SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure S1 Knockdown validation of siRNAs. (**A**) U251MG cells were transfected control siRNA (RLUC) or FAT1pool-siRNA. 72h later, cells were lysed and the expression of the indicated mRNAs was analysed by qPCR. Data is presented as $\log_2$-fold change after calibration to the house keeping gene *GAPDH* and normalization to RLUC-transfected cells. The mean ± SD of three independent experiments is shown.

(**B**) Cell lines were transfected with RLUC (control) or siRNA-FAT#1-4, pool. Cells were stimulated with 10ng/ml TRAIL (HepG2, U2OS) or 25ng/ml TRAIL (HeLa) or left untreated. Viability was determined by luminescence-based CellTiterGlo-Assay 24hr after treatment. Results are shown as percentage of RLUC-untreated cells. The mean ± SD of at least four independent experiments is shown.

(**C**) U251MG cells were transfected control siRNA (RLUC) or pooled siRNAs targeting FAT1, FAT2, FAT3 or FAT4. 72h later, cells were lysed and the expression of the indicated mRNAs was analysed by qPCR. Data is presented as $\log_2$-fold change after calibration to the house keeping gene *GAPDH* and normalization to RLUC-transfected cells. The mean ± SD of three independent experiments is shown.

Supplementary Figure S2 siRNA-FAT1-mediated sensitivity depends on TRAIL-R2. (**A and B**) U251MG cells were transfected with RLUC (control) , siRNA-TRAIL2pool (Supplementary Figure S2A) or siRNA-TRAIL1pool (Supplementary Figure S2B). Cells were treated with 10ng/ml TRAIL and harvested at the indicated time points for western blot analysis. β-actin serves as a loading control. (**C**) U251MG cells were transfected with indicated siRNAs. Cells were stained with IgG-PE or DR5-PE for 30min and then analyzed by flow cytometry. (**D**) U251MG cells were transfected with indicated siRNAs. One hour prior to TRAIL stimulation, cells were treated with 200nM bafilomycin A1, 10µM MG-132, 20µM Z-VAD-FMK or 10µM Z-IETD-FMK. Cells were lysed 6hr after TRAIL treatment and lysates analyzed by western blot. β-actin serves as a loading control.