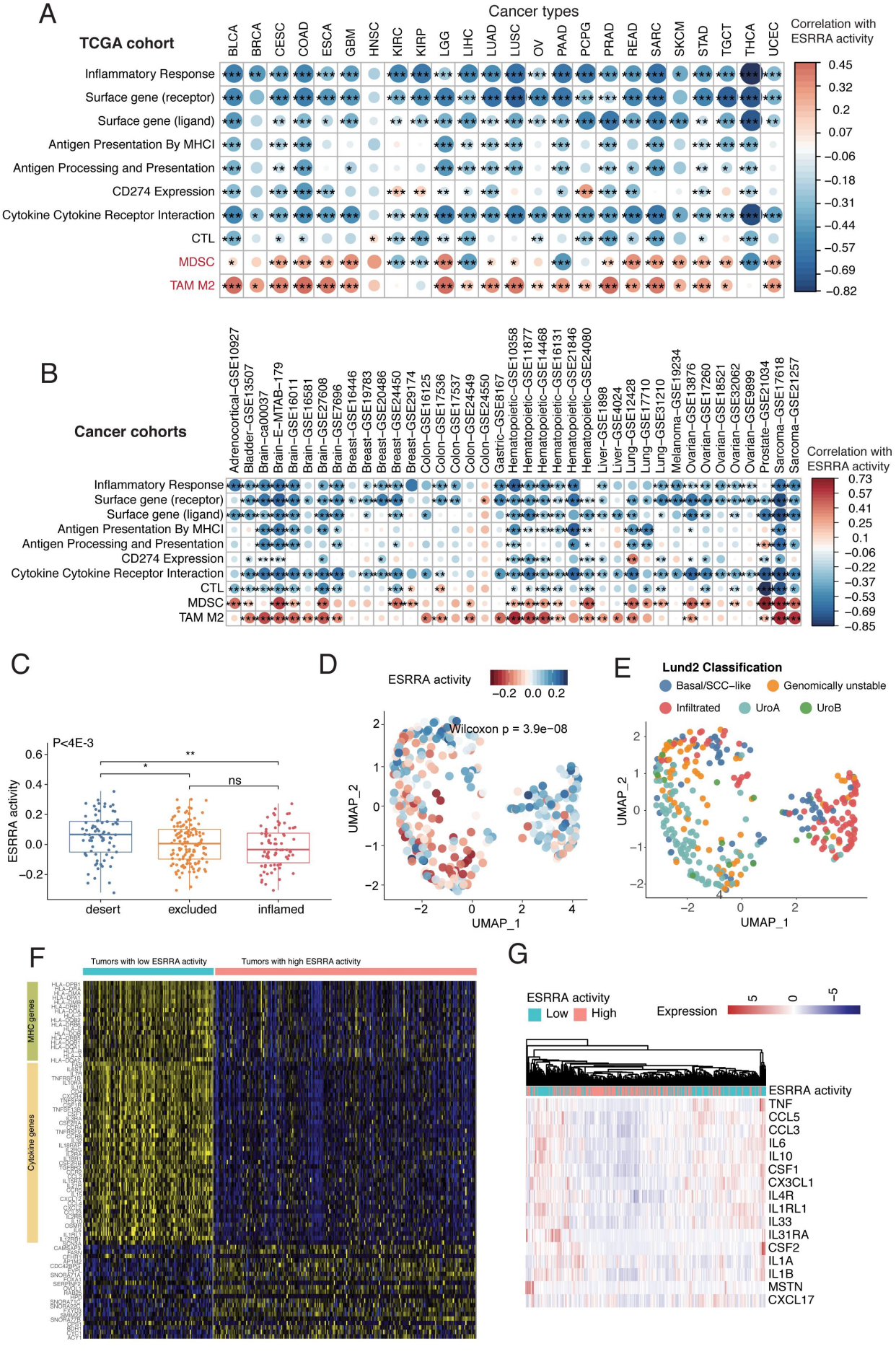
A
TCGA cohort
Cancer types
BLCA BRCA CESC COAD ESCA GBM HNSC KIRC KIRP LGG LIHC LUAD LUSC OV PAAD PCPG PRAD READ SARC SKCM STAD TGCT THCA UCEC
Correlation with ESRRA activity
0.45 0.32 0.2 0.07 −0.06 −0.18 −0.31 −0.44 −0.57 −0.69 −0.82
Inflammatory Response
Surface gene (receptor)
Surface gene (ligand)
Antigen Presentation By MHCI
Antigen Processing and Presentation
CD274 Expression
Cytokine Cytokine Receptor Interaction
CTL
MDSC
TAM M2
B
Cancer cohorts
Adrenocortical−GSE10927 Bladder−GSE13507 Brain−ca00037 Brain−E−MTAB−179 Brain−GSE16011 Brain−GSE16581 Brain−GSE27608 Brain−GSE7696 Breast−GSE16446 Breast−GSE19783 Breast−GSE20486 Breast−GSE24450 Breast−GSE29174 Colon−GSE16125 Colon−GSE17536 Colon−GSE17537 Colon−GSE24549 Colon−GSE24550 Gastric−GSE8167 Hematopoietic−GSE10358 Hematopoietic−GSE11877 Hematopoietic−GSE14468 Hematopoietic−GSE16131 Hematopoietic−GSE21846 Hematopoietic−GSE24080 Liver−GSE1898 Liver−GSE4024 Lung−GSE12428 Lung−GSE17710 Lung−GSE31210 Melanoma−GSE19234 Ovarian−GSE13876 Ovarian−GSE17260 Ovarian−GSE18521 Ovarian−GSE32062 Ovarian−GSE9899 Prostate−GSE21034 Sarcoma−GSE17618 Sarcoma−GSE21257
Correlation with ESRRA activity
0.73 0.57 0.41 0.25 0.1 −0.06 −0.22 −0.37 −0.53 −0.69 −0.85
Inflammatory Response
Surface gene (receptor)
Surface gene (ligand)
Antigen Presentation By MHCI
Antigen Processing and Presentation
CD274 Expression
Cytokine Cytokine Receptor Interaction
CTL
MDSC
TAM M2
C
P<4E-3
ESRRA activity
desert excluded inflamed
D
ESRRA activity
−0.2 0.0 0.2
Wilcoxon p = 3.9e−08
UMAP_2
UMAP_1
E
Lund2 Classification
Basal/SCC−like
Genomically unstable
Infiltrated
UroA
UroB
UMAP_2
UMAP_1
F
Tumors with low ESRRA activity
Tumors with high ESRRA activity
MHC genes
Cytokine genes
G
ESRRA activity
Low High
Expression
5 0 −5
ESRRA activity
TNF
CCL5
CCL3
IL6
IL10
CSF1
CX3CL1
IL4R
IL1RL1
IL33
IL31RA
CSF2
IL1A
IL1B
MSTN
CXCL17

Fig. S4. ESRRA inhibition correlated with immune infiltrations and proinflammatory signaling in patient tumors.

(**A, B**) Spearman correlation of ESRRA activity with levels of immune biomarkers in TCGA (**A**) and PRECOG (**B**) cancer cohorts. (**C**) ESRRA activity in bladder cancer patient (n=348; *Mariathasan et al.*) tumors with inflamed, excluded, and desert immunophenotypes (based on $CD8^{+}$T infiltration levels: inflamed > excluded > desert) in bladder cancer cohort. P-value was estimated using the Kruskal-Wallis test. (**D**) Unsupervised clustering of bladder cancer tumors identified two groups with markedly different ESRRA activities, shown by the UMAP plot. Significance is from the two-sided Wilcoxon rank-sum test. (**E**) Inflamed immunophenotype of bladder cancer patients concomitant with low ESRRA activity in tumors. Colors represent tumor classifications (Lund2) based on immunohistochemistry of tumors from bladder cancer patients. (**F**) The expression of the differentially expressed genes between two clusters with different ESRRA activities in the bladder cancer cohort. Cytokines and MHC genes are shown. (**G**) The z-score normalized expression of M1-polarizing cytokines in patients with low (green in the colorbar) and high ESRRA activity (red in the colorbar) in the bladder cancer cohort.