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Original Research

Potential predictive value of comutant LRP1B and FAT for immune response in non-small cell lung cancer
LRP1B and FAT comutation enhance immune response

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ABSTRACT

Background: Preliminary investigation revealed that Low-density lipoprotein receptor-related protein 1b (LRP1B) and FAT atypical cadherin (FAT) family mutation might serve as immune regulators under certain tumor microenvironment.
Experimental design: We curated a total of 70 non-small cell lung cancer (NSCLC) patients who harbored alterations in LRP1B and/or FAT family (FAT1/2/3/4) based on next-generation sequencing (NGS) to analyze multiple-dimensional data types, including comutant status, tumor mutation burden (TMB), programmed death receptor ligand 1 (PD-L1) expression, T cell-inflamed gene expression profiling (GEP) and therapy response.
Results: 20 patients with co-occurring mutations in LRP1B and FAT1/2/3/4 revealed a relatively higher TMB level of 17.05 mut/Mb compared with 7.60 mut/Mb and 8.80 mut/Mb in single LRP1B and FAT mutation groups, respectively. LRP1B and FAT members showed specifically enriched T cell-inflamed genes and the co-occurring mutant TP53 status in NSCLC patients who harbor LRP1B/FAT comutations.
Conclusions: This work provides evidence that co-occurring mutations of LRP1B and FAT in NSCLC may serve as a group of potential predictive factors in guiding immunotherapy on the basis of their association with TMB status.

Introduction

Lung cancer is one of the leading causes of cancer-related mortality worldwide, with a poor 5-year survival rate of only 19% [1]. Despite major advances in early detection and treatment, survival rate remains unsatisfactory owing to wide dissemination in majority of patients at the time of diagnosis. There are two main forms of lung cancer: small cell lung cancer (SCLC, ~15% of patients) and non-small cell lung cancer (NSCLC, ~85% of patients), with the latter further subdivided into 2 main types: lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) [2]. In the past decade, treatment landscape of NSCLC had dramatically changed due to advances in the identification of key mutational alterations and introduction of immune checkpoint blockade [3]. Tumor mutational burden (TMB), T cell infiltrates, and the level of programmed death receptor ligand 1 (PD-L1) protein on the surface of tumor tissue have been proposed as biomarkers of response to immunotherapy [4,5]. However, a substantial of tumor either exhibits low level of PD-L1 protein or do not sustain durable clinical benefit from immune checkpoint inhibitors [6]. Therefore, novel modulators are urgently needed to distinguish responders from non-responders and will most likely arise from a more elaborate understanding of tumor-immune microenvironment and the identification of genetic abnormalities in NSCLC.

Low-density lipoprotein receptor-related protein 1b (LRP1B) belongs to LDLR family and is identified as a likely putative tumor suppressor [7]. A battery of evidence suggests mutant LRP1B may exhibit elevated PD-L1 expression and improved outcomes with immune checkpoint inhibitors (ICIs) [8,9]. According to Catalog of Somatic Mutations in Cancer (COSMIC, https://cancer.sanger.ac.uk/cosmic), a large-scale database curated by the Wellcome Trust Sanger Institute, LRP1B is one of the top abundantly mutated genes in NSCLC and the patterns of its somatic mutations are 28% and 37% in LUAD and LUSC, respectively. Another potential predictive biomarker candidate is FAT atypical cadherin (FAT) family, consisting of FAT1, FAT2, FAT3 and FAT4, exhibits

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tumor suppressive or promoting effect under certain context on the basis of its interaction with Hippo-YAP pathway and planar cell polarity (PCP) [10], inhibition of epithelial-to-mesenchymal transition (EMT) and involvement in lymphovascular permeation [11]. Different from FAT4 with an EGF-like domain followed by two Laminin-G-like domains, human FAT1, FAT2, and FAT3 have a Laminin-G-like domain followed by multiple EGF-like domains. Particularly, FAT1 is involved in promotion of actin-mediated cell migration as well as inhibition of YAP1-mediated cell proliferation [12]. In line with COSMIC, FAT1 is also one of the top 20 abundantly mutated genes in NSCLC and the patterns of its somatic mutations are 8% and 12% in LUAD and LUSC, respectively.

Interestingly, research revealed that dissemination of LRP1B-silenced renal cancer cells was possibly due to actin cytoskeleton remodeling regulated by Rho/Cdc42 pathway and the alteration of focal adhesion complex components [13]. FAT1 and FAT4 suppress tumor growth through Hippo signaling activation, while FAT1 promotes tumor invasion through actin polymerization at lamellipodia and filopodia under certain condition [14]. Previous investigation revealed a strong co-expression of FAT1 with molecular components of low-density lipoprotein (LRP) 5 and molecular targeting of FAT1 re-sensitizes cisplatin-resistant OSCC cells to cisplatin treatment by deregulating the LRP/WNT pathway [15]. Both LRP1B and FAT members are involved in YAP regulation via Hippo-dependent and independent pathway and activated YAP act as a transcriptional driver of cytokines in bolstering T-regulatory cells (Tregs) recruitment and escaping from innate and adaptive arms of immune system [16]. Thus, it is urgently needed to explore their regulation on tumor immunology. Here, we delineated 70 NSLCL patients with LRP1B and/or FAT family (FAT1/2/3/4) alterations to determine their potential immune signature in NSCLC.

Materials and methods

Patients and eligibility

We curated patients with LRP1B and/or FAT family (FAT1/2/3/4) alterations reported on tissue-based next-generation sequencing (NGS) panels at our Center between October 2019 and November 2021. Limited or advanced NSCLC patients with LRP1B and/or FAT1/2/3/4 alterations were eligible.

Tissue-based NGS

Genomic alterations, such as deletion, truncation or loss of function (e.g., nonsense mutation, homozygous loss, frame shift mutation, intragenic rearrangement, splice acceptor/donor mutation) were identified with Tissue-based NGS (Supplementary Materials).

Patient variables

The variables collected included patient demographics (such as age and gender), metastatic stages, PD-L1, TMB, and microsatellite status. Patient outcomes included best radiographic response, which was characterized by RECIST V.1.1 criteria in combination with clinical notes.

Gene expression profiling (GEP)

The GEP consists of 18 genes associated with chemokine expression, cytolytic activity, antigen presentation, and adaptive immune resistance, including CD274 (PD-L1), CD276 (B7-H3), CCL5, CD27, CD8A, CMKLR1, CXCL9, CXCR6, IDO1, LAG3, NKG7, PDCD1LG2 (PDL2), PSMB10, HLA-DQA1, HLA-DRB1, HLAE, STAT1, and TIGIT.

TCGA Data and cBioPortal

The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancers and matched normal samples spanning 33 cancer types. LRP1B and FAT mutant LUAD (TCGA, Firehose Legacy; 586 cases) and LUSC (TCGA, Firehose Legacy; 511 cases) datasets were selected for further analyses using cBioPortal for Cancer Genomics, which is a comprehensive portal for exploring, visualizing, and analyzing multidimensional cancer genomics database (http://www.cbioportal.org/).

Statistical analysis

Statistical analyses were conducted using GraphPad Prism (version 9.0). Scatter dot plots indicate median and 95% confidence interval (CI). All tests were two-sided, and p-values of <0.05 indicated statistical significance.

Data availability

The data generated in this study are available within the article.

Results

Patient outcomes

A total of 70 patients of NSCLC were identified who harbored alterations in LRP1B and/or FAT family (FAT1/2/3/4) by NGS in our center. Demographics were shown in Table 1 according to genomics alterations, metastatic stages, PD-L1, TMB and microsatellite status. LRP1B gene was evident in 49 mutations, including 38 missense mutations, 7 nonsense mutations and 4 splice site mutations. Notably, FAT1/2/3/4 genes were identified in 60 mutations, including missense, nonsense, frame shift, splice site mutation, deletion, deletion-insert and

Table 1
Demographics.

	All Patients (n=70)	LUAD(n=46)	LUSC(n=24)
Gender			
Male(%)	54(70%)	31(67%)	23(96%)
Age,median(range)			
<65	29	23	6
≥65	41	23	18
PD-L1 expression			
≥1%	49	28	21
0% or <1%	13	12	1
Not availbable	8	6	2
TMB status			
<5/MB	17	11	6
5-10/MB	15	9	6
>10MB	31	21	10
Not availbable	7	5	2
Gene Mut			
FAT FAMILY	52	35	17
LRP1B	38	25	13
Both	20	13	7
Microsatellite			
MSI-H	0	0	0
MSI-L	3	2	1
MSS	51	33	18
Not availbable	16	10	6
M Stage			
M0	19	8	11
M1a	10	7	3
M1b	24	20	4
M1c	9	7	2
Mx	8	4	4

PD-L1, programed death receptor ligand 1; TMB, Tumor mutation burden; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-high; MSS, microsatellite stable.

insert mutation (Fig. 1 A and B). Co-occurring mutations in LRP1B and FAT1/2/3/4 were identified in 13 LUAD and 7 LUSC patients, respectively.

Association with TMB and PD-L1 expression

Scatter plots for TMB and PD-L1 were shown in Fig. 2 A and B. 20 patients with co-occurring mutations in LRP1B and FAT1/2/3/4 revealed a relatively higher TMB level of 17.05 mut/Mb compared with 7.60 mut/Mb and 8.80 mut/Mb in single LRP1B and FAT mutation groups, respectively. The comutant group showed more outliers with TMB >10 mut/Mb in 12 patients (60%) compared with 2 and 7 patients in single LRP1B (12.5%) and FAT (25%) mutant groups, respectively. Nevertheless, PD-L1 expression in our study did no show significant differences in all three groups.

Comparison between LRP1B/FAT and EGFR mutation

Therapeutic regimen of NSCLC has been transformed due to identification of the oncogenic drivers, especially tumors harbor activating mutations in Epidermal growth factor receptor (EGFR) [17]. We next determined the correlation between LRP1B/FAT and EGFR mutations. A total of 10 patients with single LRP1B/FAT mutations accompanied EGFR comutation were treated with osimertinib or almonertinib. Meanwhile, 15 out of 20 patients with co-occurring mutations in LRP1B and FAT1/2/3/4 received immunotherapy and revealed a relatively higher TMB level compared to EGFR-targeted group (Fig. 3A). Up to February 25, 2022, 9 patients experienced partial response (PR). 3 of them concomitantly harbored EGFR mutation and 6 patients with co-occurring mutations in LRP1B and FAT1/2/3/4. 9 patients were evaluated as stable disease (SD) after 2 or 3 cycles of immunotherapy or targeted therapy and 5 of them harbored comutation of LRP1B and FAT1/2/3/4. Besides, 3 patients were evaluated as progression disease (PD) and 1 of them harbored EGFR mutation (Fig. 3B).

NSCLC harboring LRP1B/FAT mutations are co-occurring mutant TP53

A series of studies demonstrate that P53 is a central tumor suppressor and the TP53 mutations display substantial immune cells composition and increased PD-L1 level. Notably, of 48 patients with FAT family mutations 45 (93.8%) showed evidence of TP53 mutation and 38 in 42 (90.5%) patients with LRP1B mutations are comutant TP53. Here, we also revealed that NSCLC harboring LRP1B/FAT comutations are co-occurring mutant TP53 (Fig. 4).

Inflammatory genes associated with LRP1B and FAT mutations

We applied the T cell-inflamed Gene expression profiling (GEP) to identify correlation between LRP1B/FAT mutations and inflammatory genes [18]. In our study, T cell-inflamed gene expression profile were analyzed and found a higher correlation between FAT1/2/3/4 and GEP genes in LUSC compared to LUAD with TCGA database (Table 2).

Discussion

Tumors have long been recognized as wounds that do not heal [19]. A battery of investigation now paints a complex landscape in which unresolved inflammation is a potent driver of carcinogenesis. Immunotherapy, alone, or in combination with other therapeutics, is employed to improve NSCLC survival and reduce mortality rate. However, a subset of patients might not benefit from immunotherapy by virtue of an immunologically "cold" state and some responders would develop acquired resistance after initial responses. Considering intricate tumor microenvironment, it is difficult to discriminate between an immunologically "cold" and "hot" state just using PD-L1 expression and TMB status [20,21]. Recent studies also revealed that tumor infiltrating lymphocytes associated with effector T-cell signature are responsible for immune response [22,23]. Here, we first introduce a group of possible tumor suppressive mutations-LRP1B and FAT family-of NSCLC that distinctively correlated with T cell-inflamed gene expression and tumor mutation burden. To some extent, anti–PD-1/PD-L1 therapy may also been introduced in PD-L1 negative but LRP1B and FAT comutant group since an irrelevant relation between PD-L1 expression and co-occurring mutations in LRP1B and FAT family. Accordingly, patients with EGFR mutation were prone to produce a weaker TMB level and less co-occurring mutation in LRP1B and FAT1/2/3/4, which might be correlated with immunosuppressive tumor microenvironment [24].

According to cbioPortal, most LRP1B somatic mutations are recognized as missense mutation, deletion, splice mutation and inframe mutation. FAT1/2/3/4 genetic alterations are identified as missense mutation, truncating mutation, deletion and amplification. Here, genetic mechanisms of majority NSCLC patients accompanied LRP1B and FAT1/2/3/4 were deletion and missense point mutations. As to their pathogenic, likely pathogenic, and variant of unknown significance (VUS) alterations are still need further study in our later investigation.

Several studies have evaluated the TP53 status as a prognostic biomarker of therapy and its communication with other genetic alterations, such as KRAS, LKB1, KEAP1 and EGFR, may affect tumor-immune microenvironment and influence TMB and PD-L1 status [25,

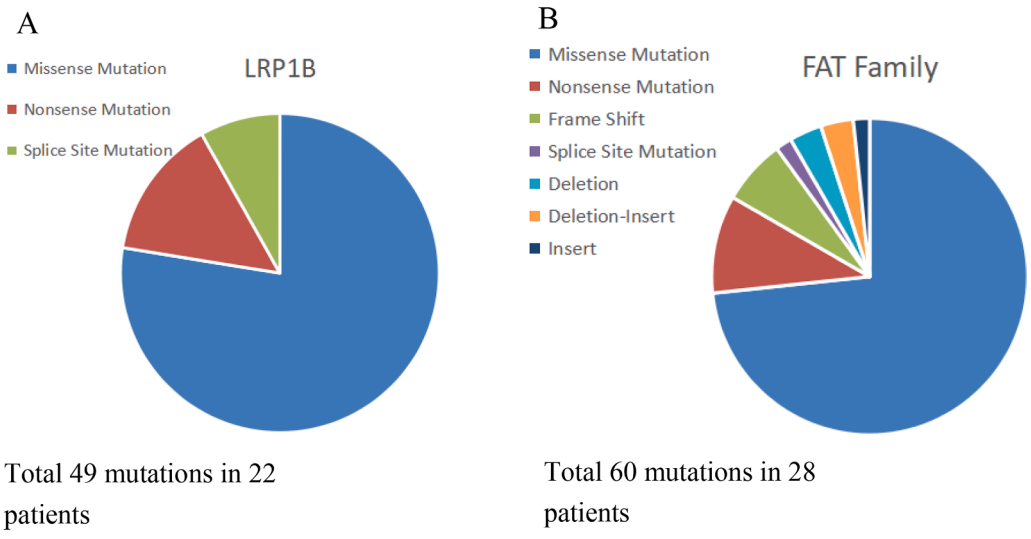

Fig. 1. Distribution of LRP1B (A) and/or FAT family (B) alterations identified by Tissue-based NGS in our center.

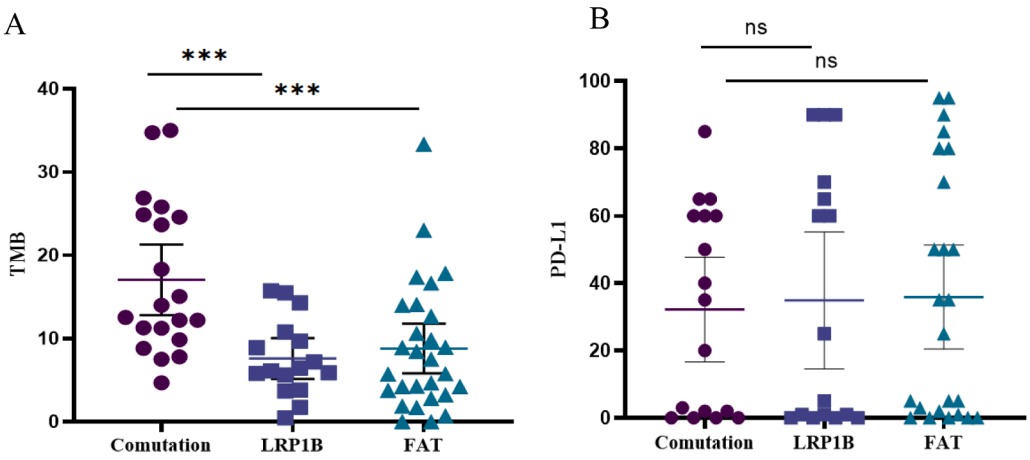

Fig. 2. Scatter plots for TMB (E) and PD-L1(F) levels among molecular subtypes were evaluated.

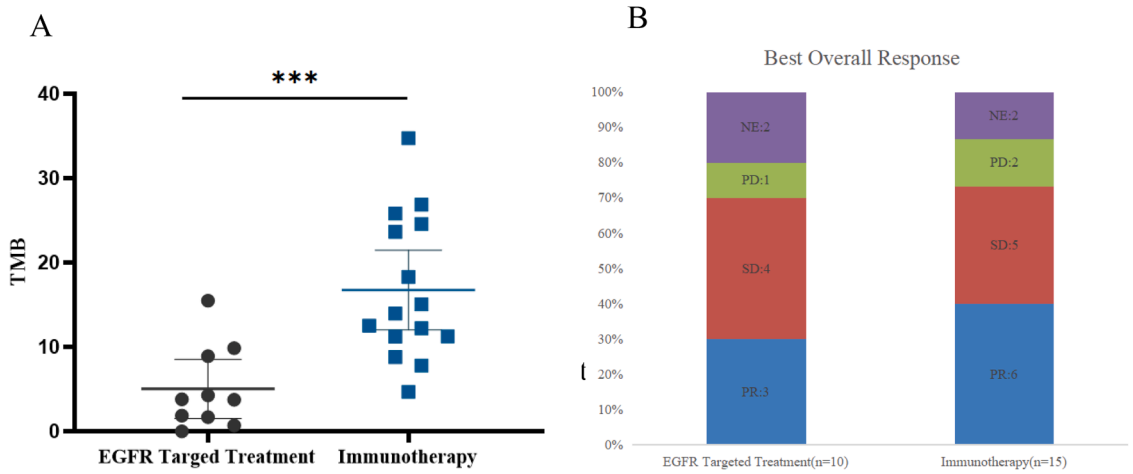

Fig. 3. 10 patients with single LRP1B/FAT mutations accompanied EGFR mutation were received targeted treatment. 15 out of 20 patients with co-occurring mutations in LRP1B and FAT1/2/3/4 underwent immunotherapy. TMB status (A) and radiographic response rates (B) were employed to compare these two groups. PR, partial response; NE, not evaluable; PD, progressive disease; SD, stable disease.

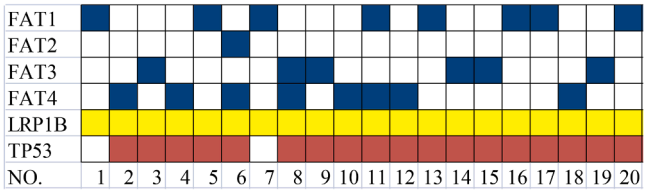

Fig. 4. Status of TP53 mutation in 20 patients with comutant LRP1B/FAT.

26,27]. Notably, we revealed that the co-occurring mutant TP53 status in NSCLC patients who harbor LRP1B/FAT comutations and exhibit high level of TMB. Previous research combined with our study identified P53/FAT/LRP1B might serve as tumor suppressor and play key roles in YAP inhibition, which might be related with RHO GTPase and cell-cell adhesion. A wealth of evidence indicates that an overarching determinant of YAP/TAZ activity in tumor initiation and progression, sustained activation of YAP/TAZ promotes aberrant cell proliferation, epithelial to mesenchymal transition, invasion, drug resistance, metastasis, and poor prognosis [28]. Even though its rarely gene alteration, increased protein level of YAP was detected in more than half of NSCLC tissues and predominantly correlated with tumour, node and metastasis (TNM) stage and inferior prognosis [29]. As an upstream signal, FAT negatively regulates YAP/TAZ oncogenic function and FAT1 re-sensitizes cisplatin-resistant OSCC cells to cisplatin treatment by deregulating the LRP/WNT signaling pathway [16]. How P53/FAT/LRP1B regulates YAP remained elusive and further studies are need to understand their regulation in T infiltrating cells.

However, This study has several limitations. First, this is a small, retrospective study curated patients who were only diagnosed as LUAD and LUSC with tissue-based NGS testing. Additionally, loss of patient primary outcomes because of short-term follow up. Thus, long-term follow-up will be conducted to identify OS and PFS in comutant group and potential predictive value LRP1B and FAT comutation in immune response will be verified in our prospective pan-cancer studies.

Conclusion

In summary, in the study, we observed that concurrent mutations in LRP1B and FAT might serve as a group of potential predictive factors to guide immunotherapy and patients harboring LRP1B/FAT comutations are co-occurring mutant TP53. The P53/LRP1B/FAT axis may present a role in establishing vastly distinct T cell microenvironment. Further exploration is needed to determine the deep immune phenotyping of these co-mutations and long-term follow-up data related with LRP1B/FAT comutations are just underway.

Table 2
GFP gene expression associated with LRP1B and FAT mutations in LUAD and LUSC. Cor, R value of Spearman's correlation; Purity, correlation adjusted by purity. *p<0.1, **p<0.01, ***p< 0.001.

GEP	LUAD									
	LRP1B		FAT1		FAT2		FAT3		FAT4	
	Purity		Purity		Purity		Purity		Purity	
	Cor	P	Cor	P	Cor	P	Cor	P	Cor	P
CD274 (PD-L1)	-0.099	*	-0.021	0.642	0.298	***	0.064	0.153	0.2	***
CD276 (B7-H3)	-0.004	0.922	0.326	***	0.164	***	0.137	**	0.019	0.68
CCL5	0.001	0.975	-0.126	**	0.03	0.503	-0.03	0.507	-0.013	0.779
CD27	-0.036	0.419	-0.066	0.146	0.026	0.561	0.1	*	0.185	***
CD8A	-0.001	0.983	-0.113	*	0.038	0.404	0.007	0.875	0.062	0.168
CMKLR1	0.004	0.921	-0.012	0.795	0.193	***	0.378	***	0.425	***
CXCL9	-0.024	0.596	-0.078	*	0.059	0.191	-0.016	0.724	-0.016	0.724
CXCR6	-0.05	0.272	-0.095	*	0.03	0.506	0.072	0.108	0.16	***
IDO1	-0.006	0.896	0.035	0.435	0.183	***	-0.004	0.923	-0.018	0.686
LAG3	0.053	0.243	-0.043	0.344	0.084	*	-0.013	0.765	-0.056	0.215
NKG7	0.025	0.574	-0.139	**	-0.023	0.614	-0.075	*	-0.101	*
PDCD1LG2 (PDL2)	-0.039	0.392	-0.084	*	0.182	***	0.134	**	0.226	***
PSMB10	-0.026	0.56	-0.104	*	0.176	***	-0.18	***	-0.078	*
HLA-DQA1	-0.078	*	-0.111	*	0.299	***	0.142	**	0.36	***
HLA-DRB1	-0.111	*	-0.201	***	0.277	***	0.091	*	0.378	***
HLA-E	0.029	0.515	-0.071	0.117	0.251	***	0.173	***	0.396	***
STAT1	-0.066	0.141	0.076	*	0.155	***	-0.015	0.733	0.054	0.235
TIGIT	-0.024	0.593	0.013	0.779	0.169	***	0.094	*	0.182	***

GEP	LUSC									
	LRP1B		FAT1		FAT2		FAT3		FAT4	
	Purity		Purity		Purity		Purity		Purity	
	Cor	P	Cor	P	Cor	P	Cor	P	Cor	P
CD274 (PD-L1)	0.204	***	-0.125	**	-0.038	0.408	0.013	0.78	0.048	0.297
CD276 (B7-H3)	0.074	0.106	0.335	***	0.243	***	0.259	***	0.134	**
CCL5	-0.117	*	-0.047	0.307	-0.232	***	0.169	***	0.206	***
CD27	-0.006	0.887	-0.141	**	-0.307	***	0.226	***	0.302	***
CD8A	-0.007	0.878	-0.152	***	-0.31	***	0.141	**	0.216	***
CMKLR1	-0.01	0.825	-0.044	0.336	-0.213	***	0.254	***	0.432	***
CXCL9	-0.008	0.859	-0.117	*	-0.248	***	0.084	*	0.076	*
CXCR6	-0.022	0.628	-0.144	**	-0.317	***	0.154	***	0.249	***
IDO1	-0.19	***	-0.042	-0.366	-0.263	***	0.088	*	0.175	***
LAG3	-0.054	0.243	-0.081	*	-0.213	***	0.105	*	0.124	**
NKG7	-0.048	0.292	-0.147	**	-0.296	***	0.107	*	0.145	**
PDCD1LG2 (PDL2)	0.028	0.548	-0.099	*	-0.185	***	0.124	**	0.208	***
PSMB10	-0.127	**	-0.071	0.119	-0.183	***	0.031	0.493	0.034	0.462
HLA-DQA1	-0.046	0.317	-0.122	**	-0.276	***	0.12	**	0.246	***
HLA-DRB1	-0.099	*	-0.107	*	-0.332	***	0.158	***	0.277	***
HLA-E	-0.177	***	0.086	*	-0.06	0.194	0.07	0.129	0.336	***
STAT1	0.013	0.784	0.034	0.456	-0.086	*	0.027	0.55	0.139	**
TIGIT	0.038	0.412	-0.086	*	-0.214	***	0.218	***	0.293	***

Author contribution

Fang Hao: Conceptualization, Methodology, Software, Data collection, Writing- Original draft preparation. Qing Ma: Visualization, Investigation. Diansheng Zhong: Supervision, Writing- Reviewing and Editing.

CRediT authorship contribution statement

Fang Hao: Conceptualization, Methodology, Software, Data curation, Writing – original draft. **Qing Ma:** Visualization, Investigation. **Diansheng Zhong:** Supervision, Writing – review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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