

# Association of Elevated Expression Levels of *COL4A1* in Stromal Cells with Immunosuppressive Tumor Microenvironment in Low-Grade Glioma, Pancreatic Adenocarcinoma, Skin Cutaneous Melanoma, and Stomach Adenocarcinoma

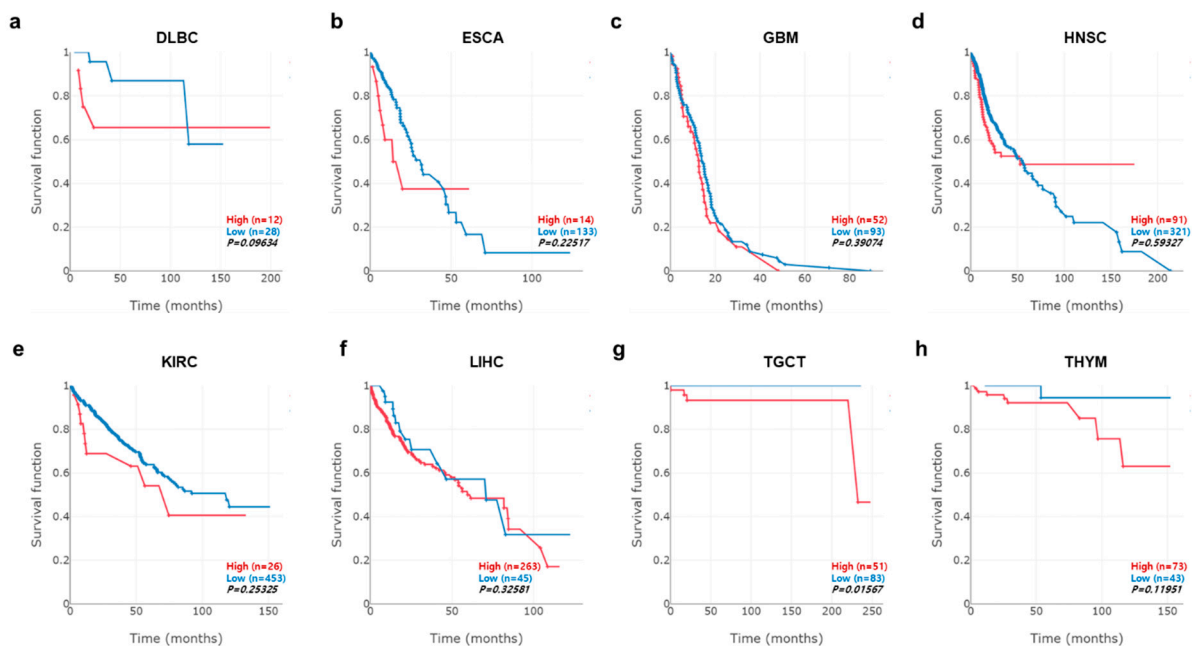
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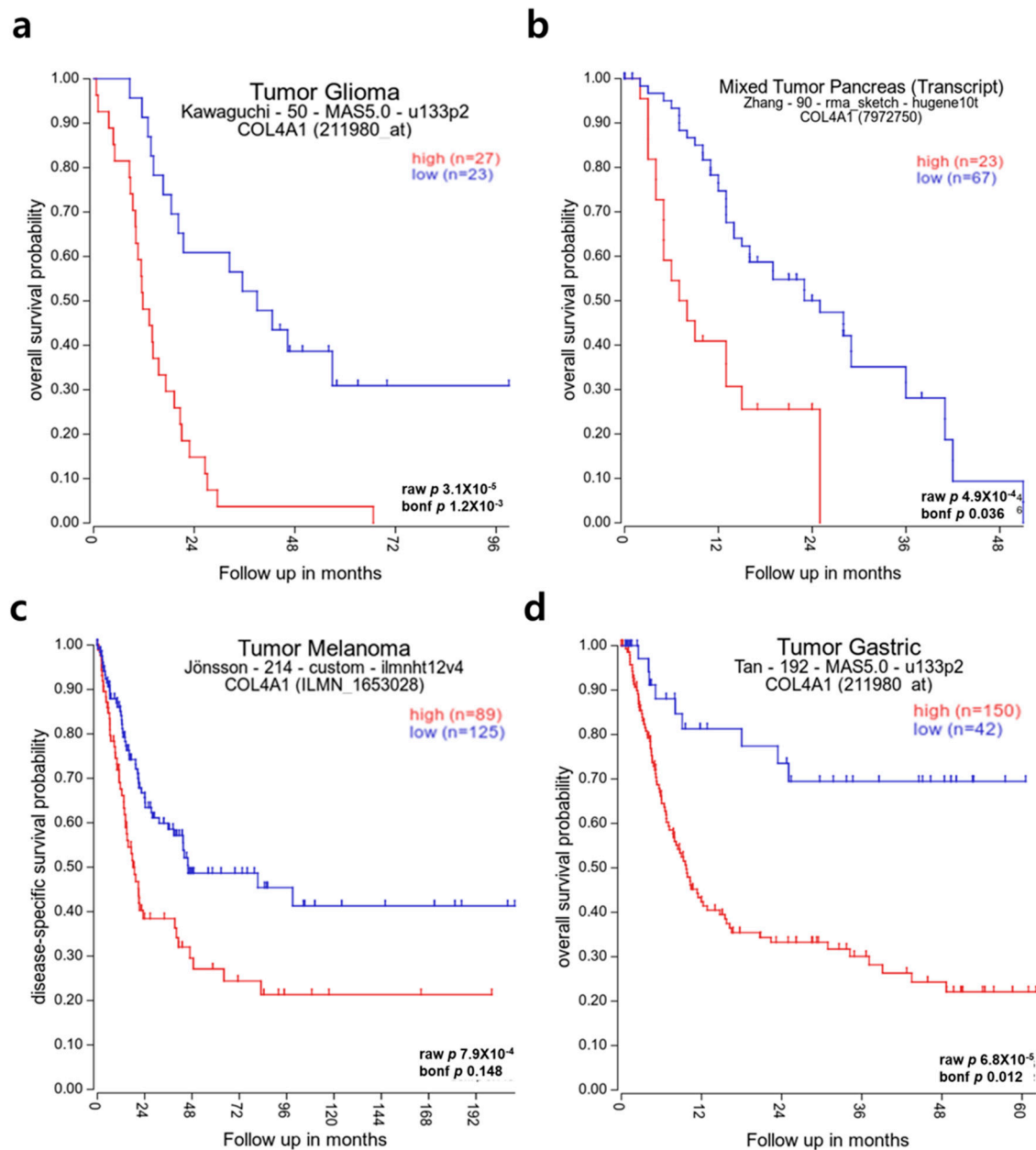
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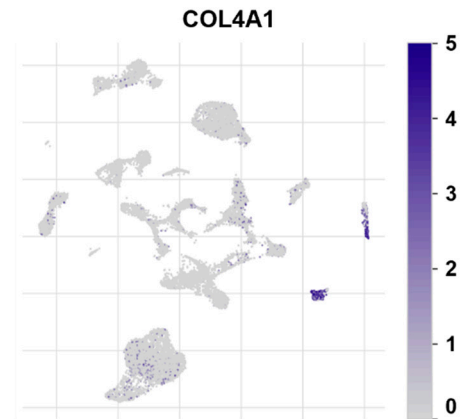
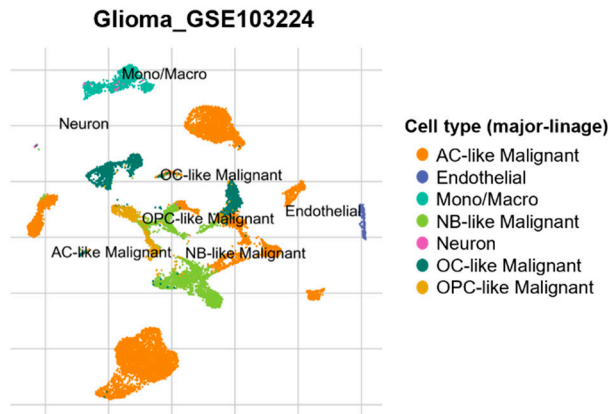
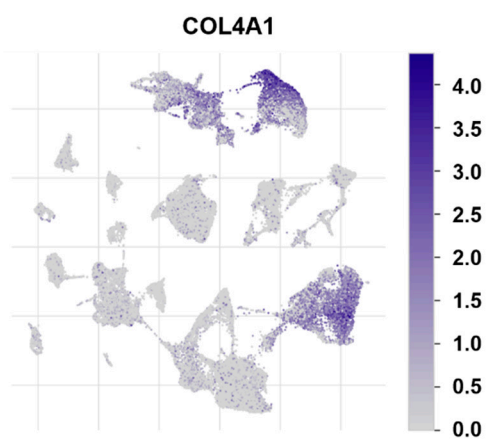
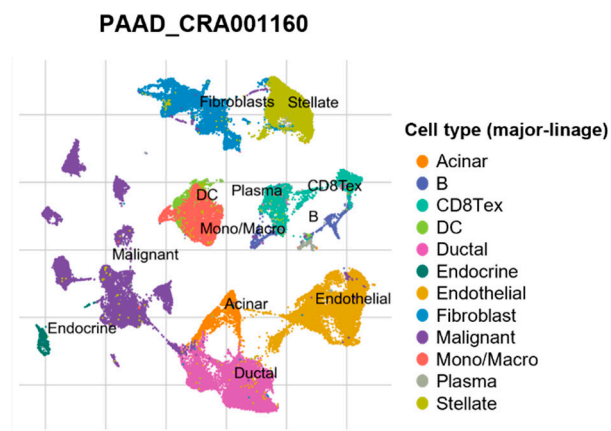
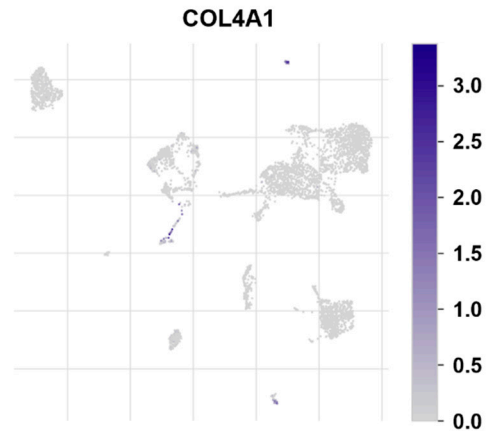
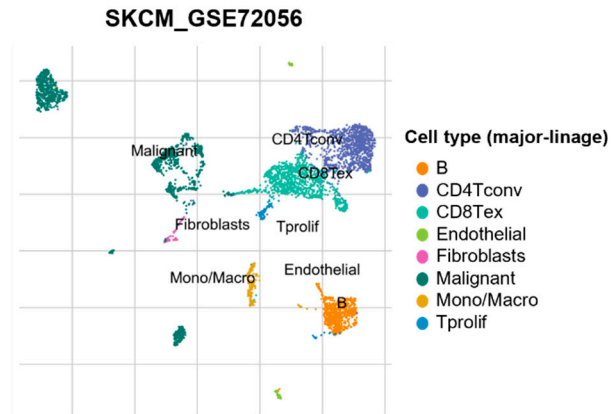
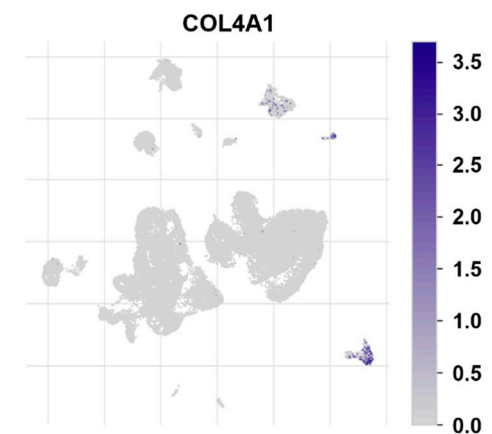
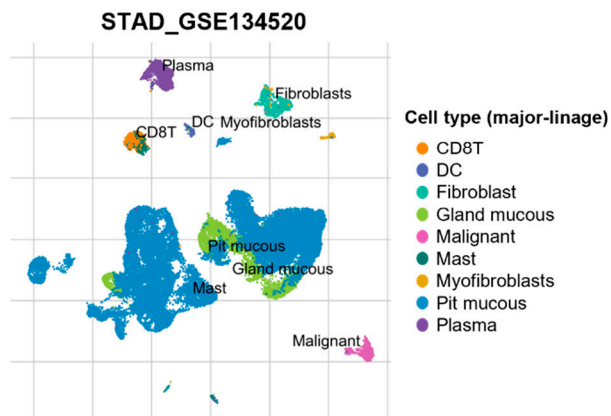
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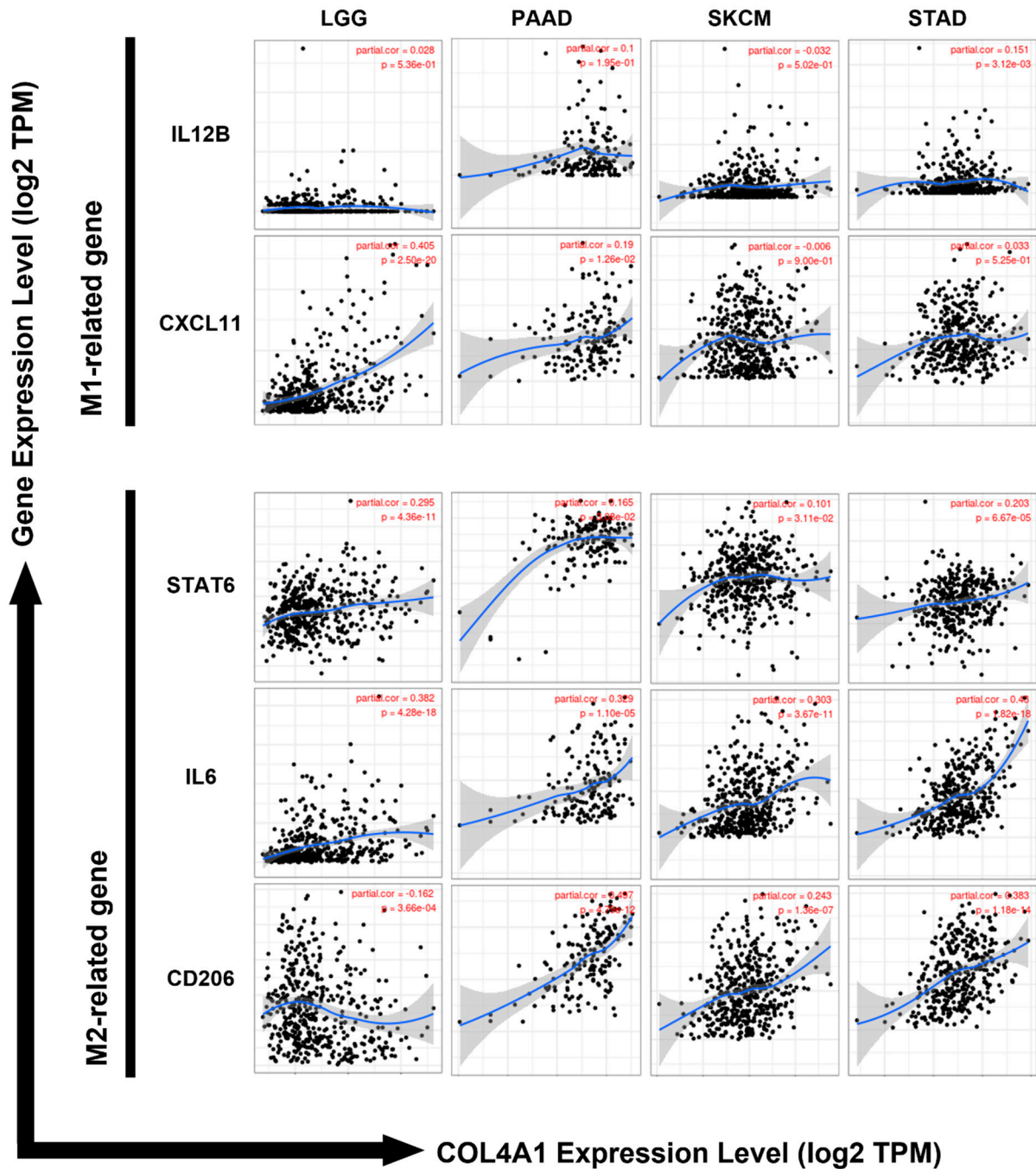
**Figure S1.** Overall patient survival according to the expression levels of collagen type IV alpha1 chain 1 (*COL4A1*) in diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), testicular germ cell tumors (TGCT), and thymoma (THYM). Kaplan-Meier survival curves of patient groups with high (red) and low (blue) *COL4A1* expression levels split by optimal cut-off to minimize the *p*-value were retrieved from The Cancer Genome Atlas (TCGA) datasets using the ESurv online analysis tool. (a) DLBC (n = 40), (b) ESCA (n = 147), (c) GBM (n = 145), and (d) HNSC (n = 412), (e) KIRC (n = 479), (f) LIHC (n = 308), (g) TGCA (n = 134), (h) THYM (n = 116).



**Figure S2.** Kaplan–Meier survival curves of patient groups with high and low *COL4A1* expression levels retrieved from the R2 platform. Kaplan–Meier survival curves of the patient groups with high (red) or low (blue) *COL4A1* expression levels were retrieved from the R2 platform. Patients were divided into two groups based on *COL4A1* expression levels to maximize the survival difference. The analyzed datasets were as follows: (a) tumor glioma (GSE43378,  $n = 50$ ), (b) mixed tumor pancreas (GSE28735,  $n = 90$ ), (c) tumor melanoma (GSE65904,  $n = 214$ ), and (d) tumor gastric (GSE15459,  $n = 192$ ).

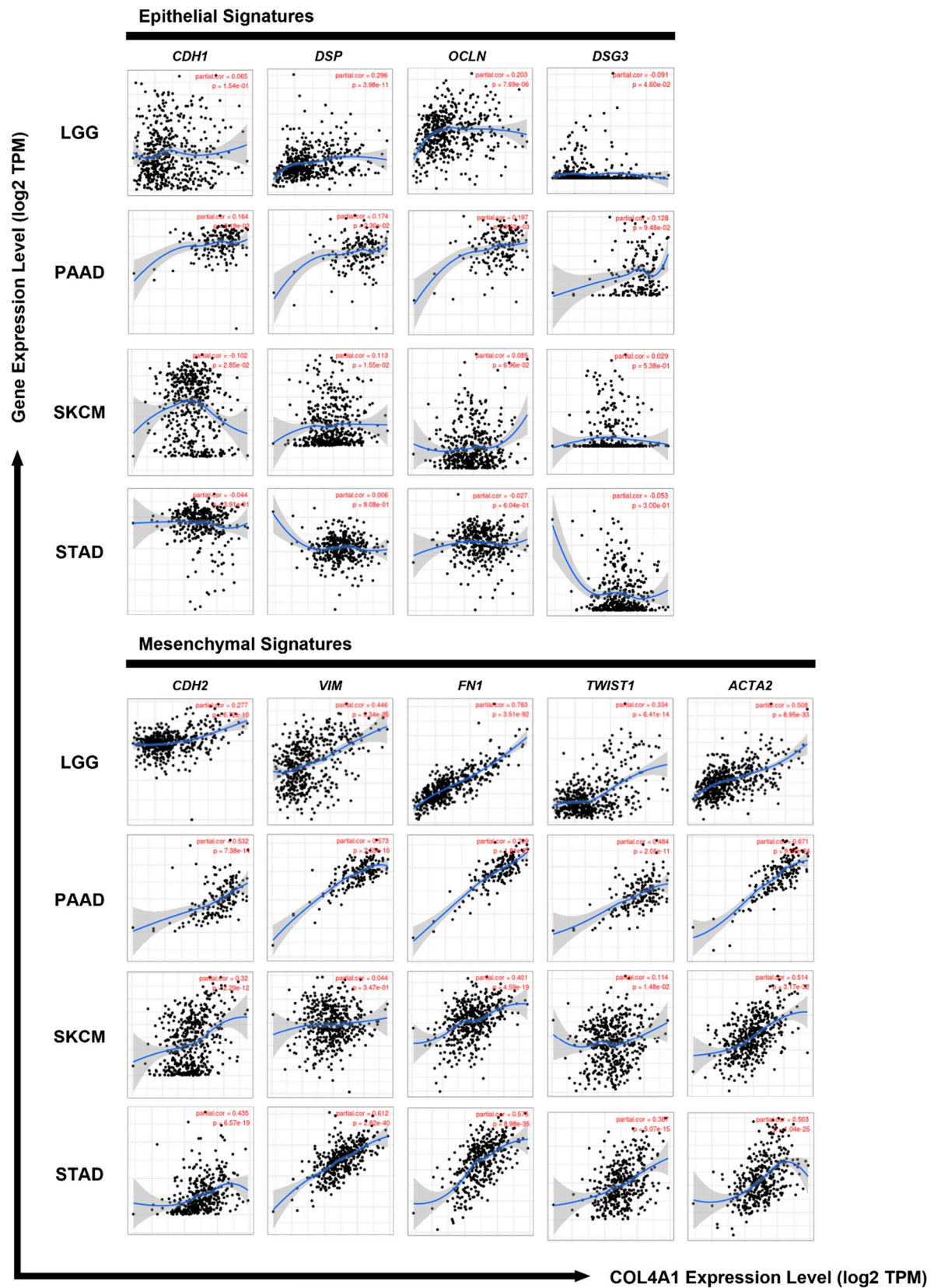
**a****b****c****d**

**Figure S3.** Single cell RNA-sequencing analysis of the *COL4A1* gene in TME cells of LGG, PAAD, SKCM, and STAD. Single cell RNA-sequencing plots of individual type of cancers with the expression of COL4A1 were retrieved from TISCH dataset browser. Analyzed cancer types were: (a) Glioma (GSE103224; 8 patients, 17185 cells), (b) PAAD (CRA001160; 35 patients, 57443 cells), (c) SKCM (GSE72056; 19 patients, 4645 cells), and (d) STAD (GSE134520; 13 patients, 41554 cells).



**Figure S4.** The correlation of *COL4A1* expression with the expression levels of various polarized macrophage-related genes in LGG, PAAD, SKCM, and STAD. Correlation analysis of individual type of cancers were retrieved from TIMER tool. Interleukin-12 subunit beta (*IL12B*) and C-X-C motif chemokine ligand 11 (*CXCL11*) were used as M1-related genes; Signal transducer and activator of transcription 6 (*STAT6*), interleukin-6 (*IL6*), and cluster of differentiation 206 (*CD206*) were used as M2-related genes.





**Figure S5.** The correlation of *COL4A1* expression with the expression levels of various EMT signature genes in LGG, PAAD, SKCM, and STAD. Correlation analysis of individual type of cancers were retrieved from TIMER tool. Cadherin 1 (*CDH1*, E-cadherin), desmoplakin (*DSP*), occludin (*OCLN*),

and desmoglein 3 (*DSG3*) were used for epithelial signature genes; Cadherin 2 (*CDH2*, N-cadherin), vimentin (*VIM*), fibronectin 1 (*FN1*), twist family bHLH transcription factor (*TWIST1*), and alpha smooth muscle actin (*ACTA2*) were used for mesenchymal signatures.

**Table S1.** List of The Cancer Genome Atlas (TCGA) abbreviations for different types of cancer.

Abbreviation	Name
ACC	Adrenocortical carcinoma
BLCA	Bladder urothelial carcinoma
BRCA	Breast invasive carcinoma
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangiocarcinoma
COAD	Colon adenocarcinoma
DLBC	Lymphoid neoplasm diffuse large B-cell lymphoma
ESCA	Esophageal carcinoma
GBM	Glioblastoma multiforme
HNSC	Head and neck squamous cell carcinoma
KICH	Kidney chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma
LAML	Acute myeloid leukemia
LGG	Low-grade glioma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MESO	Mesothelioma
OV	Ovarian serous cystadenocarcinoma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
SARC	Sarcoma
SKCM	Skin cutaneous melanoma
STAD	Stomach adenocarcinoma
TGCT	Testicular germ cell tumors
THCA	Thyroid carcinoma
THYM	Thymoma
UCEC	Uterine corpus endometrial carcinoma
UCS	Uterine carcinosarcoma
UVM	Uveal melanoma



**Table S2.** Correlation analyses among the expression levels of collagen type IV alpha chain 1 (*COL4A1*) and related marker genes of T, B, monocytes, natural killer (NK), dendritic, Th2, Tfh, Th17, and exhausted T cells in low-grade glioma (LGG), pancreatic adenocarcinoma (PAAD), skin cutaneous melanoma (SKCM), and stomach adenocarcinoma (STAD)-TCGA datasets using the Tumor Immune Estimation Resource (TIMER) web tool.

Description	Gene Markers	LGG				PAAD				SKCM				STAD			
		None		Purity		None		Purity		None		Purity		None		Purity	
		Cor	P	Cor	P	Cor	P	Cor	P	Cor	P	Cor	P	Cor	P	Cor	P
T cells (general)	<i>CD3D</i>	0.382	***	0.427	***	0.322	***	0.253	***	-0.006	0.901	-0.118	*	0.093	0.059	0.069	0.182
	<i>CD3E</i>	0.403	***	0.438	***	0.358	***	0.29	***	0.009	0.842	-0.095	*	0.127	**	0.109	*
	<i>CD2</i>	0.448	***	0.477	***	0.367	***	0.292	***	0.021	0.654	-0.078	0.097	0.141	**	0.125	*
B cells	<i>CD19</i>	0.365	***	0.36	***	0.232	**	0.179	*	0.005	0.907	-0.059	0.207	0.147	**	0.134	**
	<i>CD79A</i>	0.2	***	0.208	***	0.275	***	0.213	**	-0.05	0.28	-0.133	**	0.108	*	0.077	0.135
Monocytes	<i>CD86</i>	0.262	***	0.303	***	0.611	***	0.562	***	0.218	***	0.188	***	0.284	***	0.271	***
	<i>CSF1R</i>	0.111	*	0.141	**	0.581	***	0.524	***	0.317	***	0.308	***	0.418	***	0.399	***
NK cells	<i>KIR2DL1</i>	0.203	***	0.204	***	0.22	**	0.219	**	0.003	0.949	-0.049	0.299	0.119	*	0.118	*
	<i>KIR2DL3</i>	0.274	***	0.288	***	0.279	***	0.291	***	0.037	0.42	-0.029	0.542	0.081	0.099	0.07	0.174
	<i>KIR2DL4</i>	0.249	***	0.243	***	0.15	*	0.164	*	-0.045	0.332	-0.127	**	-0.061	0.214	-0.087	0.089
	<i>KIR3DL1</i>	0.168	***	0.171	***	0.204	**	0.187	*	0.042	0.367	-0.015	0.751	0.085	0.085	0.06	0.242
	<i>KIR3DL2</i>	0.178	***	0.19	***	0.223	**	0.174	*	0.045	0.329	-0.029	0.533	0.122	*	0.128	*
	<i>KIR3DL3</i>	0.013	0.771	0.017	0.707	0.194	**	0.144	0.06	-0.061	0.183	-0.087	0.062	-0.029	0.555	-0.008	0.878
	<i>KIR2DS4</i>	0.188	***	0.213	***	0.047	0.531	0.053	0.487	0.055	0.23	0.005	0.914	0.102	*	0.099	0.055
	<i>KLRK1</i>	-0.083	0.059	-0.106	*	0.22	**	0.182	*	-0.001	0.988	-0.074	0.116	0.112	*	0.089	0.085
	<i>NCR1</i>	0.24	***	0.228	***	0.364	***	0.405	***	0.147	**	0.105	*	0.161	**	0.16	**
	<i>NCR2</i>	0.05	0.254	0.045	0.325	-0.098	0.193	-0.091	0.237	0.048	0.296	0.025	0.593	-0.089	0.07	-0.1	0.053
	<i>NCR3</i>	0.07	0.113	0.084	0.065	0.173	*	0.129	0.094	0.092	*	0.023	0.621	0.106	*	0.098	0.056
Dendritic cells	<i>HLA-DPB1</i>	0.444	***	0.472	***	0.471	***	0.412	***	0.112	*	0.052	0.27	0.135	**	0.117	*
	<i>HLA-DQB1</i>	0.392	***	0.415	***	0.392	***	0.335	***	0.101	*	0.046	0.329	0.1	*	0.079	0.124

	<i>HLA-DRA</i>	0.465	***	0.491	***	0.549	***	0.498	***	0.114	*	0.056	0.229	0.1	*	0.088	0.088
	<i>HLA-DPA1</i>	0.478	***	0.508	***	0.548	***	0.503	***	0.079	0.087	0.014	0.768	0.094	0.056	0.078	0.131
	<i>CD1C</i>	0.278	***	0.271	***	0.283	***	0.227	**	0.127	**	0.083	0.076	0.186	***	0.169	***
	<i>NRP1</i>	0.616	***	0.604	***	0.741	***	0.716	***	0.67	***	0.665	***	0.662	***	0.638	***
	<i>ITGAX</i>	0.219	***	0.262	***	0.497	***	0.434	***	0.175	***	0.128	**	0.395	***	0.381	***
Th2	<i>GATA3</i>	0.379	***	0.411	***	0.264	***	0.238	**	0.13	**	0.065	0.168	0.156	**	0.143	**
	<i>STAT6</i>	0.185	***	0.295	***	0.183	*	0.165	*	0.095	*	0.101	*	0.206	***	0.203	***
	<i>STAT5A</i>	0.28	***	0.32	***	0.361	***	0.313	***	-0.104	*	-0.109	*	0.312	***	0.299	***
	<i>IL13</i>	-0.022	0.62	-0.008	0.855	0.04	0.595	0.049	0.525	0.02	0.658	0.002	0.965	0.123	*	0.148	**
Tfh	<i>BCL6</i>	0.084	0.058	0.052	0.252	0.417	***	0.389	***	0.136	**	0.119	*	0.389	***	0.351	***
	<i>IL21</i>	0.098	*	0.082	0.073	0.156	*	0.134	0.081	0.044	0.336	0.003	0.943	0.009	0.858	0.003	0.956
Th17	<i>STAT3</i>	0.569	***	0.555	***	0.619	***	0.589	***	0.26	***	0.246	***	0.459	***	0.435	***
	<i>IL17A</i>	0.07	0.114	0.055	0.226	0.097	0.197	0.074	0.335	-0.035	0.445	-0.045	0.342	0.032	0.518	0.035	0.494
Exhausted T cells	<i>PDCD1</i>	0.409	***	0.42	***	0.283	***	0.209	**	-0.032	0.484	-0.133	**	0.13	**	0.127	*
	<i>CTLA4</i>	0.264	***	0.264	***	0.356	***	0.29	***	0.081	0.078	0.026	0.581	0.182	***	0.177	***
	<i>LAG3</i>	0.248	***	0.247	***	0.219	**	0.185	*	-0.03	0.518	-0.122	**	0.1	*	0.078	0.129
	<i>HAVCR2</i>	0.295	***	0.347	***	0.618	***	0.568	***	0.211	***	0.179	***	0.3	***	0.284	***

Asterisks denote the significance level of the correlation between the expression levels of *COL4A1* and each marker gene (\*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ ).

**Table S3.** Correlation analyses among the expression levels of *COL4A1* and related marker genes of the tumor microenvironment (TME) immune cells of four tumor groups from different origins using the R2 tool.

Description	Gene Markers	Tumor Glioma (GSE43378, n = 50)		Mixed Tumor Pancreas (GSE28735, n = 90)		Tumor Melanoma (GSE65904, n = 214)		Tumor Gastric (GSE15459, n = 192)	
		r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value
CD8+ T cell	<i>CD8A</i>	0.075	$6.04 \times 10^{-1}$	-0.103	$3.36 \times 10^{-1}$	-0.077	$2.65 \times 10^{-1}$	-0.133	$6.60 \times 10^{-2}$
	<i>CD8B</i>	-0.082	$5.69 \times 10^{-1}$	0.116	$2.74 \times 10^{-1}$	-0.143	<b><math>3.70 \times 10^{-2}</math></b>	-0.123	$9.00 \times 10^{-2}$
T cells (general)	<i>CD3D</i>	0.290	<b><math>4.10 \times 10^{-2}</math></b>	0.320	<b><math>2.08 \times 10^{-3}</math></b>	-0.004	$9.59 \times 10^{-1}$	-0.077	$2.89 \times 10^{-1}$
	<i>CD3E</i>	-0.111	$4.43 \times 10^{-1}$	0.251	<b><math>1.70 \times 10^{-2}</math></b>	0.049	$4.75 \times 10^{-1}$	0.010	$8.86 \times 10^{-1}$
	<i>CD2</i>	0.329	<b><math>2.00 \times 10^{-2}</math></b>	0.353	<b><math>6.41 \times 10^{-4}</math></b>	0.003	$9.67 \times 10^{-1}$	-0.028	$6.97 \times 10^{-1}$
B cells	<i>CD19</i>	-0.218	$1.28 \times 10^{-1}$	-0.284	<b><math>6.64 \times 10^{-3}</math></b>	-0.014	$8.39 \times 10^{-1}$	-0.168	<b><math>2.00 \times 10^{-2}</math></b>
	<i>CD79A</i>	-0.145	$3.14 \times 10^{-1}$	0.099	$3.53 \times 10^{-1}$	0.010	$8.79 \times 10^{-1}$	-0.145	<b><math>4.40 \times 10^{-2}</math></b>
Monocytes	<i>CD86</i>	0.412	<b><math>2.97 \times 10^{-3}</math></b>	0.674	<b><math>3.49 \times 10^{-13}</math></b>	0.162	<b><math>1.80 \times 10^{-2}</math></b>	0.205	<b><math>4.43 \times 10^{-3}</math></b>
	<i>CSF1R</i>	0.111	$4.42 \times 10^{-1}$	0.686	<b><math>8.11 \times 10^{-14}</math></b>	0.478	<b><math>1.33 \times 10^{-13}</math></b>	0.419	<b><math>1.41 \times 10^{-9}</math></b>
TAMs	<i>CCL2</i>	0.233	$1.03 \times 10^{-1}$	0.254	<b><math>1.60 \times 10^{-2}</math></b>	0.355	<b><math>9.09 \times 10^{-8}</math></b>	0.452	<b><math>4.78 \times 10^{-11}</math></b>
	<i>CD68</i>	N/A	N/A	N/A	N/A	0.208	<b><math>2.20 \times 10^{-3}</math></b>	N/A	N/A
	<i>IL10</i>	0.305	<b><math>3.10 \times 10^{-2}</math></b>	0.219	<b><math>3.80 \times 10^{-2}</math></b>	0.201	<b><math>3.09 \times 10^{-3}</math></b>	0.107	$1.38 \times 10^{-1}$
M1 macrophages	<i>NOS2</i>	0.090	$5.33 \times 10^{-1}$	-0.327	<b><math>1.69 \times 10^{-3}</math></b>	0.118	$8.50 \times 10^{-2}$	-0.190	<b><math>8.16 \times 10^{-3}</math></b>
	<i>IRF5</i>	0.034	$8.12 \times 10^{-1}$	0.207	$5.00 \times 10^{-2}$	-0.026	$7.03 \times 10^{-1}$	-0.051	$4.85 \times 10^{-1}$
	<i>PTGS2</i>	0.328	<b><math>2.00 \times 10^{-2}</math></b>	0.584	<b><math>1.55 \times 10^{-9}</math></b>	0.362	<b><math>5.17 \times 10^{-8}</math></b>	0.461	<b><math>1.75 \times 10^{-11}</math></b>
M2 macrophages	<i>CD163</i>	0.777	<b><math>3.16 \times 10^{-11}</math></b>	0.684	<b><math>1.06 \times 10^{-13}</math></b>	0.375	<b><math>1.50 \times 10^{-8}</math></b>	0.369	<b><math>1.43 \times 10^{-7}</math></b>
	<i>VSIG4</i>	0.413	<b><math>2.88 \times 10^{-3}</math></b>	0.624	<b><math>5.10 \times 10^{-11}</math></b>	0.326	<b><math>1.05 \times 10^{-6}</math></b>	0.307	<b><math>1.45 \times 10^{-5}</math></b>
	<i>MS4A4A</i>	0.558	<b><math>2.52 \times 10^{-5}</math></b>	0.521	<b><math>1.41 \times 10^{-7}</math></b>	0.279	<b><math>3.46 \times 10^{-5}</math></b>	0.290	<b><math>4.45 \times 10^{-5}</math></b>
Neutrophils	<i>CEACAM8</i>	0.334	<b><math>1.80 \times 10^{-2}</math></b>	0.248	<b><math>1.80 \times 10^{-2}</math></b>	-0.015	$8.26 \times 10^{-1}$	0.004	$9.53 \times 10^{-1}$
	<i>ITGAM</i>	0.134	$3.55 \times 10^{-1}$	0.768	<b><math>1.09 \times 10^{-18}</math></b>	0.344	<b><math>2.42 \times 10^{-7}</math></b>	0.278	<b><math>9.33 \times 10^{-5}</math></b>

	<i>CCR7</i>	0.478	<b>4.50×10<sup>-4</sup></b>	0.370	<b>3.32×10<sup>-4</sup></b>	0.108	1.14×10 <sup>-1</sup>	0.003	9.67×10 <sup>-1</sup>
	<i>KIR2DL1</i>	0.032	8.27×10 <sup>-1</sup>	N/A	N/A	-0.067	3.33×10 <sup>-1</sup>	0.001	9.85×10 <sup>-1</sup>
	<i>KIR2DL3</i>	-0.370	<b>8.23×10<sup>-3</sup></b>	N/A	N/A	-0.143	3.70×10 <sup>-2</sup>	-0.153	<b>3.40×10<sup>-2</sup></b>
	<i>KIR2DL4</i>	-0.135	3.52×10 <sup>-1</sup>	N/A	N/A	-0.174	<b>1.10×10<sup>-2</sup></b>	-0.011	8.76×10 <sup>-1</sup>
	<i>KIR3DL1</i>	-0.156	2.81×10 <sup>-1</sup>	N/A	N/A	-0.052	4.53×10 <sup>-1</sup>	-0.046	5.26×10 <sup>-1</sup>
	<i>KIR3DL2</i>	N/A	N/A	N/A	N/A	-0.063	3.61×10 <sup>-1</sup>	N/A	N/A
NK cells	<i>KIR3DL3</i>	0.034	8.15×10 <sup>-1</sup>	N/A	N/A	-0.078	2.55×10 <sup>-1</sup>	-0.029	6.94×10 <sup>-1</sup>
	<i>KIR2DS4</i>	0.132	3.59×10 <sup>-1</sup>	N/A	N/A	-0.126	6.50×10 <sup>-2</sup>	-0.184	<b>1.10×10<sup>-2</sup></b>
	<i>KLRK1</i>	N/A	N/A	-0.019	8.58×10 <sup>-1</sup>	-0.060	3.81×10 <sup>-1</sup>	N/A	N/A
	<i>NCR1</i>	0.002	9.90×10 <sup>-1</sup>	-0.203	5.60×10 <sup>-2</sup>	-0.074	2.84×10 <sup>-1</sup>	-0.105	1.49×10 <sup>-1</sup>
	<i>NCR2</i>	-0.390	<b>5.16×10<sup>-3</sup></b>	-0.616	<b>1.02×10<sup>-10</sup></b>	-0.090	1.91×10 <sup>-1</sup>	-0.058	4.27×10 <sup>-1</sup>
	<i>NCR3</i>	0.078	5.90×10 <sup>-1</sup>	-0.389	<b>1.50×10<sup>-4</sup></b>	0.018	7.91×10 <sup>-1</sup>	-0.076	2.95×10 <sup>-1</sup>
	<i>HLA-DPB1</i>	0.537	<b>5.74×10<sup>-5</sup></b>	0.572	<b>3.96×10<sup>-9</sup></b>	0.084	2.21×10 <sup>-1</sup>	0.023	7.55×10 <sup>-1</sup>
	<i>HLA-DQB1</i>	0.513	<b>1.39×10<sup>-4</sup></b>	0.612	<b>1.43×10<sup>-10</sup></b>	0.048	4.86×10 <sup>-1</sup>	-0.041	5.72×10 <sup>-1</sup>
	<i>HLA-DRA</i>	0.548	<b>3.83×10<sup>-5</sup></b>	0.659	<b>1.73×10<sup>-12</sup></b>	0.197	<b>3.74×10<sup>-3</sup></b>	-0.121	9.40×10 <sup>-2</sup>
Dendritic cells	<i>HLA-DPA1</i>	0.457	<b>8.59×10<sup>-4</sup></b>	0.615	<b>1.18×10<sup>-10</sup></b>	0.124	7.00×10 <sup>-2</sup>	-0.023	7.52×10 <sup>-1</sup>
	<i>CD1C</i>	0.047	7.45×10 <sup>-1</sup>	0.445	<b>1.11×10<sup>-5</sup></b>	0.204	<b>2.67×10<sup>-3</sup></b>	0.097	1.80×10 <sup>-1</sup>
	<i>NRP1</i>	0.722	<b>3.25×10<sup>-9</sup></b>	0.760	<b>3.49×10<sup>-18</sup></b>	0.704	<b>2.62×10<sup>-33</sup></b>	0.577	<b>1.82×10<sup>-18</sup></b>
	<i>ITGAX</i>	0.315	<b>2.60×10<sup>-2</sup></b>	0.698	<b>2.11×10<sup>-14</sup></b>	0.096	1.62×10 <sup>-1</sup>	0.331	<b>2.75×10<sup>-6</sup></b>
	<i>TBX21</i>	0.323	<b>2.20×10<sup>-2</sup></b>	-0.487	<b>1.16×10<sup>-6</sup></b>	-0.240	<b>3.91×10<sup>-4</sup></b>	-0.066	3.64×10 <sup>-1</sup>
	<i>STAT4</i>	-0.542	<b>4.72×10<sup>-5</sup></b>	0.294	<b>4.89×10<sup>-3</sup></b>	0.081	2.38×10 <sup>-1</sup>	0.069	3.42×10 <sup>-1</sup>
Th1	<i>STAT1</i>	0.478	<b>4.43×10<sup>-4</sup></b>	0.294	<b>4.89×10<sup>-3</sup></b>	-0.167	<b>1.40×10<sup>-2</sup></b>	-0.218	<b>2.38×10<sup>-3</sup></b>
	<i>IFNG</i>	0.338	<b>1.60×10<sup>-2</sup></b>	0.095	3.71×10 <sup>-1</sup>	-0.184	<b>6.87×10<sup>-3</sup></b>	-0.086	2.35×10 <sup>-1</sup>
	<i>TNF</i>	-0.352	<b>1.20×10<sup>-2</sup></b>	-0.205	<b>5.30×10<sup>-2</sup></b>	0.048	4.82×10 <sup>-1</sup>	0.043	5.57×10 <sup>-1</sup>
	<i>GATA3</i>	0.385	<b>5.79×10<sup>-3</sup></b>	0.426	<b>2.83×10<sup>-5</sup></b>	-0.013	8.54×10 <sup>-1</sup>	0.034	6.36×10 <sup>-1</sup>
Th2	<i>STAT6</i>	0.103	4.78×10 <sup>-1</sup>	0.698	<b>1.96×10<sup>-14</sup></b>	-0.012	8.59×10 <sup>-1</sup>	0.156	<b>3.10×10<sup>-2</sup></b>

Tfh	<i>STAT5A</i>	0.121	4.03×10 <sup>-1</sup>	0.619	<b>8.00×10<sup>-11</sup></b>	0.064	3.54×10 <sup>-1</sup>	0.184	<b>1.10×10<sup>-2</sup></b>
	<i>IL13</i>	0.072	6.20×10 <sup>-1</sup>	-0.207	5.00×10 <sup>-2</sup>	-0.065	3.41×10 <sup>-1</sup>	-0.123	9.00×10 <sup>-2</sup>
	<i>BCL6</i>	0.375	<b>7.27×10<sup>-3</sup></b>	0.629	<b>3.04×10<sup>-11</sup></b>	0.433	<b>3.48×10<sup>-11</sup></b>	0.412	<b>2.77×10<sup>-9</sup></b>
	<i>IL21</i>	0.065	6.52×10 <sup>-1</sup>	-0.316	<b>2.41×10<sup>-3</sup></b>	-0.075	2.73×10 <sup>-1</sup>	-0.099	1.74×10 <sup>-1</sup>
Th17	<i>STAT3</i>	0.548	<b>3.82×10<sup>-5</sup></b>	0.785	<b>5.09×10<sup>-20</sup></b>	0.509	<b>1.73×10<sup>-15</sup></b>	0.266	1.89×10 <sup>-4</sup>
	<i>IL17A</i>	-0.075	6.05×10 <sup>-1</sup>	-0.343	<b>9.45×10<sup>-4</sup></b>	-0.235	<b>5.21×10<sup>-4</sup></b>	-0.021	7.70×10 <sup>-1</sup>
Treg	<i>FOXP3</i>	-0.299	<b>3.50×10<sup>-2</sup></b>	-0.164	1.24×10 <sup>-1</sup>	0.005	9.39×10 <sup>-1</sup>	-0.147	<b>4.20×10<sup>-2</sup></b>
	<i>CCR8</i>	0.117	4.20×10 <sup>-1</sup>	0.343	<b>9.27×10<sup>-4</sup></b>	-0.047	4.90×10 <sup>-1</sup>	-0.113	1.20×10 <sup>-1</sup>
	<i>STAT5B</i>	-0.112	4.38×10 <sup>-1</sup>	0.620	<b>7.18×10<sup>-11</sup></b>	0.199	<b>3.39×10<sup>-3</sup></b>	0.259	<b>2.78×10<sup>-4</sup></b>
	<i>TGFB1</i>	0.107	4.59×10 <sup>-1</sup>	0.855	<b>6.98×10<sup>-27</sup></b>	-0.019	7.81×10 <sup>-1</sup>	0.445	<b>1.01×10<sup>-10</sup></b>
Exhausted T cells	<i>PDCD1</i>	0.211	1.41×10 <sup>-1</sup>	-0.040	7.11×10 <sup>-1</sup>	-0.107	1.18×10 <sup>-1</sup>	-0.064	3.77×10 <sup>-1</sup>
	<i>CTLA4</i>	-0.149	3.02×10 <sup>-1</sup>	0.509	<b>3.02×10<sup>-7</sup></b>	-0.176	<b>9.68×10<sup>-3</sup></b>	-0.012	8.69×10 <sup>-1</sup>
	<i>LAG3</i>	-0.152	2.92×10 <sup>-1</sup>	-0.403	<b>8.17×10<sup>-5</sup></b>	-0.178	<b>9.02×10<sup>-3</sup></b>	-0.025	7.31×10 <sup>-1</sup>
	<i>HAVCR2</i>	0.253	7.60×10 <sup>-2</sup>	0.664	<b>9.43×10<sup>-13</sup></b>	0.194	<b>4.46×10<sup>-3</sup></b>	0.232	<b>1.21×10<sup>-3</sup></b>

Bold values indicate the statistical significance at  $p < 0.05$ .