Role of lipid-associated fibroblasts and their signature genes FABP4, CD36 and ABCA8 in gastric cancer progression

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Abstract. Cancer-associated fibroblasts (CAFs) serve key roles in gastric cancer progression, however, the role of specific CAF subsets, particularly lipid-rich CAFs (lipo-CAFs), remains unclear. Therefore, the present study aimed to investigate whether lipo-CAFs are associated with gastric cancer progression. A total of 28 lipo-CAF-associated genes was used to classify patients with gastric cancer in The Cancer Genome Atlas Stomach Adenocarcinoma dataset. Differential expression analysis was subsequently performed to identify biological processes and pathways associated with the lipo-CAF phenotype. Validation analyses were conducted using the GSE84437 dataset and expression and survival analyses of the signature genes were performed using data from the Human Protein Atlas database and Tumor-Immune System Interaction Database. Finally, NIH-3T3 cells were transduced with lentiviral vectors to knock down the candidate genes and were co-cultured with mouse gastric cancer MFC cells to evaluate the fibroblast-mediated effects of these genes on gastric cancer cell behavior *in vitro*. The majority of lipo-CAF-associated genes were highly expressed in gastric cancer. Patients were stratified into high- and low-risk groups based on gene expression patterns and these groups exhibited differences in prognosis, energy metabolism-associated pathways and immune infiltration. A prognostic model was constructed using these genes and externally validated. Findings indicated that fatty acid-binding protein 4 (FABP4), CD36 and ATP-binding cassette subfamily A member 8 (ABCA8) may exert tumor-promoting roles in gastric cancer. In fibroblast-based co-culture experiments, knockdown of these three genes in NIH-3T3 cells inhibited the proliferation of co-cultured gastric cancer cells. Lipo-CAF-associated genes were found to be coupled with gastric cancer progression and with distinct immune and stromal features of the tumor microenvironment. Among these genes, FABP4, CD36 and ABCA8 demonstrated tumor-promoting effects in fibroblast-based co-culture experiments, highlighting their potential relevance for prognostic stratification and future therapeutic investigation in gastric cancer.

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Introduction

Gastric cancer is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality. Gastric cancer is one of the most common malignancies worldwide, with ~1.09 million new cases and ~769,000 deaths reported globally in 2020 (1). The pathogenesis of gastric cancer is complex and involves interactions among numerous genetic, environmental and lifestyle factors. Established risk factors include a high-salt diet, smoking, *Helicobacter pylori* infection, alcohol consumption, poor nutrition and gastric polyps. Current treatment strategies for gastric cancer include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, administered either alone or in combination. Despite recent therapeutic advances (1), patients with advanced-stage, metastatic, recurrent or treatment-resistant gastric cancer experience poor clinical outcomes. Therefore, identifying potential prognostic markers and therapeutic targets remains key.

In recent years, increasing attention has been directed toward cancer-associated fibroblasts (CAFs) in gastric cancer. CAFs are key components of the tumor microenvironment and serve key roles in tumor growth, dissemination, metastasis and drug resistance (2). A number of advances have been reported in this field. CAFs in gastric cancer may originate from resident fibroblasts in adjacent tissues, bone marrow-derived mesenchymal cells, adipocytes or other cell types (3). CAFs secrete

extracellular matrix (ECM) components, growth factors, cytokines and other soluble mediators, thereby contributing to the regulation of tumor growth, invasion and metastasis. Second, research has revealed a complex interaction network between CAFs and other cell types (such as tumor and immune cells) within the gastric cancer microenvironment (4). These reciprocal interactions shape both the phenotype and function of CAFs and contribute to tumor progression. Third, CAFs have increasingly been recognized as potential therapeutic targets and strategies aimed at inhibiting or reprogramming CAF function may remodel the tumor microenvironment and restrict tumor growth and dissemination (5-7).

Research regarding lipid metabolism in gastric cancer progression has also begun to attract increasing attention (8,9) Lipid metabolism is a central biological process required for cell proliferation, differentiation and survival, serving an important role in the initiation and progression of gastric cancer. Abnormalities in lipid metabolism may promote the proliferation of gastric cancer cells and influence their invasive and metastatic potential (10); second, the role of lipid metabolism in regulating the tumor microenvironment has been increasingly recognized as lipid metabolites such as free fatty acids, lysophosphatidic acid and prostaglandin E2 influence CAF activation, extracellular matrix remodeling and tumor-cell interactions with the surrounding matrix (11,12); and third, abnormalities in lipid metabolism are associated with resistance to chemotherapy and targeted therapy in gastric cancer (13). Therefore, understanding the role of lipid metabolism in gastric cancer progression may facilitate the development of improved treatment strategies.

Given the importance of both CAF biology and lipid metabolic remodeling in gastric cancer, a lipid-associated CAF state may represent a clinically relevant but insufficiently characterized stromal component (6,12). Therefore, the present study aimed to characterize lipo-CAF-associated genes in gastric cancer and evaluate their association with prognosis, metabolic features and immune features of the tumor microenvironment. Public gastric cancer datasets were used to construct and validate a lipo-CAF-associated prognostic model, and selected candidate genes were further examined in fibroblast-based co-culture experiments to assess their potential influence on gastric cancer cell behavior. The present study was designed to clarify the clinical and functional relevance of lipo-CAF-associated genes and to provide a basis for future studies of stromal lipid metabolism in gastric cancer.

Methods and materials

Patient data acquisition. RNA sequencing data and corresponding clinical information for patients with gastric cancer were obtained from The Cancer Genome Atlas Stomach adenocarcinoma (TCGA-STAD, portal.gdc.cancer.gov/projects/TCGA-STAD) cohort. A total of 443 patients were initially identified. Subsequently, 5 patients were excluded due to incomplete follow-up information required for survival analysis, including missing survival time or survival status. Therefore, 438 patients were retained for follow-up and prognostic analyses. No newly collected patient data were included in the present study for the first time. All patient-level data were obtained from TCGA-GDC (portal.gdc.cancer.gov/), GEO (https://www.ncbi.nlm.nih.gov/geo/), HPA (proteinatlas.org/), TISIDB (cis.hku.hk/TISIDB/), TIDE (tide.dfci.harvard.edu/) and STRING (https://string-db.org/). GO (http://geneontology.org/) and KEGG (https://www.genome.jp/kegg/) databases were used for enrichment analyses (14-19). The external validation cohort GSE84437 (20) was downloaded from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/) and included transcriptomic and clinical information from 483 patients with gastric cancer. The GSE84437 SuperSeries contains 483 gastric cancer samples and was generated using the GPL6947 Illumina HumanHT-12 V3.0 expression beadchip platform. Gene expression matrices were annotated using the GPL6947 Illumina HumanHT-12 V3.0 expression beadchip platform annotation file.. When multiple probes corresponded to the same gene symbol, the mean expression value was used for downstream analysis with gastric cancer.

Lipo-CAF-associated gene co-expression network. A total of 28 lipo-CAF-associated genes were selected through a structured literature review. Genes were included if previous studies reported their association with lipid metabolism, lipid transport, fatty acid handling, adipocyte-like stromal features, lipid-rich fibroblast phenotypes, CF-associated stromal remodeling or cancer-associated lipid metabolic programs. The selected genes and information regarding their supporting studies are listed in Table I (21-48). This literature-derived gene set was used as an initial biologically informed signature to evaluate lipid-associated CAF-associated features in gastric cancer. To identify gastric cancer phenotype-associated biological processes, differential expression analysis was performed between the lipo-CAF-high and -low groups using the limma package (version 3.52.0) in R software version 4.2.1 (49). Genes with adjusted P-value <0.05 and $|\log2 \text{ fold change}| > 1$ were considered significantly differentially expressed. followed by Gene Ontology (50) and Kyoto Encyclopedia of Genes and Genomes (51) enrichment analyses. A protein-protein interaction (PPI) network of lipo-CAF-associated genes was constructed and visualized using the STRING database (19).

Construction of a lipo-CAF gene prognostic signature in gastric cancer. Any association between lipo-CAF gene expression and overall survival (OS) was evaluated using univariate Cox regression analysis. To identify a prognosis-associated signature, Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression analysis was performed. Lipo-CAF genes were selected based on the Akaike information criterion (52), which was used for model selection by balancing model fit and complexity. The risk score for each patient was calculated as the sum of the expression value of each selected gene multiplied by its corresponding regression coefficient. Univariate and multivariate Cox regression analyses were performed to evaluate independent prognostic factors, including clinical features and risk score, in gastric cancer. Kaplan-Meier survival analysis was performed using mRNA expression and overall survival data from TCGA-STAD and GSE84437 gastric cancer cohorts. Patients were stratified into high- and low-risk groups according to the

Table I. Lipid rich cancer associated fibroblast-associated genes.

First author, year	Gene	Function	(Refs.)
Yoshida *et al*, 2024	CFD	Hydrolase, protease and serine protease	(21)
Dai *et al*, 2008	CA3	Lyase	(22)
Luis *et al*, 2021	FABP4	Lipid transport protein in adipocytes	(23)
Wang *et al*, 2019	APOC3	Lipid degradation, lipid metabolism and transport	(24)
Gu *et al*, 2023	APOC1	Lipid transport	(25)
Dwivedi *et al*, 2022	APOA2	Host-virus interaction, lipid transport	(26)
Wang *et al*, 2021	APOC2	Lipid degradation, lipid metabolism, lipid transport	(27)
Yamanaka *et al*, 2022	ROBO4	Developmental protein and receptor	(28)
Hagemann *et al*, 2022	SERPINF2	Protease inhibitor and serine protease inhibitor	(29)
Qiu *et al*, 2023	FABP5	Lipid transport and transport	(30)
Duan *et al*, 2016	FASN	Fatty acid biosynthesis, fatty acid metabolism, lipid biosynthesis and lipid metabolism	(31)
Nishimoto *et al*, 2018	CBR1	Oxidoreductase	(32)
Djurec *et al*, 2018	SAA3P	Major acute phase reactant	(33)
Zhu *et al*, 2023	CD36	Cell adhesion, lipid transport	(34)
Wiltshire *et al*, 2002	SH3BP5	Guanine-nucleotide releasing factor	(35)
Yagi *et al*, 2011	ARAP3	GTPase activation	(36)
Yang *et al*, 2021	ABCA8	Lipid transport and transport	(37)
Nieminen *et al*, 2011	BMPR1A	Kinase, receptor, serine/threonine-protein kinase and transferase	(38)
Saetrom *et al*, 2009	BMPR1B	Kinase, receptor, serine/threonine-protein kinase and transferase	(39)
Owens *et al*, 2012	BMPR2	Kinase, receptor, serine/threonine-protein kinase and transferase	(40)
Deng *et al*, 2020	BMP4	Cytokine, developmental protein and growth factor	(41)
Li *et al*, 2023	TFCP2	Transcription and transcription regulation	(42)
Zhang *et al*, 2020	WNT5B	Developmental protein	(43)
Mizokami *et al*, 2008	HIF1A	Host-virus interaction, transcription and transcription regulation	(44)
Lin *et al*, 2019	PTGS2	Fatty acid biosynthesis, fatty acid metabolism, lipid biosynthesis, lipid metabolism, prostaglandin biosynthesis and prostaglandin metabolism	(45)
Wang *et al*, 2023	HILPDA	Increases intracellular lipid accumulation	(46)
Zhang *et al*, 2022	PNPLA2	Lipid degradation and lipid metabolism	(47)
Zhang *et al*, 2022	IL1R1	Interleukin-1 receptor involved in inflammatory cytokine signaling	(48)

median risk score cutoff of 2.20 and survival differences were compared using the log-rank test.

Tumor microenvironment analysis. Stromal, immune and ESTIMATE score and tumor purity were calculated using the ESTIMATE algorithm (53). ESTIMATE is an expression-based method that infers the levels of stromal and immune cell infiltration in tumor tissue based on gene expression signatures. The ESTIMATE algorithm was implemented using the estimate package in R software, and normalized gene expression data from TCGA-STAD cohort were used as input. The stromal score, immune score, ESTIMATE score and tumor purity were compared between the lipo-CAF-high and lipo-CAF-low groups.

Immune escape analysis. Tumor Immune Dysfunction and Exclusion (https://tide.dfci.harvard.edu) was used to evaluate immune escape in patients classified into high- and low-risk groups according to the prognostic signature. The expression levels of human leukocyte antigen (HLA) family genes and immune checkpoint molecules (TIGIT, PDCD1, SIGLEC15, CTLA4, CD274, PDCD1LG2, LAG3 and HAVCR2) were compared between the high- and low-risk groups. Spearman correlation analysis was conducted to assess the association between immune cell infiltration and risk score.

Cell lines and culture conditions. NIH-3T3 mouse fibroblasts were obtained from the American Type Culture Collection (cat. no. CRL-1658) and mouse forestomach carcinoma (MFC) gastric cancer cells were obtained from Procell Life Science & Technology Co., Ltd. (cat. no. CL-0156). NIH-3T3 cells were cultured in high-glucose DMEM supplemented with 10% FBS and 1% penicillin-streptomycin. MFC cells were cultured in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin-streptomycin. Cells were maintained at 37˚C in a humidified incubator containing 5% CO_2. Cells were used within 10 passages after thawing and were determined to be free of *Mycoplasma* contamination. NIH-3T3 cells were used as a technically tractable fibroblast-based model to evaluate whether knockdown of candidate lipo-CAF-associated genes in fibroblasts could affect gastric cancer cell behavior in co-culture. Given that the gastric cancer cells used in the

co-culture system were mouse MFC cells, NIH-3T3 cells were selected to maintain species compatibility.

Cell Counting Kit-8 (CCK-8) assay. 3xxTransduced NIH-3T3 mouse fibroblasts were co-cultured with MFC mouse gastric cancer cells in 96-well plates. Briefly, NIH-3T3 cells were seeded into 96-well plates and allowed to adhere overnight at 37˚C. MFC cells were added, and co-cultured in complete medium at 37˚C. CCK-8 assays were performed at 0, 24, 48 and 72 h after co-culture. CCK-8 (Beyotime Biotechnology, cat. no. C0038) was added to each well and incubated for 2 h at 37˚C. Absorbance was measured at 450 nm using a microplate reader.

TUNEL assay. xxTransduced NIH-3T3 mouse fibroblasts were co-cultured with MFC mouse gastric cancer cells for 48 h at 37˚C. Cells were fixed with 4% paraformaldehyde for 30 min at room temperature. TUNEL assay was performed using a One Step TUNEL Apoptosis Assay kit (Beyotime Biotechnology, cat. no. C1088) according to the manufacturer's instructions. Briefly, cells were incubated with the TUNEL reaction mixture for 60 min at 37˚C in the dark. After washing with PBS, nuclei were counterstained with DAPI (1 μg/ml) for 5 min at room temperature. Samples were mounted using anti-fade fluorescence mounting medium and observed under a fluorescence microscope. In total, ≥5 randomly selected fields of view were captured for each sample. Fluorescence signals were analyzed using ImageJ software version 1.53t (National Institutes of Health). The percentage of apoptotic cells was calculated as the number of TUNEL-positive cells divided by the total number of DAPI-positive cells.

Human Protein Atlas (HPA) and Tumor-Immune System Interaction Database (TISIDB) analyses. HPA (proteinatlas.org) was used to evaluate the protein expression of candidate genes in gastric cancer tissues and normal gastric tissues. For HPA immunohistochemistry images, the corresponding HPA antibody accession numbers were recorded. The antibody accession numbers used for normal and tumor tissues were as follows: Apolipoprotein (APO)-C3 (accession no. HPA073918 for both normal and tumor tissues); APOA2 (accession no. HPA072575 for normal tissue and CAB025885 for tumor tissue); APOC2 (accession no. HPA055877 for both normal and tumor tissue); prostaglandin-endoperoxide synthase 2 (PTGS2; accession no. HPA001335 for both normal and tumor tissues); FABP4 (accession no. CAB024961 for normal tissue and HPA002188 for tumor tissue); CD36 (accession no. CAB025866 for both normal and tumor tissues); and ABCA8 (accession no. HPA044914 for both normal and tumor tissues). The TISIDB database (cis.hku.hk/TISIDB/) was used to assess the associations between candidate gene expression and clinical features in stomach adenocarcinoma. The TISIDB analyses were based on the cohort from TCGA-STAD. The source cohort was recorded as TCGA-STAD, with Genomic Data Commons project ID: TCGA-STAD (Database Of Genotypes And Phenotypes accession no. phs000178).

Western blotting analysis. Transduced NIH-3T3 mouse fibroblasts were lysed using RIPA lysis buffer (Thermo Fisher Scientific, Inc.; cat. no. 89900) supplemented with protease inhibitor cocktail. Total protein concentration was determined using a bicinchoninic acid protein assay kit. Equal amounts of protein (30 μg/lane) were loaded onto 10% SDS-PAGE gels and transferred onto PVDF membranes. The membranes were blocked with 5% skimmed milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 1 h at room temperature. The membranes were incubated with primary antibodies against FABP4 (1:1,000; cat. no. #2120S; Cell Signaling Technology, Inc.), CD36 (cat. no. #74002S; Cell Signaling Technology, Inc.), ABCA8 (all 1:1,000; cat. no. ab230896; Abcam) and GAPDH (1:5,000; cat. no. ab8245; Abcam) overnight at 4˚C. After washing three times with TBST, the membranes were incubated with HRP-conjugated anti-rabbit (1:5,000; cat. no. #7074S; Cell Signaling Technology, Inc.) and anti-mouse IgG (1:5,000; cat. no. #7076S; Cell Signaling Technology, Inc.), for 1 h at room temperature. Protein bands were detected using Pierce ECL Western Blotting Substrate (Thermo Fisher Scientific, Inc.; cat. no. 32106) and visualized using a chemiluminescence imaging system. Band intensities were quantified using ImageJ software version 1.53t (National Institutes of Health) and normalized to GAPDH.

Lentiviral transduction and co-culture assay. Lentiviral shRNA plasmids targeting mouse Fabp4, Cd36 or Abca8a were constructed using the pLKO.1-puro lentiviral vector. The pLKO.1-puro vector and psPAX2 packaging and pMD2.G envelope plasmid were obtained from Addgene, Inc. Lentiviral particles were generated using a second-generation lentiviral packaging system. Briefly, 293T cells (American Type Culture Collection; cat. no. CRL-3216) were maintained in high-glucose DMEM supplemented with 10% FBS and 1% penicillin-streptomycin at 37˚C. For lentivirus production, 293T cells were co-transfected with 10 μg pLKO.1-shRNA plasmid, 7.5 μg psPAX2 packaging plasmid and 2.5 μg pMD2.G envelope plasmid at a mass ratio of 4:3:1 using Lipofectamine 3000 transfection reagent. Transfection was performed at 37˚C for 6 h, after which the medium was replaced with fresh complete medium. Lentiviral supernatant was collected at 48 and 72 h after transfection. NIH-3T3 mouse fibroblasts were infected with the collected lentiviral particles at a multiplicity of infection of 10 in the presence of 8 μg/ml polybrene. After 24 h of transduction at 37˚C in a humidified incubator containing 5% CO_2, the medium was replaced with fresh complete medium. Cells were selected with 2 μg/ml puromycin for 72 h and maintained in medium containing 1 μg/ml puromycin. Knockdown efficiency was assessed by western blotting 72 h after transduction, and the sequence with the highest knockdown efficiency for each target gene was used for subsequent functional assays. The shRNA target sequences were as follows: shFABP4-1, 5'-CACCGAGATTTCCTTCAAA-3'; shFABP4-2, 5'-CTGGATGGAAATTTGCATCAA-3'; shFABP4-3, 5'-TGTGTGATGCCTTTGTGGG-3'; shCD36-1, 5'-GGACCATTGGTGATGAGAAGG-3'; shCD36-2, 5'-GGCTGTGTTTGGAGGTATTCT-3'; shCD36-3, 5'-GCTGTGTTTGGAGGTATTCTG-3'; shABCA8A-1, 5'-GCTGCTATGTTCTTCCTGAAA-3'; shABCA8A-2, 5'-GCAGATGATGCTGCTGATGAA-3'; shABCA8A-3, 5'-GCTGATGACCTTCTTCATCAA-3'; and sh-negative control (NC), 5'-TTCTCCGAACGTGTCACGT-3'. For co-culture assays, transduced NIH-3T3 cells were seeded into culture plates and allowed to adhere

overnight at 37˚C. MFC mouse gastric cancer cells were added and co-cultured with NIH-3T3 cells in complete medium at 37˚C. Co-culture was performed for 0, 24, 48 and 72 h for CCK-8 assays and 48 h for TUNEL assays.

Statistical analysis. Statistical analyses were performed using R software (version 4.2.1; Posit Software, PBC) and GraphPad Prism (version 9.5.1; Dotmatics). Data are presented as the mean ± SD unless otherwise stated. Data normality was assessed using the Shapiro-Wilk test. For two-group comparisons, unpaired two-tailed Student's t-tests or Wilcoxon rank-sum tests were used as appropriate. For comparisons among >2 groups, one-way ANOVAs followed by Tukey's multiple-comparison tests or Kruskal-Wallis tests followed by Dunn's multiple-comparison tests were used as appropriate. For time-course experiments, two-way ANOVA followed by Sidak's multiple-comparison tests was used. Kaplan-Meier survival curves were compared using the log-rank test. Cox regression analysis was used to evaluate prognostic factors and LASSO Cox regression was used to construct the prognostic model. Spearman correlation analysis was used to assess correlations between variables. All tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Lipid-rich CAFs are upregulated in gastric cancer. To investigate the role of lipo-CAFs in gastric cancer progression, 28 lipo-CAF-associated genes were collected (Table I). Differential expression analysis revealed that the majority of lipo-CAF-associated genes were expressed at higher levels in gastric cancer compared with in normal tissues (Fig. 1A). protein-protein interaction (PPI) analysis demonstrated that these genes were closely interconnected (Fig. 1B). Based on the expression patterns of these lipo-CAF-associated genes, patients with gastric cancer from TCGA-STAD cohort were classified into two subtypes (Fig. 1C-E). Significant differences in lipo-CAF gene expression were observed between the two subtypes (Fig. 1F). In addition, patients with the C2 subtype (lipo-CAF-high) exhibited significantly shorter OS compared with those with the C1 subtype (Fig. 1G).

Differential gene expression and gene enrichment analyses were performed to compare the two subtypes (Fig. 2A and B). GO enrichment analysis showed that differentially expressed genes between the lipo-CAF-high and -low groups were enriched in terms associated with synaptic signaling, membrane potential regulation and ion-channel activity, including 'regulation of membrane potential', 'modulation of chemical synaptic transmission', 'synapse organization', 'potassium ion transport', 'ion channel complex' and 'channel activity' (Fig. 2C). Pathway enrichment analysis further demonstrated that these genes were enriched in energy metabolism-associated pathways, including the 'calcium signaling pathway', 'cell adhesion molecules' and the 'cAMP signaling pathway' (Fig. 2D). In addition, mutation analysis revealed that patients with gastric cancer in the lipo-CAF-high group exhibited a lower overall mutation rate (Fig. 2E and F). Estimation of Stromal and Immune cells in Malignant Tumours using Expression data-based analyses showed that patients in the lipo-CAF-high group exhibited significantly higher immune and stromal scores, whereas tumor purity was significantly lower, compared with the lipo-CAF-low group (Fig. 3A-D). Immune infiltration analysis (Fig. 3E) further indicated that the lipo-CAF-high group exhibited increased infiltration of naïve B cells, $CD8^+$ T cells, monocytes, M2 macrophages, dendritic cells and mast cells (Fig. 3F). Finally, the lipo-CAF-high group demonstrated higher expression levels of HLA family genes (Fig. 4A) and immune checkpoint molecules, including T cell immunoreceptor with Ig and ITIM domains, programmed cell death 1 and cytotoxic T lymphocyte-associated protein 4 (Fig. 4B).

Lipo-CAF-associated genes to predict the prognosis of patients with gastric cancer. Based on the role of lipo-CAF-associated genes in gastric cancer as aforementioned, a prognostic model was constructed using these genes. Univariate Cox regression analysis identified nine genes with prognostic value (Fig. 4C). Subsequently, a prognostic signature was established using LASSO Cox regression analysis (Fig. 4D and E). The model was internally validated in the TCGA cohort and externally validated in the GSE84437 cohort and was significantly associated with OS in patients with gastric cancer (Fig. 4F and G). Visualization using a heatmap demonstrated that these genes were highly expressed in patients at high-risk and were associated with poor survival outcomes (Fig. 5A-C). Furthermore, univariate and multivariate Cox regression analyses showed that the prognostic model-derived risk score was an independent prognostic factor for patients with gastric cancer (Fig. 5D and E).

Lipo-CAF signature is associated with immune function. To determine whether the prognostic model was associated with immune cell infiltration, correlation analysis was performed between the risk score and immune cell infiltration levels. Results showed that the risk score was positively correlated with M2 macrophages and mast cells and negatively correlated with plasma cells (Fig. 5F-H). Immune therapy response scoring was conducted in TCGA-STAD patients with gastric cancer, with results suggesting that high-risk patients, as defined by the prognostic model, were more likely to exhibit no response to immunotherapy (Fig. 5I).

Lipo-CAF genes (FABP4, CD36 and ABCA8) promote gastric cancer progression. To determine whether the lipo-CAF genes included in the prognostic model were expressed in CAFs in gastric cancer, single-cell transcriptomic datasets GSE134520 and GSE167297 were analyzed. GSE134520 was originally generated to construct a single-cell transcriptomic atlas of gastric premalignant and early-malignant lesions, including non-atrophic gastritis, chronic atrophic gastritis, intestinal metaplasia and early gastric cancer. GSE167297 was originally generated from diffuse-type gastric cancer samples to characterize spatially distinct tumor microenvironment features The results showed that FABP4, CD36, ABCA8 and PTGS2 were expressed in CAFs (Figs. S1 and S2). Subsequently, clinical validation analyses were performed using publicly available online databases. FABP4, CD36 and ABCA8 were associated with poor prognosis in gastric cancer and showed clinicopathological associations with tumor stage and grade (Fig. S3A,

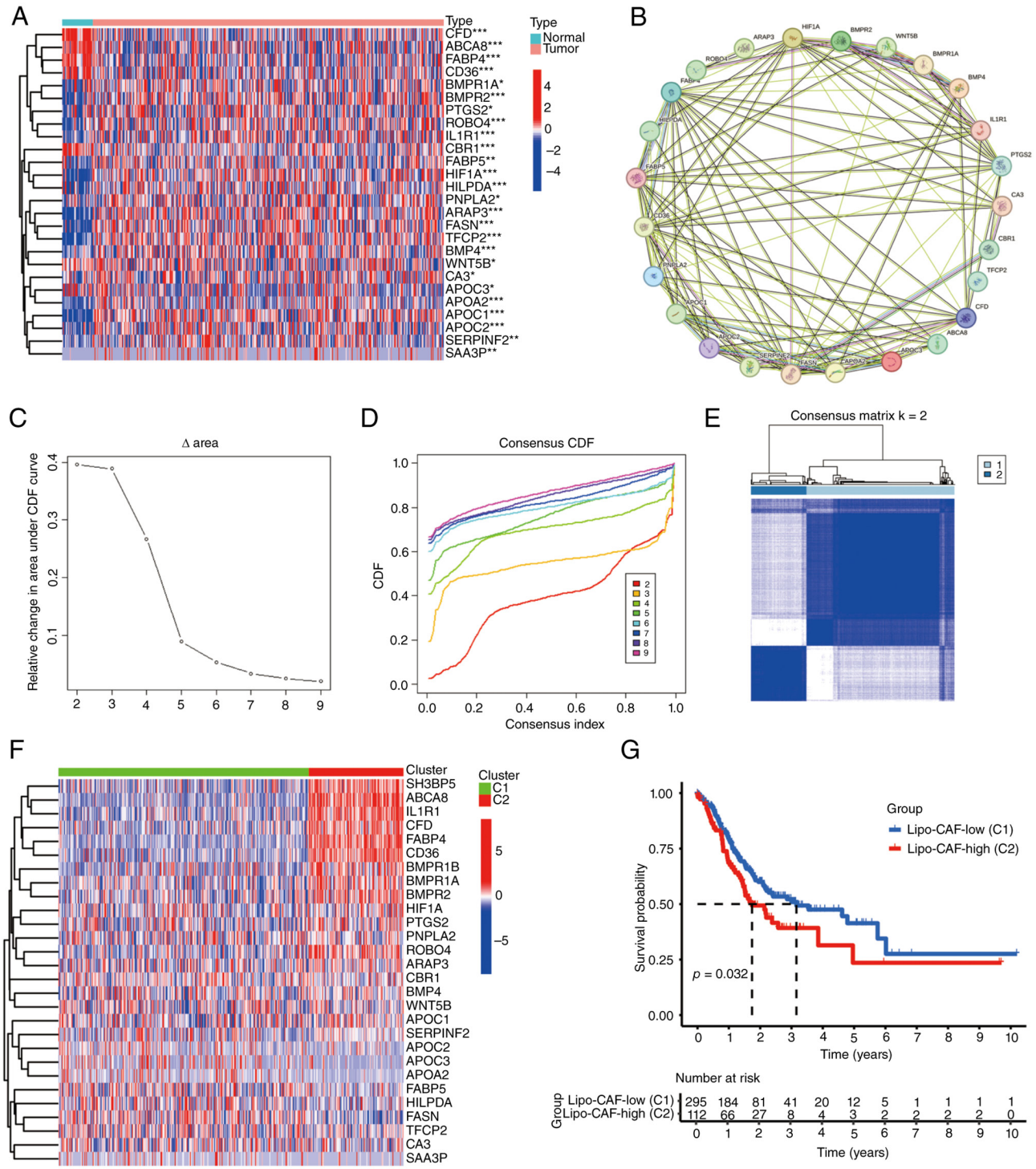

Figure 1. Identification of lipo-CAF-associated genes in gastric cancer. (A) Heatmap showing the expression of lipo-CAF-associated genes in gastric cancer and normal tissue from The Cancer Genome Atlas Stomach Adenocarcinoma cohort. (B) Protein-protein interaction network analysis of lipo-CAF-associated genes using the STRING database. (C) Consensus clustering matrix of patients with gastric cancer based on the expression of lipo-CAF-associated genes. (D) Cumulative distribution function curves for consensus clustering. (E) Relative change in the area under the cumulative distribution function curve. (F) Differentially expressed lipo-CAF-associated genes between cluster 1 and cluster 2. (G) Kaplan-Meier analysis of overall survival between the lipo-CAF-high and the lipo-CAF-low group, C1. *P<0.05, **P<0.01 and ***P<0.001. Lipo-CAF, lipid-rich cancer-associated fibroblast; CDF, cumulative distribution function; PPI, protein-protein interaction; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

F and G), whereas the remaining genes did not show significant differences (Fig. S3B-E and H). Furthermore, protein expression of lipo-CAF-associated genes was evaluated using the HPA database, which showed that FABP4, CD36 and ABCA8 were highly expressed in CAFs within gastric cancer tissue (Fig. 6A-G). To further investigate their functional roles, these three genes were individually knocked down in mouse fibroblasts using lentiviral vectors (Fig. 6H-J) and subsequently co-cultured with mouse gastric cancer MFC cells (Fig. 6K). Functional assays demonstrated that knockdown

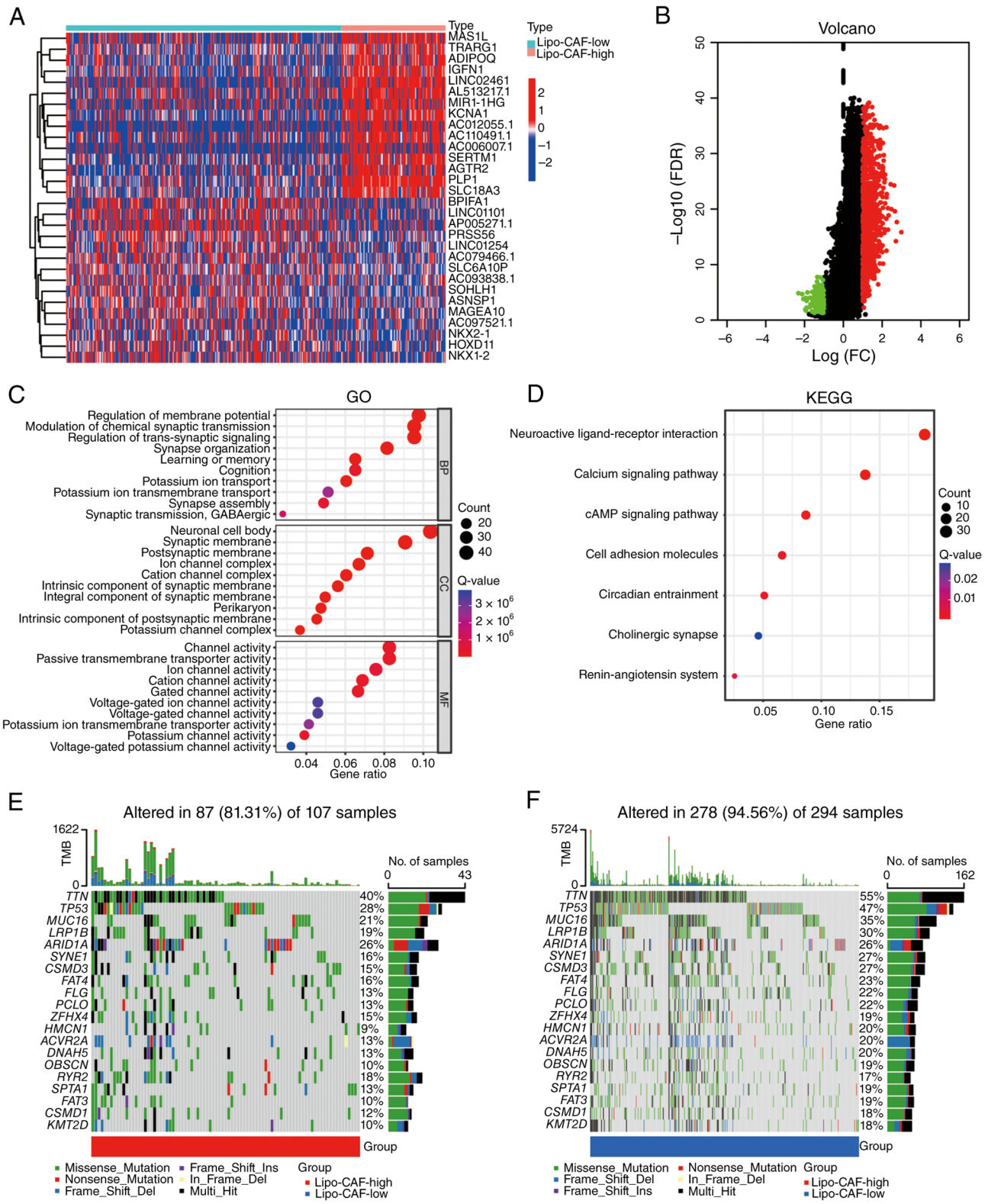

Figure 2. Lipo-CAF-associated genes are coupled with metabolic and stromal features. (A) Heatmap showing differentially expressed genes between the lipo-CAF-high and lipo-CAF-low. (B) Volcano plot showing differentially expressed genes between the lipo-CAF-high and lipo-CAF-low groups. (C) Gene Ontology enrichment analysis of differentially expressed genes between the lipo-CAF-high and lipo-CAF-low groups. (D) Kyoto Encyclopedia of Genes and Genomes enrichment analysis of differentially expressed genes between the lipo-CAF-high and lipo-CAF-low groups. (E) Waterfall plot showing the gene mutation profile in the lipo-CAF-high group. (F) Waterfall plot showing the gene mutation profile in the lipo-CAF-low group. Lipo-CAF, lipid-rich cancer-associated fibroblast; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; FDR, false discovery rate; FC, fold change; TMB, tumor mutational burden.

of these genes significantly reduced MFC cell proliferation, as measured by CCK-8 assays and was accompanied by increased TUNEL-positive staining in the co-culture system (Fig. 6L-Q). These findings indicate that lipo-CAF-associated

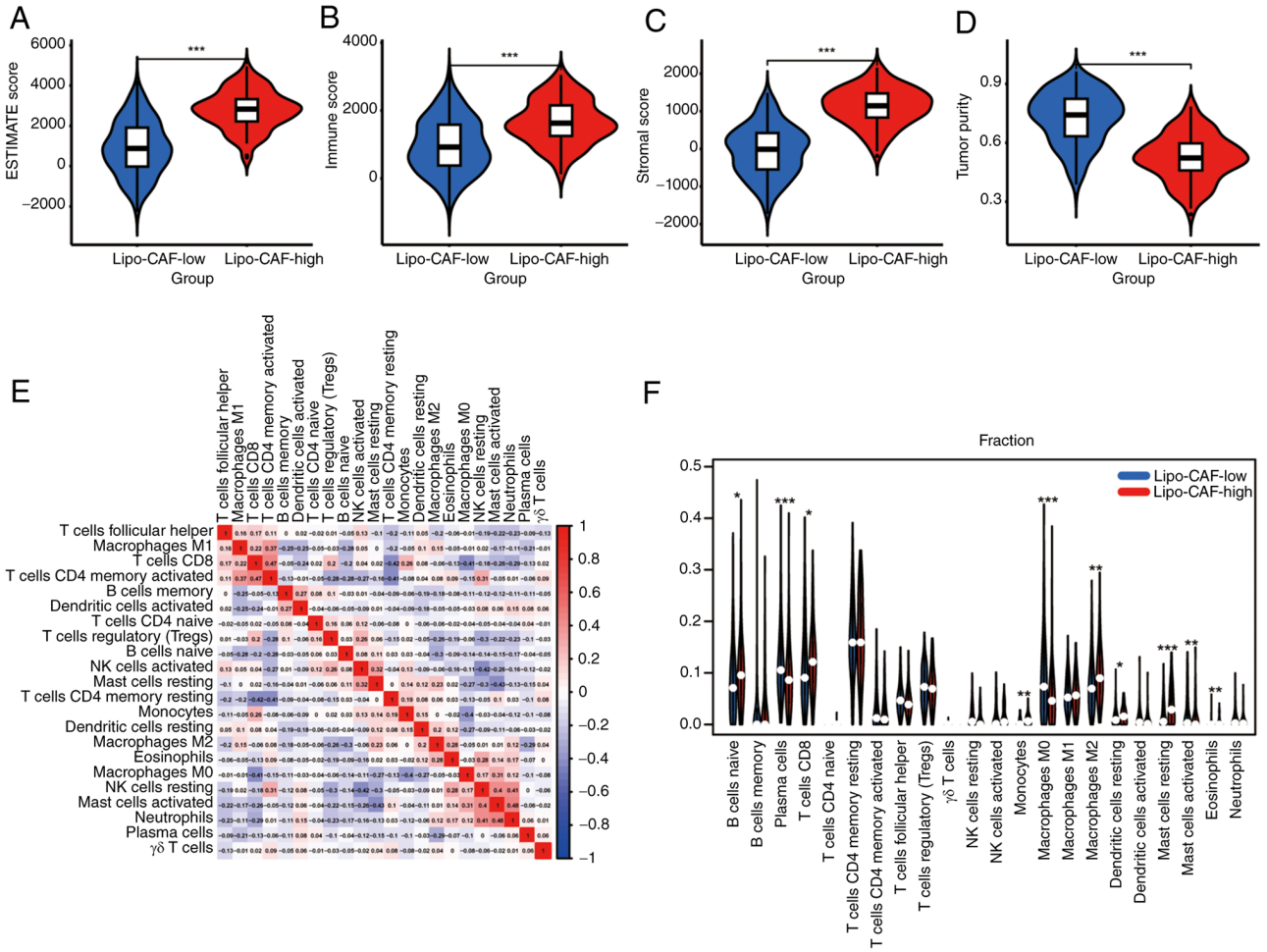

Figure 3. Lipo-CAF subtype is associated with immune infiltration. (A) ESTIMATE, (B) Immune and (C) Stromal score and (D) Tumor purity in the lipo-CAF-high and lipo-CAF-low groups. (E) Correlation matrix of immune-cell infiltration in gastric cancer. (F) Comparison of immune-cell infiltration between the lipo-CAF-high and lipo-CAF-low groups. Lipo-CAF, lipid-rich cancer-associated fibroblast; NK, natural killer; ESTIMATE, Estimation of Stromal and Immune Cells in Malignant Tumour Tissues using Expression data. *P<0.05, **P<0.01 and ***P<0.001.

genes, particularly FABP4, CD36 and ABCA8, may exert tumor-promoting effects in fibroblast-based co-culture systems.

Discussion

Marked advances have been made in understanding the role of lipid metabolism in CAFs and tumors. Fatty acids are the primary building blocks of lipids and enter metabolic pathways such as triglyceride synthesis, phospholipid and sphingolipid synthesis and cholesterol ester formation to generate more complex lipid species (54). The structural diversity of fatty acids serves a key role in regulating the cellular lipid pool and associated biochemical processes in normal cells (55). Aberrant fatty acid metabolism as a key feature of cancer, as fatty acids not only contribute to cell membrane structure but also serve central roles in cell signaling and energy metabolism (56), Pancreatic stellate cells (PSCs), which represent fibroblast-like stromal cells associated with the PDAC tumor microenvironment, undergo metabolic remodeling during activation, including loss of vitamin A-containing lipid droplets, altered lipid-droplet homeostasis and secretion of lysophosphatidylcholine (LPC) species that can be converted into lysophosphatidic acid to support pancreatic tumor progression (57). Activated PSCs lose neutral lipids, resulting in a marked increase in intracellular lysophospholipid levels (58). In addition, LPCs are abundantly secreted into the tumor microenvironment. A proportion of these LPCs is taken up by PDAC cells for membrane lipid synthesis, whereas the remaining LPCs are converted into lysophosphatidic acid (LPA) by autotaxin (ATX) secreted by PDAC cells, thereby activating LPA receptor signaling in tumor cells (59). Similarly, tumor-derived LPA promotes metabolic reprogramming in both cancer cells and stromal fibroblasts. In fibroblasts, ovarian cancer cell-derived LPA induces a glycolytic shift and CAF-like phenotype through LPA receptors, with involvement of hypoxia-inducible factor 1α signaling, highlighting metabolic crosstalk between fibroblasts and cancer cells (60). The ATX/LPA/LPA receptor signaling pathway exerts notable effects on tumor growth, cell proliferation and metabolism and has therefore been proposed as a potential therapeutic target, particularly in liver cancer, and as a signaling pathway involved in cancer-associated pain (61,62). CAFs undergo lipid metabolic reprogramming and can promote CRC cell migration and invasion through lipid-mediated metabolic crosstalk (63). Collectively, these

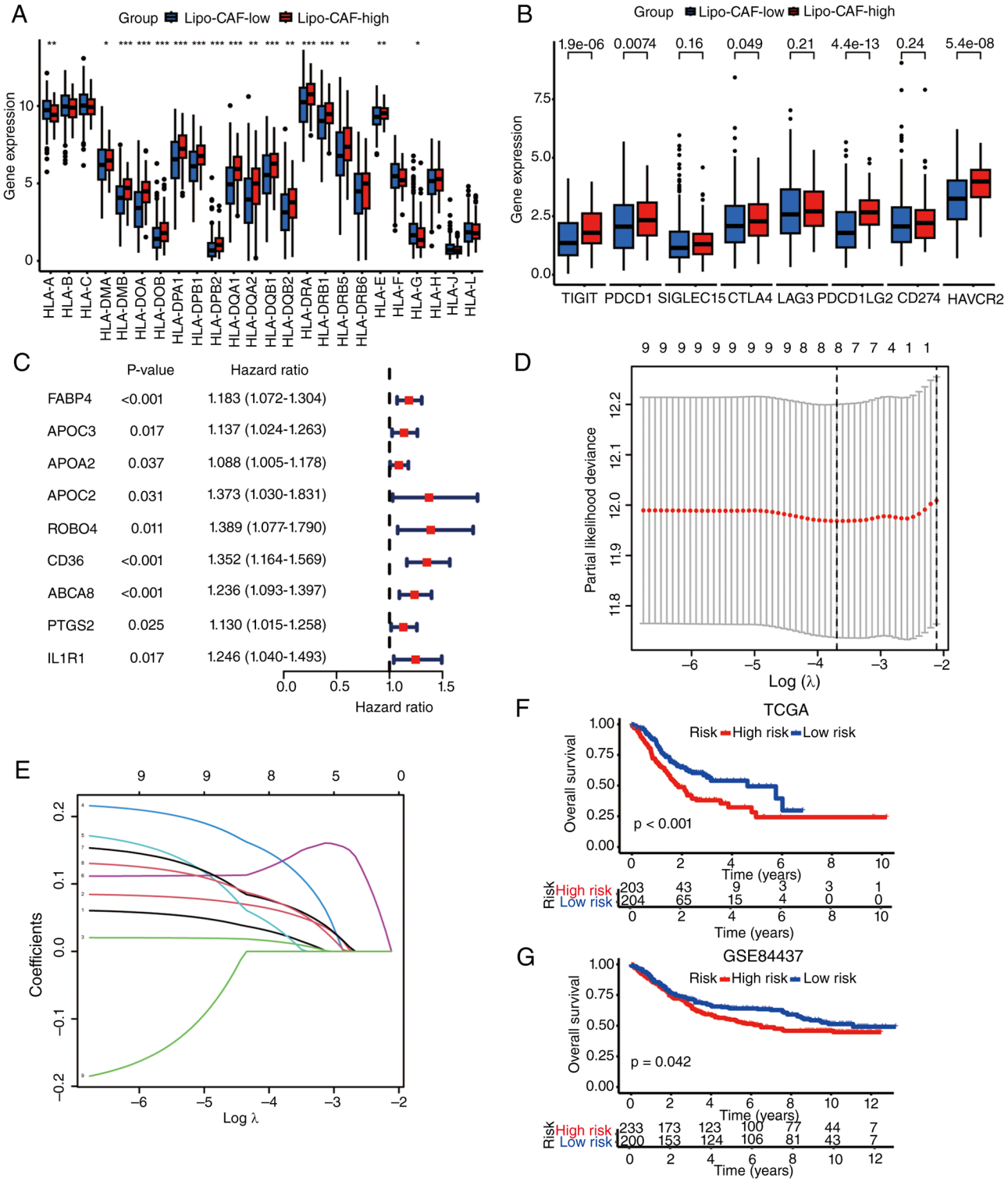

Figure 4. Construction and validation of the lipo-CAF prognostic signature in gastric cancer. (A) Expression of HLA family genes in the lipo-CAF-high and lipo-CAF-low groups. (B) Expression of immune checkpoint molecules in the lipo-CAF-high and lipo-CAF-low groups. (C) Univariate Cox regression analysis of lipo-CAF-associated genes in gastric cancer. (D) Ten-fold cross-validation curve for LASSO Cox regression. (E) LASSO coefficient profiles of lipo-CAF-associated genes. (F) Kaplan-Meier analysis of overall survival between high-risk and low-risk patients in The Cancer Genome Atlas Stomach Adenocarcinoma cohort. (G) Kaplan-Meier analysis of overall survival between high-risk and low-risk patients in the GSE84437 cohort. *P<0.05, **P<0.01 and ***P<0.001. Lipo-CAF, lipid-rich cancer-associated fibroblast; TCGA, The Cancer Genome Atlas; HLA, human leukocyte antigen; LASSO, least absolute shrinkage and selection operator.

findings advance understanding of lipid metabolic mechanisms in CAFs and tumor cells and provide insights for future research and therapeutic development. Collectively, these observations provide a biological rationale for interpreting lipo-CAF-tumor interactions in gastric cancer from the perspective of metabolic symbiosis, in which lipid-associated stromal cells may facilitate tumor growth by modulating lipid availability, transport and utilization (13).

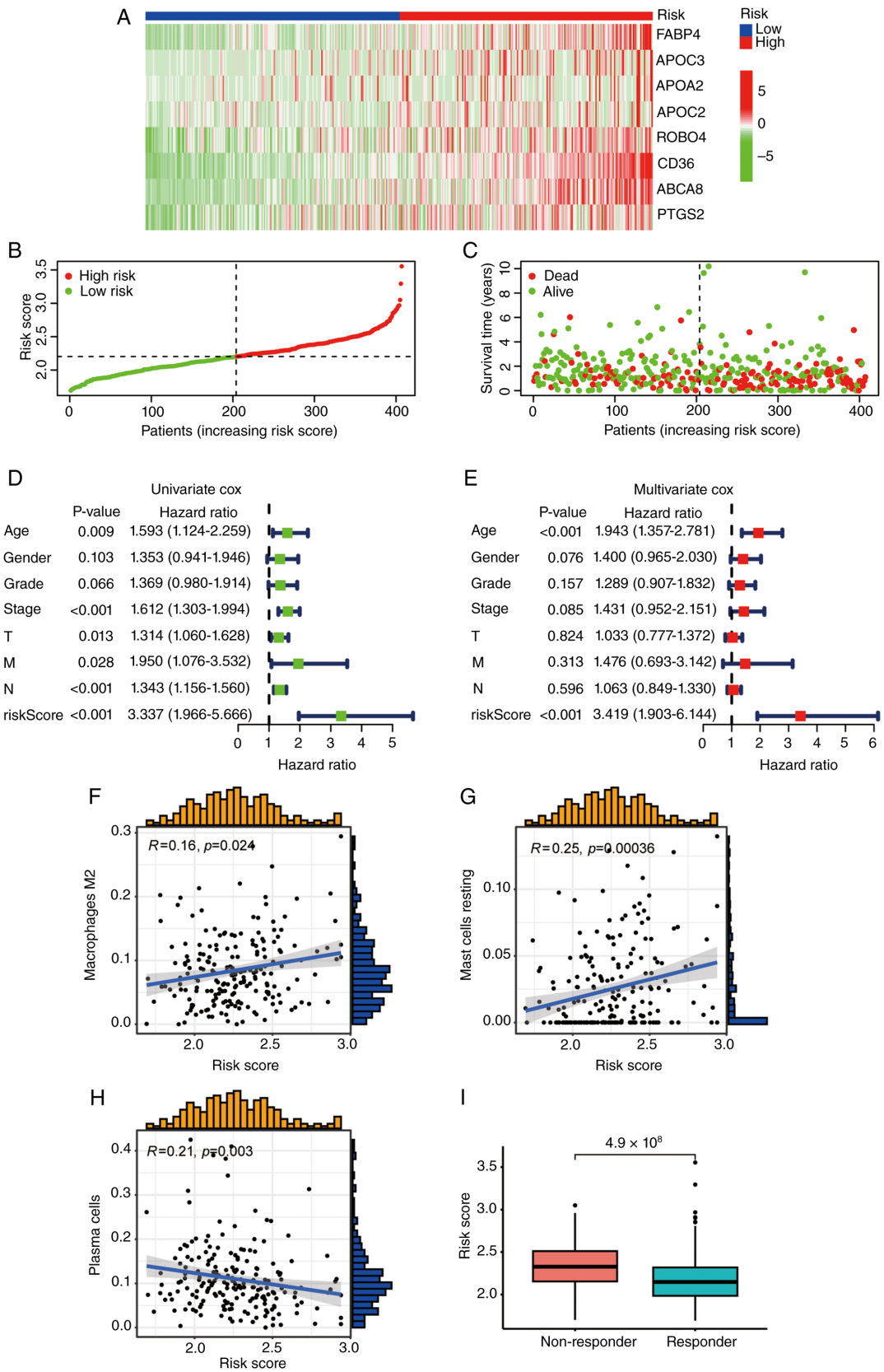

Figure 5. Lipo-CAF risk score associated with prognosis and immune features in gastric cancer. (A) Heatmap showing the expression of lipo-CAF signature genes in the high-risk and low-risk groups. (B) Survival status distribution in high-risk and low-risk patients. (C) Risk score distribution in high-risk and low-risk patients. (D) Univariate Cox regression analysis of age, sex, grade, stage, T, N stage, M stage and risk score in patients with gastric cancer. (E) Multivariate Cox regression analysis of age, sex, grade, stage, T, N stage, M stage and risk score in patients with gastric cancer. (F) Correlation between the lipo-CAF risk score and M2 macrophage infiltration. (G) Correlation between the lipo-CAF risk score and resting mast cell infiltration. (H) Correlation between the lipo-CAF risk score and plasma cell infiltration. (I) Association between the lipo-CAF risk score and predicted immunotherapy response. Lipo-CAF, lipid-rich cancer-associated fibroblast; T stage, tumor stage; N stage, lymph node stage; M stage, metastasis stage; FABP4, fatty acid-binding protein 4; APO, apolipoprotein; ROBO4, roundabout homolog 4; ABCA8, ATP-binding cassette subfamily A member 8; PTGS2, prostaglandin-endoperoxide synthase 2.

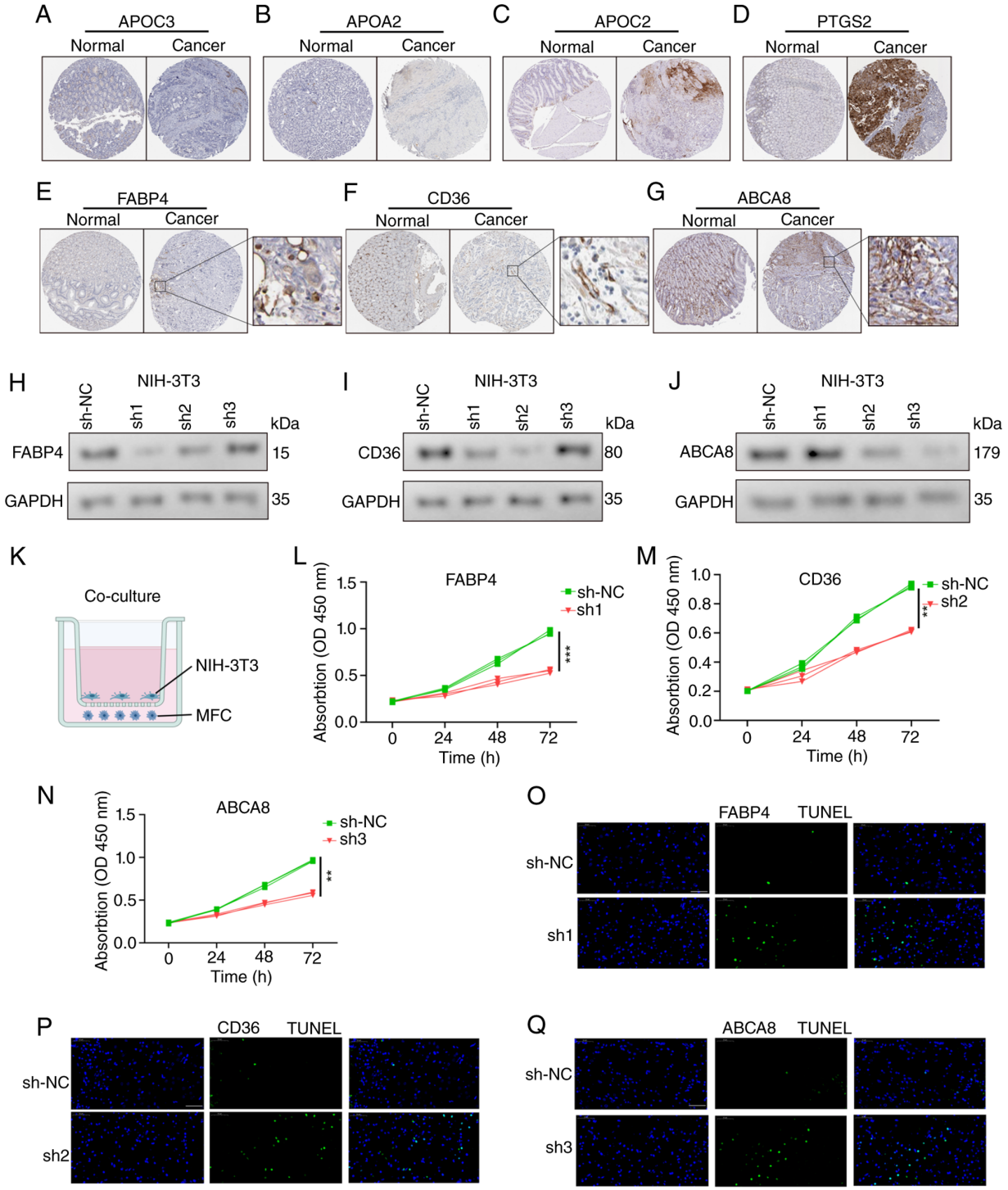

Figure 6. FABP4, CD36 and ABCA8 promote gastric cancer cell growth in a fibroblast-based co-culture system. (A) Representative HPA immunohistochemistry showing APOC3 protein expression in normal gastric tissue and gastric cancer tissue. (B) Representative HPA immunohistochemistry image showing APOA2 protein expression in normal gastric tissue and gastric cancer tissue. (C) Representative HPA immunohistochemistry showing APOC2 protein expression in normal gastric tissue and gastric cancer tissue. (D) Representative HPA immunohistochemistry image showing PTGS2 protein expression in normal gastric tissue and gastric cancer tissue. (E) Representative HPA immunohistochemistry image showing FABP4 protein expression in normal gastric tissue and gastric cancer tissue. (F) Representative HPA immunohistochemistry image showing CD36 protein expression in normal gastric tissue and gastric cancer tissue. (G) Representative HPA immunohistochemistry image showing ABCA8 protein expression in normal gastric tissue and gastric cancer tissue. (H) Western blotting analysis showing FABP4 knockdown in NIH-3T3 cells. (I) Western blotting analysis showing CD36 knockdown in NIH-3T3 cells. (J) Western blotting analysis showing ABCA8 knockdown in NIH-3T3 cells. (K) Schematic diagram of the co-culture system using NIH-3T3 mouse fibroblasts and MFC mouse gastric cancer cells.(L) Cell Counting Kit-8 assay showing the effect of FABP4 knockdown in NIH-3T3 cells on cell viability in the co-culture system. (M) Cell Counting Kit-8 assay showing the effect of CD36 knockdown in NIH-3T3 cells on cell viability in the co-culture system. (N) Cell Counting Kit-8 assay showing the effect of ABCA8 knockdown in NIH-3T3 cells on cell viability in the co-culture system. (O) TUNEL assay showing the effect of FABP4 knockdown in NIH-3T3 cells on apoptosis in the co-culture system. (P) TUNEL assay showing the effect of CD36 knockdown in NIH-3T3 cells on apoptosis in the co-culture system. (Q) TUNEL assay showing the effect of ABCA8 knockdown in NIH-3T3 cells on apoptosis in the co-culture system. **P<0.01 and ***P<0.001. Scale bar, 50 μm. FABP4, fatty acid-binding protein 4; ABCA8, ATP-binding cassette subfamily A member 8; HPA, Human Protein Atlas; lipo-CAF, lipid-rich cancer-associated fibroblast; sh, short hairpin; NC, negative control; OD, optical density; MFC, mouse forestomach carcinoma; PTGS2, prostaglandin-endoperoxide synthase 2.

In the present study, it was demonstrated that lipo-CAF-associated genes were highly expressed in gastric cancer. Based on their expression profiles, patients with gastric cancer were classified into two subtypes with distinct prognostic outcomes. Further analyses revealed that the subtype associated with poor prognosis exhibited increased tumor immune infiltration. In addition, the lipo-CAF-based prognostic model indicated that patients with high expression of lipo-CAF-associated genes were more likely to exhibit resistance to immunotherapy. Lipid-mediated cellular interactions within the tumor microenvironment may confer survival advantages to cancer cells and promote metastasis. Fatty acids secreted by adipocytes and other tumor-associated stromal cells, such as CAFs, can directly enhance tumor cell proliferation, invasion and migration, thereby exerting tumor-promoting effects. In addition, lipid metabolic remodeling may modulate tumor progression by influencing immune cells in the tumor microenvironment, including natural killer and cytotoxic $CD8^+$ T cells, tumor-associated macrophages, dendritic cells, regulatory T cells and myeloid-derived suppressor cells (64). For example, lipid transfer from lipid-laden stromal cells has been reported to impair natural killer cell function, while aberrant lipid metabolism can also affect $CD8^+$ T cell effector activity, including cytotoxic function and the production of effector cytokines such as IFN-γ and TNF-α (10,65-67). Lipid accumulation can also reduce dendritic cell activity, promote infiltration of myeloid-derived suppressor cells, and enhance regulatory T cell activity, thereby suppressing cytotoxic T cell function (68). Furthermore, lipids can induce tumor-promoting polarization of tumor-associated macrophages. Finally, lipids may facilitate communication with neural cells, such as Schwann cells, leading to increased secretion of ECM components that promote metastasis (69). In this context, the present findings suggest that lipo-CAF-associated genes may define a metabolically active stromal state that is associated not only with tumor-supportive features but also with an immunosuppressive microenvironment. The elevated expression of immune checkpoint molecules and the poorer predicted response to immunotherapy in the lipo-CAF-high group further support this interpretation (9,67). However, these observations are just associations in the present study and should not be overinterpreted as direct mechanistic evidence that lipo-CAFs drive immune evasion. Rather, the present results indicate that lipo-CAF-associated programs may be associated with gastric cancer progression partly through stromal-tumor metabolic crosstalk and partly through their association with an immunosuppressive niche.

In total, three lipo-CAF-associated genes (FABP4, CD36 and ABCA8) associated with tumor-promoting effects in gastric cancer were identified. FABP4 is a lipid-binding protein that serves a key role in lipid metabolism and intracellular fatty acid transport (23). It is upregulated in a number of cancer types, including breast, prostate and colorectal cancers (70-72). FABP4 promotes cancer cell proliferation, migration, invasion and therapy resistance by regulating fatty acid transport, lipid uptake and metabolic adaptation (73-76). In addition, FABP4 is reported to enhance tumor angiogenesis by interacting with endothelial cells and promoting vascularization within the tumor microenvironment (77,78). Furthermore, FABP4 may modulate antitumor immune responses by influencing immune cell function and facilitating immunosuppressive mechanisms in the tumor microenvironment (79,80). These findings have important implications for the efficacy of cancer immunotherapy and the overall antitumor immune response. In the context of lipo-CAFs, FABP4 may facilitate intracellular lipid trafficking and handling in stromal cells, thereby supporting the storage, buffering or delivery of lipid metabolites that can be utilized by adjacent gastric cancer cells (81).

CD36 is associated with lipid metabolism and tumor biology (34). As a lipid scavenger receptor, CD36 serves a central role in regulating lipid metabolism under physiological conditions by mediating lipid uptake, metabolism and storage. However, in tumor settings, CD36 function may be dysregulated, contributing to tumor initiation and progression. CD36 is upregulated in a number of cancer types, including breast and prostate cancer and melanoma. In addition, CD36 expression has been associated with resistance to chemotherapy and targeted therapies in certain cancer types. Previous studies (34,82,83) have examined the role of CD36 in angiogenesis and tumor vascular biology, but these effects appear to be context- and ligand-dependent. CD36 mediates thrombospondin-induced anti-angiogenic signaling, whereas CD36-mediated lipid uptake has been linked to tumor growth, metastasis, immune regulation and therapy resistance (83,84). Furthermore, CD36 may contribute to tumor immune evasion by modulating immune cell function and attenuating antitumor immune responses. From the perspective of metabolic symbiosis, CD36 may enhance the uptake and exchange of extracellular lipids within the tumor microenvironment, thereby strengthening metabolic coupling between lipo-CAFs and tumor cells.

ABCA8 is an ATP-binding cassette transporter involved in the transmembrane transport of cellular substrates under physiological conditions (37). ABCA8, an ATP-binding cassette transporter, may influence tumor-associated biological processes (37,85) by regulating substrate transport and lipid-associated signaling. For example, ABCA8-mediated efflux of taurocholic acid contributes to gemcitabine insensitivity in pancreatic cancer through the S1PR2/ERK pathway, and ABCA8-positive lipid-metabolic CAFs have been associated with immunotherapy resistance in triple-negative breast cancer (37,85). In addition, ABCA8 may be involved in the remodeling of tumor lipid metabolism, therapeutic resistance and lipid-mediated signaling within the tumor microenvironment. By regulating lipid transport and associated metabolic pathways, ABCA8 may influence tumor cell survival, proliferation and metastasis. It may also modulate intercellular signaling and treatment responsiveness within the tumor microenvironment. Compared with FABP4 and CD36, the role of ABCA8 in cancer remains less well characterized. This limitation makes ABCA8 one of the more distinctive findings within the present (85). As a transmembrane transporter, ABCA8 may contribute to gastric cancer malignancy by regulating the transport of lipid-associated molecules, altering membrane composition or facilitating stromal-tumor lipid exchange within the microenvironment. Although these mechanisms remain speculative, the present findings suggest that ABCA8 is not merely a passive marker but may represent

a distinct component of the lipo-CAF program that warrants further mechanistic investigation.

A key strength of the present study was the identification of lipo-CAF-associated genes and the successful development of a prognostic signature in gastric cancer. Despite this, a number of limitations should be acknowledged. Only *in vitro* experiments were performed for functional validation and no *in vivo* studies were conducted. In addition, further experimental validation of the effects of lipo-CAF-associated genes on tumor immunity was not undertaken. In addition, the *in vitro* functional assays were conducted using an immortalized mouse fibroblast cell line rather than primary gastric CAFs or directly isolated lipo-CAFs. Given the marked heterogeneity of fibroblasts, this model may not fully recapitulate the biological characteristics of lipo-CAFs within the gastric tumor microenvironment. Also, migration or invasion assays were not performed and the effects of these genes on tumor growth and stromal-immune interactions were not validated *in vivo*. Therefore, the present findings should be interpreted as bioinformatics-supported and *in vitro* functional evidence rather than definitive proof of lipo-CAF-specific biological activity in gastric cancer. Despite these limitations, the lipo-CAF-associated signature may provide a useful framework for prognostic stratification and for identifying tumors characterized by a metabolically remodeled stromal microenvironment. From a translational perspective, FABP4, CD36 and ABCA8 may represent candidate stromal targets for future investigation, particularly in studies aimed at disrupting tumor-supportive lipid crosstalk or enhancing immunotherapy responsiveness.

In conclusion, a lipo-CAF-associated gene prognostic model was established to predict the prognosis of gastric cancer. Patients classified as high risk by this model exhibited poorer survival and an altered immune infiltration profile. Notably, the lipo-CAF-associated genes with marked prognostic value (FABP4, CD36 and ABCA8), were all associated with gastric cancer progression. The present co-culture experiments further demonstrated that the expression of these genes in fibroblasts was associated with tumor-promoting effects on gastric cancer cells *in vitro*. Collectively, these findings suggested that lipo-CAF-associated genes exhibit notable potential for prognostic stratification and therapeutic targeting in gastric cancer. However, their precise mechanistic roles, particularly in immune regulation and stromal-tumor metabolic coupling, remain to be elucidated in future studies using primary CAF-based systems and *in vivo* models.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW and JL conceived the present study and wrote, reviewed and edited the manuscript. LZ and QL analyzed and interpreted the data. PZ performed the statistical and computational analyses, and supervised the study. LW and JL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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