Materials and methods

Animal experiment. A total of 6 male C57BL/6 mice were set as the C57BL/6 group, and 36 male NHD13 mice were divided into the NHD13, DMSO, U0126 (1 mg/kg/day), U0126 (10 mg/kg/day), Ly294002 (1 mg/kg/day) and Ly294002 (10 mg/kg/day) groups for the pre-experiments. The NHD13 mice were continuously treated with U0126 at 1 and 10 mg/kg/day or Ly294002 at 1 and 10 mg/kg/day, respectively, for 2 months. Changes in peripheral blood white blood cell (WBC) counts, red blood cell (RBC) counts and platelet (PLT) counts were assayed to determine the appropriate doses of U0126 and Ly294002 in mice *in vivo*. The method of medication *in vivo* and the method of peripheral blood cell detection were consistent with the methods described in the main manuscript.

Cell experiment. SKM-1 cells in logarithmic growth phase were seeded onto 96-well plates (5,000 cells/well). The cells were treated with various concentrations of U0126 (0, 0.5, 1, 2, 5, 10, 20 and 40 μM) or Ly294002 (0, 0.5, 1, 2, 5, 10, 20 and 40 μM) for 48 h. Cytotoxicity was detected using the MTT kit (M1020, Beijing Solarbio Science & Technology Co., Ltd.) as per the instructions provided with the kit. The optical density at 570 nm was measured using a Multiskan SkyHigh Microplate Spectrophotometer (Thermo Scientific™ SkanIt Software, Thermo Fisher Scientific, Inc.), with the results expressed as a percentage (%). The U0126 or Ly294002 treatment group with 0 concentration was set to 100%. Each group of experiments was repeated three times.

Results

U0126 or Ly294002 partially restore the number of peripheral blood cells in NHD13 mice. The peripheral blood of NHD13 mice was collected after 2 months of continuous treatment with U0126 at 1 and 10 mg/kg/day or Ly294002 at 1 and 10 mg/kg/day. WBC, RBC and PLT counts of peripheral blood were determined. Following treatment with 1 mg/kg/day of U0126 or Ly294002, the numbers of WBC, RBC and PLT in NHD13 mice were partially restored, with a tendency to increase to a certain extent; however, the improvement was minimal. U0126 or Ly294002 at 10 mg/kg/day significantly increased the WBC, RBC and PLT numbers relative to 1 mg/kg/day of U0126 or Ly294002 (all $P<0.05$; Fig. S1). Therefore, treatment with U0126 or Ly294002 at 10 mg/kg/day was selected.

Suppressive effects of U0126 or Ly294002 to SKM-1 cells. To determine the appropriate concentrations of U0126 or Ly294002, the SKM-1 cells were treated with various concentrations of U0126 (0, 0.5, 1, 2, 5, 10, 20 and 40 μM) or Ly294002 (0, 0.5, 1, 2, 5, 10, 20 and 40 μM) for 48 h. The results of the MTT assay revealed that 0.5-40 μM U0126 or 1-40 μM Ly294002 inhibited SKM-1 cell viability, and 5 μM U0126 was close to its half-inhibitory concentration (IC50) for SKM-1 cells (Fig. S2A), and 5 μM Ly294002 was also close to its IC50 for SKM-1 cells (Fig. 2B). Therefore, 5 μM U0126 or 5 μM Ly294002 were selected as the concentrations for use in formal experiments.

Figure S1. U0126 or Ly294002 treatment partially restores the peripheral blood cell count of NHD13 mice. (A-C) An automatic blood cell analyzer was used to determine the number of WBCs, RBCs and PLTs in the peripheral blood of C57B/L6 or NHD13 mice subjected to the different treatments; n=6. Comparisons among groups were conducted using one-way ANOVA with Tukey's post hoc test. *P<0.05 and ***P<0.001. WBC, white blood cells; RBC, red blood cell; PLT, platelet.

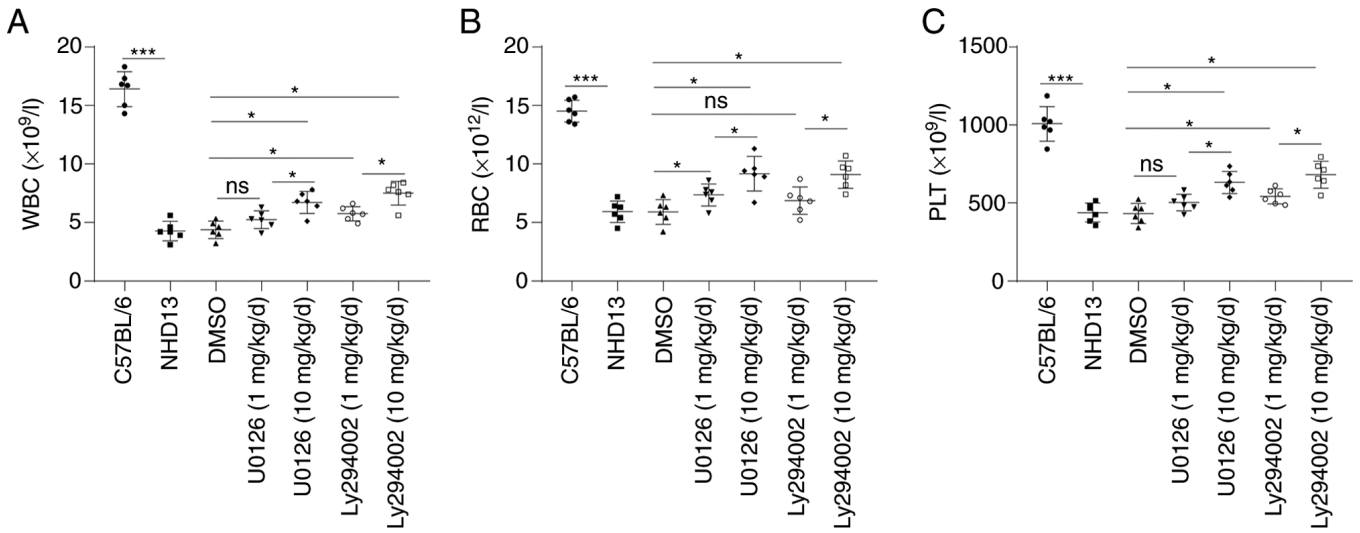

Figure S2. Inhibition of SKM-1 cells by U0126 or Ly294002. (A and B) SKM-1 cells were treated with 0, 0.5, 1, 2, 5, 10, 20 and 40 μM U0126 or Ly294002 for 48 h. The relative cell viability was assessed using MTT assay. Zero concentration was utilized as the control group, and comparisons among multiple groups were made by one-way analysis of variance, *P<0.05, **P<0.01 and ***P<0.001, vs. the control.