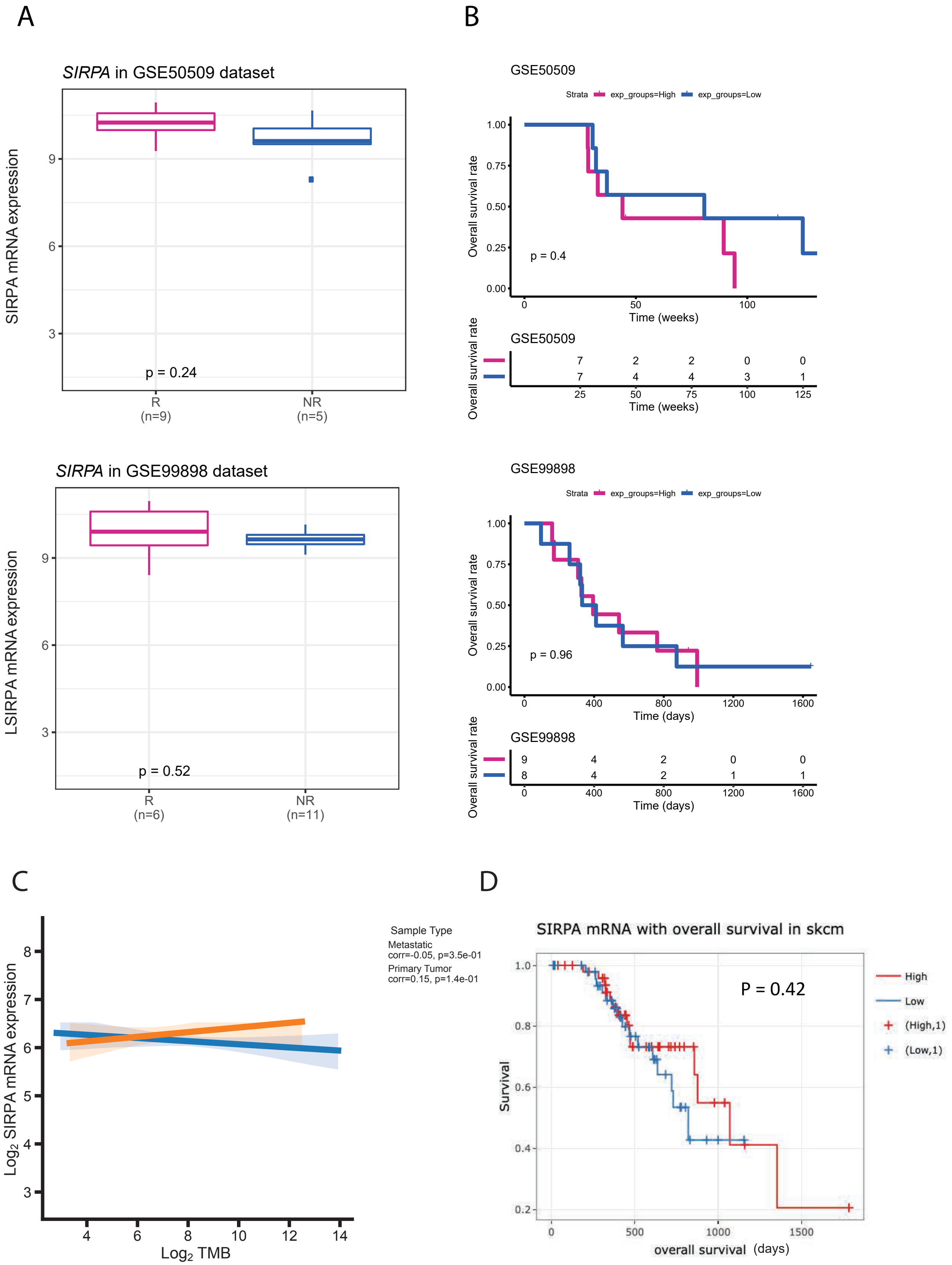

Figure S1. Correlations of SIRPA expression with response to BRAF inhibitors, TMB, and patient prognosis, related to Figure 1

(A, B) Boxplots and Kaplan-Meier (KM) plots showing the associations between the mRNA expressions of SIRPA and tumor responses to BRAF inhibitors (A) or patient survival times (B) in two patient cohorts. For box plots, the middle line in the box is the median, the bottom, and top of the box are the first and third quartiles, and the whiskers extend to the 1.5× interquartile range of the lower and the upper quartiles, respectively. The Mann-Whitney U test was used to assess the difference in SIRPA expression between the responding and non-responding groups. R, responding. NR, non-responding. For KM plots, a log-rank test was used for survival analysis. (C) Scatterplot showing the association between tumor mutation burden (TMB) and SIRPA mRNA expression by Spearman's correlation in TCGA-SKCM patients. (D) KM plot showing the association between SIRPA mRNA expression and overall survival in TCGA-SKCM patients.

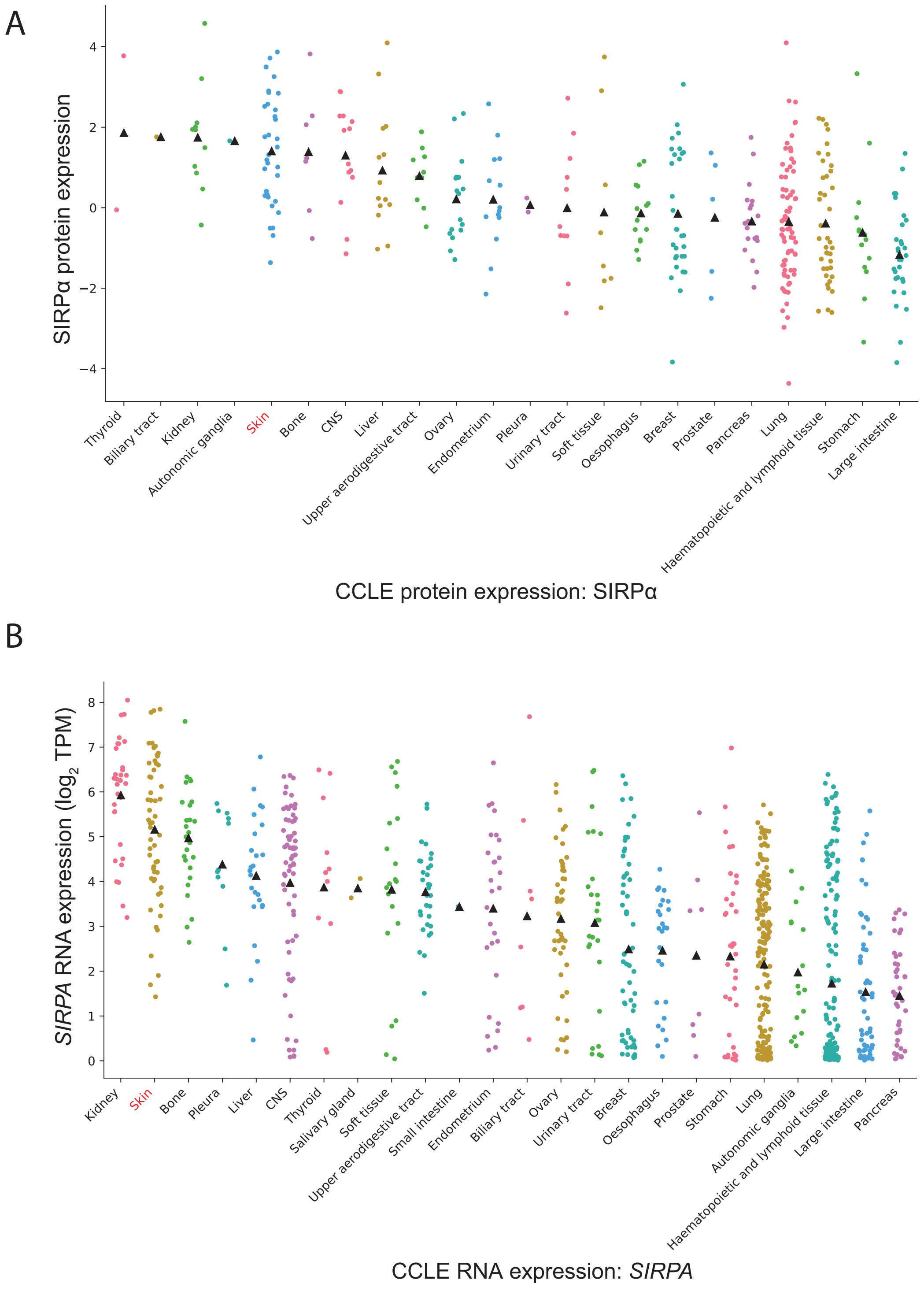

Figure S2. *SIRPA* expression in different cell components of melanoma patients and CCLE cancer cell lines, related to Figure 2

(A, B) SIRPA expression in CCLE cell lines of various lineages. (A) Protein expression. (B) RNA expression. Triangles indicate the mean values.

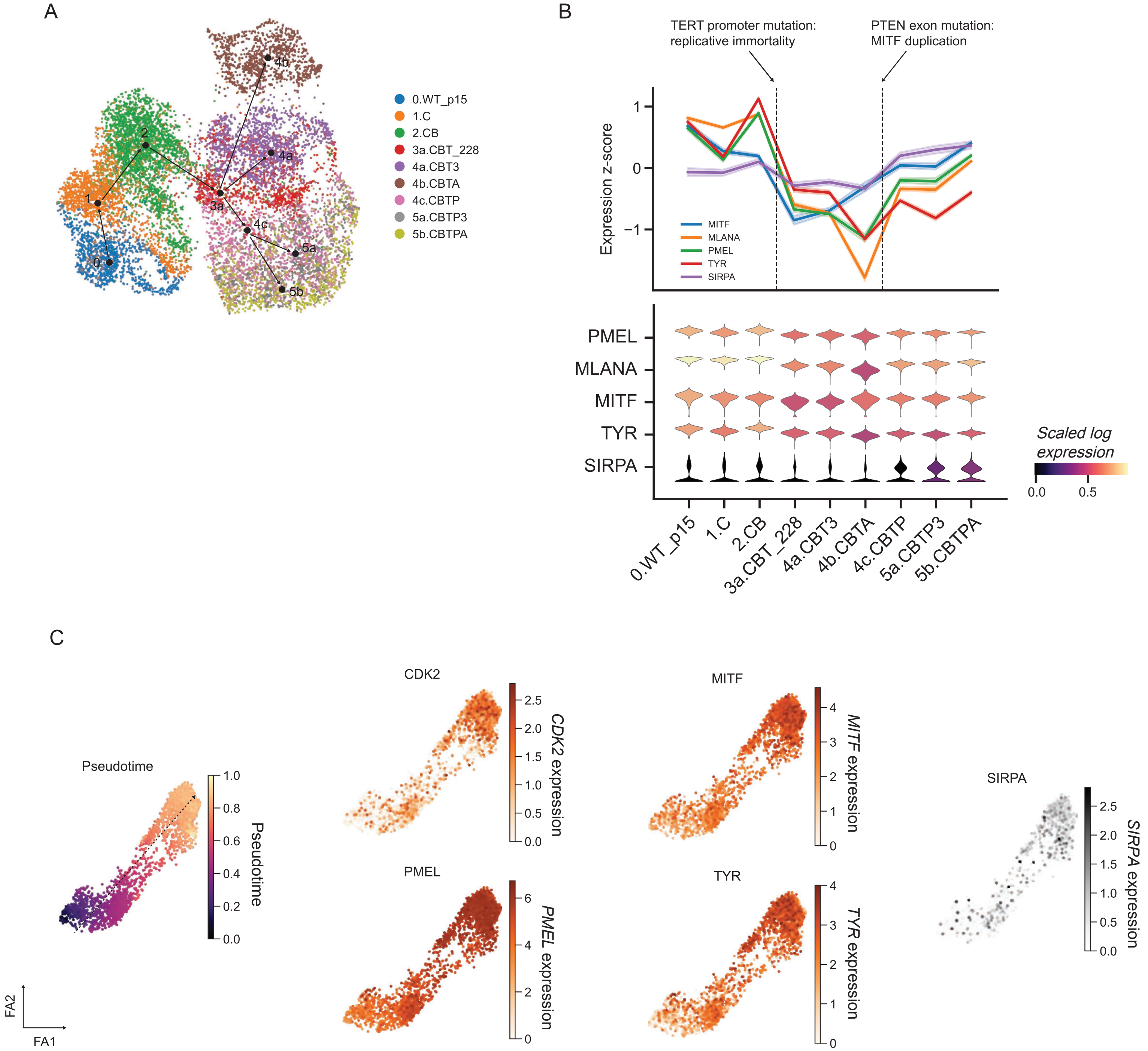

Figure S3. SIRPA expression in melanoma and melanocyte development trajectory, related to Figure 3

(A) UMAP plot showing clustering of melanoma cells with different oncogenic mutations. (B) Top panel, line plot showing normalized expression levels of SIRPA and four melanoma differentiation markers along the trajectory of melanoma development, with major oncogenic events labeled for specific time points. Bottom panel, a complementary visualization using a violin plot. The width of the violin plot represents a probability that the data points will take on the given value, and the top and bottom lines indicate the maximal and minimal data values. The color key indicates normalized gene expression.(C) Force atlas-based projection of human melanocytes at fetal stage based on the gene expression profiles, overlaid with visualizations of diffusion pseudo-time or mRNA expression levels of melanoma differentiation markers and SIRPA. Color keys indicate pseudotime or gene expression.

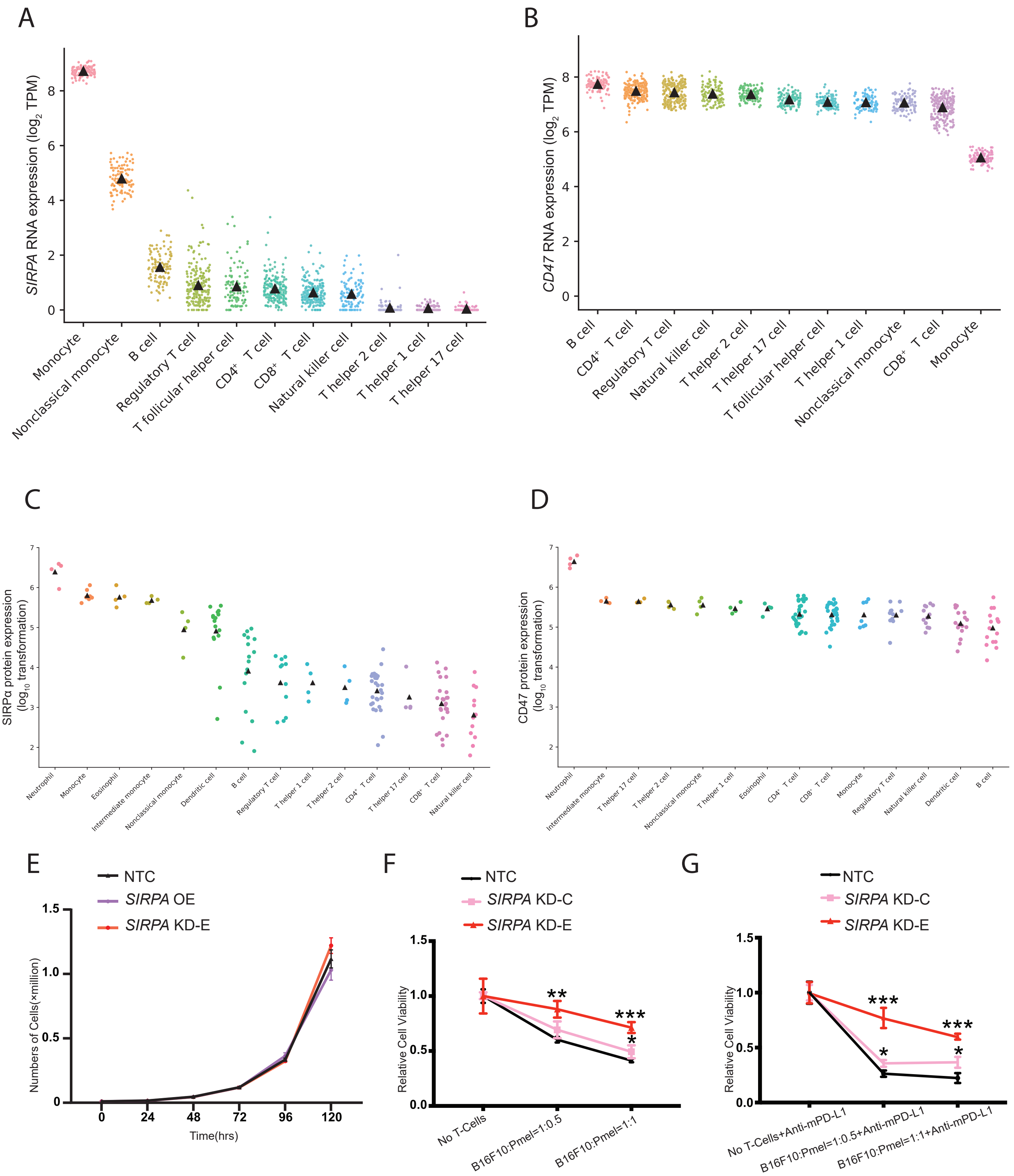

Figure S4. SIRPA and CD47 expression in immune cells and the effect of SIRPα inhibition on T cell-mediated anti-tumor response in melanoma cells, related to Figure 4

(A, B) RNA-level expression of SIRPA (A) and CD47 (B) across a diverse set of human immune cell populations. (C, D) Protein-level expression of SIRPα (C) and CD47 (D) across a diverse set of human immune cell populations. (A-D) Triangles indicate the mean values. (E) Line charts showing the growing cell numbers until 120 h. (F, G) Line charts showing relative survival rates of tumor cells at 96 h in co-cultures of different ratios of B16F10 and CD8+ T cells (Pmel-1) without (F) and with (G) the addition of mouse anti-PD-L1 antibody (mPD-L1). Results are based on three replicates per experiment, and independent experiments were repeated. The error bars indicate mean ± SD. P values are based on Student's t-test; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

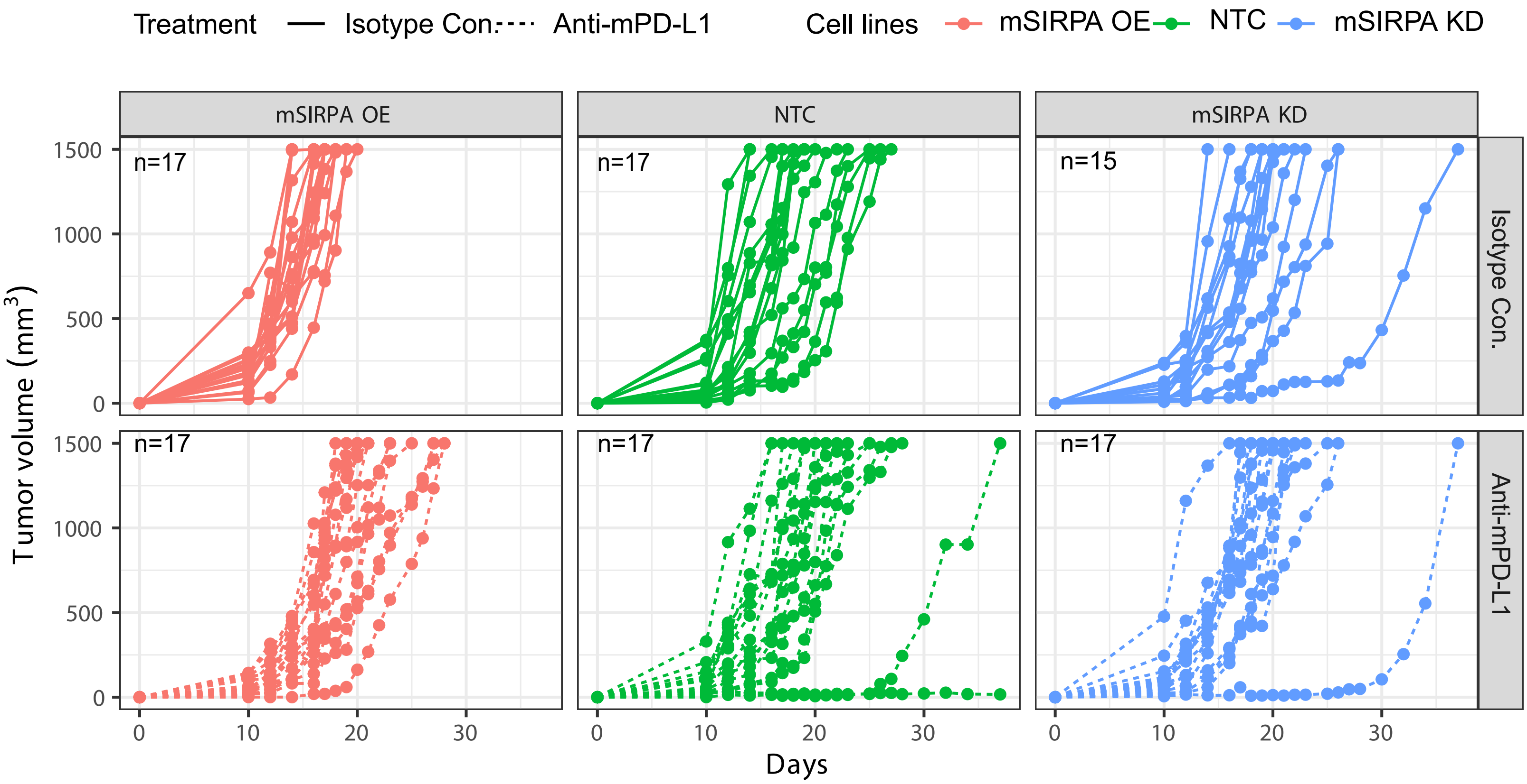

Figure S5 Tumor volume curves of different mouse groups (capped at 1500 mm^3), related to Figure 5

The number in each panel indicates the group size. Mice were sacrificed when tumors reached 20 mm in diameter or 1500 mm^3 in volume.

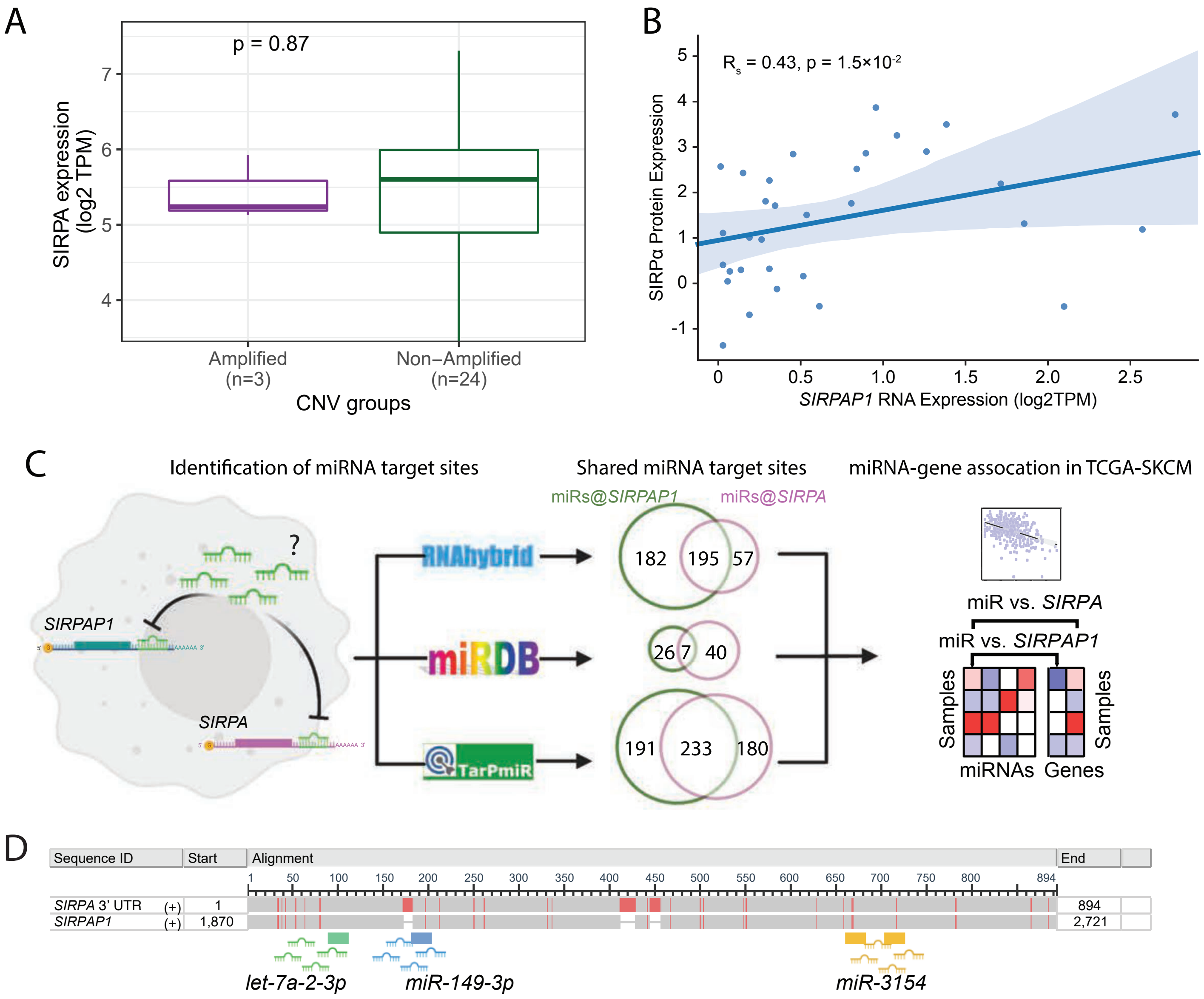

Figure S6. Co-regulation of SIRPA and SIRPAP1 expression in melanoma cohorts, related to Figure 6

(A) Boxplots showing the association between SIRPA gene amplification and mRNA expression in the Hugo cohort. Patient samples with the called somatic copy number > 3 are denoted as amplified, and the others as non-amplified. The middle line in the box is the median, the bottom and top of the box are the first and third quartiles, and the whiskers extend to the 1.5× interquartile range of the lower and the upper quartiles, respectively. (B) Scatterplot showing the correlation between SIRPAP1 RNA and SIRPα protein expression in TCGA-SKCM patients. (C) Workflow of the miRNA target analysis. (D) The target sites of the identified miRNAs shared by SIRPA (3' UTR region) and SIRPAP1 (3' end region).