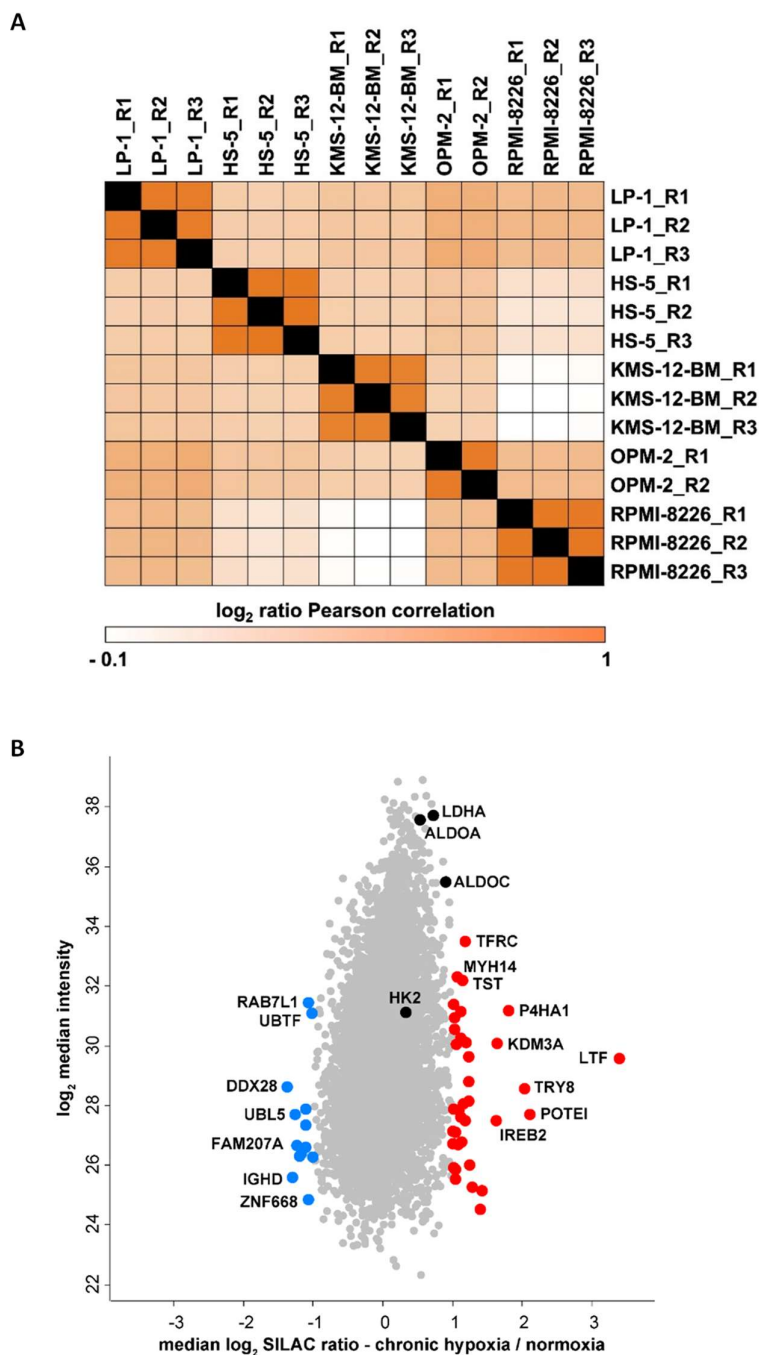
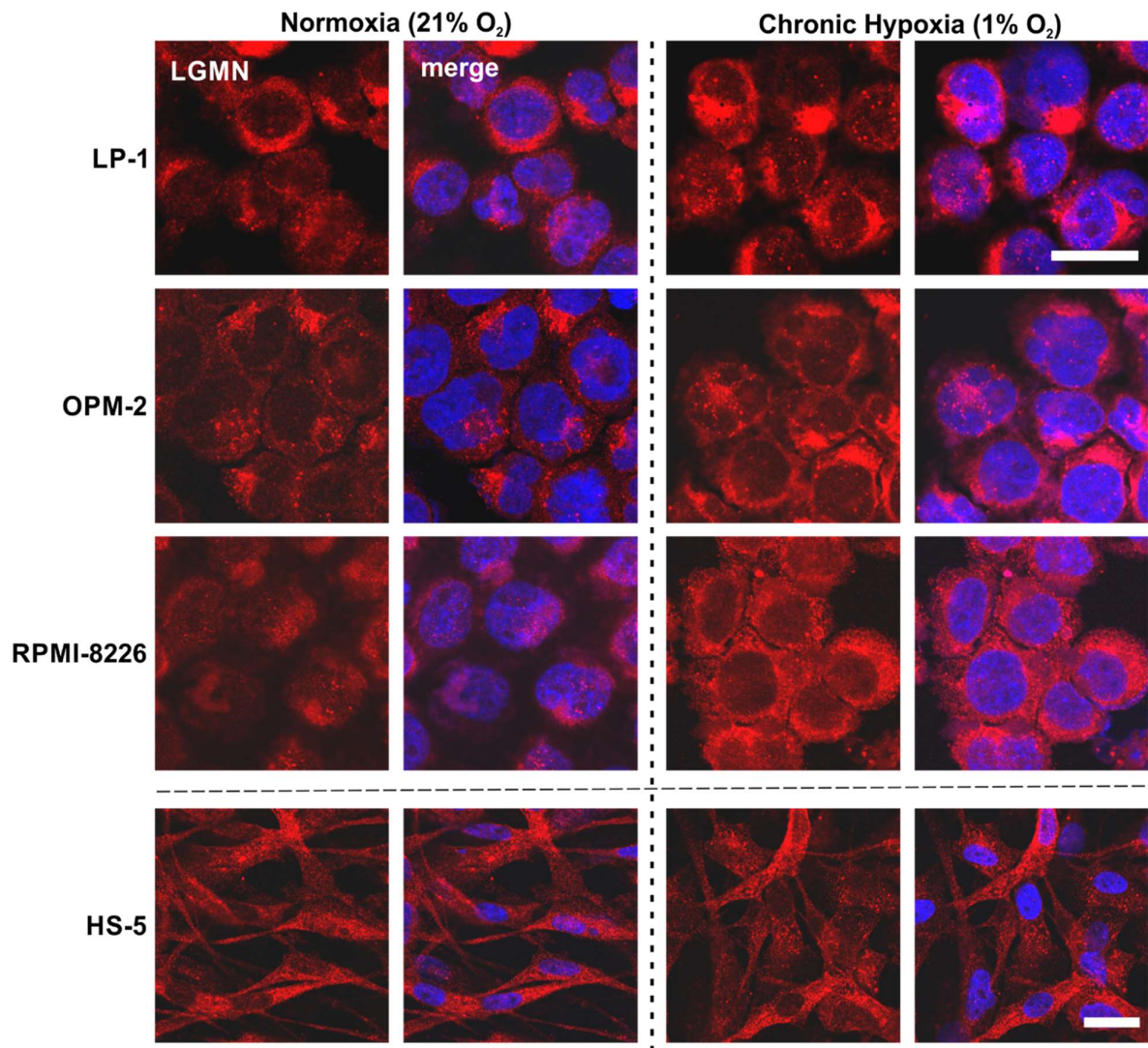


## Supplementary Figure S1



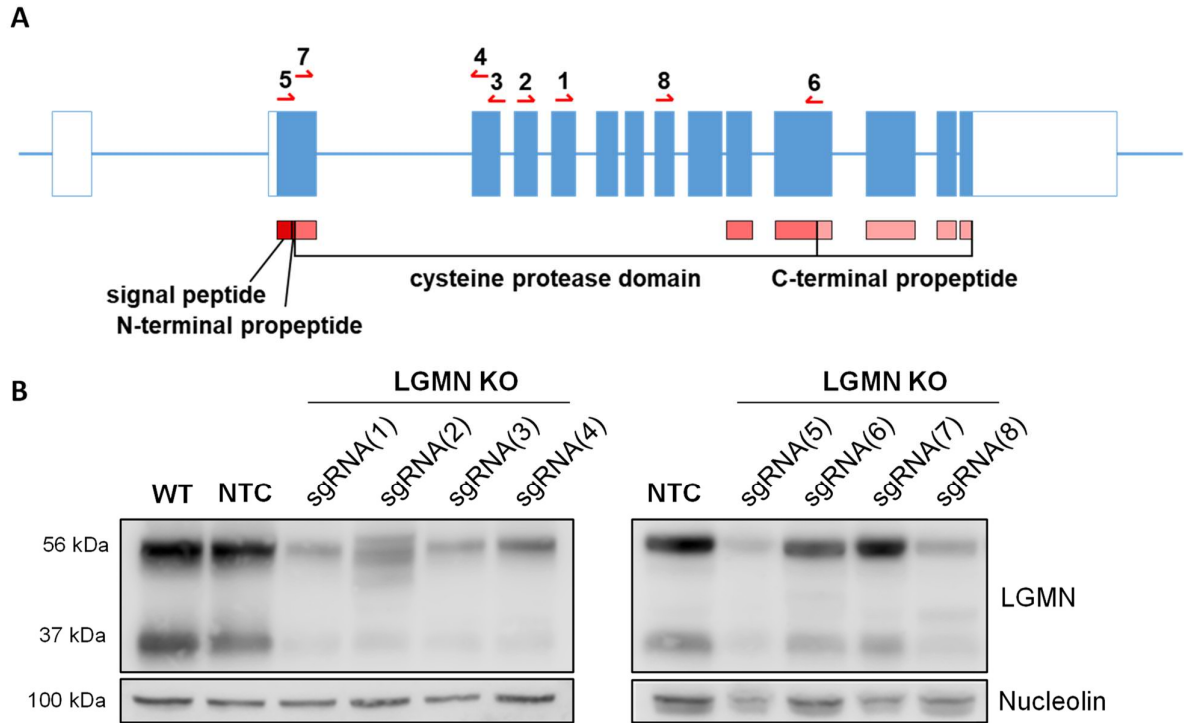
**Supplementary Figure S1:** Correlation of global proteome profiles and significantly regulated proteins in KMS-12-BM cells: **(A)** The matrix was created by plotting the Pearson correlation coefficient based on the SILAC ratios of each quantified protein in individual LC/MS analyses against all other runs. **(B)** Volcano plot showing proteins significantly regulated under hypoxic conditions KMS-12-BM cells. For statistical analysis, one-sample t-test of the  $\log_2$ -transformed SILAC ratios against zero (no change) was conducted and the  $p$ -values were adjusted for multiple hypotheses testing (Benjamini-Hochberg FDR < 5%)

## Supplementary Figure S2



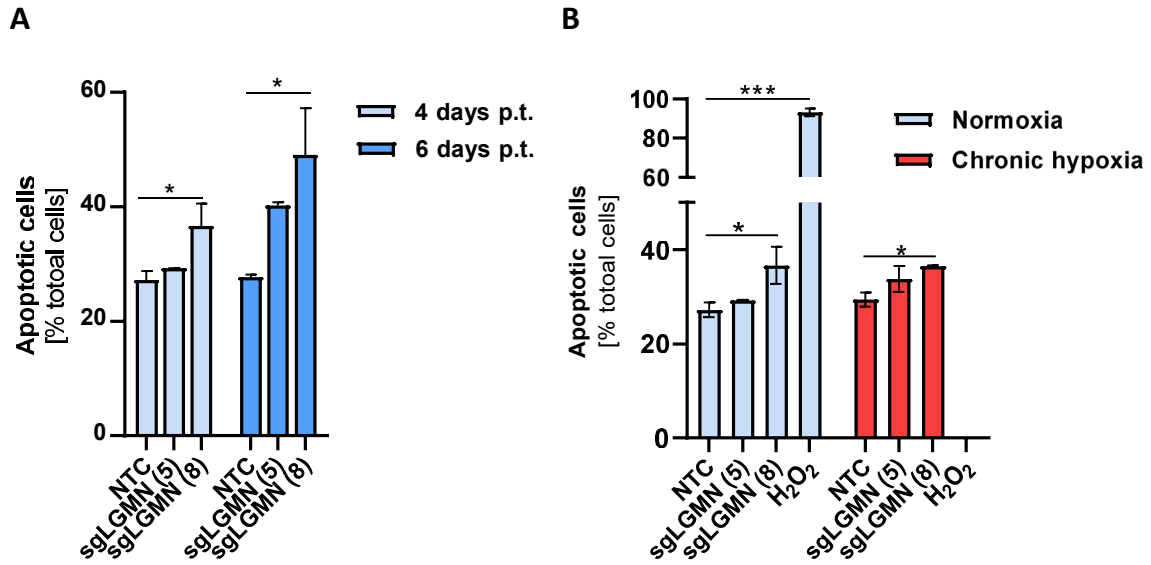
**Supplementary Figure S2:** Confocal images of the Multiple Myeloma-specific upregulation of LGMN in chronic hypoxia: Three MM cell lines and the stromal cell line HS-5 were cultured under hypoxic conditions (1% O<sub>2</sub>) for 7 days and stained for endogenous LGMN. Nuclei were visualized using DAPI. Scale bar = 20  $\mu$ M

### Supplementary Figure S3



**Supplementary Figure S3:** Knockout of LGMN in RPMI-8226 cells using eight distinct sgRNAs: **(A)** Schematic view of the gene structure of LGMN. The domains of LGMN protein, and the complementary regions of the sgRNAs used, are indicated. SP, signal peptide; NPP, N-terminal propeptide, AP, activation peptide, LSAM, LGMN stabilization and activity modulation domain (C-terminal propeptide). **(B)** Knockout of LGMN in RPMI-8226 cells using eight distinct sgRNAs. Representative Westernblot of LGMN. Loading control: Nucleolin

## Supplementary Figure S4



**Supplementary Figure S4:** Knockout of LGMN in LP-1 cells leads to an oxygen-independent induction of apoptosis: **(A)** Annexin V-PE-positive (apoptotic) LP-1 cells [% of total cells] four and six days post transduction with sgRNA NTC, sgRNA LGMN(5) and sgRNA LGMN(8) in normoxic conditions. Bar graphs represent the mean  $\pm$  SD of two independent experiments. Two-way-ANOVA with Bonferroni's post hoc test. \*,  $p < 0.05$ . Abbreviations: p.t. = post transduction. **(B)** Annexin V-PE-positive (apoptotic) LP-1 cells [% of total cells] four days post transduction with sgRNA NTC, sgRNA LGMN(5) and sgRNA LGMN(8) in normoxic and chronic hypoxic conditions. Bar graphs represent the mean  $\pm$  SD of two independent experiments. Two-way-ANOVA with Bonferroni's post-hoc test. \*  $p < 0.05$ , \*\*\*  $p < 0.001$ . Data under normoxia are the same as shown in **(A)** for four days post transduction.