857B | AACTCTTCAGGCAGGATTCCTGTGGACTT |                        |
| shKDM3A#C | TL303857C | GGTCCAGAAGAGCAATGGAGGAAGTGACA |                        |
| shKDM3A#D | TL303857D | ATTGGAGACCACTTCTGTCAAATGGTGAT |                        |

**Supplemental Table S2. List of upregulated (fold change > 2) genes for all patient samples and cell lines in hypoxia.**

| ProbeName      | GeneSymbol    | Hypoxia vs. Normoxia Log <sub>2</sub> FC |      |       |         |      |      |      |      |      |
|----------------|---------------|--|------|-------|---------|------|------|------|------|------|
|                |               | U266                                     | 8226 | KMS11 | KMS12BM | MM1S | pt1  | pt2  | pt3  | pt4  |
| A_32_P95067    | AK4           | 1.76                                     | 3.19 | 2.15  | 1.77    | 1.76 | 1.26 | 1.93 | 1.06 | 2.47 |
| A_24_P237586   | ANKRD37       | 1.79                                     | 2.38 | 3.32  | 1.31    | 3.73 | 3.41 | 1.99 | 1.47 | 1.12 |
| A_24_P268676   | BHLHE40       | 1.41                                     | 3.13 | 2.09  | 2.30    | 1.83 | 2.51 | 1.09 | 1.55 | 2.15 |
| A_33_P3247175  | C4orf47       | 2.19                                     | 3.64 | 6.35  | 1.46    | 6.67 | 2.57 | 2.93 | 1.95 | 2.48 |
| A_24_P159434   | CD300A        | 1.55                                     | 2.76 | 1.90  | 2.52    | 2.33 | 1.44 | 1.06 | 1.04 | 1.15 |
| A_23_P428129   | CDKN1C        | 2.15                                     | 2.05 | 2.11  | 3.51    | 1.50 | 2.41 | 1.49 | 1.80 | 3.31 |
| A_21_P0011857  | DARS-AS1      | 2.42                                     | 4.63 | 4.82  | 3.23    | 4.75 | 2.04 | 4.55 | 2.55 | 2.50 |
| A_21_P0014245  | DKFZp667F0711 | 1.31                                     | 2.30 | 3.37  | 2.20    | 4.57 | 2.90 | 3.65 | 4.00 | 1.15 |
| A_33_P3264042  | EFCAB3        | 1.52                                     | 3.12 | 4.95  | 1.02    | 3.72 | 1.98 | 1.64 | 1.25 | 2.27 |
| A_33_P3432135  | EPHA1-AS1     | 1.95                                     | 2.16 | 3.82  | 1.38    | 2.96 | 2.49 | 2.41 | 1.02 | 1.81 |
| A_33_P3691916  | FAM13A        | 1.14                                     | 2.29 | 1.95  | 1.01    | 2.13 | 2.93 | 2.37 | 1.74 | 2.95 |
| A_33_P3378126  | FBXO32        | 1.05                                     | 1.76 | 3.01  | 1.01    | 2.93 | 2.24 | 1.43 | 1.04 | 2.07 |
| A_23_P167683   | GDNF          | 1.88                                     | 3.33 | 2.10  | 2.59    | 1.80 | 1.54 | 1.01 | 1.05 | 1.06 |
| A_23_P20035    | GPR146        | 1.46                                     | 2.11 | 2.49  | 1.68    | 2.11 | 1.72 | 1.51 | 1.79 | 2.11 |
| A_23_P395075   | KDM3A         | 1.34                                     | 2.66 | 2.98  | 1.91    | 2.11 | 1.82 | 1.93 | 1.28 | 1.94 |
| A_33_P3252068  | KDM7A         | 1.28                                     | 1.65 | 2.29  | 2.75    | 3.53 | 1.54 | 1.12 | 2.28 | 4.17 |
| A_19_P00320226 | LINC00894     | 1.40                                     | 1.83 | 1.63  | 1.76    | 1.24 | 2.16 | 1.66 | 1.51 | 1.71 |
| A_33_P3589543  | lnc-RASSF7-1  | 1.52                                     | 1.09 | 3.37  | 1.26    | 4.53 | 2.07 | 1.86 | 1.61 | 1.36 |
| A_21_P0003797  | lnc-SCRG1-1   | 1.28                                     | 2.93 | 5.30  | 2.23    | 4.55 | 1.70 | 1.99 | 1.57 | 1.98 |
| A_33_P3373573  | lnc-UBXN4-2   | 2.25                                     | 3.73 | 3.70  | 3.61    | 4.49 | 1.62 | 2.35 | 1.96 | 1.39 |
| A_21_P0003488  | LOC101929491  | 1.34                                     | 2.79 | 2.40  | 3.62    | 1.43 | 1.43 | 1.94 | 1.03 | 1.83 |
| A_21_P0007153  | LOC143666     | 2.09                                     | 2.33 | 3.14  | 1.69    | 3.23 | 2.67 | 1.35 | 1.39 | 1.76 |
| A_24_P918907   | LOC154761     | 1.96                                     | 2.97 | 3.62  | 2.97    | 3.78 | 2.25 | 1.76 | 1.67 | 1.45 |
| A_33_P3291619  | LOC399715     | 1.07                                     | 3.21 | 3.94  | 2.08    | 4.24 | 2.06 | 2.00 | 2.15 | 4.06 |
| A_33_P3383029  | MXI1          | 1.42                                     | 2.39 | 2.94  | 2.07    | 3.21 | 1.32 | 1.40 | 1.10 | 1.78 |
| A_23_P27229    | MYO15A        | 2.86                                     | 3.92 | 3.51  | 1.48    | 3.51 | 2.06 | 3.22 | 1.70 | 2.35 |
| A_23_P20494    | NDRG1         | 2.16                                     | 4.28 | 3.69  | 1.38    | 2.21 | 2.84 | 3.31 | 1.58 | 2.03 |
| A_33_P3214481  | P4HA1         | 1.97                                     | 3.57 | 3.91  | 2.54    | 3.01 | 2.16 | 2.44 | 1.68 | 2.82 |
| A_24_P261259   | PFKFB3        | 1.91                                     | 1.46 | 2.03  | 1.63    | 1.89 | 1.68 | 1.35 | 1.27 | 2.30 |
| A_24_P206604   | PFKFB3        | 1.55                                     | 1.72 | 2.81  | 2.53    | 3.31 | 1.27 | 1.58 | 2.32 | 2.80 |
| A_24_P362904   | PFKFB4        | 2.48                                     | 4.51 | 4.76  | 2.34    | 4.35 | 2.07 | 4.83 | 2.98 | 3.41 |
| A_32_P83098    | SCNN1B        | 1.41                                     | 2.00 | 1.48  | 1.93    | 1.72 | 2.17 | 1.76 | 2.54 | 2.08 |
| A_23_P158725   | SLC16A3       | 1.98                                     | 3.02 | 1.92  | 1.40    | 2.11 | 1.14 | 1.63 | 3.37 | 1.58 |
| A_19_P00811533 | SLC2A1-AS1    | 2.63                                     | 2.16 | 3.26  | 1.90    | 2.91 | 2.77 | 2.90 | 1.34 | 1.80 |
| A_24_P237912   | TCAF2         | 1.59                                     | 4.06 | 3.55  | 1.91    | 4.88 | 2.00 | 1.73 | 1.69 | 1.57 |
| A_23_P419107   | TCP11L2       | 1.45                                     | 1.17 | 3.20  | 1.09    | 3.22 | 1.41 | 3.93 | 1.46 | 2.38 |
| A_23_P70398    | VEGFA         | 1.36                                     | 3.45 | 2.70  | 2.89    | 2.72 | 1.96 | 2.55 | 1.04 | 1.38 |
| A_23_P102117   | WNT10A        | 1.84                                     | 2.21 | 2.86  | 2.00    | 3.02 | 1.85 | 1.92 | 1.31 | 1.72 |

**Supplemental Table S3. List of downregulated (fold change < 0.5) genes for all patient samples in hypoxia.**

| ProbeName     | GeneSymbol | Hypoxia vs. Normoxia Log <sub>2</sub> FC |       |       |         |       |       |       |       |       |
|---------------|------------|--|-------|-------|---------|-------|-------|-------|-------|-------|
|               |            | U266                                     | 8226  | KMS11 | KMS12BM | MM1S  | pt1   | pt2   | pt3   | pt4   |
| A_24_P205589  | ACOT7      | -0.42                                    | -2.71 | -2.32 | -0.28   | -1.19 | -2.66 | -1.82 | -1.09 | -1.40 |
| A_33_P3240543 | AGAP3      | -0.31                                    | -0.31 | -1.21 | 0.48    | -1.50 | -1.32 | -1.04 | -1.21 | -1.67 |
| A_32_P192970  | ALDH4A1    | -2.00                                    | -4.25 | -3.36 | -2.89   | -3.08 | -3.03 | -2.70 | -1.66 | -2.29 |
| A_33_P3288159 | ASPM       | -0.85                                    | -1.75 | -1.63 | -0.95   | -1.82 | -1.29 | -1.15 | -1.12 | -1.69 |
| A_33_P3349469 | ATAD3A     | -0.51                                    | -0.35 | -2.17 | -0.58   | -1.67 | -1.01 | -1.42 | -1.01 | -1.35 |
| A_23_P164228  | ATP5G1     | -0.66                                    | -1.51 | -1.82 | -1.05   | -1.56 | -1.94 | -1.61 | -1.09 | -1.35 |
| A_23_P160537  | AUNIP      | -0.07                                    | -1.70 | -3.25 | -0.01   | -2.07 | -1.80 | -1.59 | -1.02 | -1.82 |
| A_23_P131866  | AURKA      | -1.12                                    | -0.80 | -1.59 | -0.67   | -2.00 | -1.20 | -1.27 | -1.14 | -1.68 |
| A_33_P3368301 | BOLA3      | -0.51                                    | -1.59 | -2.52 | -0.97   | -1.87 | -1.38 | -1.39 | -1.14 | -1.43 |
| A_23_P313223  | C11orf84   | -0.19                                    | -0.56 | -1.46 | -0.62   | -0.44 | -2.71 | -1.04 | -1.27 | -1.35 |
| A_33_P3258191 | C16orf91   | -0.66                                    | -0.60 | -1.16 | -0.17   | -1.20 | -1.12 | -1.31 | -1.08 | -1.01 |
| A_33_P3399433 | C20orf27   | -0.83                                    | -1.60 | -2.26 | -0.40   | -2.05 | -1.56 | -1.52 | -1.87 | -1.78 |
| A_23_P28878   | C20orf27   | -0.74                                    | -1.12 | -2.60 | -0.82   | -2.32 | -1.61 | -1.67 | -1.75 | -1.12 |
| A_24_P84428   | CACYBP     | -0.59                                    | -0.33 | -1.22 | 0.06    | -1.32 | -1.64 | -1.38 | -1.09 | -1.60 |
| A_23_P40049   | CAD        | -0.72                                    | -0.86 | -2.75 | -0.95   | -2.15 | -1.72 | -1.27 | -1.53 | -1.30 |
| A_21_P0014306 | CAPN15     | -0.86                                    | -1.10 | -2.40 | 0.19    | -1.17 | -1.99 | -1.46 | -1.98 | -2.01 |
| A_23_P58321   | CCNA2      | -0.80                                    | -1.94 | -2.43 | -0.62   | -2.19 | -1.35 | -1.80 | -1.23 | -1.68 |
| A_23_P122197  | CCNB1      | -1.44                                    | -1.03 | -2.11 | -0.15   | -2.25 | -1.29 | -1.39 | -1.43 | -1.78 |
| A_23_P208310  | CD3EAP     | -1.06                                    | -0.71 | -1.66 | -0.81   | -1.08 | -1.03 | -2.18 | -1.29 | -1.21 |
| A_23_P149200  | CDC20      | -1.19                                    | -0.84 | -2.02 | -0.31   | -2.48 | -1.04 | -1.53 | -1.36 | -1.93 |
| A_24_P397107  | CDC25A     | -0.25                                    | -3.02 | -3.32 | -2.14   | -2.29 | -2.50 | -1.88 | -1.16 | -1.70 |
| A_23_P57379   | CDC45      | -0.08                                    | -2.14 | -2.20 | -3.23   | -2.19 | -2.75 | -1.61 | -1.10 | -1.89 |
| A_23_P251421  | CDC47      | 0.25                                     | 1.18  | -1.55 | 0.71    | -1.74 | -1.62 | -1.74 | -1.57 | -1.52 |
| A_23_P254733  | CENPU      | -0.14                                    | -1.99 | -1.54 | -2.03   | -1.99 | -1.76 | -1.47 | -1.18 | -1.65 |
| A_24_P462899  | CENPW      | -1.00                                    | -1.22 | -2.22 | -0.99   | -2.06 | -1.75 | -1.05 | -1.52 | -2.13 |
| A_33_P3291831 | CEP55      | -0.54                                    | -3.20 | -2.42 | -1.05   | -1.35 | -1.02 | -1.59 | -1.26 | -1.36 |
| A_23_P57306   | CHAF1B     | 0.14                                     | -0.83 | -1.83 | 0.15    | -1.53 | -2.60 | -1.21 | -1.15 | -1.74 |
| A_33_P3349536 | CHEK1      | -0.24                                    | -2.49 | -2.19 | -2.64   | -1.85 | -1.56 | -1.67 | -1.14 | -1.45 |
| A_23_P111228  | COQ3       | -0.66                                    | -1.20 | -2.23 | -0.44   | -2.19 | -1.62 | -1.59 | -1.61 | -1.01 |
| A_33_P3221843 | COQ3       | -0.27                                    | -0.93 | -2.07 | -0.25   | -2.74 | -1.70 | -1.33 | -1.87 | -1.45 |
| A_23_P17393   | CSE1L      | -0.32                                    | -0.56 | -1.58 | 0.38    | -1.54 | -1.35 | -1.18 | -1.11 | -1.11 |
| A_23_P148372  | CSTF2      | -0.77                                    | -0.95 | -1.86 | -0.66   | -1.67 | -1.92 | -1.18 | -1.35 | -1.19 |
| A_33_P3235217 | CTPS1      | -0.73                                    | -2.02 | -3.44 | -1.43   | -2.54 | -1.48 | -2.59 | -2.04 | -1.66 |
| A_23_P21706   | CTPS1      | -0.57                                    | -1.91 | -3.50 | -1.26   | -2.63 | -1.28 | -2.27 | -1.37 | -1.44 |
| A_23_P148984  | DARS2      | -0.68                                    | -0.87 | -1.82 | -0.06   | -1.95 | -1.20 | -1.22 | -1.20 | -1.04 |
| A_24_P943358  | DBF4       | -1.03                                    | 0.45  | -2.03 | -0.24   | 1.64  | -1.88 | -1.24 | -1.12 | -1.10 |
| A_24_P54131   | DCLRE1B    | -0.33                                    | -0.50 | -1.49 | 1.65    | -0.80 | -2.95 | -1.45 | -1.23 | -1.10 |
| A_23_P33613   | DCTPP1     | -0.62                                    | -1.07 | -2.00 | -0.61   | -1.75 | -2.38 | -1.80 | -1.70 | -1.13 |
| A_23_P78664   | DDX39A     | -0.97                                    | -1.83 | -1.34 | -0.06   | -1.33 | -1.14 | -1.16 | -1.17 | -1.65 |
| A_23_P88893   | DEF8       | -1.26                                    | -1.57 | -1.83 | -1.41   | -0.72 | -1.48 | -1.06 | -1.40 | -1.26 |
| A_24_P193582  | DEF8       | -1.31                                    | -1.55 | -1.72 | -1.35   | -0.76 | -1.46 | -1.10 | -1.34 | -1.22 |
| A_23_P361419  | DEPDC1B    | -0.22                                    | -1.84 | -2.02 | -0.19   | -3.29 | -1.16 | -1.30 | -1.17 | -1.76 |
| A_24_P343095  | DHFR       | -0.33                                    | -0.77 | -2.51 | -0.19   | -1.76 | -1.73 | -1.64 | -1.20 | -1.72 |
| A_23_P103631  | EBNA1BP2   | -1.08                                    | -1.32 | -1.84 | -0.44   | -1.67 | -1.89 | -1.58 | -2.03 | -1.30 |
| A_21_P0011842 | EEF1E1     | -0.60                                    | -0.59 | -1.47 | 0.08    | -1.57 | -1.32 | -1.75 | -1.07 | -1.87 |
| A_33_P3296372 | EIF2B3     | -0.83                                    | -1.15 | -2.14 | -1.08   | -1.54 | -1.50 | -1.73 | -1.17 | -1.06 |
| A_33_P3305482 | EIF2B3     | -1.15                                    | -1.46 | -2.38 | -1.28   | -1.71 | -1.89 | -2.11 | -1.75 | -1.39 |
| A_24_P126425  | FAM188B    | -0.49                                    | -0.70 | -1.24 | -0.31   | -1.30 | -2.26 | -1.82 | -2.02 | -1.59 |
| A_24_P203407  | FITM2      | -0.81                                    | -1.70 | -1.17 | -0.57   | -0.83 | -1.91 | -1.97 | -1.59 | -1.50 |
| A_23_P12113   | FLVCR1     | -0.90                                    | -1.67 | -1.35 | -0.84   | -1.43 | -1.27 | -1.27 | -1.46 | -2.19 |
| A_23_P40657   | GCAT       | -0.59                                    | -0.47 | -1.58 | -2.28   | -2.13 | -1.32 | -1.08 | -2.85 | -1.26 |
| A_23_P42695   | GGCT       | -0.20                                    | -0.29 | -1.21 | 0.16    | -1.55 | -1.10 | -1.58 | -1.37 | -1.55 |
| A_23_P118246  | GINS2      | 0.07                                     | -2.10 | -2.11 | -2.16   | -2.01 | -3.50 | -1.80 | -2.17 | -1.40 |
| A_23_P160503  | GLRX2      | -0.71                                    | -0.97 | -1.34 | 0.48    | -1.29 | -1.15 | -1.44 | -1.49 | -1.10 |
| A_23_P97265   | GPATCH4    | -1.26                                    | -1.76 | -2.73 | -0.85   | -1.98 | -1.25 | -1.48 | -1.21 | -1.30 |
| A_23_P416036  | HAUS7      | -0.46                                    | -0.97 | -1.80 | -0.28   | -1.63 | -1.95 | -1.61 | -1.66 | -1.61 |
| A_23_P12816   | HELLS      | 0.29                                     | -2.26 | -1.62 | -1.68   | -1.27 | -2.30 | -2.09 | -1.29 | -2.87 |
| A_23_P61268   | HGH1       | -0.43                                    | -0.72 | -2.85 | -0.82   | -1.86 | -1.79 | -1.12 | -1.30 | -1.21 |
| A_33_P3237359 | HMGB3      | -0.22                                    | -0.30 | -2.02 | -0.27   | -1.90 | -1.12 | -1.09 | -1.14 | -1.49 |
| A_33_P3395321 | HN1        | -0.48                                    | -0.71 | -1.36 | 0.12    | -1.39 | -1.40 | -1.38 | -1.03 | -1.43 |
| A_23_P19084   | HNRNPAB    | -0.38                                    | -1.34 | -2.53 | 0.07    | -2.12 | -1.46 | -1.69 | -1.07 | -1.14 |
| A_33_P3294017 | HNRNPC     | -0.98                                    | -0.67 | -1.11 | -0.97   | -0.93 | -1.30 | -1.11 | -1.10 | -1.18 |
| A_23_P74449   | HPDL       | 0.61                                     | -1.75 | -2.17 | -0.98   | -2.33 | -1.85 | -2.21 | -2.13 | -1.46 |
| A_33_P3344282 | HS1BP3     | -1.27                                    | -1.88 | -1.52 | 0.88    | -1.45 | -1.54 | -2.05 | -1.87 | -1.71 |
| A_23_P10685   | HSPBP1     | -0.91                                    | -0.91 | -1.82 | -0.72   | -1.51 | -1.82 | -1.46 | -1.13 | -1.16 |
| A_23_P257956  | ILF2       | -0.59                                    | -0.25 | -1.78 | -0.86   | -1.74 | -1.29 | -1.01 | -1.20 | -1.24 |
| A_23_P434944  | ILF3       | -0.66                                    | -0.75 | -1.72 | -0.26   | -1.73 | -1.12 | -1.29 | -1.95 | -1.08 |

Supplemental Table S3. List of downregulated (fold change &lt; 0.5) genes for all patient samples in hypoxia.

Continued

| ProbeName      | GeneSymbol   | Hypoxia vs. Normoxia Log <sub>2</sub> FC |       |       |         |       |       |       |       |       |
|----------------|--------------|--|-------|-------|---------|-------|-------|-------|-------|-------|
|                |              | U266                                     | 8226  | KMS11 | KMS12BM | MM1S  | pt1   | pt2   | pt3   | pt4   |
| A_21_P0014225  | KANK1        | 0.65                                     | -0.64 | 0.37  | -0.16   | 0.61  | -1.71 | -1.07 | -1.23 | -1.11 |
| A_23_P94998    | LETM1        | -0.96                                    | -1.26 | -2.81 | -0.53   | -1.13 | -1.63 | -1.05 | -1.03 | -1.50 |
| A_33_P3632937  | LOC100131262 | -0.77                                    | -2.61 | -4.35 | -1.37   | -2.22 | -1.94 | -1.56 | -2.40 | -2.16 |
| A_33_P3253707  | LRR1         | -0.29                                    | -0.59 | -1.74 | -0.19   | -1.45 | -1.68 | -1.10 | -1.01 | -1.95 |
| A_23_P41327    | LYAR         | -1.13                                    | -0.72 | -1.42 | -0.14   | -0.51 | -1.17 | -1.92 | -1.59 | -1.40 |
| A_32_P103633   | MCM2         | 0.01                                     | -1.68 | -1.91 | -1.75   | -1.81 | -2.29 | -1.33 | -1.25 | -1.32 |
| A_23_P370989   | MCM4         | 0.05                                     | -1.66 | -2.33 | -0.83   | -2.18 | -2.71 | -1.62 | -1.20 | -1.40 |
| A_23_P047790   | METTL1       | -0.53                                    | -0.37 | -2.10 | -1.13   | -1.92 | -1.18 | -1.52 | -1.11 | -1.18 |
| A_24_P83678    | MMS22L       | -0.08                                    | -0.95 | -1.50 | -0.23   | -0.60 | -1.28 | -1.46 | -1.17 | -1.38 |
| A_23_P140848   | MPHOSPH6     | -0.44                                    | -1.28 | -2.06 | -0.41   | -1.49 | -1.63 | -1.33 | -1.52 | -1.05 |
| A_23_P165130   | MPV17L2      | -1.15                                    | -0.23 | -1.75 | -0.84   | -1.09 | -1.72 | -2.06 | -1.69 | -1.48 |
| A_33_P3223088  | MRPL19       | -1.68                                    | -1.68 | -0.97 | -0.83   | -0.02 | -1.27 | -2.08 | -1.32 | -1.23 |
| A_23_P102471   | MSH2         | -0.52                                    | -0.55 | -1.31 | 0.37    | -1.20 | -1.94 | -1.09 | -1.00 | -1.22 |
| A_33_P3287502  | MSH2         | -0.55                                    | -0.53 | -1.37 | 0.49    | -1.03 | -2.15 | -1.08 | -1.02 | -1.07 |
| A_23_P31073    | MYB          | -0.57                                    | 0.99  | -0.06 | -1.27   | -1.35 | -2.46 | -1.01 | -1.57 | -2.12 |
| A_23_P100868   | MYO19        | -1.46                                    | -1.07 | -1.37 | -0.26   | -1.80 | -1.28 | -1.25 | -1.19 | -1.88 |
| A_23_P35219    | NEK2         | -0.49                                    | -1.20 | -0.98 | -0.28   | -1.37 | -1.19 | -1.15 | -1.10 | -1.47 |
| A_33_P3394828  | NOC4L        | -0.78                                    | -0.70 | -1.05 | -0.85   | -0.46 | -1.07 | -1.35 | -1.03 | -1.10 |
| A_24_P101402   | NOP56        | -0.26                                    | -0.84 | -1.64 | -0.52   | -1.03 | -1.32 | -1.15 | -1.64 | -1.01 |
| A_23_P326844   | NOP9         | -0.43                                    | -1.07 | -1.32 | -0.03   | -2.13 | -1.84 | -1.17 | -1.49 | -1.14 |
| A_23_P52298    | NPM3         | -1.24                                    | -0.63 | -2.75 | 0.47    | -2.30 | -1.43 | -1.41 | -1.53 | -1.49 |
| A_23_P48099    | NUP37        | -0.58                                    | -0.41 | -1.51 | -0.29   | -1.71 | -1.24 | -1.04 | -1.13 | -1.09 |
| A_23_P89056    | NUP93        | -0.60                                    | -0.81 | -2.21 | -0.12   | -2.04 | -1.46 | -1.14 | -1.03 | -1.48 |
| A_23_P3775     | OGFOD1       | -0.67                                    | 0.00  | -1.63 | -0.24   | -1.36 | -1.31 | -1.04 | -1.11 | -1.14 |
| A_23_P100344   | ORC6         | -0.27                                    | -1.97 | -2.44 | -1.30   | -2.31 | -1.51 | -1.71 | -1.02 | -1.65 |
| A_23_P87769    | PARBP        | -0.93                                    | -1.31 | -1.37 | -2.59   | -1.83 | -1.04 | -1.26 | -1.17 | -1.75 |
| A_23_P28886    | PCNA         | 0.08                                     | -1.14 | -2.14 | 0.13    | -1.71 | -2.52 | -1.80 | -1.17 | -1.30 |
| A_33_P3258612  | PCNA         | 0.12                                     | -1.17 | -2.22 | 0.14    | -1.93 | -2.57 | -1.98 | -1.25 | -1.22 |
| A_19_P00806947 | PCNA         | 0.12                                     | -1.17 | -2.11 | 0.16    | -1.66 | -2.57 | -1.72 | -1.10 | -1.48 |
| A_23_P161152   | PDSS1        | -0.92                                    | -1.42 | -2.03 | 0.18    | -2.11 | -2.16 | -1.76 | -2.30 | -1.59 |
| A_33_P3251796  | PDSS1        | -0.89                                    | -1.41 | -1.52 | -0.03   | -1.01 | -1.93 | -1.58 | -1.84 | -1.13 |
| A_23_P118174   | PLK1         | -1.47                                    | -1.13 | -2.09 | 0.29    | -2.82 | -1.16 | -1.31 | -1.09 | -2.14 |
| A_23_P155969   | PLK4         | -0.48                                    | -1.62 | -1.61 | -0.19   | -0.16 | -1.12 | -1.12 | -1.14 | -1.45 |
| A_23_P163099   | POLE2        | -0.21                                    | -1.13 | -1.96 | -2.29   | -2.34 | -2.70 | -1.21 | -1.18 | -1.40 |
| A_23_P341275   | POP1         | -0.84                                    | -1.61 | -1.73 | -0.32   | -1.55 | -1.48 | -1.36 | -1.41 | -1.00 |
| A_33_P3298413  | PPIH         | -0.96                                    | -0.23 | -1.33 | 0.21    | -1.14 | -1.50 | -1.41 | -1.51 | -1.22 |
| A_23_P9603     | PRKDC        | -0.24                                    | -1.15 | -2.20 | -0.55   | -1.82 | -1.05 | -1.45 | -1.56 | -1.04 |
| A_33_P3337599  | PRKDC        | -0.22                                    | 0.47  | -1.11 | 0.17    | -0.19 | -1.22 | -1.41 | -1.57 | -1.38 |
| A_33_P3220643  | PTRH1        | -0.14                                    | -2.01 | -3.42 | -0.73   | -2.03 | -1.34 | -1.34 | -1.17 | -1.58 |
| A_23_P18579    | PTTG2        | -0.83                                    | -1.40 | -1.50 | -0.28   | -1.48 | -1.05 | -1.21 | -1.16 | -1.43 |
| A_23_P144697   | RAD1         | -0.73                                    | -0.37 | -1.44 | -0.30   | -1.44 | -1.60 | -1.56 | -1.40 | -1.23 |
| A_33_P3272828  | RAD1         | -0.50                                    | -0.84 | -0.98 | 0.35    | -0.94 | -1.72 | -1.47 | -1.70 | -1.32 |
| A_23_P91590    | RANBP1       | -0.26                                    | -0.49 | -2.05 | 0.17    | -1.48 | -1.52 | -1.49 | -1.26 | -1.11 |
| A_24_P276102   | RBL1         | -0.33                                    | -0.85 | -1.15 | -0.73   | -0.42 | -1.83 | -1.76 | -1.63 | -1.21 |
| A_33_P3378925  | RBM14        | -0.31                                    | -0.37 | -1.07 | -0.29   | -1.24 | -1.00 | -1.54 | -1.67 | -1.10 |
| A_23_P14193    | RFC3         | -0.49                                    | -0.68 | -2.04 | 0.19    | -1.85 | -1.71 | -1.60 | -1.53 | -1.04 |
| A_23_P18196    | RFC4         | 0.05                                     | -0.54 | -1.62 | -0.32   | -1.50 | -1.86 | -1.16 | -1.00 | -1.56 |
| A_23_P378526   | RTEL1        | -0.43                                    | -0.97 | -1.87 | -1.40   | -1.82 | -1.77 | -1.19 | -1.22 | -1.72 |
| A_23_P29723    | SGOL1        | -1.01                                    | -1.96 | -3.24 | -0.17   | -2.35 | -2.63 | -1.29 | -2.13 | -2.35 |
| A_33_P3384108  | SLC19A1      | -0.46                                    | -1.05 | -2.53 | -0.68   | -1.84 | -1.09 | -1.57 | -1.05 | -1.57 |
| A_33_P3350074  | SLC25A19     | -0.33                                    | -0.68 | -0.83 | -0.56   | -1.00 | -1.68 | -1.45 | -1.27 | -1.44 |
| A_33_P3378334  | SMC2         | -0.57                                    | -0.88 | -1.03 | -0.42   | -1.17 | -1.28 | -1.18 | -1.21 | -1.07 |
| A_21_P0000320  | SNORA30      | -1.18                                    | -0.27 | -0.32 | -0.49   | -0.19 | -1.28 | -1.11 | -1.25 | -1.33 |
| A_21_P0000500  | SNORD86      | -0.13                                    | -0.91 | -2.34 | -0.40   | -1.76 | -2.40 | -1.75 | -2.15 | -1.59 |
| A_23_P152284   | SNRNP25      | -0.50                                    | -1.83 | -2.34 | -1.04   | -1.42 | -2.54 | -1.19 | -1.04 | -1.26 |
| A_32_P148672   | SNRPD1       | -0.50                                    | -1.00 | -1.81 | -0.12   | -1.42 | -1.39 | -1.30 | -1.29 | -1.19 |
| A_23_P117068   | SNRPF        | -0.67                                    | -1.02 | -1.53 | -0.05   | -1.48 | -1.24 | -1.01 | -1.00 | -1.62 |
| A_21_P0011375  | SORD         | -0.46                                    | -0.38 | -0.73 | -1.96   | -3.59 | -1.16 | -1.91 | -1.08 | -1.42 |
| A_23_P41948    | SPDL1        | -0.69                                    | -0.97 | -1.62 | -0.43   | -1.82 | -1.34 | -1.20 | -1.49 | -1.38 |
| A_33_P3249354  | SPDL1        | -0.59                                    | -1.10 | -1.90 | -0.19   | -2.07 | -1.42 | -1.15 | -1.48 | -1.27 |
| A_23_P74269    | SRM          | -1.00                                    | -1.53 | -3.10 | -1.61   | -1.94 | -1.30 | -2.10 | -2.03 | -1.15 |
| A_23_P413761   | SRSF3        | -0.61                                    | -0.51 | -1.29 | -0.43   | -1.22 | -1.34 | -1.03 | -1.51 | -1.07 |
| A_33_P3305840  | SRSF7        | -0.57                                    | -1.12 | -2.14 | -0.75   | -1.69 | -1.55 | -1.51 | -1.76 | -1.19 |
| A_23_P202392   | SUV39H2      | -0.24                                    | -1.51 | -2.62 | -1.33   | -2.11 | -1.59 | -1.31 | -1.36 | -1.19 |
| A_24_P391431   | TAF9B        | -1.51                                    | -0.10 | -1.95 | -0.16   | -1.89 | -2.20 | -1.41 | -2.98 | -1.08 |
| A_33_P3292919  | TCOF1        | -0.58                                    | -0.43 | -1.60 | -0.23   | -1.20 | -1.03 | -1.55 | -1.07 | -1.28 |
| A_24_P243396   | TCOF1        | -0.52                                    | -0.84 | -1.97 | -0.72   | -0.87 | -1.53 | -1.24 | -1.26 | -1.18 |

**Supplemental Table S3. List of downregulated (fold change < 0.5) genes for all patient samples in hypoxia.**

Continued

| ProbeName     | GeneSymbol     | Hypoxia vs. Normoxia Log <sub>2</sub> FC |       |       |         |       |       |       |       |       |
|---------------|----------------|--|-------|-------|---------|-------|-------|-------|-------|-------|
|               |                | U266                                     | 8226  | KMS11 | KMS12BM | MM1S  | pt1   | pt2   | pt3   | pt4   |
| A_23_P362046  | TEX30          | 0.06                                     | 0.13  | -1.42 | 0.26    | -1.45 | -1.34 | -1.18 | -1.37 | -1.20 |
| A_23_P64343   | TIMM10         | -1.08                                    | -0.82 | -1.07 | -0.28   | -1.44 | -1.67 | -1.82 | -1.75 | -1.36 |
| A_23_P99930   | TIPIN          | -0.48                                    | -1.64 | -2.10 | -0.73   | -2.04 | -2.34 | -1.85 | -2.10 | -1.64 |
| A_23_P5339    | TMEM177        | -0.14                                    | -1.98 | -2.77 | -1.14   | -1.63 | -1.73 | -1.41 | -1.26 | -1.00 |
| A_33_P3292525 | TMEM201        | -0.28                                    | -1.33 | -2.33 | -0.48   | -1.57 | -2.04 | -1.60 | -1.66 | -2.03 |
| A_23_P370097  | TMEM237        | 0.03                                     | -1.16 | -2.39 | 1.13    | -1.95 | -1.44 | -1.00 | -1.06 | -1.11 |
| A_23_P325040  | TMPO           | -0.94                                    | -1.13 | -1.90 | -0.19   | -0.81 | -1.45 | -1.52 | -1.93 | -1.34 |
| A_21_P0000006 | TOMM40         | -0.89                                    | -0.65 | -2.12 | -0.16   | -1.46 | -1.14 | -1.52 | -1.18 | -1.32 |
| A_33_P3339212 | TRIP13         | -0.68                                    | -2.07 | -2.65 | -1.31   | -2.45 | -2.37 | -1.12 | -1.52 | -1.62 |
| A_33_P3237874 | TROAP          | -0.91                                    | -1.08 | -1.50 | -1.14   | -1.01 | -1.23 | -1.43 | -1.02 | -1.60 |
| A_23_P208880  | UHRF1          | 0.18                                     | -2.19 | -2.65 | -1.52   | -2.18 | -3.05 | -1.82 | -1.04 | -1.54 |
| A_33_P3236157 | UNG            | 0.15                                     | -1.08 | -2.06 | -0.41   | -1.65 | -3.09 | -1.71 | -1.21 | -1.54 |
| A_23_P156739  | UQCC2          | -0.51                                    | -1.45 | -2.62 | -0.24   | -2.04 | -1.39 | -1.57 | -1.12 | -1.06 |
| A_21_P0000161 | USB1           | -1.53                                    | -1.77 | -2.50 | -0.58   | -2.01 | -3.09 | -2.48 | -1.79 | -2.65 |
| A_33_P3294372 | VPS9D1-AS1     | -0.92                                    | -1.23 | -3.38 | -1.73   | -2.13 | -1.24 | -1.88 | -2.02 | -1.66 |
| A_23_P143535  | WDR4           | -1.32                                    | -1.60 | -2.49 | -0.97   | -1.58 | -2.03 | -1.34 | -2.48 | -1.42 |
| A_21_P0013815 | XLOC_I2_015738 | -0.53                                    | -1.27 | -1.97 | -1.06   | -0.56 | -1.91 | -1.32 | -1.21 | -1.59 |
| A_33_P3301524 | XRCC3          | -0.62                                    | -1.31 | -2.35 | -1.38   | -1.66 | -2.16 | -1.49 | -1.20 | -1.89 |
| A_23_P87591   | YEATS4         | -0.29                                    | 0.05  | -0.91 | -0.18   | -1.32 | -1.13 | -1.01 | -1.22 | -1.03 |
| A_23_P129659  | ZNF689         | -0.80                                    | -0.73 | -1.53 | -1.12   | -1.71 | -1.50 | -1.21 | -1.15 | -1.17 |
| A_33_P3433873 | ZWILCH         | -0.74                                    | -1.26 | -2.21 | -0.48   | -2.17 | -1.15 | -1.32 | -1.27 | -1.52 |

**Supplemental Table S4. Primers used in chromatin immunoprecipitation (ChIP)**

| Primer name | Forward                    | Reverse                   | Ref.                |
|-------------|----------------------------|---------------------------|---------------------|
| KDM3A       | TCTCAATCCCACCTTTGGAGAA     | TAGGCTGCTGGGCGAAAT        | Pollard et al. (23) |
| MALAT1      | CCTGGA ACTCTCCATTTTAGGTCAT | AATCAGAACACAAACCTCGTGTAGC | Tee AE et al. (32)  |

**Supplemental Table S5. List of candidate genes of KDM3A-regulation genes only under hypoxia.**

| ProbeName     | GeneSymbol   | Log <sub>2</sub> FC |                           |                          |
|---------------|--------------|---------------------|---------------------------|--------------------------|
|               |              | hypoxia scr<br>vs.  | normoxia shKDM3A#C<br>vs. | hypoxia shKDM3A#C<br>vs. |
|               |              | normoxia scr        | normoxia scr              | hypoxia scr              |
| A_23_P395075  | KDM3A        | 1.48                | -1.15                     | -1.28                    |
| A_33_P3500167 | ACAN         | 1.36                | 0.27                      | -1.07                    |
| A_33_P3310929 | ADAM12       | 0.80                | -0.09                     | -1.13                    |
| A_23_P337658  | ALPI         | 1.06                | 0.26                      | -1.02                    |
| A_33_P3252099 | ANKLE1       | 0.73                | 0.08                      | -0.86                    |
| A_33_P3346628 | ANKRD63      | 0.69                | -0.06                     | -0.78                    |
| A_24_P8109    | ANO9         | 0.69                | -0.28                     | -0.62                    |
| A_23_P170733  | ANTXR2       | 0.65                | 0.35                      | -0.98                    |
| A_33_P3311863 | AP2A2        | 1.18                | 0.48                      | -0.78                    |
| A_23_P75630   | APOA5        | 0.90                | 0.60                      | -1.22                    |
| A_32_P213330  | ARHGEF28     | 0.60                | 0.29                      | -0.98                    |
| A_32_P146113  | ARMC12       | 0.95                | 0.19                      | -0.79                    |
| A_23_P163209  | BCL2L10      | 0.83                | -0.15                     | -0.76                    |
| A_33_P3267760 | BCOR         | 0.79                | 0.01                      | -0.91                    |
| A_23_P383915  | BTBD16       | 0.70                | 0.45                      | -0.74                    |
| A_33_P3270559 | C12orf42     | 1.05                | 0.19                      | -1.28                    |
| A_33_P3355708 | C14orf180    | 1.28                | -0.16                     | -1.60                    |
| A_21_P0009620 | C18orf61     | 1.52                | 0.13                      | -1.01                    |
| A_23_P303803  | C19orf18     | 1.15                | 0.15                      | -0.82                    |
| A_23_P412562  | C1orf162     | 0.87                | 0.56                      | -0.82                    |
| A_33_P3405459 | C20orf195    | 1.89                | 0.37                      | -0.74                    |
| A_33_P3506553 | C21orf91-OT1 | 1.00                | 0.20                      | -1.40                    |
| A_21_P0000174 | C5orf56      | 0.72                | -0.21                     | -1.12                    |
| A_33_P3288357 | C9orf117     | 1.93                | 0.08                      | -1.76                    |
| A_33_P3825869 | CACNA1C      | 1.03                | 0.11                      | -0.65                    |
| A_24_P838448  | CASC15       | 0.69                | 0.07                      | -0.84                    |
| A_33_P3283126 | CCDC64       | 0.90                | 0.28                      | -0.61                    |
| A_23_P17065   | CCL20        | 1.05                | 0.11                      | -0.66                    |
| A_23_P17593   | CDH4         | 0.68                | -0.20                     | -1.06                    |
| A_33_P3297321 | CDRT15P2     | 0.76                | 0.34                      | -0.59                    |
| A_23_P102351  | CHST10       | 0.68                | 0.46                      | -0.61                    |
| A_23_P151895  | CILP         | 0.86                | -0.02                     | -0.84                    |
| A_33_P3236071 | CLEC1B       | 1.68                | -0.01                     | -1.91                    |
| A_32_P185637  | COL20A1      | 1.17                | -0.21                     | -0.84                    |
| A_24_P257478  | COL25A1      | 0.77                | 0.49                      | -0.97                    |
| A_21_P0012396 | COL6A4P2     | 0.72                | -0.51                     | -0.79                    |
| A_23_P215331  | CRHR2        | 0.68                | 0.04                      | -1.19                    |
| A_23_P67932   | CXCR1        | 0.67                | 0.51                      | -0.91                    |
| A_23_P215828  | CYP3A43      | 0.84                | 0.32                      | -0.80                    |
| A_24_P42693   | CYP4F11      | 1.25                | 0.39                      | -1.53                    |
| A_21_P0006375 | CYSRT1       | 0.69                | -0.25                     | -1.89                    |
| A_21_P0014400 | DBNDD2       | 1.14                | 0.45                      | -1.54                    |
| A_23_P81441   | DCANP1       | 0.88                | 0.47                      | -0.73                    |
| A_24_P355145  | DNAJC5B      | 1.25                | 0.32                      | -1.48                    |
| A_33_P3289576 | EFHC2        | 1.27                | -0.14                     | -2.07                    |
| A_23_P46936   | EGR2         | 1.42                | -0.07                     | -0.82                    |
| A_21_P0011329 | EWSAT1       | 0.84                | -0.56                     | -0.97                    |
| A_23_P41145   | FAM3D        | 4.08                | 0.04                      | -2.36                    |
| A_33_P3249872 | FBLN1        | 0.81                | -0.11                     | -1.07                    |
| A_33_P3340808 | FLJ46026     | 0.60                | 0.36                      | -0.93                    |
| A_23_P91552   | FTCD         | 0.65                | 0.28                      | -0.69                    |
| A_23_P30983   | GJB7         | 0.82                | -0.25                     | -0.75                    |
| A_32_P78681   | GLP2R        | 0.59                | 0.01                      | -0.89                    |
| A_33_P3349265 | GLYATL3      | 1.01                | 0.36                      | -0.85                    |
| A_33_P3321642 | GRHL2        | 0.59                | 0.02                      | -0.67                    |
| A_23_P69573   | GUCY1A3      | 1.13                | 0.39                      | -1.57                    |
| A_33_P3378354 | GUCY1B2      | 0.85                | -0.33                     | -0.81                    |
| A_24_P52697   | H19          | 2.83                | 0.05                      | -0.59                    |
| A_33_P3216694 | HIVEP3       | 0.97                | 0.17                      | -0.90                    |
| A_33_P3324206 | HR           | 0.74                | 0.21                      | -1.40                    |
| A_23_P57658   | HRASLS       | 0.88                | -0.20                     | -0.60                    |
| A_33_P3270776 | HTRA3        | 1.43                | -0.13                     | -0.71                    |
| A_24_P304423  | IGF1         | 2.31                | -0.09                     | -0.59                    |
| A_23_P501713  | IL1F10       | 1.59                | 0.09                      | -1.63                    |
| A_33_P3221234 | IPP          | 1.10                | 0.01                      | -1.10                    |



**Supplemental Table S5. List of candidate genes of KDM3A-regulation genes only under hypoxia.**

Continued

| ProbeName      | GeneSymbol            | Log <sub>2</sub> FC |                           |                          |
|----------------|-----------------------|---------------------|---------------------------|--------------------------|
|                |                       | hypoxia scr<br>vs.  | normoxia shKDM3A#C<br>vs. | hypoxia shKDM3A#C<br>vs. |
|                |                       | normoxia scr        | normoxia scr              | hypoxia scr              |
| A_23_P312132   | ITGAX                 | 1.78                | -0.06                     | -0.61                    |
| A_23_P430411   | ITGB2                 | 0.61                | 0.31                      | -0.67                    |
| A_23_P111978   | KCNK9                 | 1.15                | -0.39                     | -1.26                    |
| A_33_P3281606  | KCNT1                 | 2.12                | -0.19                     | -0.64                    |
| A_23_P218025   | KIF5A                 | 1.28                | -0.02                     | -0.85                    |
| A_24_P288298   | KIR2DL4               | 0.65                | 0.37                      | -0.79                    |
| A_23_P363769   | KRT86                 | 0.65                | -0.21                     | -0.63                    |
| A_32_P481377   | KRTAP11-1             | 0.69                | 0.36                      | -1.56                    |
| A_24_P314534   | KRTAP13-2             | 0.90                | -0.52                     | -1.61                    |
| A_23_P32175    | LHX6                  | 1.11                | -0.29                     | -0.78                    |
| A_23_P165921   | LINC00029             | 0.89                | 0.47                      | -1.43                    |
| A_23_P401024   | LINC00304             | 1.04                | -0.23                     | -0.61                    |
| A_33_P3299165  | LINC00544             | 0.96                | 0.49                      | -2.12                    |
| A_32_P479743   | LINC00593             | 0.74                | 0.67                      | -1.00                    |
| A_19_P00320275 | LINC00632             | 1.43                | -0.11                     | -1.17                    |
| A_21_P0010308  | LINC00649             | 0.91                | 0.06                      | -0.62                    |
| A_21_P0012372  | LINC00693             | 0.62                | 0.41                      | -0.92                    |
| A_19_P00319765 | LINC00870             | 1.04                | 0.39                      | -1.42                    |
| A_21_P0012542  | LINC00877             | 2.36                | 0.27                      | -1.00                    |
| A_23_P302302   | LINC00917             | 1.23                | 0.01                      | -1.15                    |
| A_21_P0000606  | LINC00927             | 0.81                | 0.25                      | -1.28                    |
| A_21_P0005443  | LINC00996             | 1.68                | -0.26                     | -0.62                    |
| A_33_P3714477  | LINC00996             | 1.03                | 0.20                      | -0.68                    |
| A_19_P00319335 | LINC01094             | 0.70                | -0.03                     | -0.72                    |
| A_21_P0010511  | LINC01134             | 0.77                | 0.33                      | -0.59                    |
| A_33_P3861634  | LINC01305             | 0.84                | 0.62                      | -0.74                    |
| A_21_P0013404  | LINC01393             | 0.70                | -0.32                     | -0.70                    |
| A_33_P3883985  | LMF1                  | 1.65                | -0.01                     | -0.69                    |
| A_21_P0009252  | lnc-ABI3-1            | 0.87                | 0.04                      | -1.06                    |
| A_21_P0002696  | lnc-AC131097.4.1-3    | 0.90                | -0.31                     | -1.52                    |
| A_21_P0006109  | lnc-ANGPTL2-2         | 0.60                | -1.36                     | -1.61                    |
| A_33_P3774867  | lnc-AP002478.1-1      | 0.71                | -0.01                     | -0.92                    |
| A_21_P0005248  | lnc-ASB4-3            | 0.96                | 0.31                      | -0.91                    |
| A_21_P0006478  | lnc-ASMT-5            | 0.63                | -0.51                     | -0.63                    |
| A_21_P0004270  | lnc-ATG10-1           | 0.74                | -0.32                     | -0.87                    |
| A_19_P00319276 | lnc-BMP7-2            | 0.61                | 0.02                      | -0.59                    |
| A_21_P0001300  | lnc-BSND-1            | 0.77                | 0.12                      | -0.98                    |
| A_21_P0004861  | lnc-BTN1A1-1          | 2.01                | -0.13                     | -1.99                    |
| A_21_P0001616  | lnc-C1orf133-1        | 0.59                | 0.40                      | -0.76                    |
| A_21_P0007507  | lnc-C1QL4-3           | 1.10                | 0.59                      | -1.29                    |
| A_21_P0010098  | lnc-C20orf166-2       | 0.62                | -0.13                     | -0.62                    |
| A_21_P0005692  | lnc-C8orf4-1          | 1.17                | 0.57                      | -0.64                    |
| A_21_P0006366  | lnc-C9orf91-1         | 0.66                | -0.26                     | -0.84                    |
| A_21_P0006014  | lnc-CBWD3-1           | 0.68                | -0.26                     | -1.29                    |
| A_21_P0005160  | lnc-CCHCR1-1          | 0.64                | 0.07                      | -0.82                    |
| A_21_P0005109  | lnc-CD83-2            | 0.68                | -1.14                     | -1.67                    |
| A_33_P3631491  | lnc-CECR2-1           | 1.35                | 0.12                      | -1.73                    |
| A_21_P0009134  | lnc-CLEC18B-1         | 1.18                | 0.20                      | -0.89                    |
| A_21_P0008539  | lnc-CTD-2014B16.3.1-1 | 1.23                | 0.15                      | -1.39                    |
| A_21_P0009375  | lnc-CYB5D2-1          | 1.09                | -0.15                     | -1.17                    |
| A_21_P0005097  | lnc-DLL1-3            | 1.37                | 0.62                      | -1.23                    |
| A_21_P0001751  | lnc-FAIM3-2           | 0.91                | -1.13                     | -1.71                    |
| A_21_P0014229  | lnc-FAM125B-3         | 0.89                | 0.16                      | -0.92                    |
| A_21_P0009346  | lnc-GNA13-1           | 1.22                | 0.29                      | -0.59                    |
| A_21_P0005195  | lnc-GNB2-1            | 0.75                | 0.22                      | -0.89                    |
| A_21_P0010068  | lnc-HRH3-1            | 0.76                | 0.36                      | -1.02                    |
| A_21_P0008137  | lnc-KATNAL1-3         | 1.42                | -0.26                     | -0.63                    |
| A_21_P0005611  | lnc-KIAA1147-3        | 0.81                | 0.28                      | -0.75                    |
| A_21_P0003161  | lnc-LRRC58-1          | 1.09                | 0.73                      | -0.91                    |
| A_21_P0001337  | lnc-LRRC8D-2          | 1.02                | 0.05                      | -0.63                    |
| A_19_P00318443 | lnc-MAGI2-1           | 0.69                | 0.38                      | -0.63                    |
| A_21_P0009268  | lnc-MAP2K6-2          | 1.26                | -0.53                     | -0.84                    |
| A_21_P0001407  | lnc-MFSD4-2           | 0.60                | -0.73                     | -1.65                    |
| A_21_P0005027  | lnc-MRPS18A-1         | 0.95                | 0.06                      | -0.83                    |
| A_21_P0006742  | lnc-MTPAP-2           | 1.05                | 0.02                      | -0.78                    |

**Supplemental Table S5. List of candidate genes of KDM3A-regulation genes only under hypoxia.**

Continued

| ProbeName      | GeneSymbol          | Log <sub>2</sub> FC                |   |   |
|----------------|---------------------|------------------------------------|---|---|
|                |                     | hypoxia scr<br>vs.<br>normoxia scr | normoxia shKDM3A#C<br>vs.<br>normoxia scr | hypoxia shKDM3A#C<br>vs.<br>hypoxia scr |
| A_21_P0008435  | lnc-NEMF-1          | 0.62                               | -0.12                                     | -0.61                                   |
| A_21_P0001579  | lnc-OTUD7B-1        | 0.90                               | 0.08                                      | -0.63                                   |
| A_21_P0008444  | lnc-OTX2-3          | 1.25                               | 0.35                                      | -0.98                                   |
| A_21_P0008799  | lnc-PGPEP1L-1       | 1.05                               | -0.34                                     | -2.02                                   |
| A_33_P3318963  | lnc-POLR2F-1        | 1.69                               | 0.25                                      | -1.76                                   |
| A_21_P0010127  | lnc-PPP1R3D-2       | 0.92                               | 0.34                                      | -0.93                                   |
| A_21_P0008920  | lnc-PRR14-1         | 0.69                               | 0.81                                      | -0.61                                   |
| A_21_P0005143  | lnc-QKI-2           | 1.94                               | -0.06                                     | -1.87                                   |
| A_21_P0003632  | lnc-RAP1GDS1-3      | 0.63                               | 0.04                                      | -0.63                                   |
| A_21_P0002981  | lnc-ROBO2-1         | 1.50                               | 0.21                                      | -0.69                                   |
| A_19_P00320144 | lnc-RP3-368B9.1.1-1 | 1.39                               | 0.87                                      | -0.72                                   |
| A_21_P0001348  | lnc-RWDD3-2         | 1.07                               | 0.64                                      | -0.90                                   |
| A_21_P0001449  | lnc-SCCPDH-1        | 0.91                               | -0.09                                     | -1.12                                   |
| A_21_P0009279  | lnc-SEPT9-3         | 1.80                               | 0.22                                      | -1.87                                   |
| A_21_P0002494  | lnc-SLC35F5-2       | 1.32                               | -0.57                                     | -1.08                                   |
| A_21_P0001727  | lnc-SLC6A9-1        | 0.98                               | 0.73                                      | -0.94                                   |
| A_21_P0002156  | lnc-SNTG2-4         | 0.83                               | 0.00                                      | -0.93                                   |
| A_21_P0010928  | lnc-SORCS3-7        | 1.14                               | -0.19                                     | -1.27                                   |
| A_21_P0008124  | lnc-SPACA7-2        | 0.93                               | 1.35                                      | -0.93                                   |
| A_21_P0005392  | lnc-STAG3L4-1       | 1.12                               | -0.67                                     | -1.12                                   |
| A_21_P0010120  | lnc-STAU1-1         | 0.73                               | -0.02                                     | -0.83                                   |
| A_21_P0006915  | lnc-TCF7L2-1        | 0.72                               | 0.10                                      | -0.82                                   |
| A_21_P0001989  | lnc-TMEM18-11       | 0.65                               | 0.05                                      | -0.82                                   |
| A_21_P0005075  | lnc-TMEM242-1       | 0.79                               | 0.22                                      | -1.98                                   |
| A_33_P3354214  | lnc-TNFRSF14-2      | 1.84                               | 0.29                                      | -0.63                                   |
| A_21_P0002930  | lnc-TSEN2-1         | 0.84                               | 0.01                                      | -0.62                                   |
| A_21_P0002284  | lnc-TSN-6           | 1.50                               | -0.05                                     | -1.53                                   |
| A_21_P0008980  | lnc-WFDC1-1         | 0.74                               | -0.30                                     | -0.64                                   |
| A_21_P0005680  | lnc-WRN-4           | 1.25                               | -0.20                                     | -1.21                                   |
| A_21_P0003874  | lnc-ZFP42-2         | 1.05                               | 0.26                                      | -0.85                                   |
| A_21_P0009053  | lnc-ZNF23-2         | 0.95                               | 0.33                                      | -1.10                                   |
| A_21_P0009662  | lnc-ZNF507-4        | 1.62                               | 0.01                                      | -1.25                                   |
| A_33_P3304883  | LOC100131372        | 1.08                               | -0.06                                     | -1.27                                   |
| A_33_P3346807  | LOC100131581        | 0.60                               | 0.16                                      | -1.01                                   |
| A_21_P0000569  | LOC100303749        | 1.06                               | 0.45                                      | -1.10                                   |
| A_19_P00803441 | LOC100499194        | 0.98                               | 0.22                                      | -0.62                                   |
| A_21_P0007569  | LOC100506869        | 0.66                               | 0.04                                      | -1.17                                   |
| A_21_P0005202  | LOC100507642        | 0.73                               | 0.66                                      | -0.77                                   |
| A_21_P0013968  | LOC100507656        | 0.77                               | -0.49                                     | -0.80                                   |
| A_33_P3286929  | LOC100653133        | 0.95                               | 0.29                                      | -0.72                                   |
| A_21_P0003419  | LOC100996286        | 0.73                               | -0.43                                     | -1.07                                   |
| A_21_P0010508  | LOC100996583        | 2.26                               | 0.11                                      | -0.70                                   |
| A_33_P3287862  | LOC101060524        | 0.60                               | 0.31                                      | -0.99                                   |
| A_19_P00321360 | LOC101927136        | 0.94                               | 0.51                                      | -0.67                                   |
| A_21_P0002688  | LOC101927252        | 0.83                               | 0.03                                      | -0.71                                   |
| A_21_P0012411  | LOC101928430        | 0.78                               | 0.16                                      | -0.80                                   |
| A_19_P00809030 | LOC101929378        | 1.02                               | -1.00                                     | -1.16                                   |
| A_21_P0008768  | LOC101929641        | 1.17                               | -0.30                                     | -0.68                                   |
| A_33_P3372600  | LOC102723640        | 1.70                               | 0.20                                      | -1.51                                   |
| A_21_P0013050  | LOC102724511        | 0.65                               | 0.12                                      | -0.72                                   |
| A_21_P0012769  | LOC102724794        | 0.94                               | -0.59                                     | -1.24                                   |
| A_33_P3649472  | LOC283856           | 1.15                               | -0.07                                     | -0.76                                   |
| A_33_P3429242  | LOC339988           | 1.46                               | -0.03                                     | -0.86                                   |
| A_33_P3425296  | LRRC37A6P           | 0.59                               | 0.07                                      | -0.93                                   |
| A_33_P3227482  | LRRC37A8P           | 1.57                               | 0.79                                      | -0.97                                   |
| A_23_P166848   | LTF                 | 0.69                               | -0.51                                     | -0.87                                   |
| A_23_P53884    | MAB21L1             | 0.61                               | 0.03                                      | -0.61                                   |
| A_23_P397376   | MAF                 | 0.94                               | 0.29                                      | -0.68                                   |
| A_23_P370054   | MAGEB18             | 0.84                               | 0.09                                      | -1.30                                   |
| A_19_P00324839 | MALAT1              | 0.65                               | -0.17                                     | -0.77                                   |
| A_21_P0014031  | MAPT                | 0.74                               | -0.49                                     | -0.70                                   |
| A_33_P3335735  | MAPT-AS1            | 1.34                               | -0.25                                     | -1.39                                   |
| A_33_P3888629  | MECOM               | 1.09                               | -0.21                                     | -0.84                                   |
| A_23_P138105   | MED18               | 0.85                               | 0.20                                      | -0.98                                   |
| A_21_P0000117  | MID1                | 0.95                               | 0.24                                      | -1.18                                   |

**Supplemental Table S5. List of candidate genes of KDM3A-regulation genes only under hypoxia.**

Continued

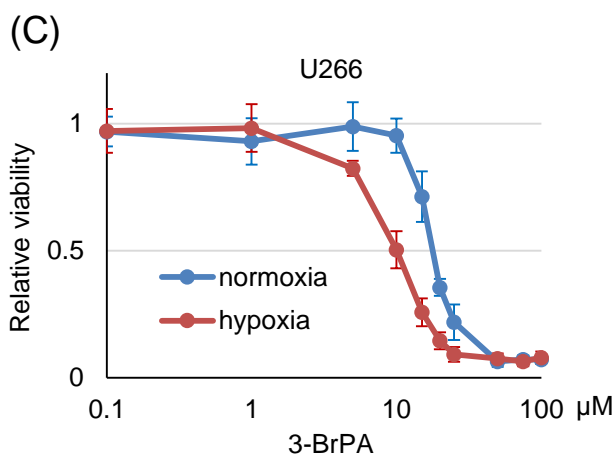
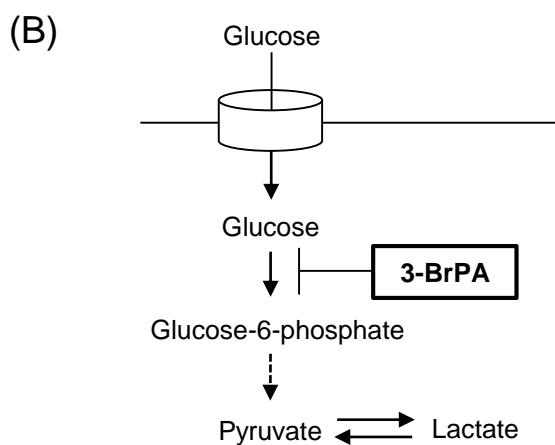
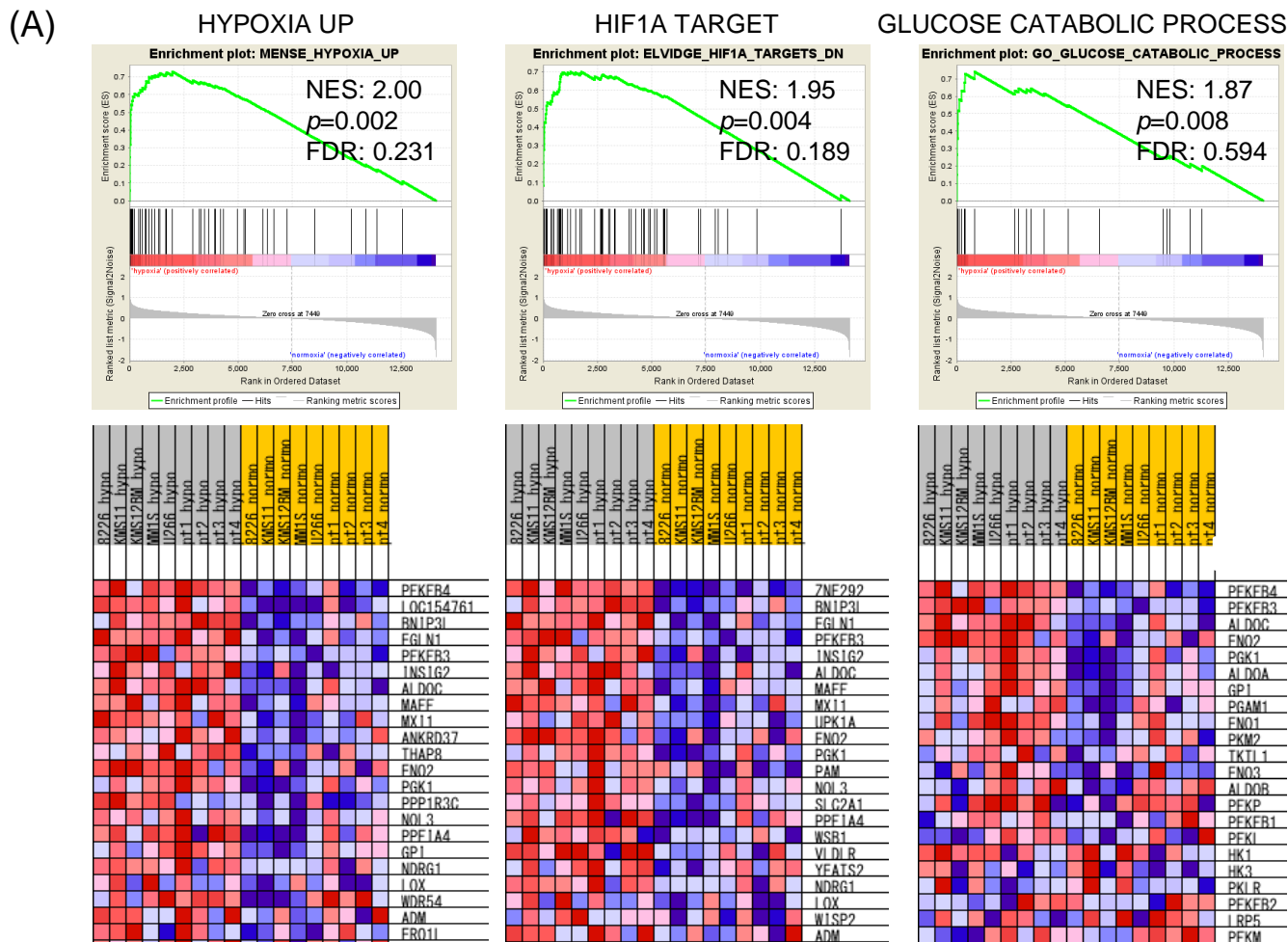
| ProbeName      | GeneSymbol    | Log <sub>2</sub> FC |                           |                          |
|----------------|---------------|---------------------|---------------------------|--------------------------|
|                |               | hypoxia scr<br>vs.  | normoxia shKDM3A#C<br>vs. | hypoxia shKDM3A#C<br>vs. |
|                |               | normoxia scr        | normoxia scr              | hypoxia scr              |
| A_24_P165205   | MORN1         | 1.07                | -0.29                     | -1.64                    |
| A_24_P160413   | MTMR9LP       | 0.84                | -0.12                     | -1.15                    |
| A_33_P3331752  | MUC3A         | 1.15                | -0.40                     | -1.11                    |
| A_23_P148737   | MYBPH         | 1.78                | -0.14                     | -0.62                    |
| A_21_P0002574  | MYCNUT        | 0.67                | 0.20                      | -1.57                    |
| A_23_P86411    | MYO3A         | 1.07                | -0.01                     | -1.82                    |
| A_33_P3788355  | NAV2-AS4      | 1.01                | 0.70                      | -1.52                    |
| A_19_P00320362 | NBAT1         | 0.63                | -0.16                     | -1.35                    |
| A_21_P0005721  | NCRNA00249    | 0.66                | 0.35                      | -1.49                    |
| A_33_P3884230  | NFIX          | 1.97                | -0.13                     | -0.96                    |
| A_23_P340019   | NLRC3         | 1.27                | -0.17                     | -0.61                    |
| A_23_P254353   | NOXA1         | 0.87                | 0.22                      | -0.59                    |
| A_33_P3297415  | NRP2          | 1.18                | 0.31                      | -0.92                    |
| A_23_P112327   | OBP2A         | 0.78                | -0.05                     | -0.98                    |
| A_33_P3383205  | OK/SW-CL.58   | 1.07                | 0.29                      | -1.83                    |
| A_23_P345564   | OPRL1         | 1.28                | 0.51                      | -1.17                    |
| A_23_P130281   | OR1A2         | 1.19                | -0.07                     | -0.70                    |
| A_33_P3365077  | OR2G2         | 0.71                | 0.00                      | -0.61                    |
| A_23_P372848   | P2RX1         | 0.89                | 0.27                      | -1.03                    |
| A_21_P0006426  | PABPC1L2B-AS1 | 0.97                | 0.05                      | -0.72                    |
| A_33_P3367924  | PABPN1L       | 1.36                | -0.18                     | -0.69                    |
| A_19_P00320718 | PCAT19        | 0.95                | 0.13                      | -1.12                    |
| A_23_P121851   | PCDHB15       | 1.16                | 0.24                      | -1.26                    |
| A_23_P151907   | PCSK6         | 1.20                | 0.34                      | -0.97                    |
| A_33_P3419383  | PDLIM3        | 1.12                | 0.29                      | -0.87                    |
| A_33_P3360412  | PIGQ          | 1.67                | 0.28                      | -0.73                    |
| A_23_P50646    | PINLYP        | 1.36                | -0.05                     | -1.85                    |
| A_32_P112493   | PKDCC         | 0.86                | -0.06                     | -0.60                    |
| A_23_P88767    | PLA2G10       | 1.16                | 0.20                      | -1.08                    |
| A_23_P17821    | PLA2G3        | 0.89                | 0.05                      | -0.64                    |
| A_23_P50508    | PLA2G4C       | 0.84                | 0.58                      | -1.24                    |
| A_21_P0014399  | PLCG1-AS1     | 1.64                | 0.29                      | -0.59                    |
| A_33_P3407643  | PLET1         | 0.83                | 0.22                      | -0.74                    |
| A_33_P3296366  | PODXL2        | 0.91                | 0.32                      | -0.81                    |
| A_33_P3272568  | PRDX4         | 1.11                | -0.22                     | -0.73                    |
| A_23_P1473     | PRF1          | 1.23                | -0.43                     | -2.55                    |
| A_23_P310274   | PRSS3P2       | 0.61                | 0.06                      | -0.74                    |
| A_33_P3259373  | PWAR1         | 1.72                | -0.34                     | -1.43                    |
| A_23_P396062   | RAB40C        | 1.10                | 0.33                      | -0.76                    |
| A_21_P0013163  | RAET1K        | 1.84                | -0.04                     | -1.09                    |
| A_33_P3230818  | RCAN2         | 0.83                | -0.03                     | -1.81                    |
| A_21_P0004969  | RPS6KA2-AS1   | 1.74                | 0.57                      | -1.39                    |
| A_24_P65941    | RUNX1-IT1     | 1.42                | -0.21                     | -0.59                    |
| A_33_P3238410  | SBF1          | 1.34                | 0.16                      | -1.63                    |
| A_33_P3241884  | SDC3          | 0.71                | 0.10                      | -0.67                    |
| A_33_P3358745  | SEPP1         | 2.14                | 0.43                      | -2.22                    |
| A_23_P207003   | SEPT4         | 1.73                | 0.24                      | -1.16                    |
| A_23_P44663    | SERPINA2      | 1.91                | 0.49                      | -2.92                    |
| A_32_P107617   | SFTPD         | 0.66                | 0.11                      | -1.16                    |
| A_23_P47199    | SLC22A11      | 1.54                | 1.31                      | -1.91                    |
| A_21_P0011492  | SLC22A31      | 0.83                | 0.29                      | -0.63                    |
| A_23_P168551   | SLC29A4       | 0.65                | 0.34                      | -1.19                    |
| A_21_P0006388  | SMC2-AS1      | 0.88                | -0.03                     | -0.73                    |
| A_33_P3263497  | SNED1         | 0.85                | 0.54                      | -0.70                    |
| A_23_P319783   | SPAG17        | 0.59                | -0.36                     | -0.66                    |
| A_33_P3319957  | SPATA1        | 0.81                | 0.15                      | -0.63                    |
| A_21_P0014795  | SPATA8-AS1    | 0.71                | 0.28                      | -1.63                    |
| A_33_P3401459  | SPTBN4        | 0.73                | 0.30                      | -0.71                    |
| A_33_P3393931  | SSBP3-AS1     | 0.74                | -0.23                     | -0.94                    |
| A_24_P64329    | STK32C        | 1.35                | 0.44                      | -1.03                    |
| A_23_P145711   | SUGCT         | 0.73                | -0.87                     | -1.32                    |
| A_23_P35349    | SVIL          | 0.92                | -0.28                     | -0.90                    |
| A_23_P211522   | SYNGR1        | 1.63                | 0.06                      | -1.56                    |
| A_23_P252082   | TMEM176A      | 2.09                | 0.45                      | -2.05                    |

**Supplemental Table S5. List of candidate genes of KDM3A-regulation genes only under hypoxia.**

Continued

| ProbeName      | GeneSymbol     | Log <sub>2</sub> FC                |   |   |
|----------------|----------------|------------------------------------|---|---|
|                |                | hypoxia scr<br>vs.<br>normoxia scr | normoxia shKDM3A#C<br>vs.<br>normoxia scr | hypoxia shKDM3A#C<br>vs.<br>hypoxia scr |
| A_21_P0000113  | TNFSF10        | 1.52                               | -0.25                                     | -1.03                                   |
| A_24_P237036   | TNFSF14        | 0.96                               | 0.56                                      | -0.73                                   |
| A_33_P3286846  | TP53TG3C       | 0.65                               | 0.21                                      | -1.23                                   |
| A_33_P3296831  | TP73           | 0.64                               | 0.07                                      | -0.76                                   |
| A_33_P3371999  | TPPP           | 1.54                               | -0.48                                     | -0.61                                   |
| A_33_P3235048  | TRIM77         | 0.83                               | 0.68                                      | -0.90                                   |
| A_33_P3354678  | TRIM78P        | 0.69                               | 0.28                                      | -0.60                                   |
| A_33_P3314952  | TRPV1          | 0.81                               | 0.11                                      | -0.61                                   |
| A_33_P3655775  | TTC34          | 0.79                               | 0.03                                      | -0.64                                   |
| A_33_P3416171  | TUNAR          | 1.08                               | 0.24                                      | -1.34                                   |
| A_33_P3276678  | VSX1           | 0.77                               | -0.13                                     | -1.08                                   |
| A_23_P338410   | WFDC9          | 1.41                               | -0.55                                     | -0.87                                   |
| A_33_P3605352  | WWTR1          | 2.12                               | -0.06                                     | -2.34                                   |
| A_21_P0010607  | XLOC_I2_000866 | 0.65                               | 0.40                                      | -0.94                                   |
| A_21_P0010611  | XLOC_I2_000900 | 0.93                               | -0.12                                     | -0.89                                   |
| A_21_P0010801  | XLOC_I2_001421 | 1.12                               | 0.16                                      | -1.80                                   |
| A_21_P0010858  | XLOC_I2_001875 | 1.03                               | -0.26                                     | -0.66                                   |
| A_21_P0010868  | XLOC_I2_001945 | 0.60                               | -0.10                                     | -0.73                                   |
| A_21_P0011432  | XLOC_I2_005187 | 0.64                               | 0.14                                      | -0.59                                   |
| A_21_P0011547  | XLOC_I2_005814 | 0.61                               | 0.46                                      | -1.33                                   |
| A_19_P00808794 | XLOC_I2_008221 | 0.85                               | 1.93                                      | -0.73                                   |
| A_21_P0011955  | XLOC_I2_008221 | 0.75                               | -0.10                                     | -0.96                                   |
| A_21_P0012385  | XLOC_I2_009804 | 1.14                               | -0.17                                     | -0.83                                   |
| A_21_P0012837  | XLOC_I2_011669 | 1.12                               | 0.28                                      | -0.76                                   |
| A_21_P0013038  | XLOC_I2_012727 | 1.91                               | 0.01                                      | -1.68                                   |
| A_21_P0013249  | XLOC_I2_013485 | 0.60                               | 0.34                                      | -0.91                                   |
| A_21_P0013265  | XLOC_I2_013583 | 1.32                               | 0.18                                      | -2.21                                   |
| A_21_P0013819  | XLOC_I2_015760 | 0.68                               | -0.08                                     | -1.01                                   |
| A_24_P71700    | ZBTB47         | 1.09                               | 0.63                                      | -0.79                                   |
| A_21_P0000780  | ZNF345         | 1.39                               | 0.31                                      | -1.03                                   |
| A_33_P3225690  | ZNF516         | 0.75                               | -0.15                                     | -0.61                                   |

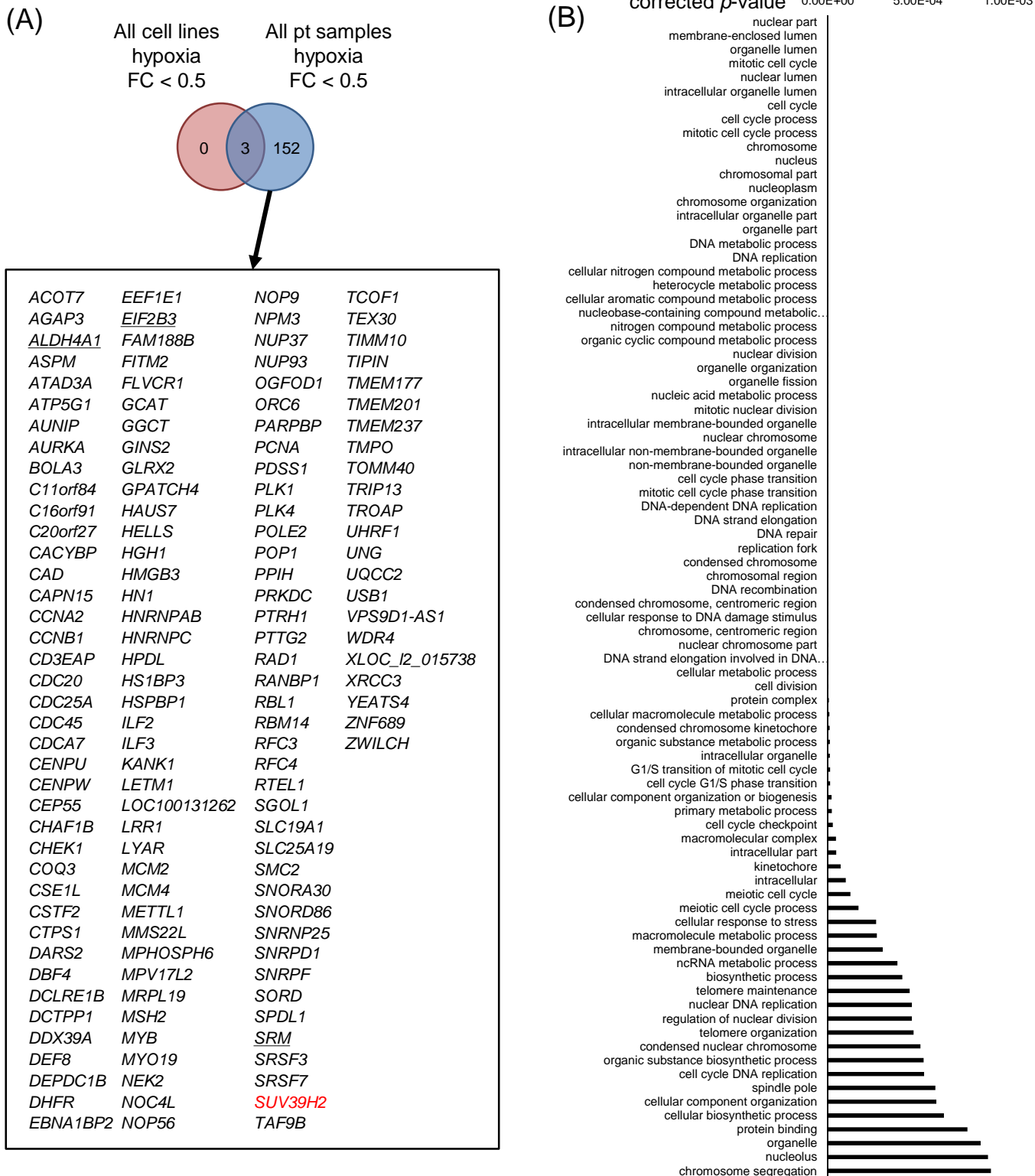
# Supplemental Figure S1



## Supplemental Figure S1. The survival of myeloma cells in a hypoxic environment may depend on glycolysis.

(A) Gene Set Enrichment Analysis (GSEA) plots of hypoxia and HIF-1 $\alpha$  targets, and glucose catabolic process based on the gene expression profiles of five MM cell lines (RPMI-8226, KMS-11, KMS-12-BM, MM.1S, and U266) and MM samples ( $n = 4$ ) cultured under normoxia or hypoxia (1%  $\text{O}_2$ ) for 48 hours. NES, normalized enrichment score. P-values refer to the nominal p-values generated after 1,000 permutations. FDR, false discovery rate. (B) A schematic diagram of glycolytic pathway. 3-bromopyruvic acid (3-BrPA), a hexokinase II inhibitor, inhibits glycolysis. (C) XTT assay of U266 cells treated with 3-BrPA (0.1~100  $\mu\text{M}$ ) under normoxia (blue line) or hypoxia (red line, 1%  $\text{O}_2$ ) for 48 hours. Bars represent mean  $\pm$  95% CI of three independent experiments.

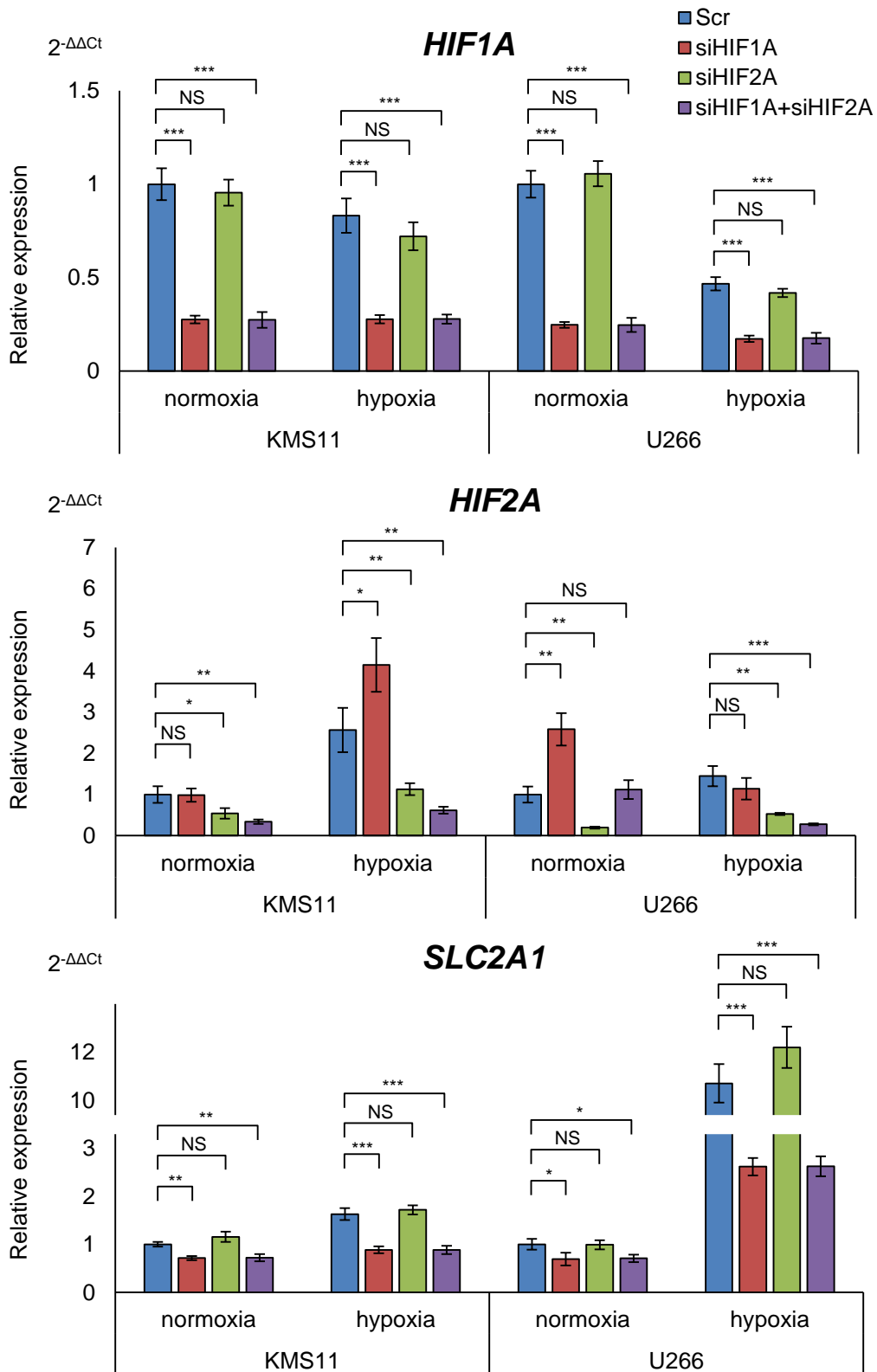
## Supplemental Figure S2



### Supplemental Figure S2. Cell cycle-associated genes are downregulated under hypoxia in MM.

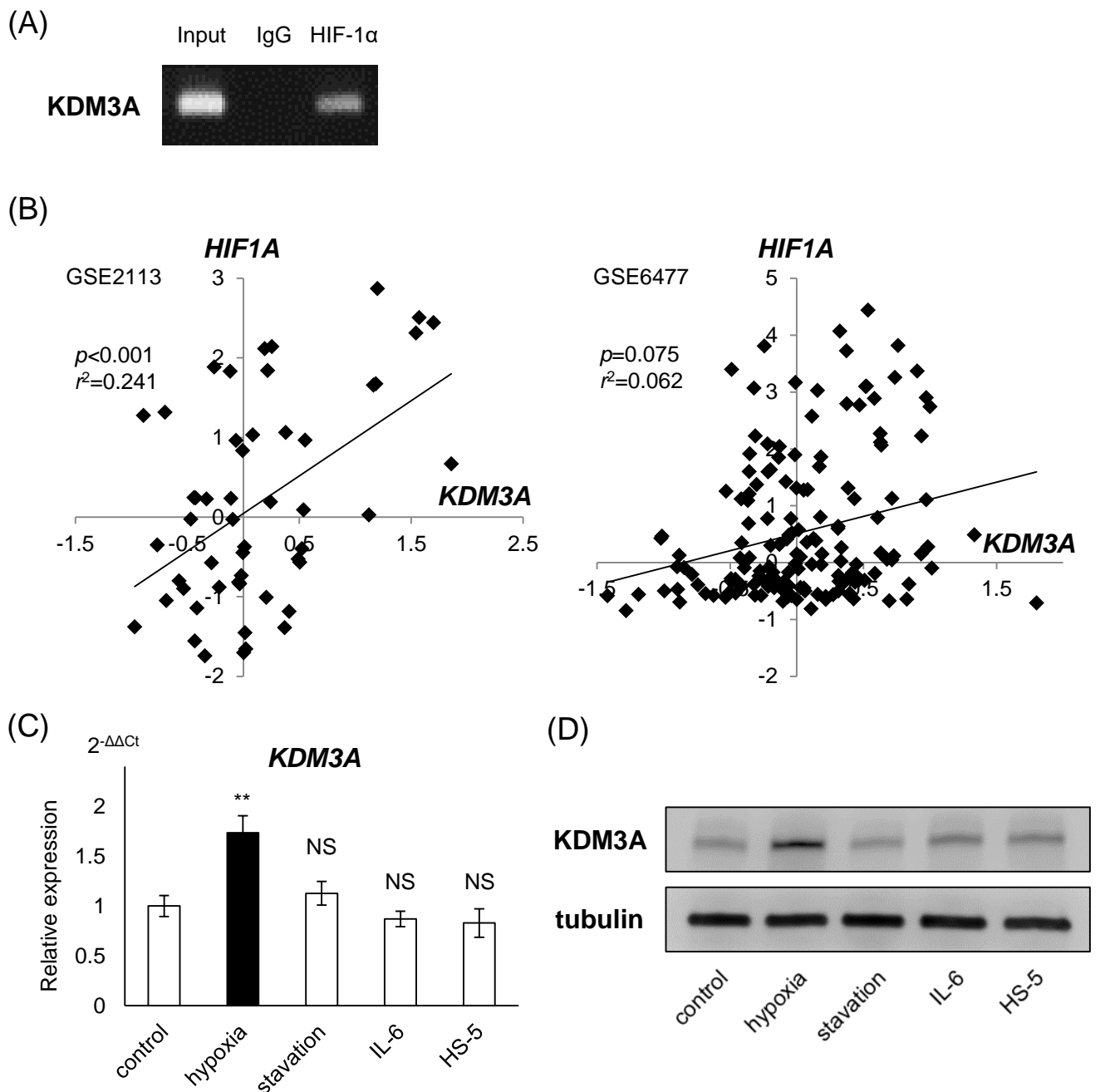
(A) Downregulated genes (normoxia vs. hypoxia expression, fold change < 0.5) in five cell lines (RPMI-8226, KMS-11, KMS-12-BM, MM.1S, and U266) and MM patient samples (n = 4). Upper panel: diagram showing number of downregulated probes. Lower panel: gene symbols of downregulated genes. Red gene: H3K9 methylase. Underlined genes: commonly downregulated genes in both myeloma cell lines and primary samples. FC: fold change. (B) GO analysis of genes listed in Figure A that are downregulated under hypoxia (FC < 0.5).

Supplemental Figure S3



**Supplemental Figure S3. Graphs show knockdown effects of siHIF1A and/or siHIF2A and SLC2A1(Glut1) expression under normoxia or hypoxia.**

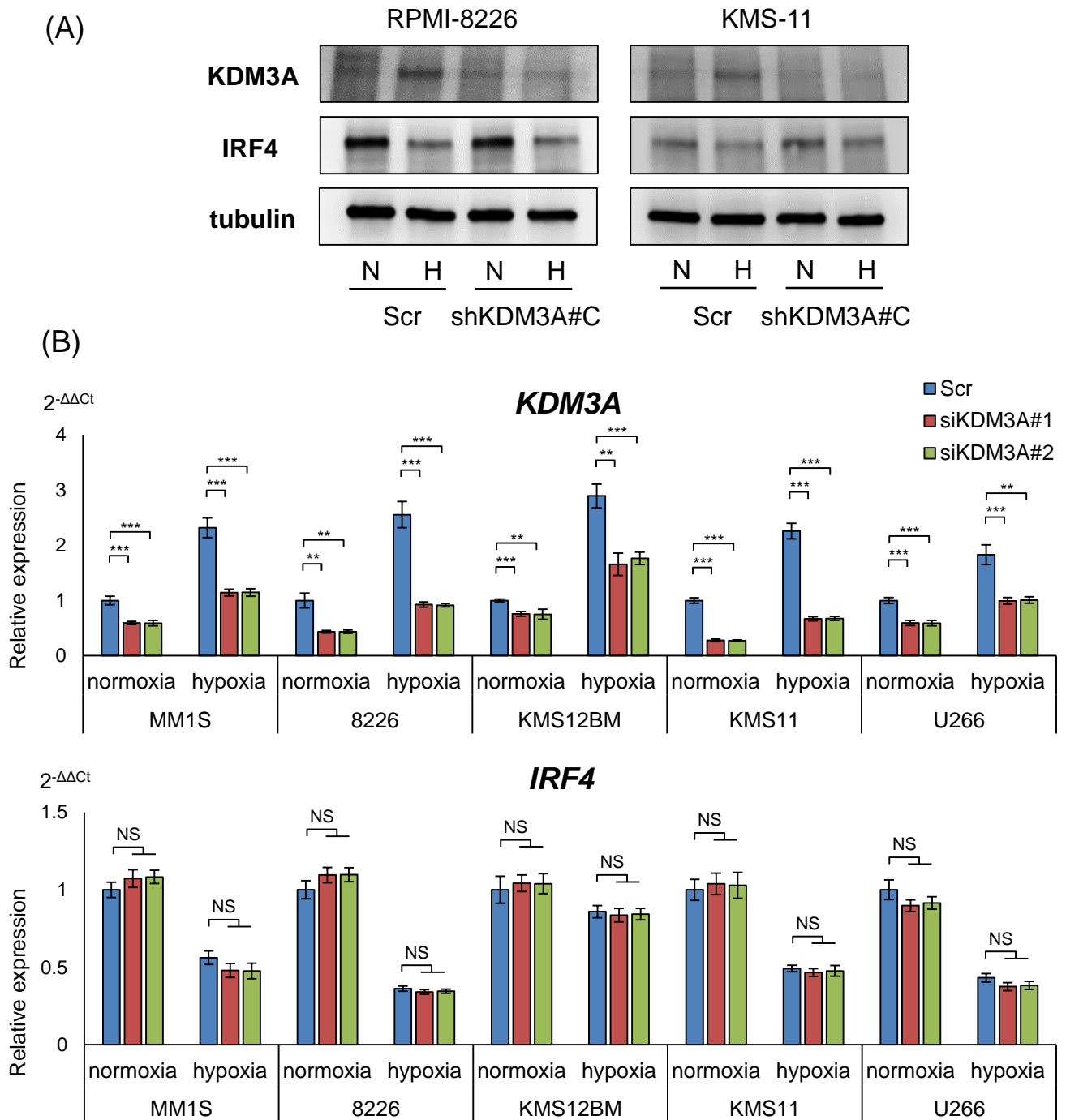
Bars represent mean  $\pm$  95% CI of three independent experiments. Asterisks (\*) indicate statistical significance: \*0.01  $\leq$  P < 0.05; \*\*0.001  $\leq$  P < 0.01; \*\*\*P < 0.001; NS, not significant. Student's *t*-test was used to test for significance.



### Supplemental Figure S4. HIF-1 $\alpha$ regulates KDM3A directory in MM.

(A) Chromatin immunoprecipitation (ChIP) of the *KDM3A* promoter from KMS-11 cells was performed using HIF-1 $\alpha$  antibody. IgG (mouse) was used as negative control, and 10% input chromatin was used as positive control for PCR. (B) Correlation of *KDM3A* with *HIF1A* expressions from the data set GSE2113 and GSE6477.  $r^2$ : correlation coefficient. (C) qRT-PCR of *KDM3A* for U266 cell line cultured under hypoxia (1% O<sub>2</sub>), serum starvation, with recombinant IL-6 (4 ng/mL), co-cultured with HS-5 for 24 hours. Bars represent mean  $\pm$  95% CI of three independent experiments. Asterisks (\*) indicate statistical significance: \*\*0.001  $\leq$  P < 0.01; NS, not significant. Student's *t*-test was used to test for significance. (D) Western blot analysis of *KDM3A* for U266 cell line cultured under hypoxia (1% O<sub>2</sub>), serum starvation, with recombinant IL-6 (4 ng/mL), co-cultured with HS-5 for 24 hours.

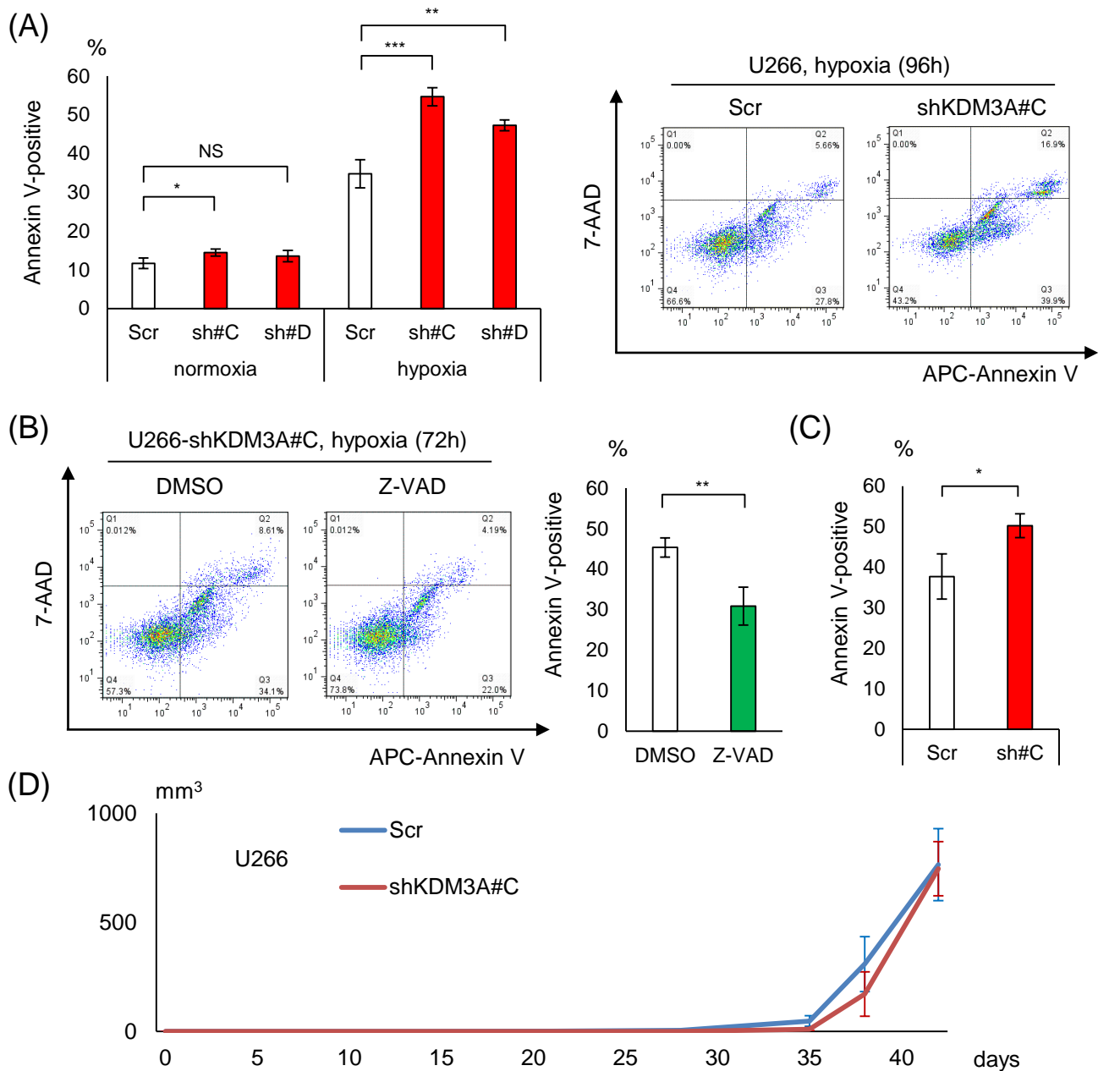




**Supplemental Figure S5. IRF4 expression was not affected by sh/siKDM3A in myeloma cells.**

(A) Western blot analysis of KDM3A and IRF4 for RPMI-8226 and KMS-11 cell lines stably transduced with shKDM3A#C and control scrambled shRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 48 hours. N: normoxia. H: hypoxia. (B) qRT-PCR of *KDM3A* and *IRF4* for five indicated MM cell lines transiently transduced with siKDM3A#1, #2, and control scrambled siRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 48 hours. Bars represent mean ± 95% CI of three independent experiments. Asterisks (\*) indicate statistical significance: \*\*0.001 ≤ P < 0.01; \*\*\*P < 0.001; NS, not significant. Student's *t*-test was used to test for significance.

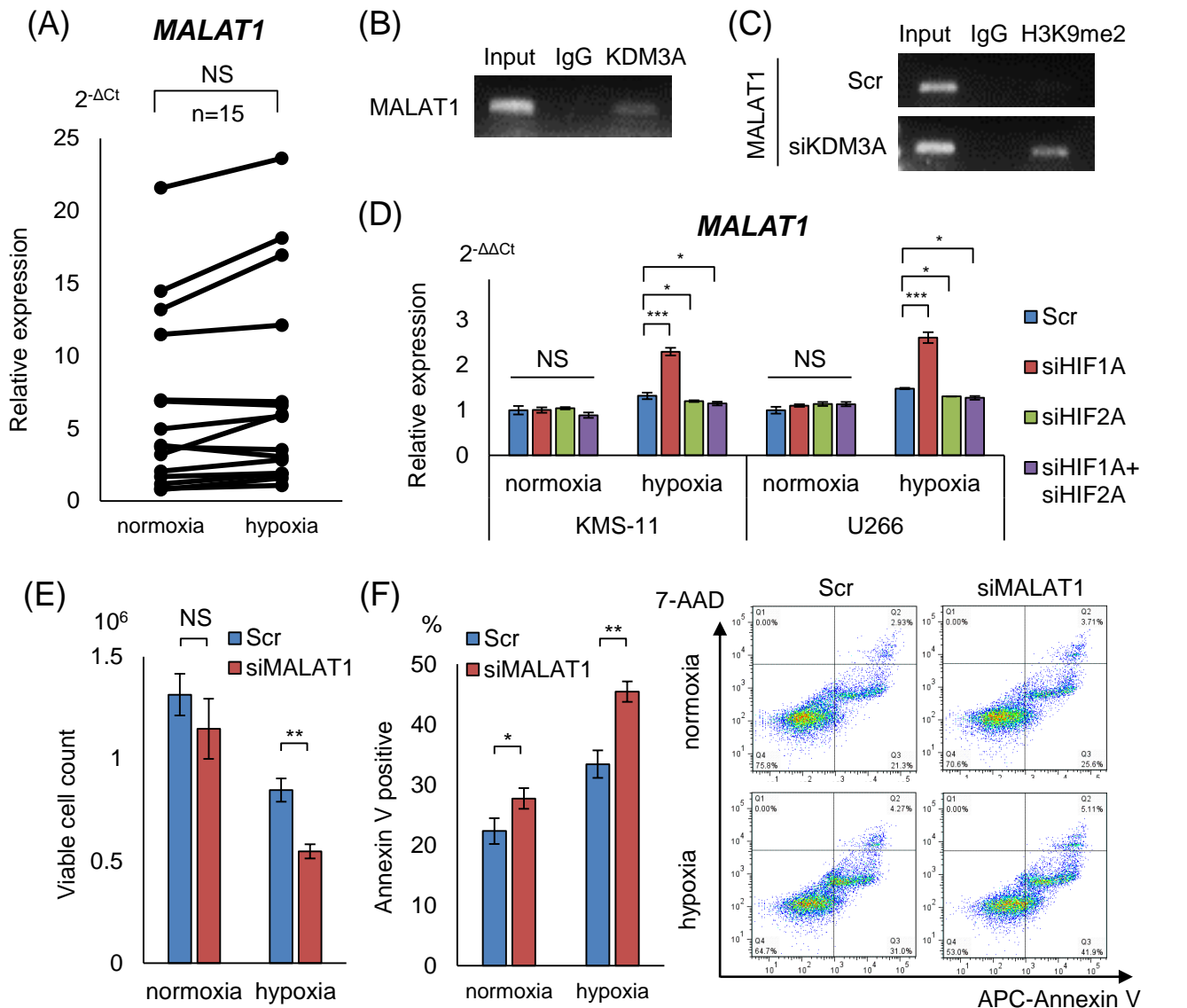
## Supplemental Figure S6



### Supplemental Figure S6. Knockdown of KDM3A leads myeloma cells to induce caspase-dependent apoptosis under chronic hypoxia.

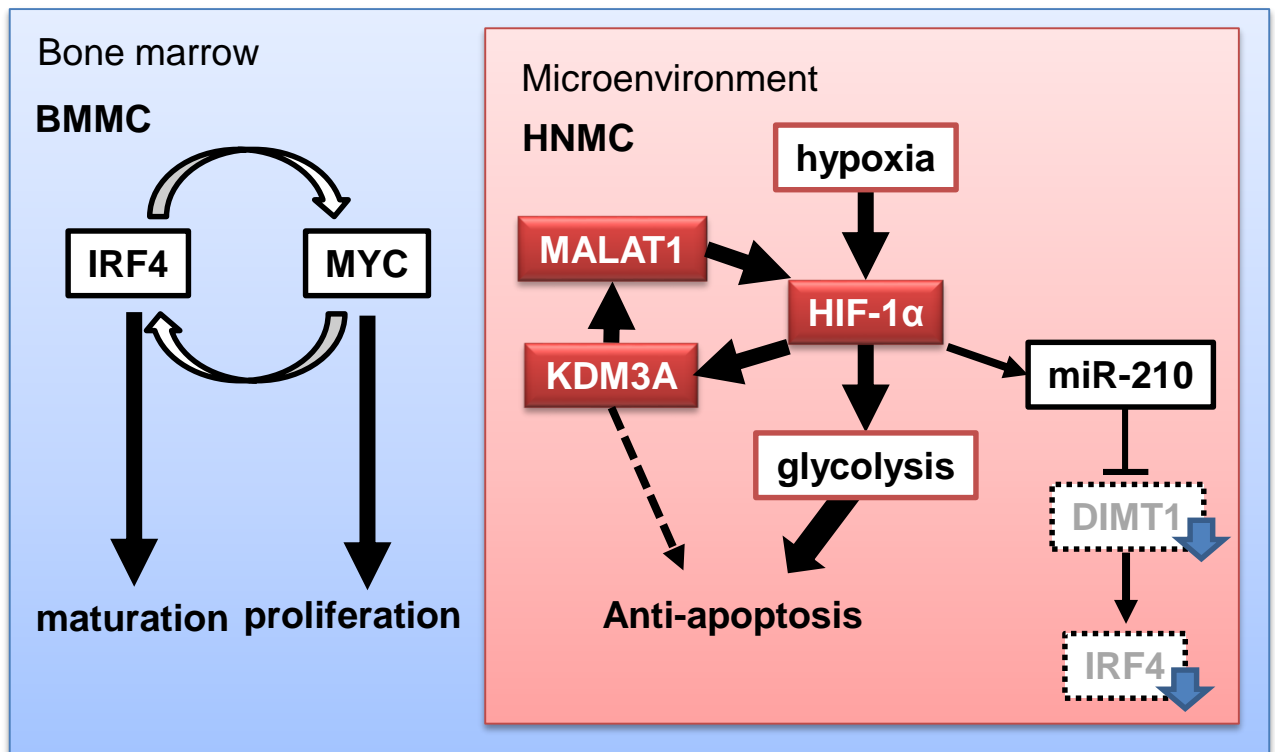
(A) Apoptosis assay in U266 cell line stably transduced with shKDM3A#C, #D, and control scrambled shRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 96 hours. X-axis: Annexin V; Y-axis: 7-AAD. Asterisks (\*) indicate statistical significance: \*0.01 ≤ P < 0.05; \*\*0.001 ≤ P < 0.01; \*\*\*P < 0.001; NS, not significant. Student's *t*-test was used to test for significance. (B) Apoptosis assay in U266 cell line stably transduced with shKDM3A#C and control scrambled shRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 72 hours with or without Z-VAD, a pan caspase inhibitor. X-axis: Annexin V; Y-axis: 7-AAD. Asterisks (\*) indicate statistical significance: \*\*0.001 ≤ P < 0.01. Student's *t*-test was used to test for significance. (C) Apoptosis assay in RPMI-8226 cell line stably transduced with shKDM3A#C and control scrambled shRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 96 hours. Asterisks (\*) indicate statistical significance: \*0.01 ≤ P < 0.05. Student's *t*-test was used to test for significance. (D) *In vivo* transplantation of U266 cell line stably transduced with shKDM3A#C and control scrambled shRNA (Scr) into NOG mice (n = 6 each). X-axis: day after transplantation. Y-axis: tumor volume (mm<sup>3</sup>, major × minor<sup>2</sup>/2).

## Supplemental Figure S7



### Supplemental Figure S7. Expression of *MALAT1* is maintained independently of HIF-1α and may contribute to survival under hypoxia in MM.

(A) qRT-PCR of *MALAT1* for primary myeloma samples (n = 15) cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 48 hours. Bars represent mean ± 95% CI of three independent experiments. NS, not significant. Paired *t*-test was used to test for significance. (B) Chromatin immunoprecipitation (ChIP) of the *MALAT1* promoter from KMS-11 cells was performed using KDM3A antibody. IgG (mouse) was used as negative control, and 10% input chromatin was used as positive control for PCR. (C) ChIP of the *MALAT1* promoter from KMS-11 cells transiently transfected with siKDM3A#1 or control scrambled siRNA (Scr) and cultured for 72 hours was performed using H3K9me2 antibody. IgG (rabbit) was used as negative control, and 10% input chromatin was used as positive control for PCR. (D) qRT-PCR of *MALAT1* for KMS-11 and U266 cell lines transiently transfected with siHIF1A and/or siHIF2A and control scrambled siRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 48 hours. Bars represent mean ± 95% CI of three independent experiments. Asterisks (\*) indicate statistical significance: \*0.01 ≤ P < 0.05; \*\*\*P < 0.001; NS, not significant. Student's *t*-test was used to test for significance. (E) Cell count of KMS-11 cells transiently transfected with siMALAT1 or control scrambled siRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 72 hours. Cells (0.5 × 10<sup>6</sup>) were cultured at 0 hours. Bars represent mean ± 95% CI of three independent experiments. Asterisks (\*) indicate statistical significance: \*\*0.001 ≤ P < 0.01; NS, not significant. Student's *t*-test was used to test for significance. (F) Apoptosis assay in KMS-11 cell line transiently transfected with siMALAT1 and control scrambled siRNA (Scr) and cultured in normoxia or hypoxia (1% O<sub>2</sub>) for 72 hours. X-axis: Annexin V; Y-axis: 7-AAD. Asterisks (\*) indicate statistical significance: \*0.01 ≤ P < 0.05; \*\*0.001 ≤ P < 0.01. Student's *t*-test was used to test for significance.



**Supplemental Figure S8. Schematic diagram: IRF4, DIMT1, HIF-1 $\alpha$ , KDM3A, and miR-210 have oncogenic roles in MM.**

We define a myeloma cell existing in the hypoxia niche as a "hypoxia niche myeloma cell" (HNMC) and a myeloma cell existing in other bone marrow regions as a "bone marrow myeloma cell" (BMMC).