Supplementary methods

Patients and Tissues

Pancreatic tissue samples were obtained from patients diagnosed with PDAC following tumor resection at Xi Jing Hospital and Tangdu Hospital. All specimens were confirmed to be PDAC by histopathology, and all patients were not treated with radiotherapy, chemotherapy, or targeted therapy before operation. Ethics approval was granted by the Ethics Committee of the Air Force Medical University, and all patients provided informed consent to participate in the study. The clinical and pathological characteristics of the patients are presented in Table S1 in the Supplementary Material. Immediately after collection, the tissue samples were frozen in liquid nitrogen for storage until further use in experiments.

RNA sequencing

RNA sequencing was performed on 51 samples, 2 samples were not included because there was insufficient RNA or the RNA quality was low. In brief, RNA was extracted and sheared followed by sequencing library preparation using NEBNext® UltraTM RNA Library Prep Kit, according to the manufacturer's instructions Sequencing was performed on Illumina HiSeq platform and 125 bp/150 bp paired-end reads were generated. Raw data (raw reads) of fastq format were first processed through in-house perlscripts. The reference genome index was built using Hisat2 v2.0.5 and paired-end clean reads were aligned to the reference genome using Hisat2 v2.0.5 and Hisat2 was selected as the mapping tool. FeatureCounts v1.5.0-p3 was then used to count the reads numbers mapped to each gene. TPM of each gene was calculated based on the gene length and reads count mapped to this gene.

Immune cell infiltration analysis via a single-sample gene set enrichment analysis (ssGSEA) algorithm

The infiltration of 24 immune cell types in the TME was quantified via ssGSEA.

Marker genes for each cell type were selected based on previous publications[1-3]. The deconvolution approach used in our study included 24 immune cell types[4]. Immune-related genes were identified as previously described[5, 6]. Unsupervised clustering was applied to categorize PAC patients into high-, moderate-, and low-infiltration subtypes based on immune cell infiltration levels.

Dimension reduction and MBS

We identified 112 metabolism-related pathways via the IOBR[7] and KEGG database, quantifying them through ssGSEA using the GSVA package[8]. Differential enrichment scores in tumor tissues and non-tumor tissues in PAC patients were assessed for GSE71729 dataset. Unsupervised clustering was employed to classify patients into distinct metabolism (MB) clusters using the "ConsensusClusterPlus" package, repeated 1000 times to ensure classification stability.[9] We extracted differentially expressed genes (DEGs) between normal and tumor tissues of PAC patients from GEPIA. Then we obtained differentially expressed genes among different MB clusters using the limma package in R, which were intersected with DEGs to harvest differentially expressed metabolism-related genes (DEMBGs)[10]. Unsupervised clustering was employed to classify the training cohort into gene cluster subtypes based on DEMBGs expression. Furthermore, DEMBGs with expression patterns that was positively and negatively correlated with the gene cluster were termed as MB gene signatures A and B, respectively. In order to reduce the noise or redundant genes, the Boruta algorithm was used to perform dimension reduction for the MB gene signatures A and B. To examine quantitative indicators of MB landscape, PCA was utilized to construct the MBS from the gene signatures A and B. Principal component 1 was extracted as the signature score termed MBS, via PCA, as previously reported[6, 11]. (1) $PC1_A$ represents the first component of gene signature A, and (2) $PC1_B$ represents the first component of gene signature B. We calculated the MBS per patient as: $MBS = \sum PC1_A - \sum PC1_B$.

Quantification of the immune response predictors: Tumor immune dysfunction

and exclusion (TIDE), immunophenoscore (IPS), and drug sensitivity analysis

The TIDE algorithm was used to model distinct tumor immune evasion mechanisms, with higher TIDE scores predicting immune evasion and poor immunotherapy response[12]. The IPS was also determined to predict immunotherapy response.[2] The Pan-F-TBRs signature is positively correlated with a poor immunotherapy response and unfavorable prognosis[13]. Immunosuppressive cell types, including cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) restrict antitumor T cells, thus promoting immune escape[12]. Tertiary lymphoid structures (TLSs) promote antigen presentation and are significantly correlated with immunotherapy response[14, 15].

Cancer cell line drug sensitivity data were obtained from the Cancer Therapeutics Response Portal (CTRP, https://portals.broadinstitute.org/ctrp.v2.1/)[16] and the PRISM database (https://www.theprismlab.org/)[17]. Both datasets provide the area under the dose-response curve (AUC) as a measure of drug sensitivity, and lower AUC values indicate greater sensitivity. K-Nearest Neighbor (K-NN) imputation was applied to obtain missing AUC values. Compounds with more than 20% missing data and haematopoietic_and_lymphoid_tissue cell lines were excluded[18]. The sensitivity of every PAC patient to chemotherapeutic was assessed based on the IC50 value, as quantified by the pRRophetic package based on the Genomics of Drug Sensitivity in Cancer (GDSC) database[19, 20]. A ridge regression model was applied to yield drug sensitivity estimates for every patient the three datasets. Expression profile data of human cancer cell lines were obtained from the Broad Institute Cancer Cell Line Encyclopedia (CCLE) database (https://sites.broadinstitute.org/ccle)[21].

Immunotherapy cohorts

Thirteen cohorts that received immunotherapy, including the IMvigor210 dataset, GSE91061, GSE78220, GSE63557, GSE117358, GSE148476, GSE173839, GSE165252, GSE168204, and four PAC immunotherapy cohorts were included for analysis. The IMvigor210 dataset includes data from metastatic urothelial cancer patients receiving atezolizumab (PD-L1 blockade,

http://research-pub.gene.com/IMvigor210CoreBiologies)[13]. The GSE91061 and GSE78220 datasets include data from anti-PD-1-treated melanoma patients[22, 23]. GSE63557 includes data from BALB/c mice treated with anti-CTLA-4[24]. Data from mice receiving anti-CTLA-4 and anti-PD-L1 were included in GSE117358[25]. Mice treated with anti-PD-1 and anti-PD-L1 were included in GSE148476[26]. Two scRNA-seq Immunotherapy cohort, including melanoma (SKCM-GSE115978) and basal cell carcinoma (BCC-GSE123813) were also included[27, 28], and the related-data obtained from previously paper[29]. Four pancreatic cancer immunotherapy cohorts: Parikh[30] conducted a single-arm, non-randomized, phase 2 trial combining radiation and immunotherapy in patients with CRC and PDAC. Balachandran et al[31] reported tumors of long-term survivors (LTS) exhibited an activated, polyclonal, tumor-specific T-cell infiltrate, suggesting differential antigenic targets. And pancreatic cancer survivors display enhanced T-cell immunity, with greater densities of CD8+ T cells (3-fold), cytolytic CD8+ cells (12-fold), mature dendritic cells, regulatory T cells, macrophages. Lutz[32] designed a neoadjuvant and adjuvant clinical trial comparing an irradiated, granulocyte macrophage colony-stimulating factor (GM-CSF)–secreting, allogeneic PDAC vaccine (GVAX) given as a single agent or in combination with low-dose cyclophosphamide to deplete regulatory T cells (Treg) as a means to study how the TME is altered by immunotherapy. And examination of resected PDACs revealed the formation of vaccine induced intratumoral tertiary lymphoid aggregates in most patients 2 weeks after vaccine treatment. And vaccine-primed PDAC may be better candidates than vaccine-naive patients for immune checkpoint and other immunomodulatory therapies. Li et al[33] performed whole-transcriptome RNA sequencing (RNA-seq) on tumor-infiltrating leukocytes (TILs) isolated from the post-treatment, surgically resected PDACs of nine patients treated with GVAX and eight patients treated with GVAX and nivolumab. These cells were sorted by flow cytometry into four immune cell subtypes: $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD11b^+$, and $CD3^-CD11b^-CD19^+$ cells prior to RNA-seq analysis. And Reported Bulk and single-cell RNA sequencing found that nivolumab alters CD4+T cell chemotaxis signaling in association with CD11b+ neutrophil

degranulation, and CD8+ T cell expression of CD137 was required for optimal T cell activation.

Comparing MBS with other published signatures

To compare the performance of MBS with other signatures, we comprehensively retrieved prognostic signatures from published papers. And we obtained 66 signatures, including lncRNA and mRNA (Supplementary Table S20). We compared the performance of MBS and other already acknowledge score, including MIAS[34], GEP[35] , IMPRES[36], CD274, PDCD1, CTLA4, and IDO1, for predicting immunotherapy response in kinds of cancer datasets using ROC curves. Furthermore, we analyzed the correlation between MBS and 5 cancer stemness signature[37-39]

Collection of somatic mutation data

The corresponding somatic mutation data of patients in the TCGA-PAAD cohort were downloaded from the cBioPortal database (http://www.cbioportal.org/study/summary?id=paad_tcga_pan_can_atlas_2018)[40]. To determine mutational burden, we analyzed all mutation counts, including synonymous and non-synonymous mutations. Significantly mutated genes between the MBS-high and -low groups and gene mutation co-occurrences were examined with the "maftools" package. The mutation proportion was statistically tested with the z-test and Chi-square test, with significance set at $p < 0.05$.

Functional mechanism analysis

The potential mechanisms underlying MBS-high and -low subtypes in PAC were explored using gene set variation analysis (GSVA). The hallmark gene set (h.all.v6.2.entrez.gmt) was obtained from the Molecular Signatures Database (MSigDB) using GSEA V3.0 (http://software.broadinstitute.org/gsea/msigdb/index.jsp)[41] and the clusterProfiler[42] package in R. The cancer immunity cycle and immunotherapy-predicted pathways were also explored as previously described[43, 44]. Cancer driver genes were obtained

from the Integrative OncoGenomics database (IntOGen, https://www.intogen.org/)[45] to compare their expression between MBS-high and -low groups. To identify pathways most differentially regulated between dasatinib-treated and non-dasatinib-treated, genes were ranked in order of differential induction and gene set enrichment analysis was performed with the R package Pi[46] using the MsigdbH ontology and pathways containing 20–5,000 genes, with 20,000 permutations used.

Western blotting

Pancreatic cancer and control tissues were obtained from the Department of General Surgery at Tangdu Hospital of Fourth Military Medical University (Xi'an, Shaanxi, People's Republic of China). All procedures performed on patient tissues were approved by the Research Ethics Committee of Tangdu Hospital, and written informed consent was obtained from all patients. Tissues were cut into small pieces and lysed with lysis buffer (P0013C, Beyotime, Shanghai, China) at 4℃ for 0.5 h. the samples were centrifuged at 10,000 rpm for 10 min, and the supernatants were harvested. Protein concentration was determined using the BCA kit. The protein samples were subjected to 10% SDS gel electrophoresis, transferred to polyvinylidene fluoride membranes, and blocked with 5% non-fat milk. The blots were incubated with primary antibodies at 4℃ overnight: anti-BIP (11587-1-AP), anti-ATF4 (10835-1-AP), anti-ATF6 (24169-1-AP), anti-XBP1 (24868-1-AP), anti-E-cadherin (20874-1-AP), anti-N-cadherin (22018-1-AP), anti-Vimentin (10366-1-AP), anti-Snail2 (12129-1-AP) and anti-GAPDH were purchased from Proteintech (Wuhan, China). Membranes were then incubated with secondary horseradish peroxidase antibodies (SA00001-1 and SA00001-2, Proteintech, Wuhan, China) for 2h at room temperature**.** The blots were visualized using ECL (ChemiDoc MP, Bio-Rad, USA).

Immunohistochemistry

Pancreatic cancer and control tissues were fixed in 4% paraformaldehyde and deparaffinized using xylene. Tissue sections were then rehydrated using different

concentrations of ethanol. To inhibit peroxide activity, tissue sections were treated with 3% hydrogen peroxide and blocked with 5% normal goat serum. The sections were then incubated overnight at 4 °C with primary antibodies against EPHA2 (A7183, Abclonal, Wuhan, China), CHST11 (D224558, BBI life science, Shanghai, China), CTLA-4 (D260213, BBI life science, Shanghai, China), PD1 (D161077, BBI life science, Shanghai, China), CD8A (#85336, Cell Signaling Technology), CD4 (#48274, Cell Signaling Technology), and CD80 (66406-1-Ig, Proteintech, Wuhan, China). Sections were stained with diaminobenzidine and hematoxylin.

Immunofluorescence

Pancreatic cancer and control tissue slides were fixed with 4% formaldehyde and then treated slides with 0.5% Triton X-100 for 30 min at room temperature. Bovine serum albumin (BSA, 5%) was used to block the samples for 1 h at room temperature. Samples were incubated with primary antibodies at 4℃ overnight, including anti-LOXL2 (67139-1-Ig), anti-MMP14 (29111-1-AP), anti-MYOF (19548-1-AP), anti-PLAU (17968-1-AP), and anti-PD-1(18106-1-AP), purchased from Proteintech (Wuhan, China). The samples were washed with PBS, incubated with secondary antibodies for 2 h, and counterstained with DAPI for 5 min. Slides were observed and analyzed under a confocal microscope (NikonA1, Tokyo, Japan)

Colony-formation assay

Cells were seeded into six-well plates (5-6*10^3 cells per well) and drugs agents or vehicle control was added after 24 hours. Cells were treated with agents as described for 10 days and replaced the culture media every 72 hours. Lastly, we stained cells using 1% crystal violet for 0.5 hours and rinsed with PBS 3 times.

Statistical analysis

All data processing, plotting, and statistical analyses were performed using R-4.0.4. Normally distributed variables were analyzed via the student's t-test.

Non-normally distributed variables were analyzed via the Wilcoxon rank-sum test. Adjusted $p<0.05$ was set as the cutoff for differentially expressed genes analysis. The Kruskal-Wallis test and one-way ANOVA were used as non-parametric and parametric methods for multi-group comparisons, respectively. Survival analysis was performed via the Kaplan-Meier method and the cox proportional hazards model to analyze associations between factors and prognosis using the "survival" and "Survminer" packages. The surv-cutpoint function from the "survival" package was applied to divide the samples into different subtypes. Pearson or Spearman correlation coefficients were determined using the corrplot[47] package in R. Principal coordinate analysis (PCoA) was performed using PERM-ANOVA. All comparisons were two-sided with an alpha level of 0.05, and the Bonferroni method was used to control the false discovery rate (FDR) for multiple hypothesis testing.

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