Integrative Analysis of TNFRSF18 in Immunogenomics: Implications as a Predictive Biomarker and Therapeutic Target in Precision Immunotherapy

Miao Sun [1†], Mengmeng Zhang [2†], Shuangshuang Duan [1], Lijun Zhang [1], Huibin Liu [2*]

[1]College of Pharmacy, Xinjiang Medical University, Urumqi 830011, China, [2]Clinical Trial Office, Cancer Hospital of Xinjiang Medical University, Urumqi 830011, China

†These authors contributed equally to this work.
*Corresponding author's e-mail: liuhuibinedu@163.com.

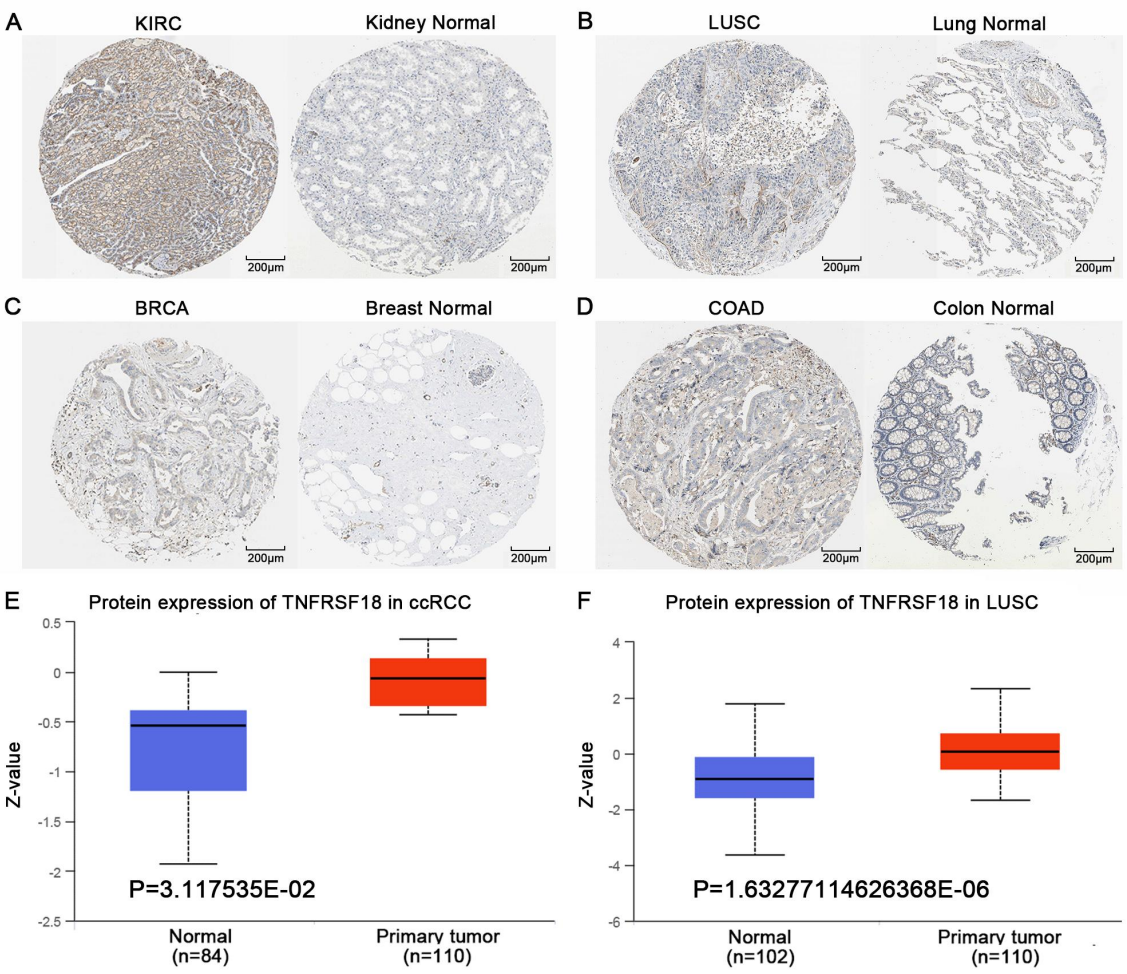

Fig. S1. Differential protein expression of TNFRSF18 in tumor versus normal tissues. Representative IHC staining of TNFRSF18 in paired clinical specimens: (A) kidney, (B) lung, (C) breast, and (D) colon (scale bars: 200 μm). (E-F) Bioinformatics validation of pan-cancer TNFRSF18 protein expression patterns using the UALCAN database.

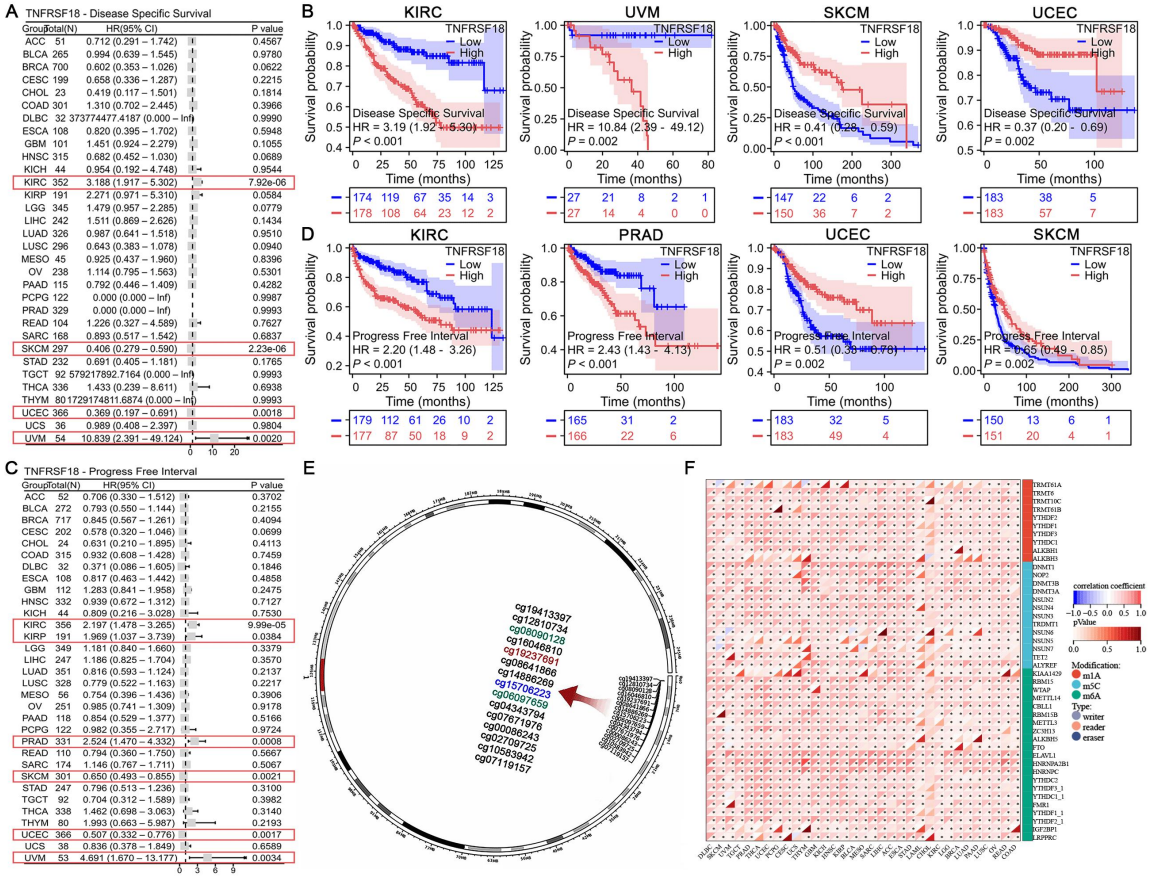

Fig. S2. Prognostic and epigenetic associations of TNFRSF18 across cancer types. (A) Univariate Cox analysis of TNFRSF18 association with disease-specific survival (DSS). (B) Kaplan-Meier curves for disease-specific survival (DSS) stratified by TNFRSF18 expression in KIRC, UVM, SKCM, UCEC and PCPG. (C) Univariate Cox analysis of TNFRSF18 association with progression-free interval (PFI). (D) Kaplan-Meier curves for PFI in KIRC, PRAD, UVM, KIRP, UCEC and SKCM. (E) Chromosomal distribution of the methylation probes associated with TNFRSF18. (F) The correlation between TNFRSF18 expression and m1A, m5C, m6A regulatory genes. * $P < 0.05$.

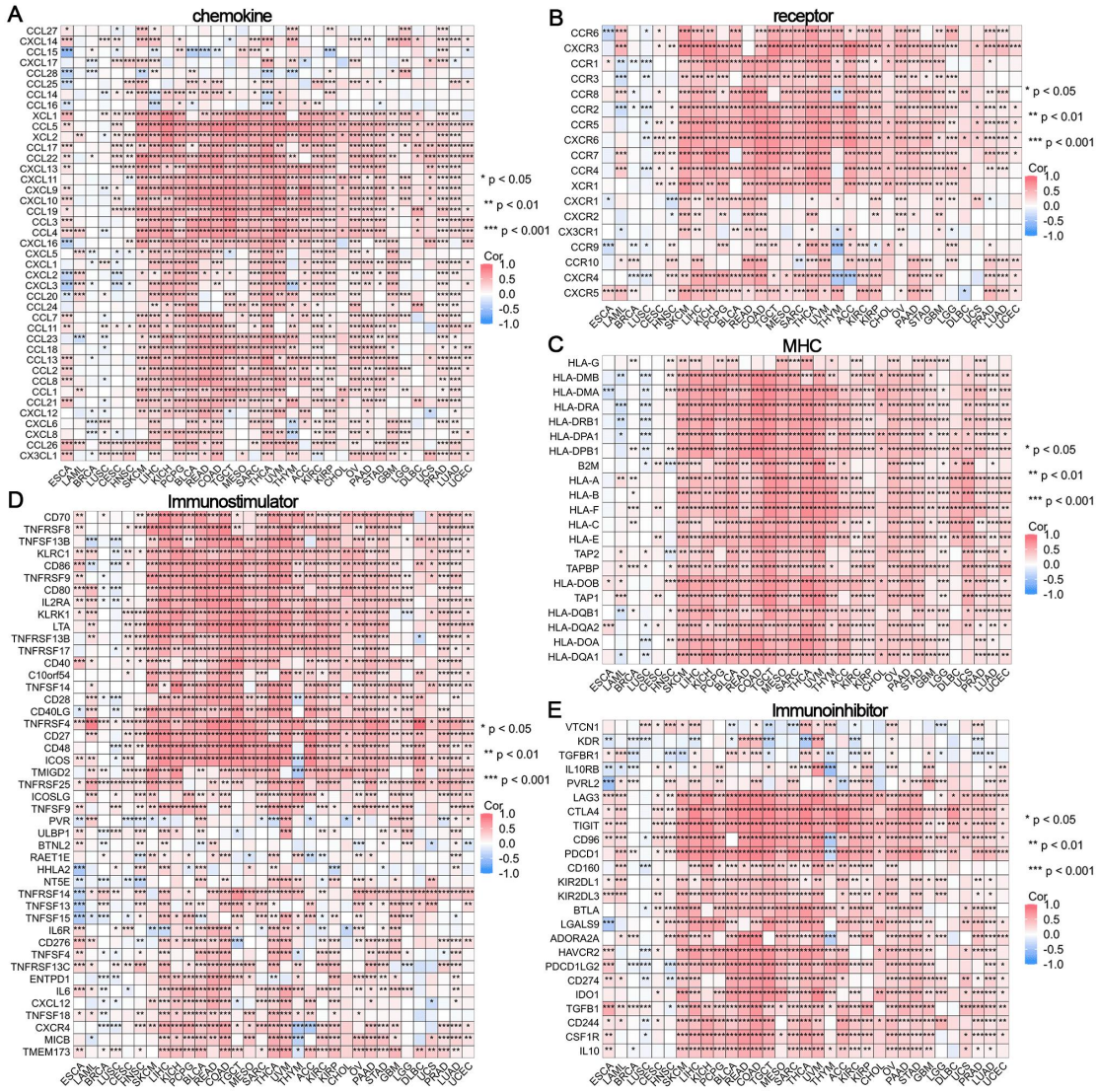

Fig. S3. Pan-cancer correlation analysis of TNFRSF18 with immune modulatory genes. Expression levels of TNFRSF18 were analyzed for significant correlations (Spearman's r) with five categories of immune-related genes across multiple cancer types: (A) Chemokine, (B) Immune stimulators, (C) Chemokine receptors, (D) MHC molecules, and (E) Immune inhibitors.

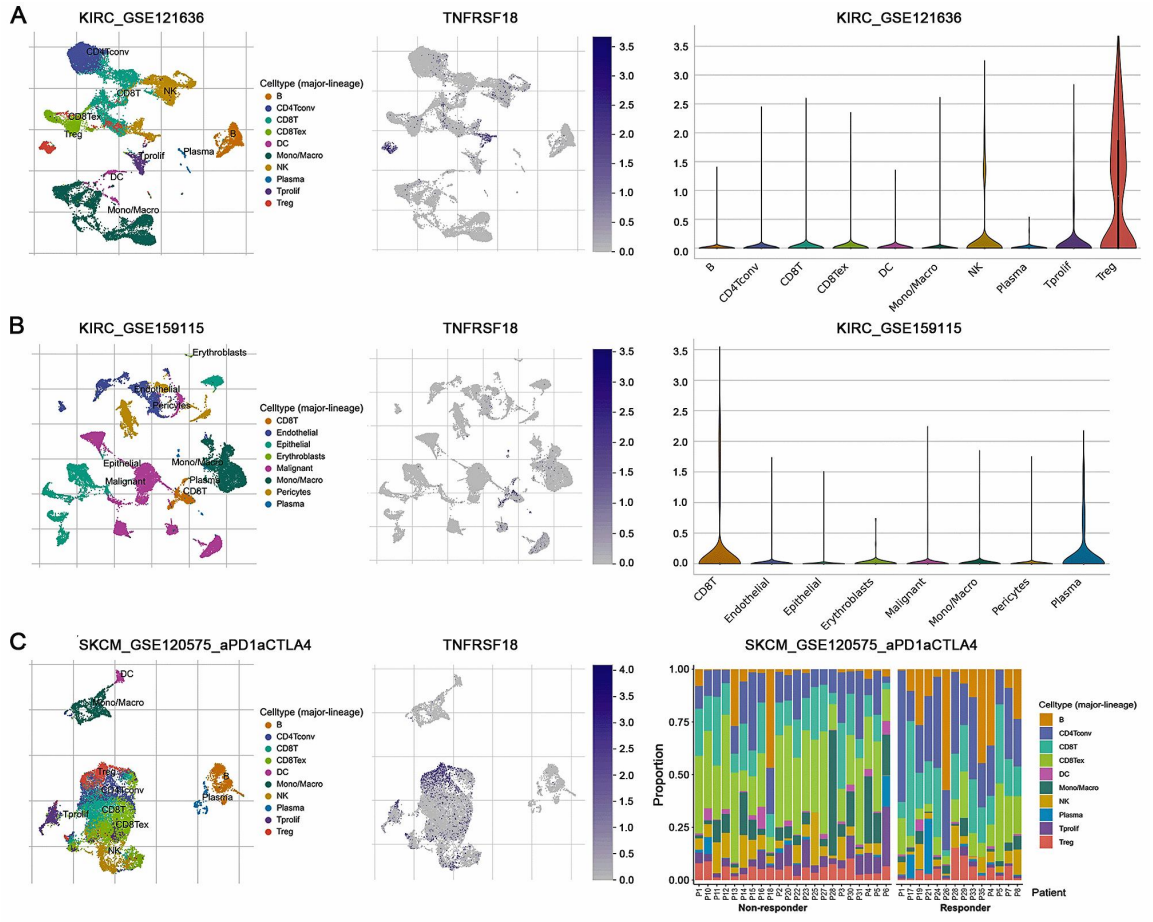

Fig. S4. Single-cell TNFRSF18 expression profiles. (A-B) Single-cell transcriptional profiles of TNFRSF18 across distinct KIRC cohorts (GSE121636 and GSE159115). (C) Comparative single-cell expression patterns of TNFRSF18 between immunotherapy responders and non-responders.

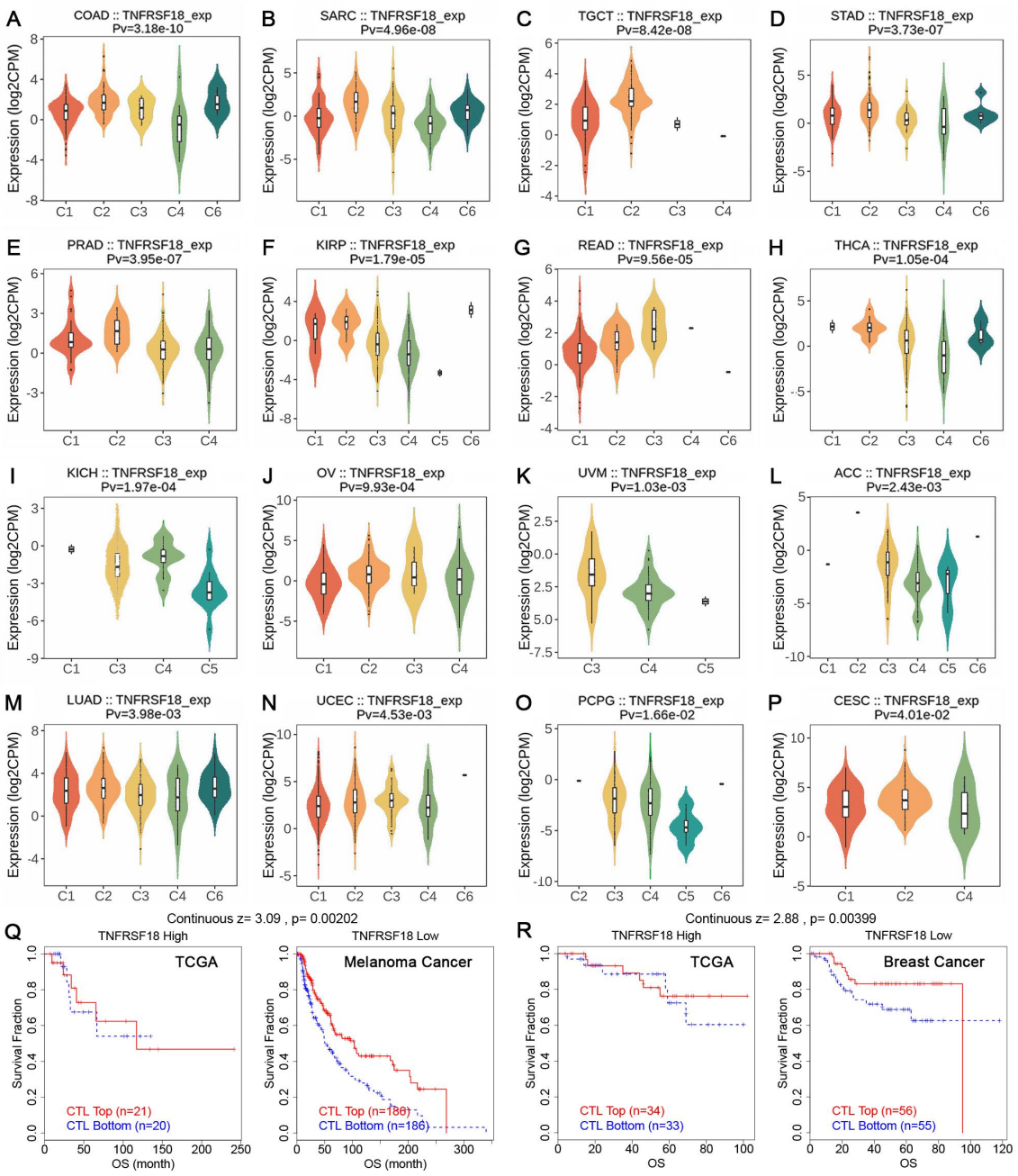

Fig. S5. Pan-cancer analysis of TNFRSF18 expression across immune subtypes and CTL. TNFRSF18 expression levels among six consensus molecular immune subtypes (C1: wound healing; C2: IFN-γ dominant; C3: inflammatory; C4: lymphocyte depleted; C5: immunologically quiet; C6: TGF-β dominant) in multiple cancer types: (A) COAD, (B) SARC, (C) TGCT, (D) STAD, (E) PEAD, (F) KIRP, (G) READ, (H) THCA, (I) KICH, (J) OV, (K) UVM, (L) ACC, (M) LUAD, (N) UCEC, (O) PCPG, and (P) CESC. (Q-R) Kaplan-Meier survival curves stratified by combined TNFRSF18 expression (high/low) and cytotoxic T lymphocyte (CTL) infiltration levels.

Abbreviations:

Adrenocortical carcinoma	ACC
Bladder urothelial carcinoma	BLCA
Breast invasive carcinoma	BRCA
Cervical squamous cell carcinoma and endocervical adenocarcinoma	CESC
Cholangiocarcinoma	CHOL
Colon adenocarcinoma	COAD
Rectum adenocarcinoma	READ
Lymphoid neoplasm diffuse large B-cell lymphoma	DLBC
Disease-specific survival	DSS
Esophageal carcinoma	ESCA
Glioblastoma multiforme	GBM
Multiplex Immunohistochemistry	mIHC
Head and neck squamous cell carcinoma	HNSC
Kyoto encyclopedia of genes and genomes	KEGG
Kidney chromophobe	KICH
Kidney renal clear cell carcinoma	KIRC
Kidney renal papillary cell carcinoma	KIRP
Acute myeloid leukemia	LAML
Brain lower-grade glioma	LGG
Liver hepatocellular carcinoma	LIHC
Lung adenocarcinoma	LUAD
Lung squamous cell carcinoma	LUSC
Mesothelioma	MESO
major histocompatibility complex	MHC

Microsatellite instability	MSI
Overall survival	OS
Pancreatic adenocarcinoma	PAAD
Pheochromocytoma and paraganglioma	PCPG
Progression-free interval	PFI
Protein-protein interaction	PPI
Prostate adenocarcinoma	PRAD
Sarcoma	SARC
Skin cutaneous melanoma	SKCM
Stomach adenocarcinoma	STAD
Testicular germ cell tumors	TGCT
Thyroid carcinoma	THCA
Thymoma	THYM
Tumor mutational burden	TMB
Tumor microenvironment	TME
Tumor Necrosis Factor Receptor Superfamily Member 18	TNFRSF18
Regulatory T cells	Tregs
Uterine corpus endometrial carcinoma	UCEC
Uterine carcinosarcoma	UCS
Uveal melanoma	UVM