Figure S1 Prognostic expression of SHMT2, MTHFD1 and TYMS in human lung cancer samples. Human lun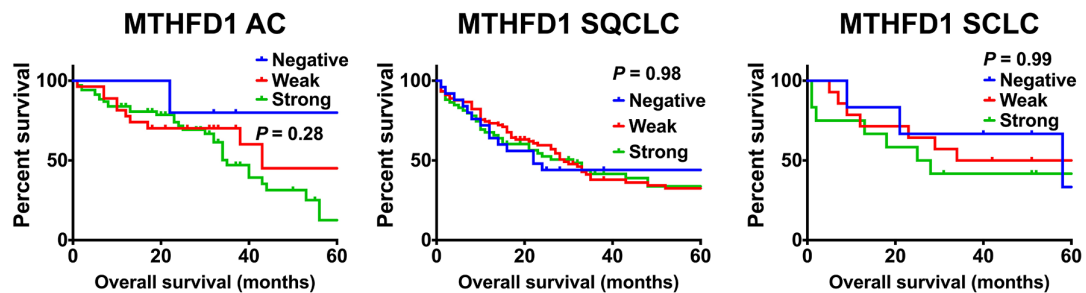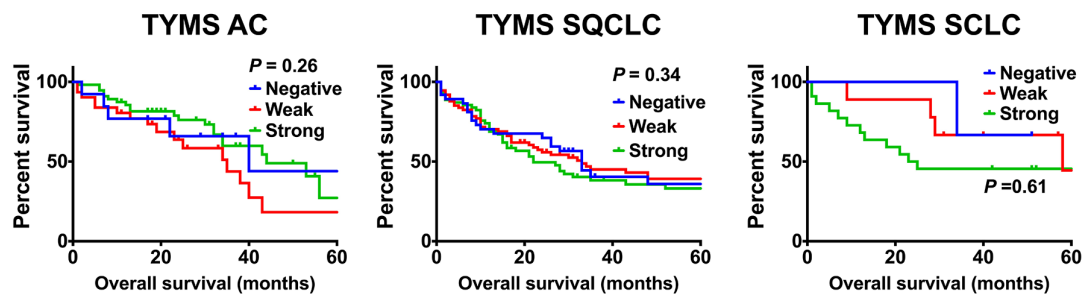g cancer tissues were immunohistochemically stained to show expression of SHMT2, MTHFD1, TYMS protein (A). Survival analysis using Kaplan-Meier estimate and log-rank test grouped by IHC score between SHMT2, MTHFD1 and TYMS protein levels in AC, SQCLC and SCLC patients (B,C,D). Blue, red and green lines depict survival curves of patients with cancer tissues that express negative, weak and strong levels of SHMT2, MTHFD1 and TYMS protein, respectively. P-values were calculated with a log-rank test.
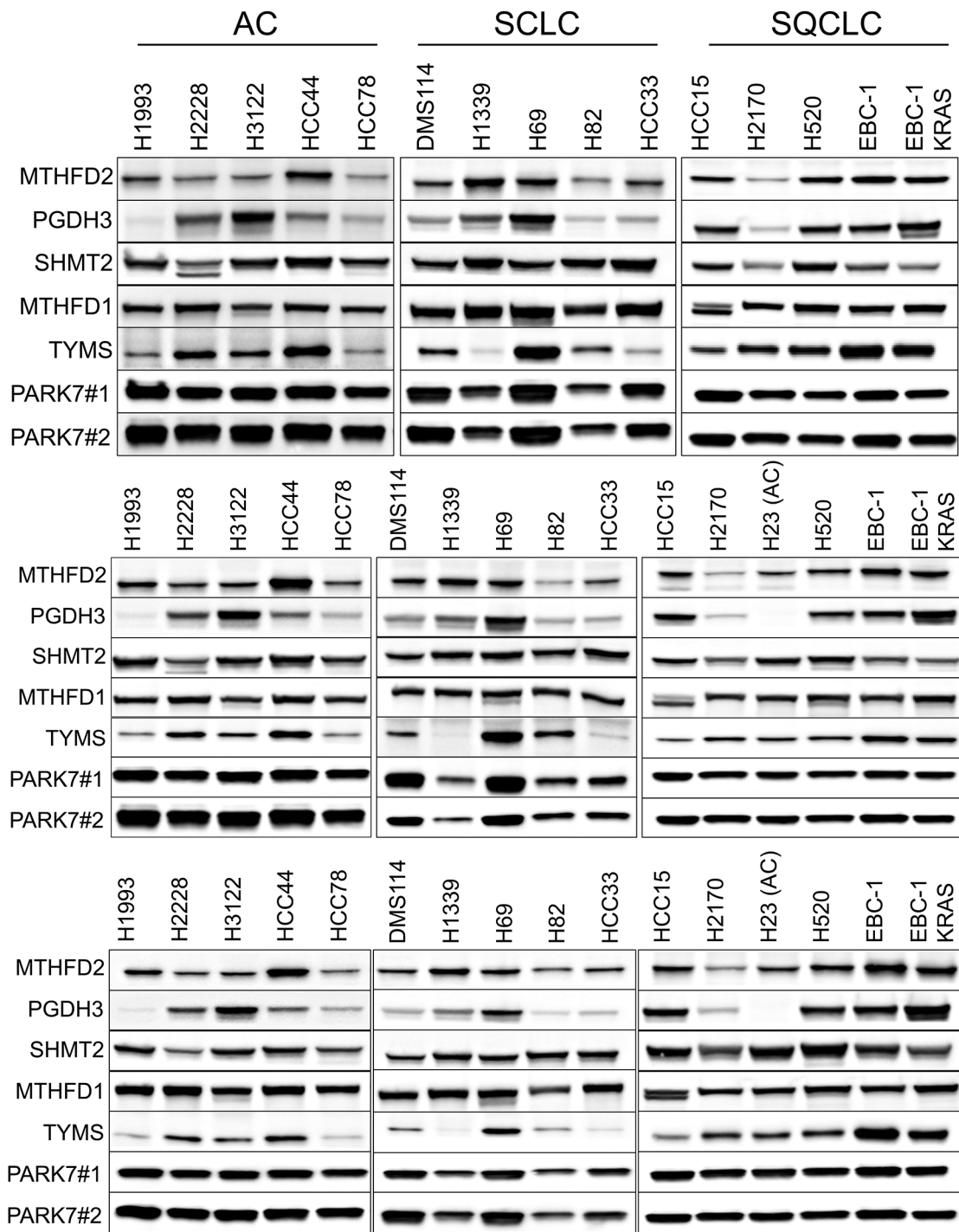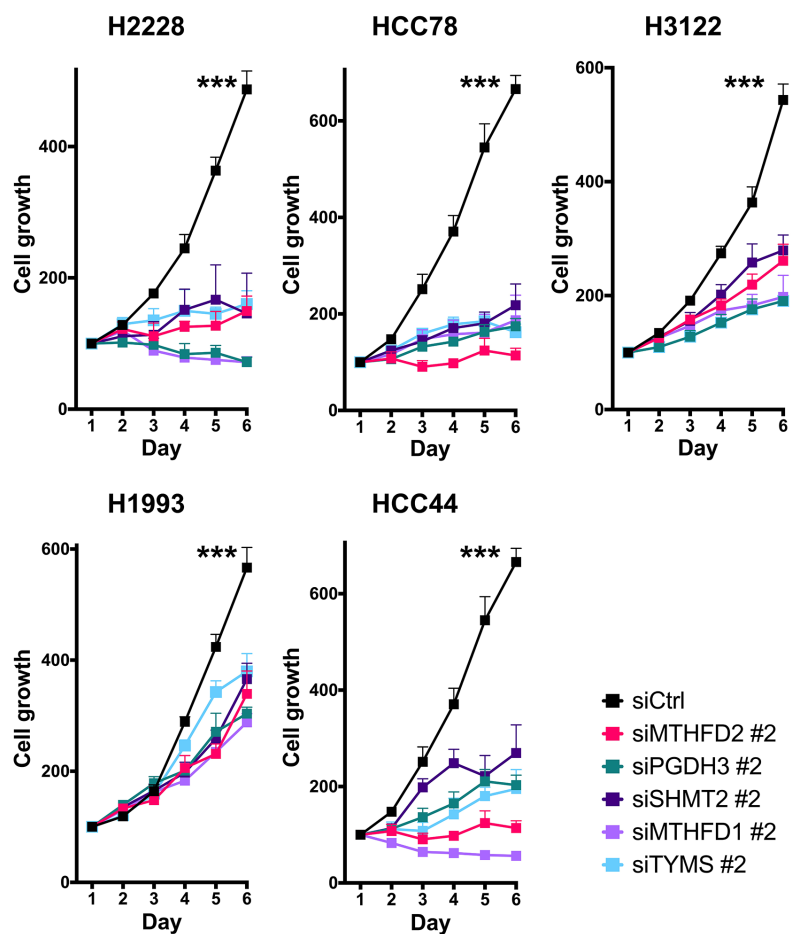
Figure S2 Expression of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS in AC, SQCLC and SCLC cell lines. Immunoblot analysis of the expression levels of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS in AC, SQCLC and SCLC cell lines. PARK7 was used as loading control.
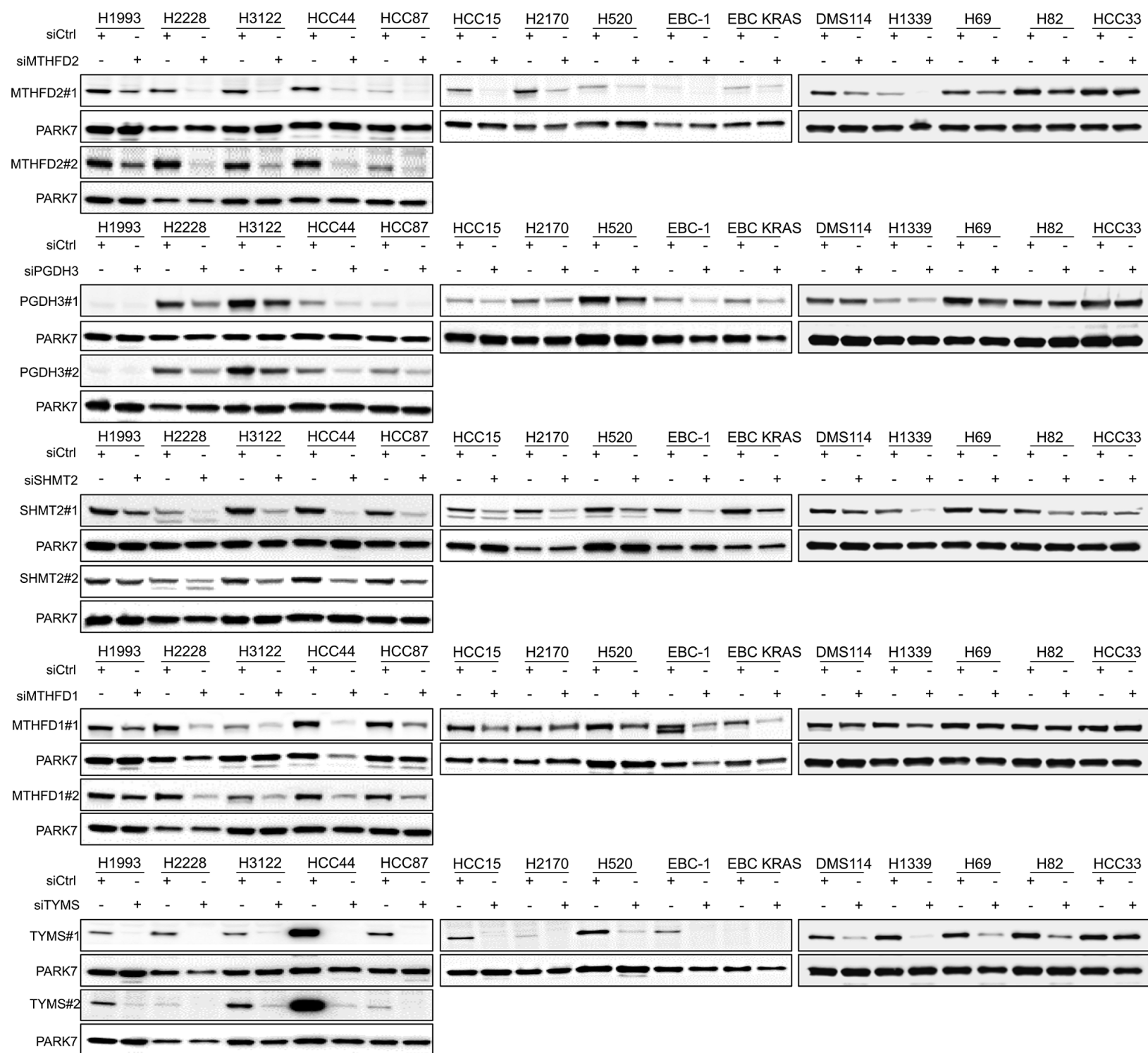
Figure S3 Genetic silencing of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS in AC, SQCLC and SCLC cell lines. Immunoblot analysis of lung cancer cells treated with targeted siRNAs/negative control siRNA for 72 h to determine the expression levels of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS. PARK7 was used as loading control.

Figure S4 Knockdown of 1CM enzymes reduced cell proliferation in pulmonary adenocarcinoma. Growth curve of AC cell lines transfected with siRNA against MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS. The data are represented as mean ± SEM of three independent experiments. ***P<0.001.
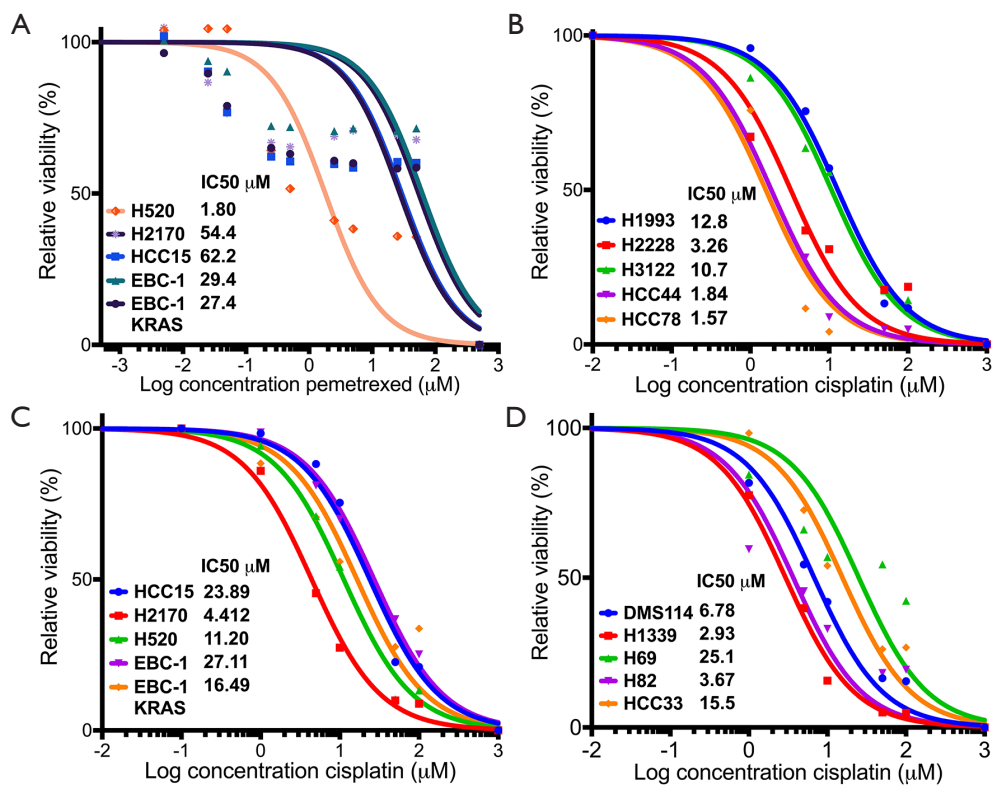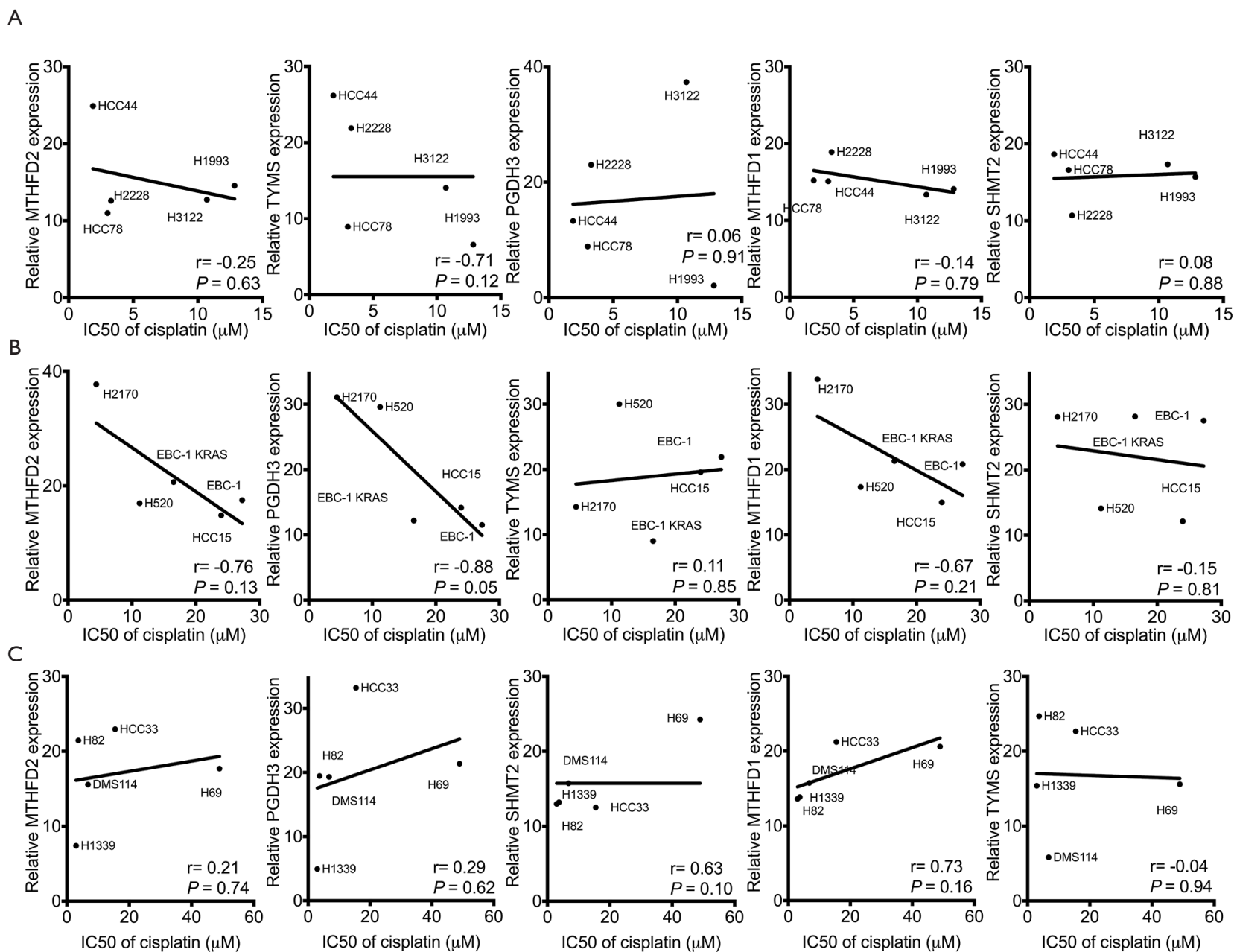
Figure S5 The IC50 values and inhibitory curve in lung cancer cell lines with drugs tested. Curves showing the correlation of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS expression and the IC50 values of pemetrexed in SQCLC cells (A) or cisplatin in AC, SQCLC and SCLC cells (B,C,D). Data is represented as mean ± SEM of at least three independent experiments.
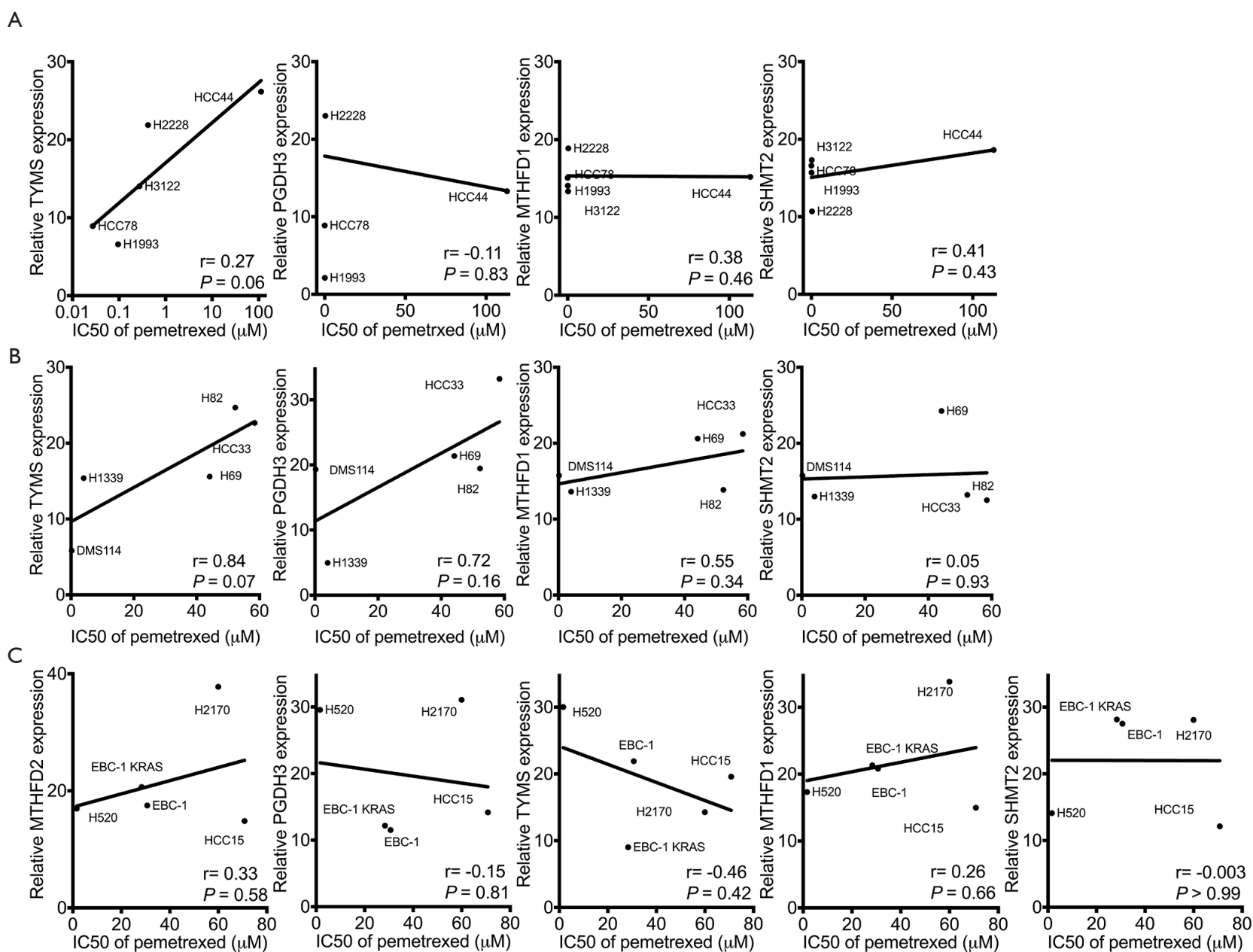
Figure S6 Correlation between pemetrexed sensitivity and the expression levels of 1CM enzymes. (A,B,C) Scatterplots of related 1CM enzymes expression vs IC50 values and pemetrexed in AC (n=5), SQCLC (n=5) and SCLC (n=5) cell lines. Pearson correlation coefficient (r) and P value are displayed. Data is represented as mean ± SEM of at least three independent experiments.

Figure S7 Correlation between cisplatin sensitivity and the expression levels of 1CM enzymes. Curves showing the correlation of MTHFD2, PGDH3, SHMT2, MTHFD1 and TYMS expression and the IC50 values of cisplatin in AC, SQCLC and SCLC cells (A,B,C). Pearson correlation coefficient (r) and P value are displayed. Data is represented as mean ± SEM of at least three independent experiments.
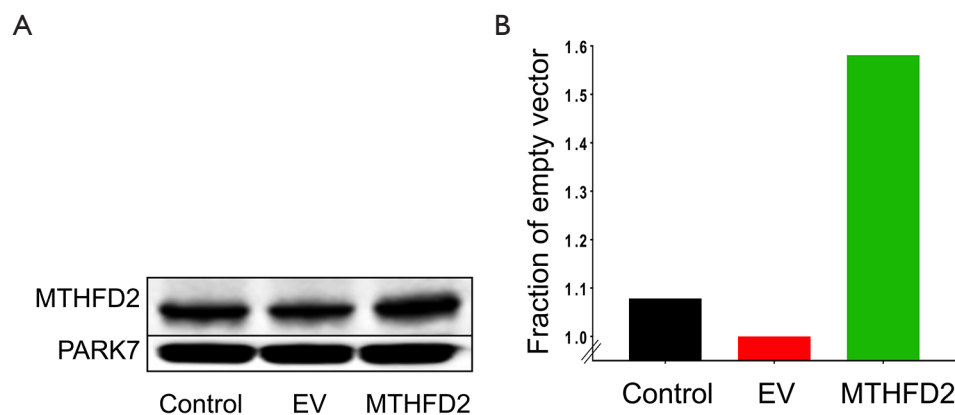
Figure S8 Overexpression of MTHFD2 *in vitro* H1993 cells. (A) H1993 cells were stably transfected with a human MTHFD2 gene expression vector or an empty vector (EV). (B) Bar chart showed quantification of protein levels compared to PARK7 control. Data is represented as mean ± SEM of three independent experiments.