Cell lines

Human pancreatic adenocarcinoma cells (BXPC3), human ovarian carcinoma cells (SKOV3), and human non-small-cell lung carcinoma cells (A549) were cultured in RPMI 1640 Medium (Shanghai BasalMediaTechnologies), and human colon carcinoma cells (SW48) were cultured in DMEM medium (Shanghai BasalMedia Technologies), supplemented with 10% FBS (Gibco) and 1% penicillin/streptomycin (Gibco). Mouse colon adenocarcinoma cell lines MC38 and CT26 were cultured in RPMI 1640 Medium (Shanghai BasalMedia Technologies) and RPMI 1640 Medium (ATCC modification) (Shanghai BasalMedia Technologies) respectively, supplemented with 10% FBS and 1% penicillin/streptomycin. The MC38 $^{Pd\text{-}l1\text{-}/\text{-}}$ cell line was a previous gift from the Yongjun Dang Lab. All cells were cultured in a 37°C incubator with 5% CO2.

Chemical agents

All chemical agents were purchased from MedChem Express Company (Shanghai, China).

Cell-based flow cytometry screening system

BXPC3 cells were seeded in 96-well plate by Multidrop Combi robotic dispenser (Thermo Fisher) overnight and then treated with/without in-house metabolic molecules and 500 IU/mL IFN-γ for 48h. After trypsinization for 3 min, the single cell suspension was directly incubated with APC-conjugated anti-human CD274 antibodies (Biolegend, Cat: 329708) at room temperature for 30 min. Samples were analyzed by iQue Screener PLUS (IntelliCyt).

Isolation of primary T cells

CD8 T cells were isolated from the spleen and lymph nodes of OT-I TCR transgenic mice. Single cell suspension was obtained after dissociation. Red blood cells were lysed, and freshly isolated cells were stimulated with 2 μg/mL OVA peptide (InvivoGen, OVA 257-264). After 48h stimulation, cells were split into new medium supplemented with IL-2. Cells were ready to use for proliferation and PD-1 *in vitro* detection assays after another 48h. For investigation of T cell proliferation, cell viability was detected with or without L-5-HTP treatment by the CellTiter-Glo luminescent assay as instructed by the manufacturer (Promega). For PD-1 detection, cells were stained with mouse PD-1 antibody (Biolegend, Cat: 135220) for 30 min on ice and analyzed by iQue Screener PLUS (IntelliCyt).

UHPLC-MS/MS analysis of L-5-HTP concentration in serum and tumor tissue

For serum analysis, a 100 μL aliquot of each individual sample was precisely transferred to an Eppendorf tube. After the addition of 400 μL of extract solution (1:1 methanol: acetonitrile, precooled at -40°C, containing 0.1% formic acid and isotopically-labeled internal standard mixture), the samples were vortexed for 30 s and sonicated for 5 min in an ice-water bath, followed by incubation at -40°C for 1 h. After centrifugation (15 min, 12000 rpm, and 4°C), a 400 μL aliquot of the supernatant was transferred to an Eppendorf tube. Then the supernatant was evaporated to dryness under a gentle stream of nitrogen and was reconstituted in 100 μL water containing 0.1% formic acid. After centrifugation

(15 min, 12000 rpm, and 4°C), the clear supernatant was subjected to UHPLC-MS/MS analysis. For tumor tissue, a 50 mg aliquot of each individual sample was precisely weighed and transferred to an Eppendorf tube. After the addition of 500 μL of extraction solution (2:2:1 methanol:acetonitrile:H_2O, precooled at -40°C, containing 0.1% formic acid and isotopically-labeled internal standard mixture), the samples were vortexed for 30 s, homogenized at 35 Hz for 4 min, and sonicated for 5 min in an ice-water bath. Homogenization and sonication were repeated twice, followed by incubation at -40°C for 1 h. After centrifugation (15 min, 12000 rpm, and 4°C), a 400 μL aliquot of the supernatant was transferred to an Eppendorf tube. Then the supernatant was evaporated to dryness under a gentle stream of nitrogen and reconstituted in 100 μL water containing 0.1% formic acid. After centrifugation (15 min, 12000rpm, and 4°C), the clear supernatant was subjected to UHPLC-MS/MS analysis.

The UHPLC separation was carried out using an EXIONLC System (Sciex), equipped with a Waters ACQUITY UPLC HSS T3 column (100 × 2.1 mm, 1.8 μL, Waters). A SCIEX 6500 QTRAP+ triple quadrupole mass spectrometer (Sciex), equipped with an IonDrive Turbo V electrospray ionization interface, was used for assay development. SCIEX Analyst Work Station Software (Version 1.6.3) and SciexMultiQuant software (Version 3.0.3) were employed for MRM data acquisition and processing.

CSDS-conditioned tumor model and behavior test

MC38 cells were implanted into male C57BL/6 mice on day 3. From day 0 to day 10, a CSDS paradigm was used as a stress model. In this paradigm, experimental mice were

subjected to bouts of defeat by a larger CD1 mouse that had screened positive for aggressive behavior. Every day, the experimental mouse was introduced into the home cage of a CD-1 aggressor mouse. Once the experimental mouse had been physically defeated in three attacks, both animals were separated with a perforated plexiglass divider for 24h, allowing for 24h of sensory interaction. Each C57BL/6 mouse was exposed to a new aggressor daily for 10 consecutive days. Control mice were individually housed in equivalent cages but with a member of the same strain in the other half of the cage.

Investigators were blinded to group allocation when testing animal behaviors. During the sucrose preference test (SPT), mice were provided two bottles in their home cages, one containing sucrose (1% w/v) and one containing water. The mice were left with these two bottles for 24h. The position of the two bottles (right/left) was varied in the middle times. After adaptation, all the food and water bottles were removed for 24h to allow the mice to become hungry. The two bottles were returned to the cage for 6h and the position of two bottles was exchanged in the middle times. The fluid intake of sucrose and water was calculated separately. Sucrose preference was measured as the amount of consumed sucrose solution relative to the total amount of liquid intake. For the tail suspension test (TST), mice were individually suspended by the distal portion of their tails with adhesive tape for a period of 5 min, and the total immobility time was used as a measure of depression behavior.

Table S1. Antibodies used in immunoblotting

NF-κB p65	#10745-1-AP, Proteintech
phospho-NF-κB p65 (Ser536)	#3033, CST
MEK	#4694, CST
Phospho-MEK (Ser217/221)	#9154, CST
ERK1/2	#9102, CST
Phospho-ERK1/2 (Thr202/Tyr204)	#4370, CST
c-JUN	#9165, CST
Phospho-c-Jun (Ser63)	#91952, CST
JAK1	#50996, CST
Phospho-JAK1 (Tyr1034/1035)	#74129, CST
STAT1	#9172, CST
Phospho-STAT1 (Tyr701)	#9167, CST
EGFR	#2232, CST
Phospho-EGFR (Tyr1068)	#2234, CST
c-MET	#3127,CST
Phospho-c-MET (Tyr1234/1235)	#3077, CST
PD-L1	#13684, CST
GAPDH	#D110016-0200, BBI

Table S2. Primers used in the qPCR study

Gene	Primer-Forward (5'-3')	Primer-Reverse (3'-5')
GAPDH	ACCCAGAAGACTGTGGATGG	TTCAGCTCAGGGATGACCTT
PD-L1	GGTGCCGACTACAAGCGAAT	AGCCCTCAGCCTGACATGTC
HGF	CTCACACCCGCTGGGAGTAC	TCCTTGACCTTGGATGCATTC
AREG	GCAGTAACATGCAAATGTCAGC	CGTTCCTCAGCTTCTCCTTCA
TGFA	AGATAGACAGCAGCCAACCCTGA	CTAGGGCCATTCTGCCCATC
VEGFC	GGTCTCTTCATCCAGCTCCTT	CTCGGATGCTGGAGATGACTC
VEGFA	CATCTTCAAGCCATCCTGTGTG	TCTCTCCTATGTGCTGGCCTTG
ANGPT4	ACCAGCTATACAGGGTGGTG	CAGCTGCTCGTTAGATGTCC

PD-L2	AGTGAACAGTGCTGTGAATCTGAA	CAAGTTTCATGGCCAGGTGT
Gapdh	GGTGAAGGTCGGTGTGAACGGA	CCAAAGTTGTCATGGATGACCTTGG
Pd-l1	GCTCCAAAGGACTTGTACGTG	TGATCTGAAGGGCAGCATTTC
Pd-l2	GCTGGGTGCTGATATTGACA	TTCAGTGCATTCTCTGCGGT

Table S3. Sequence of small interfering RNA targeting *c-JUN*

Gene	Sense (5'-3')	Antisense (3'-5')
si *c-JUN* #1	GCAAACCUCAGCAACUUCATT	UGAAGUUGCUGAGGUUUGCTT
si *c-JUN* #2	GGCACAGCUUAAACAGAAATT	UUUCUGUUUAAGCUGUGCCTT

Table S4. Antibodies used in flow cytometry

mouse CD3	BD Biosciences, Cat:553061
mouse CD274	BD Biosciences, Cat:558091
mouse PD-1	Biolegend, Cat:135220
mouse CD45	BD Horizon,Cat:557659
mouse CD8	BD Biosciences, Cat:553035
mouse granzyme B	eBioScience, Cat:12-8898-82
mouse CD11c	BD Biosciences, Cat:558079
mouse MHC-Ⅱ	BD Horizon,Cat:565254
mouse CD11b	BD Pharmingen, Cat:561688
mouse F4/80	BD Horizon, Cat:565411

Table S5. Antibodies used in immunohistochemistry

mouse PD-L1	Abcam, Cat:213480
mouse CD45	Proteintech, Cat:20103-1-AP
mouse granzyme B	Abcam, Cat:4059
mouse CD8	Abcam, Cat:217344