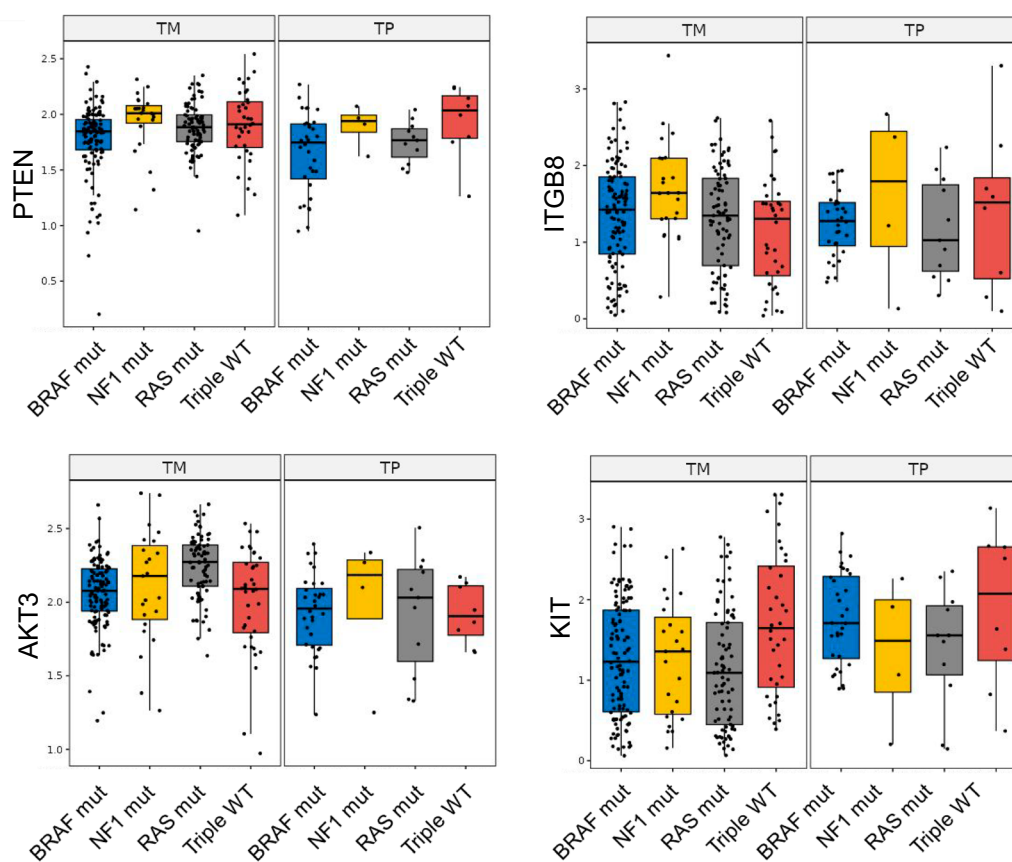
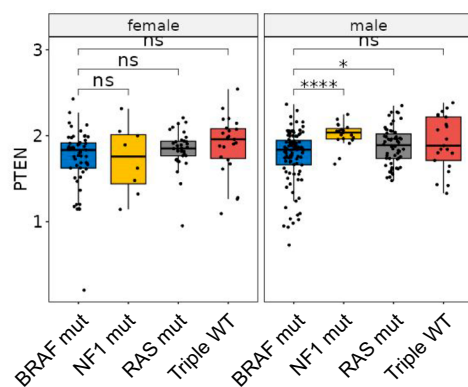
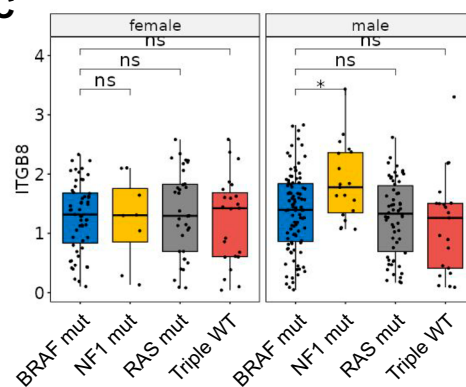
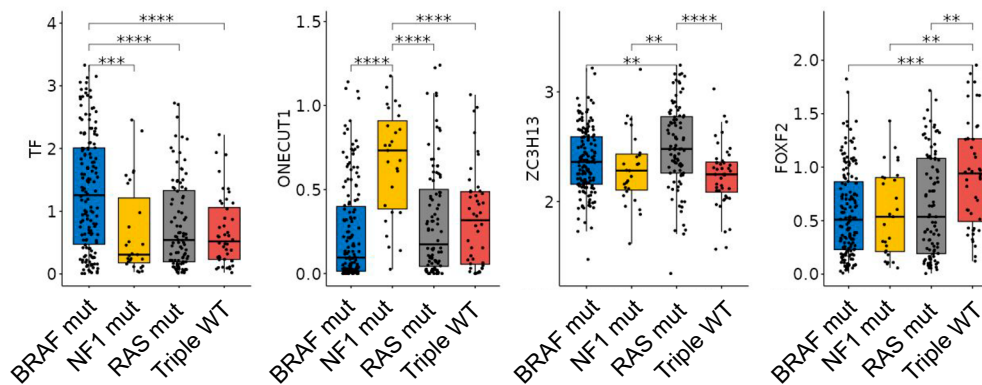
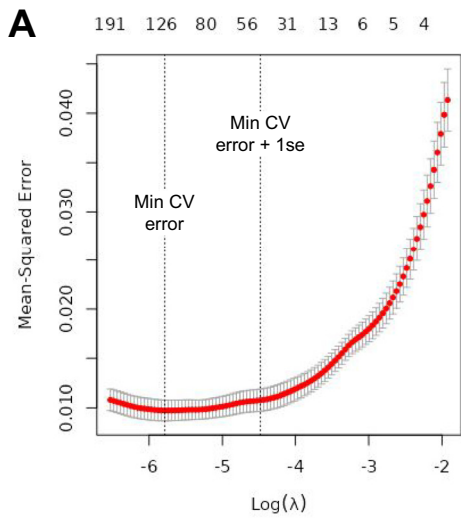


Expanded View Figures

Figure EV1. Expression profiles of subtype-selective genes in melanoma (related to Fig. 2).

(A) Expression of selected genes demonstrates comparable patterns between metastatic (TM) and primary (TP) tumor samples in SKCM (TM $n = 368$, TP $n = 103$, BRAF mutants $n = 146$, NF1 mutants $n = 27$, RAS mutants $n = 91$, Triple WT $n = 44$). (B, C) Expression of previously reported genes distinguishing melanoma mutational subtypes may show sex-specific expression patterns (female $n = 180$, male $n = 291$, BRAF mutants $n = 146$, NF1 mutants $n = 27$, RAS mutants $n = 91$, Triple WT $n = 44$). (D) Other transcripts selectively expressed in mutational subtypes of melanoma are shown (BRAF mutants $n = 146$, NF1 mutants $n = 27$, RAS mutants $n = 91$, Triple WT $n = 44$). The box represents the interquartile range (IQR), spanning from the 25th percentile (lower bound) to the 75th percentile (upper bound). The horizontal line within the box indicates the median (50th percentile). Whiskers extend to the smallest and largest values within $1.5 \times$ IQR from the lower (Q1) and upper (Q3) quartiles, respectively. T test P values are adjusted for multiple comparisons ($P < 0.0001$, "****"; $P < 0.001$, "****"; $P < 0.01$, "***"; $P < 0.05$, "**"; $P > 0.05$, "ns").

A**B****C****D**



B

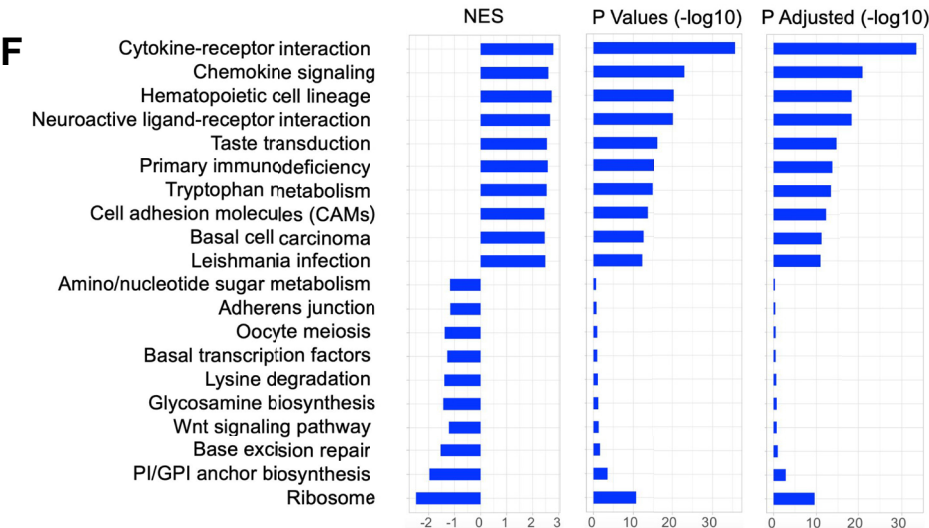
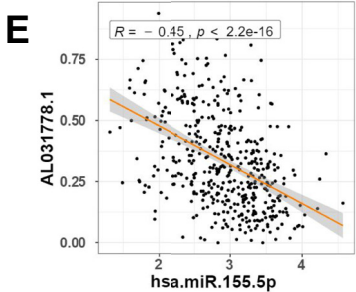
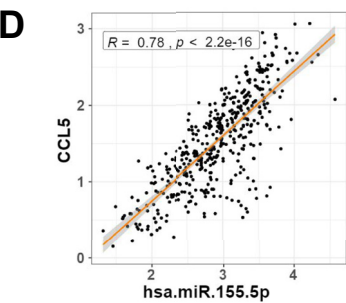
miRNA	Coefficient	miRNA	Coefficient
hsa.miR.7702	0.0792	hsa.miR.3170	-0.0360
hsa.miR.3614.5p	0.0719	hsa.miR.6509.5p	-0.0235
hsa.miR.155.5p	0.0512	hsa.miR.4636	-0.0204
hsa.miR.142.3p	0.0469	hsa.miR.3680.3p	-0.0191
hsa.miR.5586.5p	0.0324	hsa.miR.92a.3p	-0.0187
hsa.miR.181a.3p	0.0307	hsa.miR.340.3p	-0.0172
hsa.miR.100.5p	0.0266	hsa.miR.187.3p	-0.0144
hsa.miR.6125	0.0262	hsa.miR.19a.3p	-0.0140
hsa.miR.503.5p	0.0260	hsa.miR.5699.5p	-0.0133
hsa.miR.150.5p	0.0246	hsa.miR.1.3p	-0.0101
hsa.miR.29b.2.5p	0.0245	hsa.miR.6783.3p	-0.0048
hsa.miR.150.3p	0.0203	hsa.miR.129.5p	-0.0047
hsa.miR.342.5p	0.0186	hsa.miR.3150b.3p	-0.0045
hsa.miR.4728.3p	0.0162	hsa.miR.4677.3p	-0.0032
hsa.miR.3614.3p	0.0119	hsa.miR.219a.2.3p	-0.0029
hsa.miR.181c.5p	0.0100	hsa.miR.6854.5p	-0.0012
hsa.miR.29c.5p	0.0094	hsa.miR.144.5p	-0.0005
hsa.miR.342.3p	0.0080	hsa.miR.17.3p	-0.0002
hsa.let.7b.3p	0.0069		
hsa.miR.1228.3p	0.0067		
hsa.miR.542.5p	0.0057		
hsa.miR.598.3p	0.0048		
hsa.miR.424.3p	0.0039		
hsa.miR.21.3p	0.0026		
hsa.miR.30a.5p	0.0024		
hsa.miR.29c.3p	0.0017		

C

Genes	P-value	Pearson cor. coef.
CCL5	6.59E-92	0.778
NKG7	2.24E-86	0.763
CD2	1.68E-85	0.76
TRAC	2.89E-84	0.756
TRBC2	1.87E-83	0.754
CD8A	7.18E-83	0.752
MIR155HG	9.23E-83	0.752
CD3D	1.22E-82	0.752
CD8B	1.35E-82	0.752
TIGIT	3.33E-82	0.75
UCK2	1.66E-15	-0.364
CASKIN1	1.45E-15	-0.365
SNHG29	1.02E-15	-0.367
PTK7	5.52E-16	-0.37
KCTD15	5.20E-16	-0.37
KIAA1549	3.07E-17	-0.385
GTF2IRD1	1.47E-17	-0.388
SOC7	6.11E-18	-0.392
ADGRA3	1.88E-23	-0.448
AL031778.1	1.09E-23	-0.45

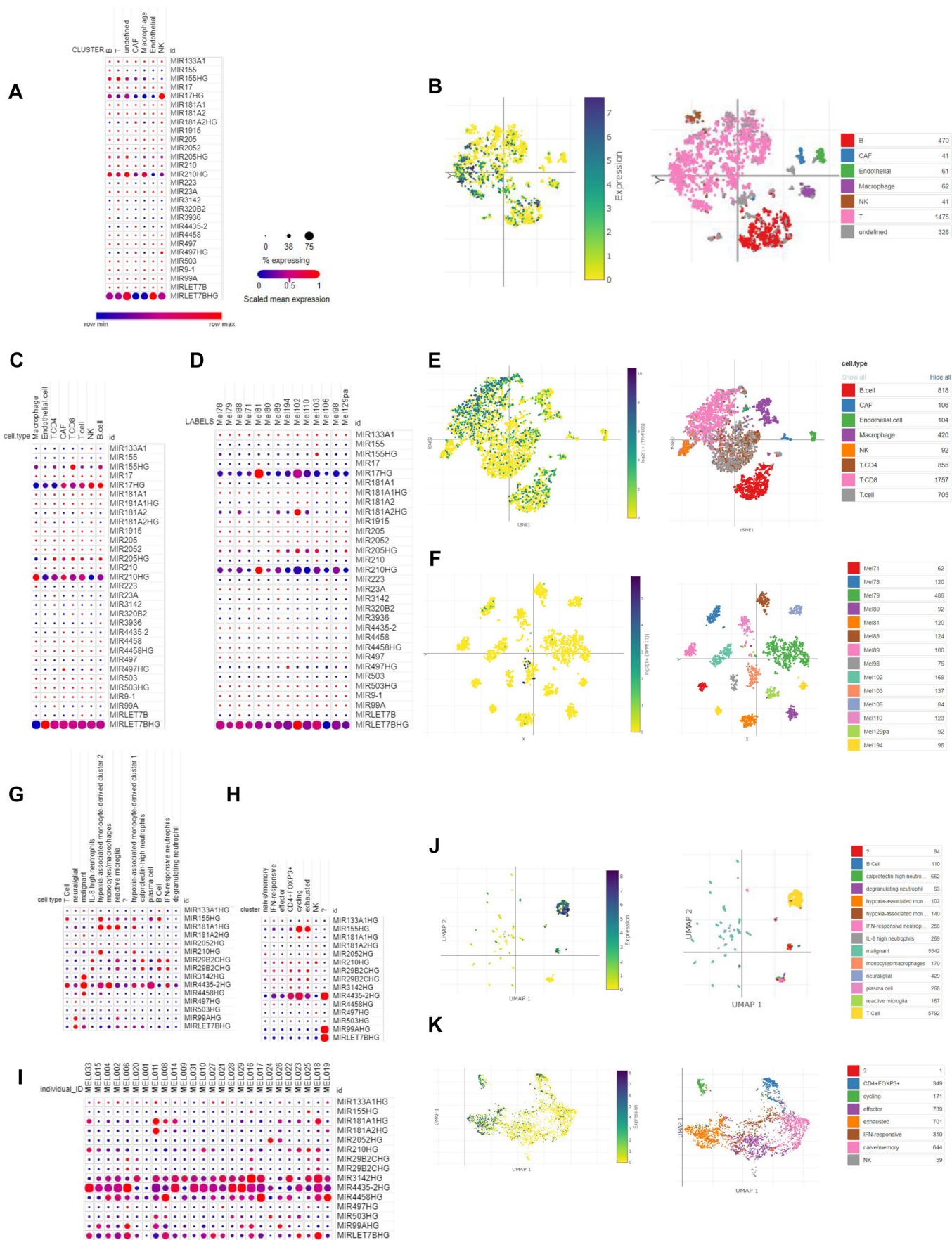
Positive correlation with miR-155-5p

Negative correlation with miR-155-5p



**Figure EV2. Lasso analysis of miRNAs against IFN γ signaling in melanoma (related to Fig. 4).**

(A) Mean-squared cross-validation (CV) error as a factor of increasing model penalty is shown ($n = 471$). (B) miRNA predictors with positive and negative coefficients at the lambda value corresponding to minimum CV error + 1 standard error are shown. (C) Transcripts with the top positive and negative correlations with miR-155-5p are shown. (D, E) TCGEx scatter plot module was used to visualize top correlators of miR-155-5p. Statistical analysis was performed using Pearson correlation test, and the corresponding P values are shown. (F) The GSEA results shown in Fig. 4E were exported from the TCGEx platform and plotted elsewhere to demonstrate that the numeric outputs can be reused by the users, if preferred.



**Figure EV3. Publicly available scRNAseq data sets on Broad Single-Cell Portal were examined to investigate the expression patterns of ML-selected miRNAs.**

Three separate data sets were analyzed: SCP11 (A, B), SCP109 (C–F), and SCP1493 (G–K); and the Single-Cell Portal interface was used to generate the plots (query URLs can be found in the Appendix). (A, C, D, G–I). Dot plots indicate the expression of miRNAs in immune (A, C, G, H) and in melanoma (D, G, I) cell clusters. Some miRNAs show immune cell-selective expression patterns whereas others are more specific to melanoma cells within the TME. (B, E, F, J, K). UMAP plots showing the expression profile of MIR155HG in immune and tumor cell clusters reveals the T and B cell-selective expression of MIR155HG within the TME (E, J). MIR155HG was particularly elevated in cycling and exhausted T-cell clusters (K). In contrast, melanoma cells did not broadly express MIR155HG (F, J) across three studies.

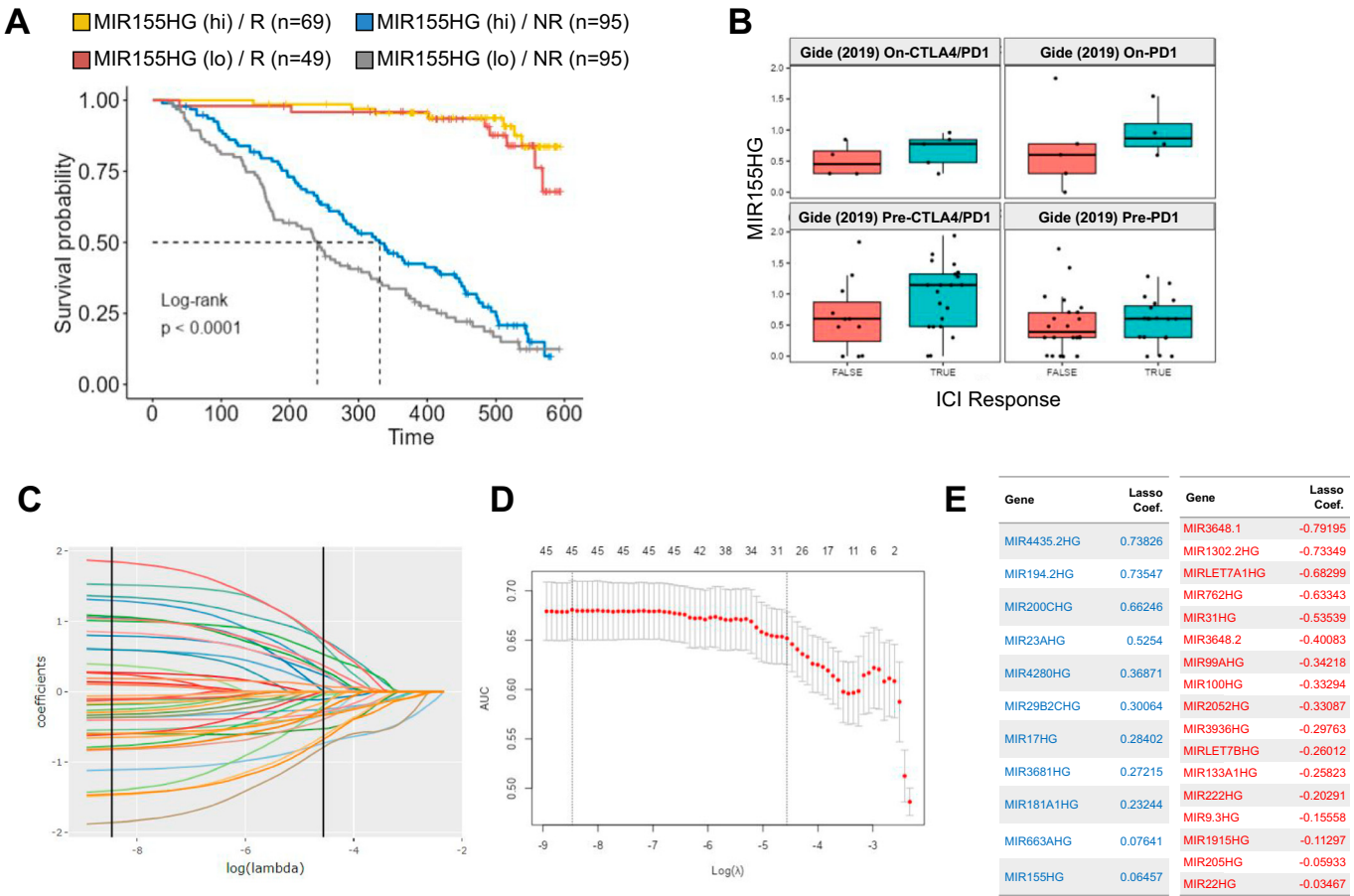
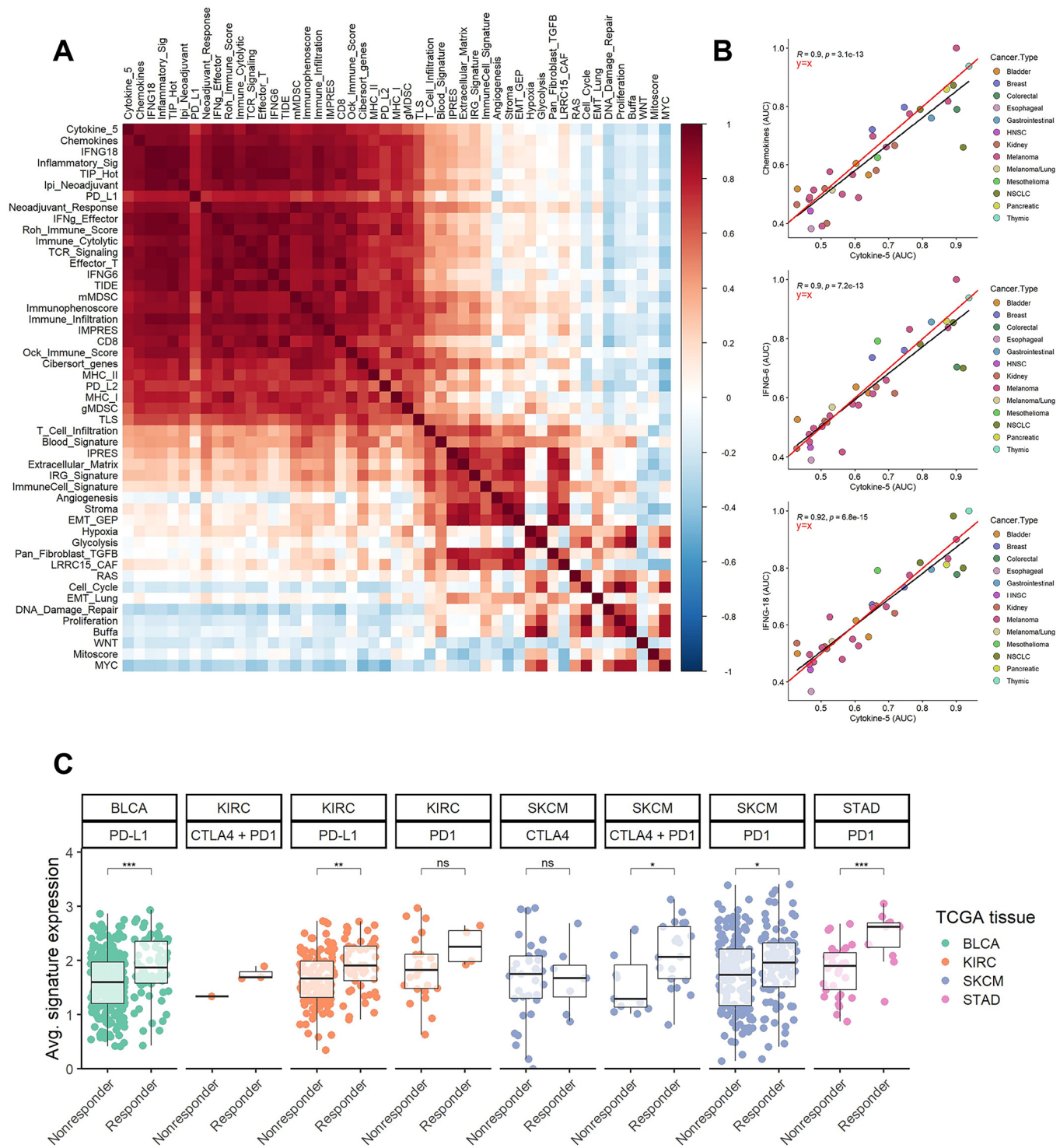


Figure EV4. Investigating the relationship between immunotherapy response and MIR155HG and other miRNA host genes (related to Fig. 6).

(A) Kaplan-Meier survival analysis demonstrates that higher MIR155HG levels (categorized at median) prior to treatment correspond to improved survival in melanoma patients ($n = 313$); however, this trend was more emphasized in non-responders. (B) Boxplots show the MIR155HG transcript levels in responders and non-responders during or prior to ICI treatment (On-CTLA4/PD1 $n = 9$, Pre-CTLA4/PD1 $n = 32$, On-PD1 $n = 9$, Pre-PD1 $n = 41$). The box represents the interquartile range (IQR), spanning from the 25th percentile (lower bound) to the 75th percentile (upper bound). The horizontal line within the box indicates the median (50th percentile). Whiskers extend to the smallest and largest values within $1.5 \times$ IQR from the lower (Q1) and upper (Q3) quartiles, respectively. (C-E) Binomial lasso was performed using binarized response (CR/PR vs PD) as response variable and 45 miRNA host genes as predictors after low-expression filtering. Regularized coefficients (C), the cross-validated AUC of the penalized model (D), and nonzero coefficients at the minimum value of lambda within 1 standard error of the highest AUC (E) are shown in pre-treatment melanoma patients ($n = 313$). Error bars indicate the lambda values within one standard error of the highest cross-validated AUC.



◀ **Figure EV5. Examination of the Cytokine-5 signature as a new marker for immunotherapy response (related to Fig. 7).**

(A) The pairwise correlations between various signatures predicting immunotherapy response are depicted in a heatmap (figure was generated using the IOSig platform). The Pearson correlation coefficients were calculated by using the AUROC values across the studies in the IOSig database. (B) Pairwise correlations between the Cytokine-5 and IFNG6, IFN18 and Chemokine signatures are plotted in IOSig data sets. The best-fitting line (black) and its equation is shown along with the $y = x$ diagonal line (red) indicating equality. Figure was generated in the R environment using the analysis results exported from the IOSig server. Statistical analysis was performed using Pearson correlation test, and the corresponding P values are shown. (C) The boxplots illustrate the average Cytokine-5 signature expression in immunotherapy responders and non-responders across different cancer types in TCGEx data sets (BLCA/PD-L1 $n = 348$, KIRC/CTLA4 + PD1 $n = 4$, KIRC/PD-L1 $n = 176$, KIRC/PD1 $n = 27$, SKCM/CTLA4 $n = 42$, SKCM/CTLA4 + PD1 $n = 32$, SKCM/PD1 $n = 239$, STAD $n = 45$). The box represents the interquartile range (IQR), spanning from the 25th percentile (lower bound) to the 75th percentile (upper bound). The horizontal line within the box indicates the median (50th percentile). Whiskers extend to the smallest and largest values within $1.5 \times$ IQR from the lower (Q1) and upper (Q3) quartiles, respectively. T test P values are shown ($P < 0.001$, "****"; $P < 0.01$, "***"; $P < 0.05$, "**"; $P > 0.05$, "ns")