

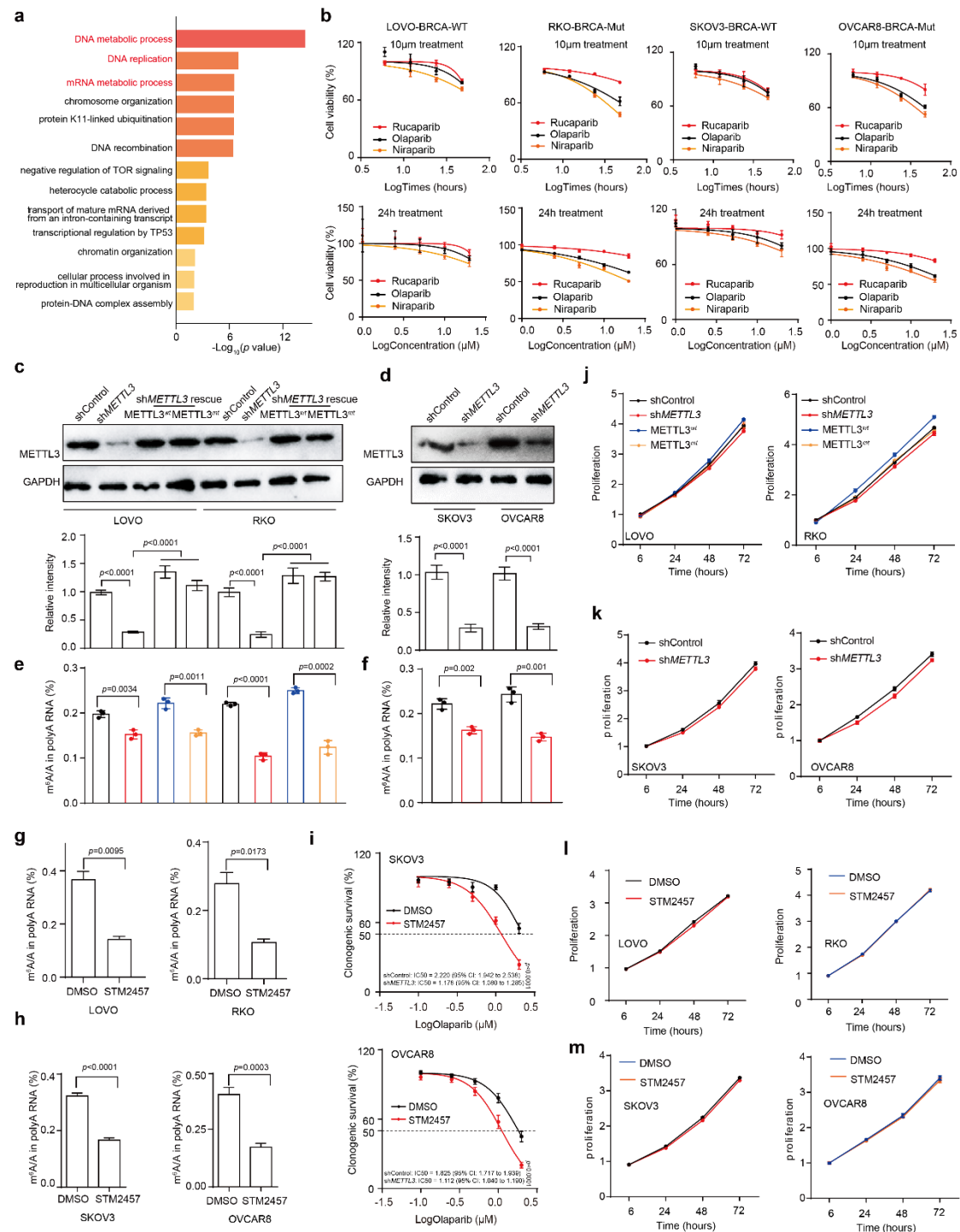


Fig. S1 *METTL3* knockdown enhances the sensitivity of both *BRCA*^{wt} and *BRCA*^{-/-} cells to PARPi. (a) Functional enrichment analysis of 58 genes (see Additional file 1: Table S1) identified from two independent genome-wide CRISPR screening datasets involving olaparib treatment in *BRCA*^{wt} (HeLa) and *BRCA*^{-/-} (SUM149PT and eHAP *MUS81*^{-/-}) cancer and normal cell lines (RPE1-hTERT), using the Metascape portal. (b) Both LOVO, SKOV3 (*BRCA*-WT) and RKO, OVCAR8 (*BRCA*-Mut) cell lines were treated with 10 μM olaparib for the indicated amount of time or for 24 h with the indicated doses of olaparib. Viability was then determined using CCK8. Data

are shown as mean $\pm$ SEM; $n = 3$ biological replicates. **(c)** Western blot analysis of METTL3 protein levels in LOVO and RKO cells following knockdown and subsequent rescue with wild-type or mutant METTL3. **(d)** The m⁶A:A ratio in mRNA was quantified by LC-MS/MS in cells subjected to *METTL3* knockdown or rescue with wild-type/mutant. **(e)** Knockdown efficiency of *METTL3* at the protein level by western blotting in SKOV3 and OVCAR8 cells. **(f)** LC-MS/MS quantification of the m⁶A:A ratio in mRNA of control or *METTL3*-knockdown SKOV3 and OVCAR8 cells. **(g, h)** LC-MS/MS quantification of the m⁶A:A ratio in mRNA of control and STM2457 (2.5 μ m) treated LOVO, RKO, SKOV3 and OVCAR8 cells. **(i)** Dose-response curves and corresponding IC₅₀ values for olaparib treatment in SKOV3 and OVCAR8 cells following STM2457 treatment. Data points represent mean $\pm$ SD of $n=3$ independent experiments. Curves were fitted using a four-parameter nonlinear regression model. IC₅₀ values with 95% CIs are indicated. Statistical significance between compared curves was determined by an extra sum-of-squares F-test (p-value shown). **(j-m)** Cell viability was assessed using the CCK-8 assay in LOVO, RKO, SKOV3, and OVCAR8 cells after *METTL3* knockdown or STM2457 treatment, as well as in LOVO and RKO cells following *METTL3* knockdown and subsequent rescue with wild-type or mutant METTL3. **(c-h)** Statistical analyses were performed using *t* test. $n = 3$ biological replicates. Data are shown as mean $\pm$ SEM.