

**Table S1** Demographic characteristics of the cohorts for exposure

GWAS	Sample size (n)	Ethnicity	Smokers (%)	Male (%)	Assay	Sample	PubMed ID
Gene expression GWAS							
eQTLGen study	31,684	Mixed	NA	NA	Illumina (55%), Illumina TruSeq (20.3%), Affymetrix U219 (8.7%), Affymetrix Hu-Ex v1.0ST (16%)	Whole blood, peripheral blood mononuclear cell	34475573
Proteome GWAS							
INTERVAL study	3,301	British	8.6 <sup>+</sup>	51.1	SOMAscan	Plasma	29875488
AGES Reykjavik study	3,200	Icelandic	12 <sup>#</sup>	42.7	SOMAscan	Serum	30072576
KORA F4 study	1,000	Germany	36.3 <sup>+</sup>	49.8 <sup>§</sup>	SOMAscan	Blood	28240269

<sup>+</sup>, percentage of current smoker. <sup>#</sup>, percentage were calculated using total participants in the AGES Reykjavik study (n=5,457). <sup>§</sup>, percentage of total participants. GWAS, genome-wide association study.

**Table S2** Characteristics of the study populations in the TRICL-ILLCO and OncoArray studies for the outcome

study	Overall		Histological types				Smoking status			
			LUAD		LUSC		Never smoking		Ever smoking	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
OnciArray	14,803	12,262	6,411	12,262	3,529	12,262	1,624	4,274	12,803	7,647
TRICL-ILLCO	14,463	44,188	4,862	43,221	3,897	43,365	731	3,230	10,420	9,317
deCODE	1,319	26,380	547	26,380	259	26,380				
GLC	481	478	186	478	97	478	35	220	433	258
Harvard	984	970	597	970	216	970	92	161	892	809
IARC	2,533	3,791	517	2,824	911	2,968	159	1,253	2,367	2,508
ICR	1,952	5,200	465	5,200	611	5,200				
MDACC	1,150	1,134	619	1,134	306	1,134			1,150	1,134
NCI	5,713	5,736	1,841	5,736	1,447	5,736	350	1,379	5,342	4,336
Toronto	331	499	90	499	50	499	95	217	236	272
Total	29,266	56,450	11,273	55,483	7,426	55,627	2,355	7,504	23,223	16,964

OnciArray, the detailed characteristics of included in OncoArray studies can be found in original article's *Table S1*; deCODE, Icelandic Lung Cancer Study, Iceland; GLC, German Lung Cancer Study, US; Harvard, Harvard Lung Cancer Study, US; IARC, the International Agency for Research on Cancer Genome-wide Association Study, France; ICR, the institute of Cancer Research Genome-wide Association Study, UK; MDACC, the MD Anderson Cancer Center Genome-wide Association Study, US; NCI, the National Cancer Institute Genome-wide Association Study, US; Toronto, the Lundenfeld-Tanenbaum Research Institute Genome-wide Association Study, Toronto, Canada. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

**Table S3** Significant mendelian randomization analyses result of the druggable genes overlapping between eQTL ( $P \leq 1.03E-05$ ) and pQTL (nominal  $P < 0.05$ )

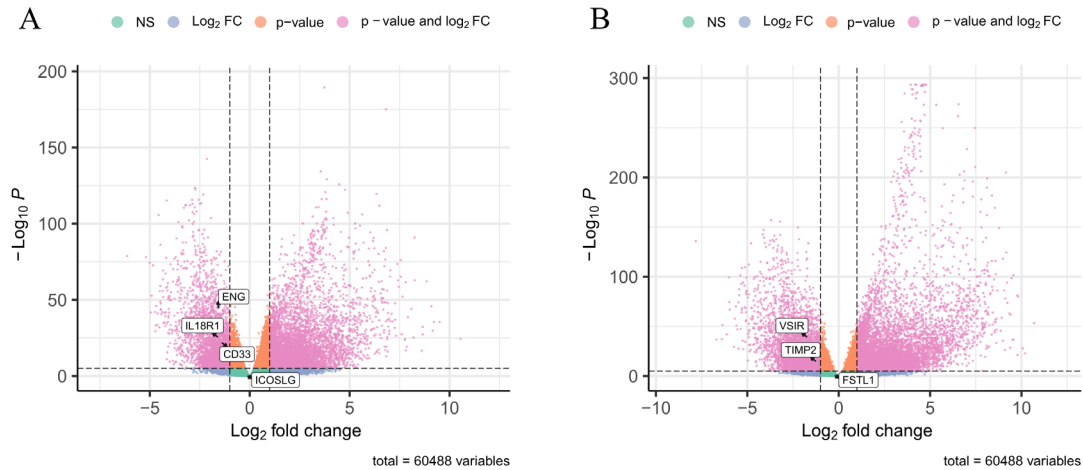
Exposure	Outcome	Gene	Method	nsnp	b	se	b_lci	b_uci	pval	OR	OR_lci	OR_uci
Suhre <i>et al.</i>	LUAD	CD33	Inverse variance weighted (multiplicative random effects)	3	-0.0165	0.0069	-0.0300	-0.0030	1.65E-02	0.9837	0.9705	0.9970
Sun <i>et al.</i>	LUAD	CD33	Wald ratio	1	0.0148	0.0186	-0.0217	0.0512	4.27E-01	1.0149	0.9786	1.0526
Vösa <i>et al.</i>	LUAD	CD33	Inverse variance weighted (multiplicative random effects)	3	-0.1304	0.0232	-0.1759	-0.0849	2.00E-08	0.8777	0.8387	0.9186
Emilsson <i>et al.</i>	LUSC	CD33	Wald ratio	1	-0.0019	0.0222	-0.0453	0.0415	9.31E-01	0.9981	0.9557	1.0424
Suhre <i>et al.</i>	LUSC	CD33	Inverse variance weighted (multiplicative random effects)	3	-0.0099	0.0074	-0.0244	0.0046	1.80E-01	0.9901	0.9758	1.0046
Sun <i>et al.</i>	LUSC	CD33	Wald ratio	1	0.0182	0.0216	-0.0241	0.0604	3.99E-01	1.0183	0.9762	1.0623
Vösa <i>et al.</i>	LUSC	CD33	Inverse variance weighted (multiplicative random effects)	3	-0.0893	0.0333	-0.1545	-0.0241	7.27E-03	0.9146	0.8568	0.9762
Emilsson <i>et al.</i>	LUAD	ENG	Wald ratio	1	0.1065	0.1062	-0.1016	0.3147	3.16E-01	1.1124	0.9034	1.3698
Suhre <i>et al.</i>	LUAD	ENG	Inverse variance weighted (multiplicative random effects)	2	-0.0895	0.0047	-0.0986	-0.0804	1.79E-82	0.9144	0.9061	0.9228
Vösa <i>et al.</i>	LUAD	ENG	Inverse variance weighted (multiplicative random effects)	2	-0.1349	0.0259	-0.1858	-0.0841	1.97E-07	0.8738	0.8304	0.9193
Emilsson <i>et al.</i>	LUSC	ENG	Wald ratio	1	-0.0115	0.1200	-0.2468	0.2238	9.24E-01	0.9885	0.7813	1.2508
Suhre <i>et al.</i>	LUSC	ENG	Inverse variance weighted (multiplicative random effects)	2	-0.0717	0.0144	-0.0999	-0.0435	6.05E-07	0.9308	0.9049	0.9574
Vösa <i>et al.</i>	LUSC	ENG	Inverse variance weighted (multiplicative random effects)	2	-0.0114	0.0637	-0.1363	0.1134	8.57E-01	0.9886	0.8726	1.1201
Suhre <i>et al.</i>	LUAD	FSTL1	Wald ratio	1	0.0119	0.0662	-0.1178	0.1415	8.58E-01	1.0119	0.8889	1.1520
Sun <i>et al.</i>	LUAD	FSTL1	Wald ratio	1	0.0156	0.0867	-0.1544	0.1856	8.58E-01	1.0157	0.8569	1.2039
Vösa <i>et al.</i>	LUAD	FSTL1	Wald ratio	1	0.0115	0.0641	-0.1142	0.1372	8.58E-01	1.0116	0.8921	1.1470
Emilsson <i>et al.</i>	LUSC	FSTL1	Wald ratio	1	-0.2379	0.0774	-0.3895	-0.0862	2.11E-03	0.7883	0.6774	0.9174
Sun <i>et al.</i>	LUSC	FSTL1	Wald ratio	1	-0.3118	0.1014	-0.5106	-0.1130	2.11E-03	0.7321	0.6001	0.8931
Vösa <i>et al.</i>	LUSC	FSTL1	Inverse variance weighted (multiplicative random effects)	2	-0.2323	0.0080	-0.2480	-0.2167	2.09E-186	0.7927	0.7804	0.8052
Emilsson <i>et al.</i>	LUAD	ICOSLG	Inverse variance weighted (multiplicative random effects)	2	-0.0075	0.0031	-0.0135	-0.0014	1.53E-02	0.9926	0.9866	0.9986
Sun <i>et al.</i>	LUAD	ICOSLG	Wald ratio	1	-0.0095	0.0313	-0.0708	0.0518	7.61E-01	0.9905	0.9316	1.0532
Vösa <i>et al.</i>	LUAD	ICOSLG	Inverse variance weighted (multiplicative random effects)	2	0.0484	0.0042	0.0401	0.0567	1.39E-30	1.0496	1.0410	1.0583
Emilsson <i>et al.</i>	LUSC	ICOSLG	Inverse variance weighted (multiplicative random effects)	2	0.0293	0.0480	-0.0646	0.1233	5.40E-01	1.0298	0.9374	1.1313
Sun <i>et al.</i>	LUSC	ICOSLG	Wald ratio	1	0.0293	0.0364	-0.0421	0.1007	4.21E-01	1.0297	0.9588	1.1059
Vösa <i>et al.</i>	LUSC	ICOSLG	Inverse variance weighted (multiplicative random effects)	2	-0.0662	0.0428	-0.1502	0.0177	1.22E-01	0.9359	0.8606	1.0179
Emilsson <i>et al.</i>	LUAD	IL18R1	Wald ratio	1	0.0332	0.0262	-0.0182	0.0846	2.06E-01	1.0338	0.9820	1.0883
Suhre <i>et al.</i>	LUAD	IL18R1	Inverse variance weighted (multiplicative random effects)	4	0.0272	0.0103	0.0071	0.0474	8.13E-03	1.0276	1.0071	1.0485
Sun <i>et al.</i>	LUAD	IL18R1	Inverse variance weighted (multiplicative random effects)	2	-0.0269	0.0169	-0.0601	0.0063	1.13E-01	0.9735	0.9417	1.0064
Vösa <i>et al.</i>	LUAD	IL18R1	Inverse variance weighted (multiplicative random effects)	2	0.0776	0.0032	0.0713	0.0839	1.90E-128	1.0807	1.0739	1.0875
Emilsson <i>et al.</i>	LUSC	IL18R1	Wald ratio	1	0.0358	0.0304	-0.0237	0.0954	2.38E-01	1.0365	0.9766	1.1000
Suhre <i>et al.</i>	LUSC	IL18R1	Inverse variance weighted (multiplicative random effects)	4	0.0174	0.0130	-0.0081	0.0429	1.81E-01	1.0176	0.9919	1.0439
Vösa <i>et al.</i>	LUSC	IL18R1	Inverse variance weighted (multiplicative random effects)	2	0.0141	0.0416	-0.0676	0.0957	7.36E-01	1.0142	0.9347	1.1004
Emilsson <i>et al.</i>	LUAD	TIMP2	Wald ratio	1	-0.0011	0.0607	-0.1200	0.1178	9.86E-01	0.9989	0.8870	1.1250
Vösa <i>et al.</i>	LUAD	TIMP2	Inverse variance weighted (multiplicative random effects)	3	-0.0504	0.0423	-0.1333	0.0324	2.33E-01	0.9508	0.8752	1.0330
Emilsson <i>et al.</i>	LUSC	TIMP2	Wald ratio	1	-0.1895	0.0701	-0.3269	-0.0520	6.89E-03	0.8274	0.7212	0.9493
Vösa <i>et al.</i>	LUSC	TIMP2	Inverse variance weighted (multiplicative random effects)	2	0.2370	0.0528	0.1335	0.3406	7.27E-06	1.2675	1.1428	1.4058
Emilsson <i>et al.</i>	LUAD	VSIR	Wald ratio	1	-0.0741	0.0892	-0.2489	0.1007	4.06E-01	0.9286	0.7797	1.1059
Sun <i>et al.</i>	LUAD	VSIR	Wald ratio	1	-0.0752	0.0848	-0.2413	0.0910	3.75E-01	0.9276	0.7856	1.0952
Vösa <i>et al.</i>	LUAD	VSIR	Inverse variance weighted (multiplicative random effects)	2	0.0955	0.0093	0.0773	0.1137	8.45E-25	1.1002	1.0803	1.1204
Emilsson <i>et al.</i>	LUSC	VSIR	Wald ratio	1	-0.1851	0.1031	-0.3873	0.0170	7.26E-02	0.8310	0.6789	1.0171
Sun <i>et al.</i>	LUSC	VSIR	Wald ratio	1	-0.1932	0.0984	-0.3860	-0.0004	4.95E-02	0.8243	0.6798	0.9996
Vösa <i>et al.</i>	LUSC	VSIR	Inverse variance weighted (multiplicative random effects)	2	-0.1279	0.0121	-0.1515	-0.1042	3.35E-26	0.8800	0.8594	0.9010

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; eQTL, expression quantitative trait locus; pQTL, protein quantitative trait locus; OR, odds ratio.

**Table S4** Sensitivity analyses of the genes in MR estimates

Exposure category	Outcome	Gene	Q	Q_pval	lsq	MR-Egger_intercept_beta	MR-Egger_intercept_se	pval
eQTL	LUAD	<i>CD33</i>	0.4340	0.8049	0.6112	0.0064	0.0381	0.8933
		<i>ENG</i>	0.2678	0.6048	0.4862			
		<i>ICOSLG</i>	0.0039	0.9502	0.0000			
		<i>IL18R1</i>	0.0047	0.9455	0.5243			
	LUSC	<i>VSIR</i>	0.0062	0.9370	0.0000			
		<i>FSTL1</i>	0.0119	0.9131	0.8162			
pQTL	LUAD	<i>CD33</i>	0.4938	0.7812	0.0000	-0.0123	0.0212	0.6661
		<i>ENG</i>	0.0262	0.8713	0.8836			
		<i>ICOSLG</i>	0.0187	0.8913	0.0000			
		<i>IL18R1</i>	1.2326	0.7452	0.2550	-0.0034	0.0221	

eQTL, expression quantitative trait locus; pQTL, protein quantitative trait locus; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MR, Mendelian randomization.

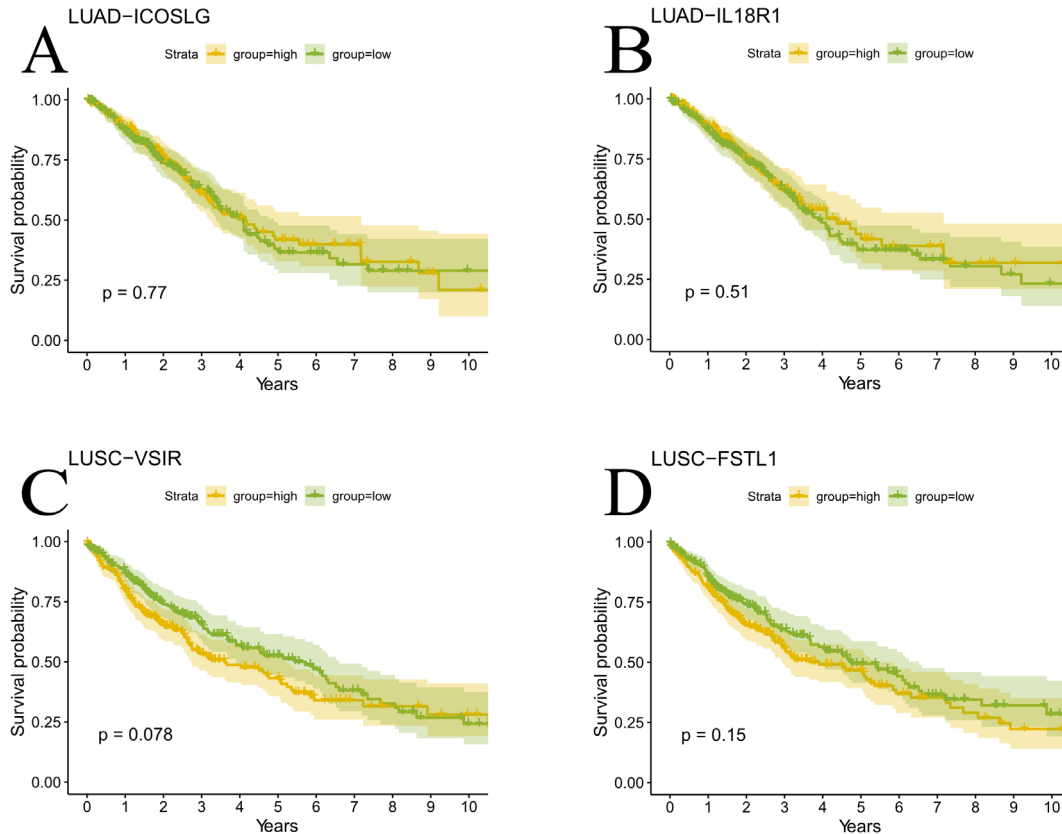


**Figure S1** Volcano plot presenting the  $-\log_{10}(P)$  and  $\log_2(\text{FC})$  of differentially expressed genes identified in LUAD and LUSC. Comparison was made between tumor tissue and normal tissue. *ENG1*, *CD33* and *IL18R1* were significantly down-regulated in tumor tissue. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; FC, fold change; NS, not significant.

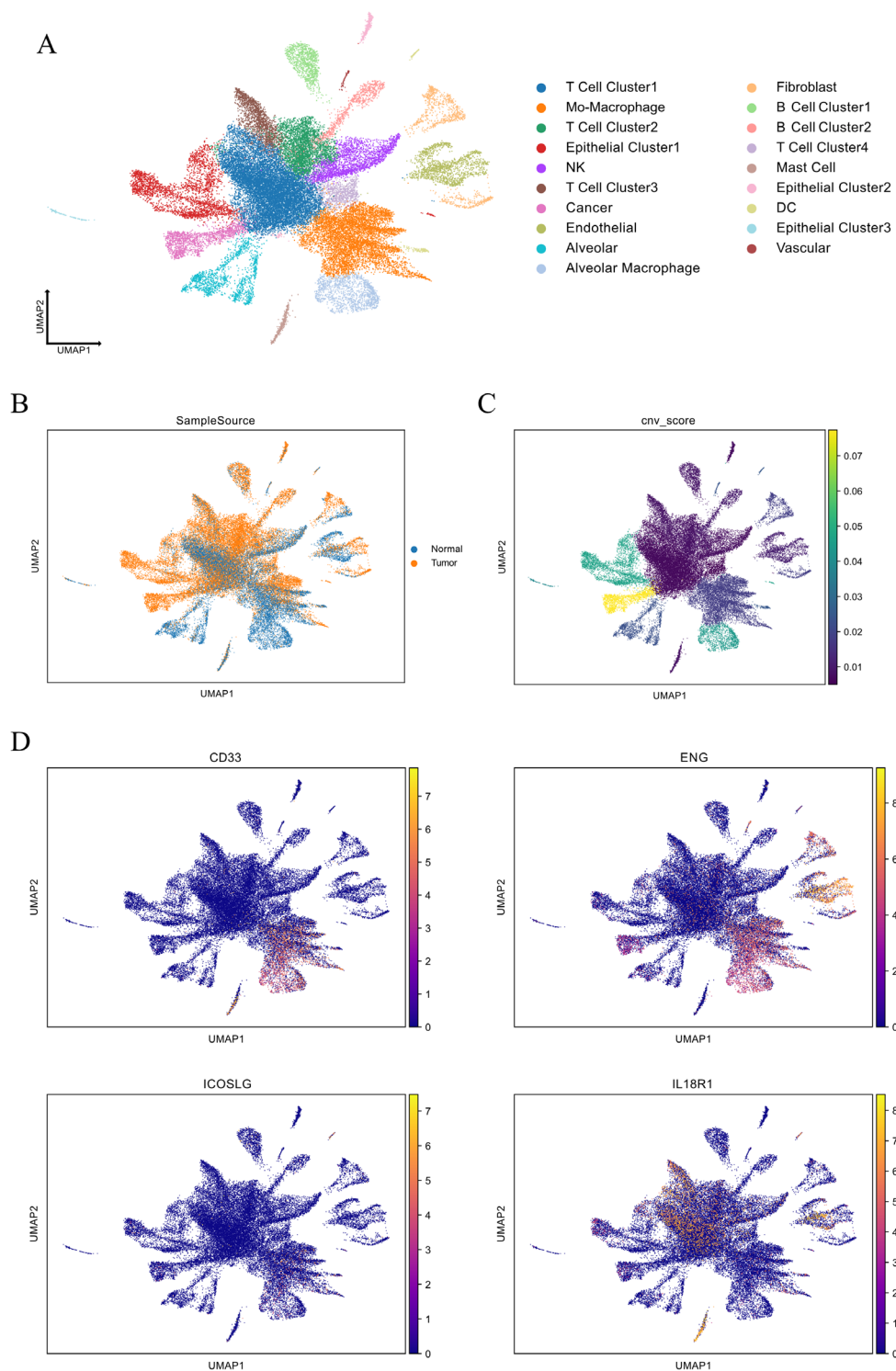
**Table S5** DESeq2 differential expressed genes analysis result between LUAD and LUSC tumor tissue and normal tissue

Category	EnsemblID	Symbol	BaseMean	Log <sub>2</sub> FoldChange	LfcSE	Stat	p.value	p.adj
LUAD	ENSG00000105383	CD33	321.9144	-1.4210	0.1408	-10.0910	6.05E-24	7.38E-23
	ENSG00000106991	ENG	8396.8961	-1.5823	0.1102	-14.3548	9.95E-47	4.36E-45
	ENSG00000115604	IL18R1	282.2041	-1.5773	0.1460	-10.8042	3.29E-27	4.90E-26
	ENSG00000160223	ICOSLG	41.6021	-0.1383	0.1940	-0.7129	4.76E-01	5.58E-01
LUSC	ENSG00000035862	TIMP2	14860.8450	-1.2214	0.1517	-8.0525	8.11E-16	4.13E-15
	ENSG00000107738	VSIR	3306.6772	-1.7052	0.1275	-13.3699	9.07E-41	1.55E-39
	ENSG00000163430	FSTL1	14987.9301	-0.2431	0.1464	-1.6608	9.68E-02	1.35E-01

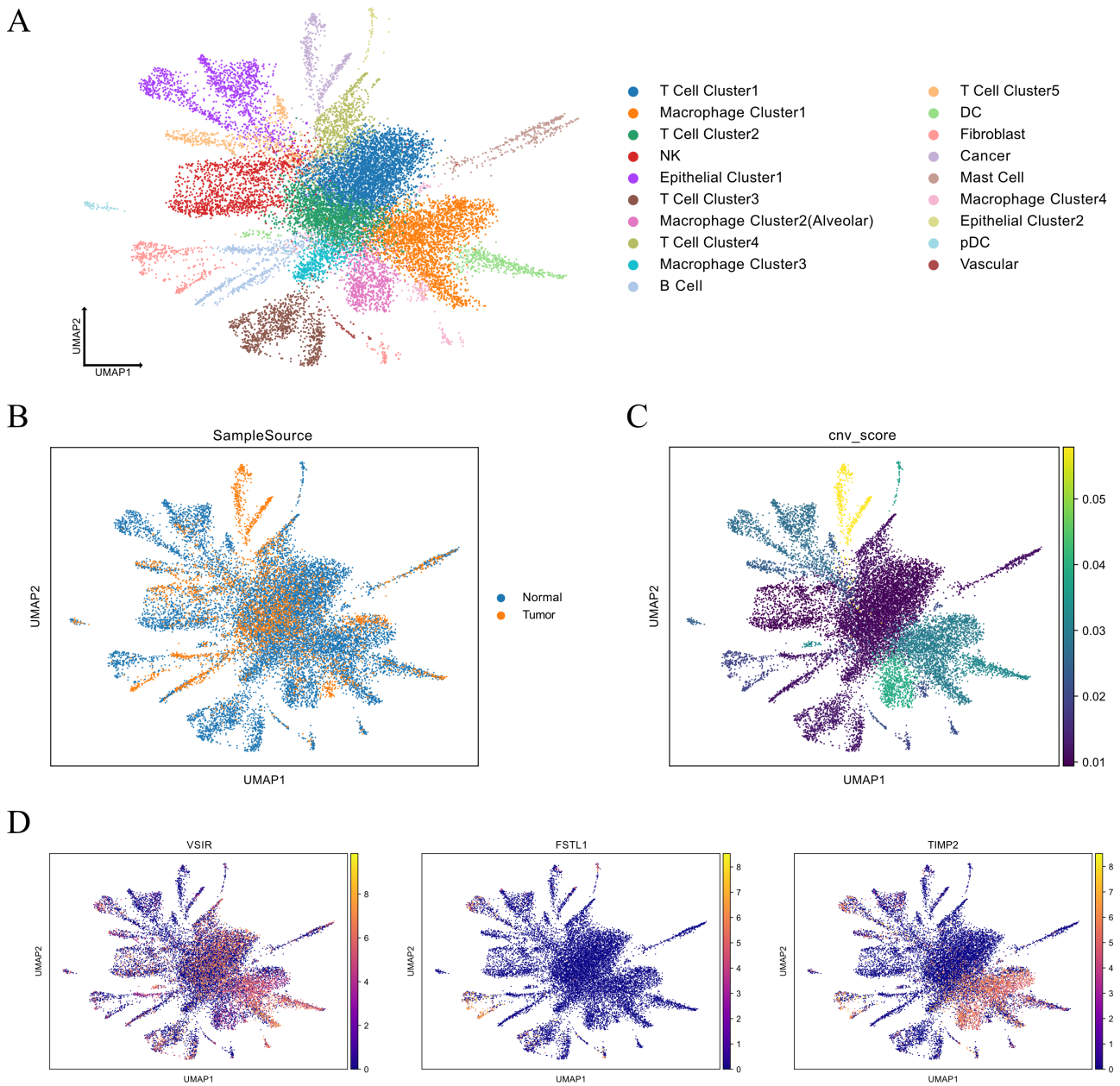
Only screened druggable genes were shown.  $|\log_2\text{FoldChange}| > 1$  and adjusted P value  $< 0.05$  were considered as statistically significant. Genes with  $\log_2\text{FoldChange} > 0$  were considered as highly expressed in tumor tissue while  $\log_2\text{FoldChange} < 0$  were considered as lowly expressed in tumor tissue. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.



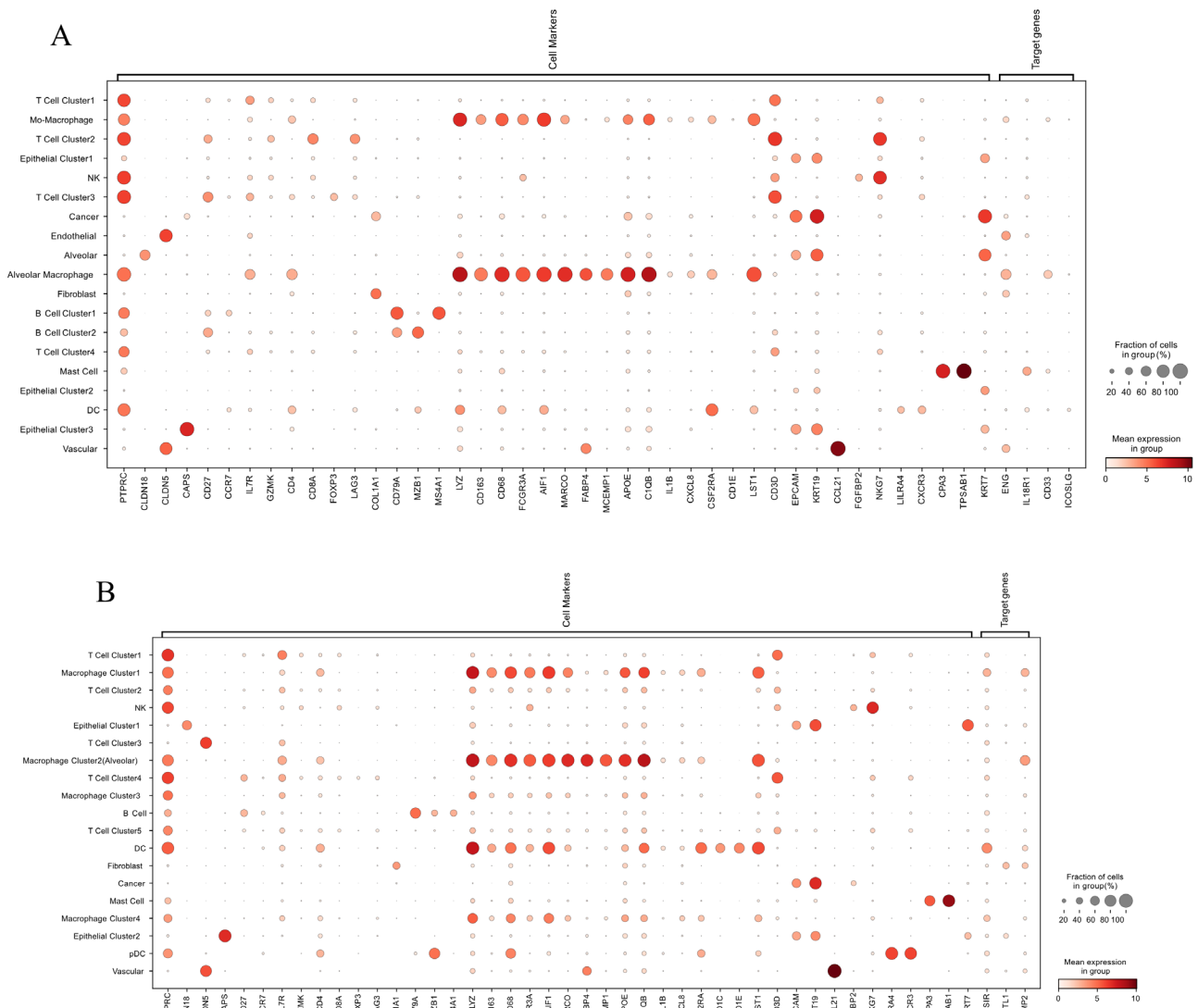
**Figure S2** Overall survival curves comparing groups with high and low expression of druggable genes. (A) ICOSLG; (B) IL18R1; (C) VSIR; (D) FSTL1. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.



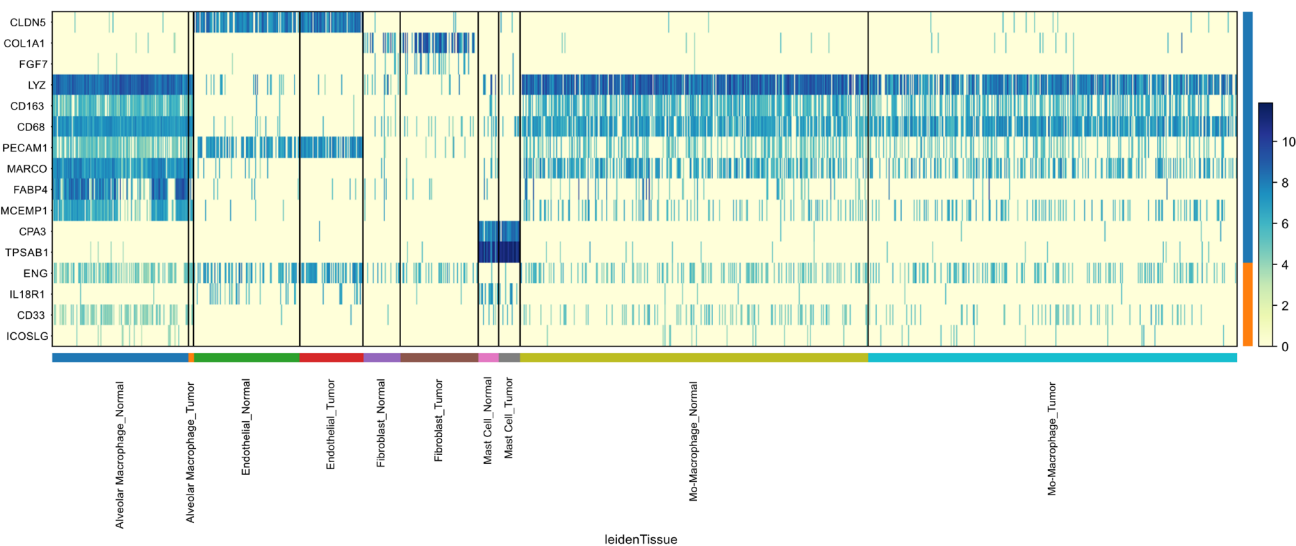
**Figure S3** UMAP representations of single-cell transcriptome in LUAD. (A) Cell clusters; (B) sample came from tumor or non-tumor tissue; (C) CNV scores generated by inferCNV analysis, with high CNV scores indicating malignant cells; (D) expression levels of screened druggable genes. UMAP, Uniform Manifold Approximation and Projection; LUAD, lung adenocarcinoma; NK, natural killer cells; DCs, dendritic cells; pDCs, plasmacytoid dendritic cells; CNV, copy number variations.



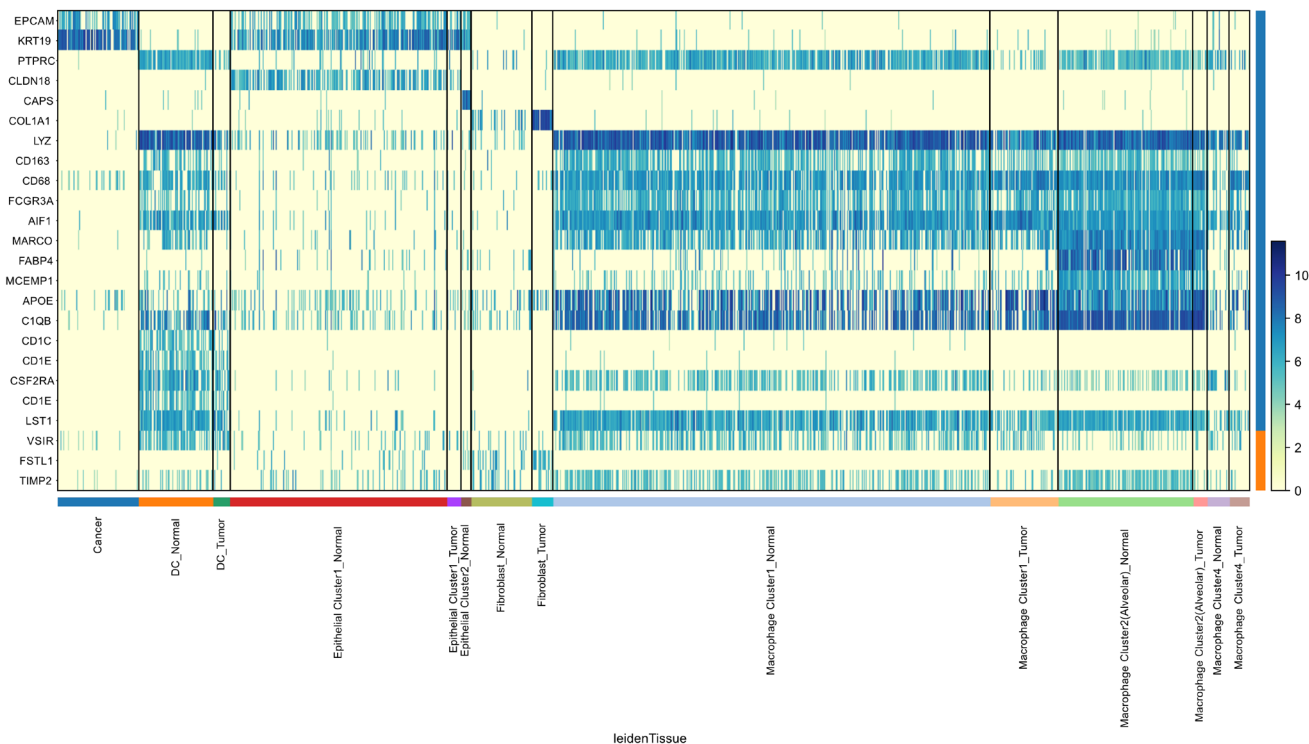
**Figure S4** UMAP representations of single-cell transcriptome in LUSC. (A) Cell clusters; (B) sample came from tumor or non-tumor tissue; (C) CNV scores generated by inferCNV analysis, with high CNV scores indicating malignant cells; (D) expression levels of screened druggable genes. UMAP, Uniform Manifold Approximation and Projection; LUSC, lung squamous cell carcinoma; CNV, copy number variations.



**Figure S5** Dot plots showing the expression levels of selected marker genes and druggable genes in various cell subpopulations in LUAD (A) and LUSC (B). The left column presents the cell subtypes identified based on Leiden clustering method. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.



**Figure S6** Heatmap showing the expression levels of marker genes and druggable genes in specific cell cluster of tumor or normal tissue in LUAD. Only cell clusters with high expression levels of druggable genes are displayed. LUAD, lung adenocarcinoma.



**Figure S7** Heatmap showing the expression levels of marker genes and the druggable genes in specific cell cluster of tumor or normal tissue in LUSC. Only cell clusters with high expression levels of druggable genes are displayed. LUSC, lung squamous cell carcinoma.