Supplementary Materials and Methods

Chemicals and reagents

All chemicals were of analytical grade. CKI were provided by Shanxi Zhendong Pharmaceutical Co.Ltd (Changzhi, China). Sorafenib was purchased from Abmole (Houston, TX). For daily injection, CKI (150 μL per mouse) was administered intraperitoneally, and sorafenib (10 or 30 mg/kg bw) was administered intragastrically. Macrophages depletion was accomplished with clodronate liposomes (FormuMax Scientific, CA). The neutralizing anti-CD8 antibody from BioXcell was used to deplete $CD8^+$ T cells. CD120a (TNF Receptor I) Monoclonal Antibody (eBioscience) and R-7050 (Target Mol, Shanghai, China) were used to block TNFR1 and the interaction between TNFR1 with TRADD and RIP1.

Cell culture

The mouse liver cancer cell line Hepa1-6 was purchased from American Type Culture Collection (ATCC); the mouse liver cancer cell line LPC-H12 was obtained from the Cell Bank of Shanghai Institutes for Biological Sciences (Chinese Academy of Science, Shanghai, China). All cell lines were routinely tested for mycoplasma by PCR and authenticated in 2018 by the analytic facility of the Cell Bank of Shanghai Institutes for Biological Sciences via STR fingerprinting. All cells were cultured in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin and maintained at 37℃ in a humidified atmosphere containing 5% CO_2. After washing with PBS, cells were harvested by using trypsin (ThermoFisher, San Diego, CA) for the individual experiment.

RBC lysis assay

Red blood cells (RBC) were lysed by using lysis buffer (BD Pharmingen, NJ). For whole blood RBC

lysis, first 2mL 1X lysis buffer was added into 100μL of whole blood plus the related monoclonal antibody mixture into each flow cytometry tube; then gently vortex each tube and incubated at room temperature for 20min protected from light; last added 2mL PBS into each tube to stop the lysis procedure and centrifuged at 1500rpm for 5min before aspirating supernatant. For tumor tissues, mouse spleen and bone marrow RBC lysis, first 1mL 1X lysis buffer was added into each tube containing the related cells; then gently pipetting up and down 2-3 times and incubated at room temperature for 5min; last added 3mL PBS into each tube to stop the lysis procedure and centrifuged at 500g for 5min before aspirating supernatant. Resuspending cells with PBS or culture medium according to each individual experiment.

Flow cytometry

Fresh mouse tumor tissues were dissociated into single-cell suspensions by using mouse tumor dissociation kits (Miltenyi Biotec, Cologne, Germany) in accordance with the manufacturer's instructions. At first, after removal of red blood cells, the single-cell suspensions were centrifuged and suspended in stain buffer (BD Pharmingen), and then incubated with the anti-mouse CD16/32 antibody (BD Pharmingen) for 15 min to prevent non-specific binding. Second, cells were incubated with Fixable viability stain 510 or Fixable Viability Stain 780 (BD Pharmingen) for discrimination of viable cells from non-viable cells. After this step, cells were stained with all relevant antibodies for 1 h at 4℃ away from the light. Then cells were washed twice with PBS and re-suspended in 200 μL stain buffer. In the end, single-cell suspensions were analyzed by BD FACS AriaII. To detecting the related tumor-infiltrated immune cells, the following antibodies were used: APC-cy7-CD45, FITC-CD45, BV421-CD3e, APC-CD4, FITC-CD4, PE-CD8, APC-CD8, BV421-CD8, FITC-Gr-1, Percpcy5.5-Ly6G, PE-CD11b, PE-NK1.1, APC-CD11c and PercpCy5.5-MHC II from BD

Pharmingen; PE-Cy7-Ly6C from eBioscience; BV421-Tim3, PE-PD1, APC-TIGIT, PE-Cy7-Lag3, BV421-F4/80 and APC-CD206 from Biolegend (San Diego, CA). According to isotype and fluorescence-minus-one (FMO), gating strategies were as follows: $CD8^+$ T cells ($CD45^+CD3e^+CD8^+$), $CD4^+$ T cells ($CD45^+CD3e^+CD4^+$), M1-TAMs ($CD45^+Ly6G^-CD11b^+F4/80^+CD206^-$), M2-TAMs ($CD45^+Ly6G^-CD11b^+F4/80^+CD206^+$), MDSCs ($CD45^+CD11b^+Gr1^+$), M-MDSCs or Monocytes ($CD45^+CD11b^+Ly6C^+$), M0 macrophages ($CD45^+Ly6G^-CD11b^+F4/80^-$), Neutrophils ($CD45^+CD11b^+Ly6G^+$), NK cells ($CD45^+CD3e^-NK1.1^+$) and DC cells ($CD45^+CD11C^+$MHC II^+).

Immunohistochemistry

Immunohistochemistry was accomplished with primary antibodies against CD8 (Abcam, Cambridge, UK), cleaved Caspase-3, F4/80, Arg-1 (Cell Signaling Technology, Danvers, MA), INOS (Abcam) and In Situ Cell Death detection kit (TUNEL, Roche, Basel, Switzerland). First, tumors were formalin-fixed and paraffin-embedded. Then paraffin sections of tumors were deparaffinized and rehydrated. After antigen retrieval, stained with primary antibodies overnight at 4℃ and HRP-conjugated secondary antibodies at 37℃ for 1 h, target proteins were visualized with diaminobenzidine staining.

Biochemical parameters

Mouse serum levels of related hepatotoxicity index and nephrotoxicity index were quantified by using standard auto-analyzer methods on chemray 240 (Rayto, USA).

Quantitative real-time PCR

Total RNA was extracted from the indicated cells with TRIzol reagent (Invitrogen, San Diego, CA)

and Direct-zol™ RNA MiniPrep (Zymo Research, Freiburg, Germany), and reverse-transcribed into cDNA by using PrimeScript^{TM} RT reagent Kit (Takara, Osaka, Japan). Quantitative real-time PCR was performed on a 7900HT Fast Real-Time PCR System (Applied biosystems) by using SYBR green as the detection fluorophore. Target gene expressions were normalized to GAPDH and β-actin. Relative mRNA expression was determined by the $\triangle\triangle C_t$ method. The primer sequences were provided in Supplementary Table 2.

ELISA assays

The concentrations of indicated cytokines and proteins in cells and cell culture supernatants were determined with corresponding ELISA Kits (Shanghai Laizhe Biotechnology Co., Ltd, Shanghai, China) according to the manufacturer's instructions. The analytes included: IL-1β, IL-6, IL-12α, TNF-α, CD14, CXCL-1, IFN-β, IFN-γ, INOS, Perforin, Granzyme-B, Arg-1, CD206, CD163, Clec10a, mMGL1, mMGL2, and Fizz-1.

***In vitro* TNFR1, TLR4 and IFN-γ receptor inhibition**

CM-educated BMDMs ($M_{hepa1-6}$) were incubated with 25 μg/mL CD120a (TNF Receptor I) Monoclonal Antibody, 10 μM R7050, 10 μM Sparstolonin B (Sigma) or 4 μg/mL CD119 (IFN-γ Receptor 1) monoclonal antibody (eBioscience) in fresh IMDM for 4 h prior to CKI incubation for another 12 h.

***In vivo* TNFR1 blocking assay**

To neutralize TNFR1 or blockade the association of TNFR1 with TRADD and RIP1, mice bearing

with LPC-H12 tumors were injected intraperitoneally with 100 μg CD120a (TNF Receptor I) Monoclonal Antibody every 4 days or 10 mg/kg R7050 every 3 days. Vehicle groups were received an equivalent amount of saline or In Vivo MAb rat IgG2a isotype (BioXcell).

Western blotting

Cells were lysed in RIPA lysis buffer (Beyotime Biotechnology, Shanghai). The total protein concentrations were determined by using bicinchoninic acid protein assay kit (Thermo Fisher Scientific). Equal quantities of boiled protein extracts were separated by 7.5% or 10% SDS-PAGE gels, then transferred to methanol preactivated-polyvinylidene difluoride membranes. Membranes were incubated with 5% skimmed milk for 1h at room temperature and then incubated with primary antibodies overnight at 4℃. The membranes were then incubated in HRP-linked secondary antibody for 1h at room temperature. The proteins in blots were visualized using an enhanced chemiluminescence regent (Thermo Fisher Scientific). Primary antibodies information was provided in Supplementary Table 3.

Immunoprecipitation assay

Cells lysates (1 mg total protein in 1 ml RIPA lysis buffer) were incubated with anti-TNF-R1 (H-5) (2 μg, Santa Cruz, sc-8436) for 6h followed by Protein A/G agarose beads (Santa Cruz, sc-2003) for overnight at 4℃. Beads were washed 3 times and eluted with SDS loading buffer. Immunoprecipitated proteins were performed by SAD-PAGE as described before.