Supplement 1

Animal experiments

Balb/c nude female mice and C57BL female mice were purchased from Chengdu Dossy Laboratory Animals Company and allowed to acclimatize for 1 week prior to the experiments. All animal procedures were approved by the Laboratory Animal Management Committee of the Affiliated Hospital of Southwest Medical University. Balb/c nude female mice were kept under specific pathogen-free conditions, and food, water, and bedding were autoclaved before use. All the animals used were housed in12 h light/12h dark cycle at constant temperature and provided food and water ad libitum.

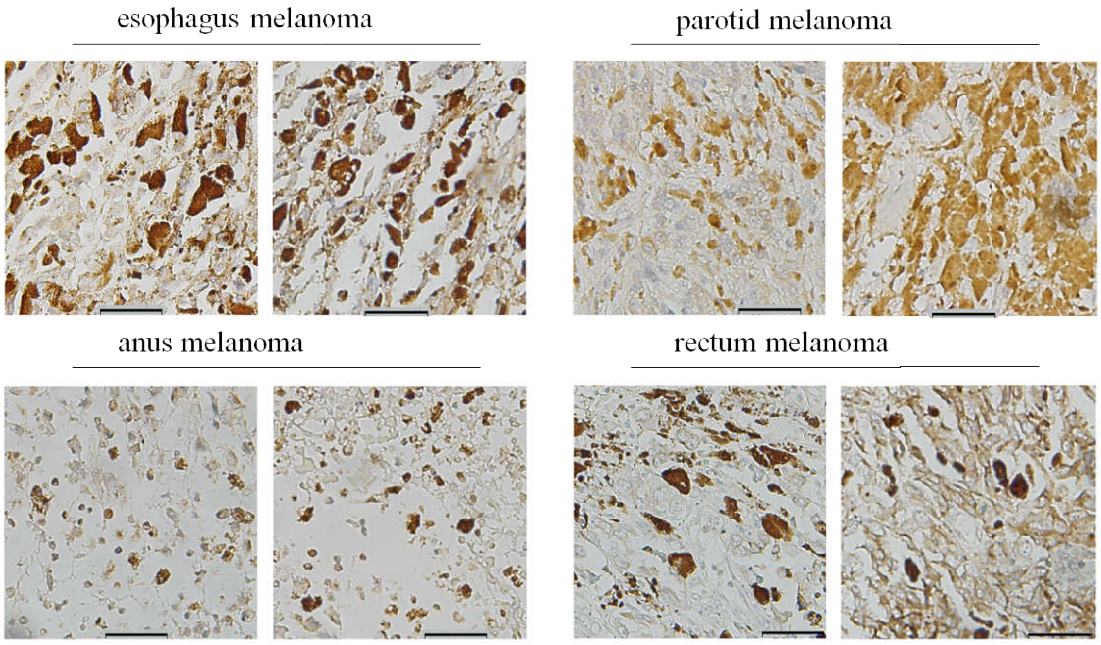
Balb/c nude female mice (body weight 14-16g, 5 weeks old) were randomly divided into two group (six mice per group). Mice were inoculated subcutaneously in the right armpit with $1x10^6$ A375 shRNA-NC cells or A375 shRNA-USP7 cells in 100 μl PBS to induce the tumor. We started to measure weight and tumor size of mice at day 6 post tumor transplantation. Then the weight and tumor size were measured every three days. Tumor volume was calculated according to the formula $V=0.5\times a^2\times b$ (a, smallest superficial diameter; b, largest superficial diameter). The mice were killed by CO_2 overdose at day 29 post treatments. The tumors were harvested, weighted, and recorded.

C57BL female mice (body weight 13-15g, 5 weeks old) were also randomly divided into two group (six mice per group). B16 WT melonoma cells or B16 USP7-KO melonoma cells were subcutaneously injected into their right armpit with the viable cell number $3x10^5$ cells. We started to measure tumor size at day 6 post tumor transplantation. Then the weight and tumor size were measured every three days. The mice were killed by CO_2 overdose at day 15 post treatments. The tumors were analyzed.

Supplement 2

Immunohistochemical analysis of USP7 in human melanoma tissues(melanoma tissue microarray ME241b, Alenabio). Scale bar, 50 μm.

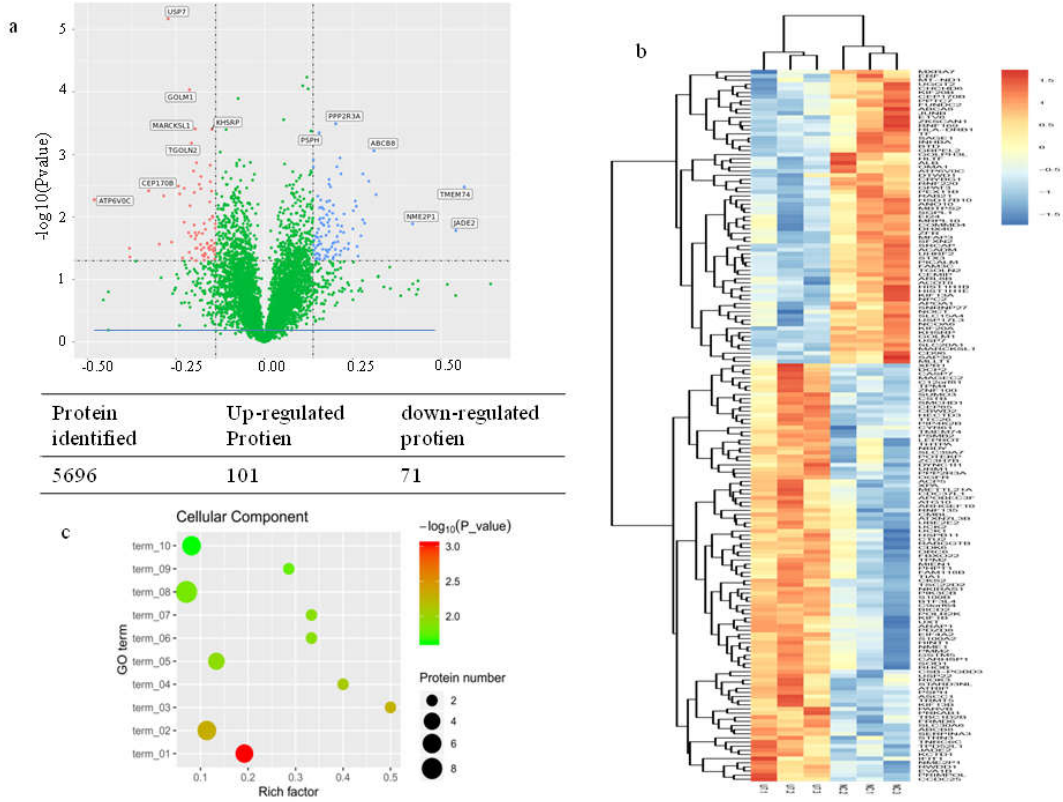
Supplement 2



Supplement 3

Integrative analysis of identified proteins.iTRAQ coupled with LC-MS/MS analysisproteins from A375 cells transfected with USP7 siRNA for 24h.(a)The ratio intensity plot representing protein fold and protein density plot.Red, blue and green clusters indicate up-, down- and unregulated proteins, respectively. (b)Heatmap shows the relative changes in abundance of the 172differentially expressed proteins.(c)Top 10 enriched GO terms “cellular components”. term01, kinesin complex; term02, P-body; term03,muscle thin filament tropomyosin; term04, platelet dense granule lumen; term05, axon cytoplasm; term06, intraciliary transport particle B; term07, striated muscle thin filament;term08,cytoplasmic ribonucleoprotein granule; term09, myofilament; term10, microtubule associated complex.

Supplement 3

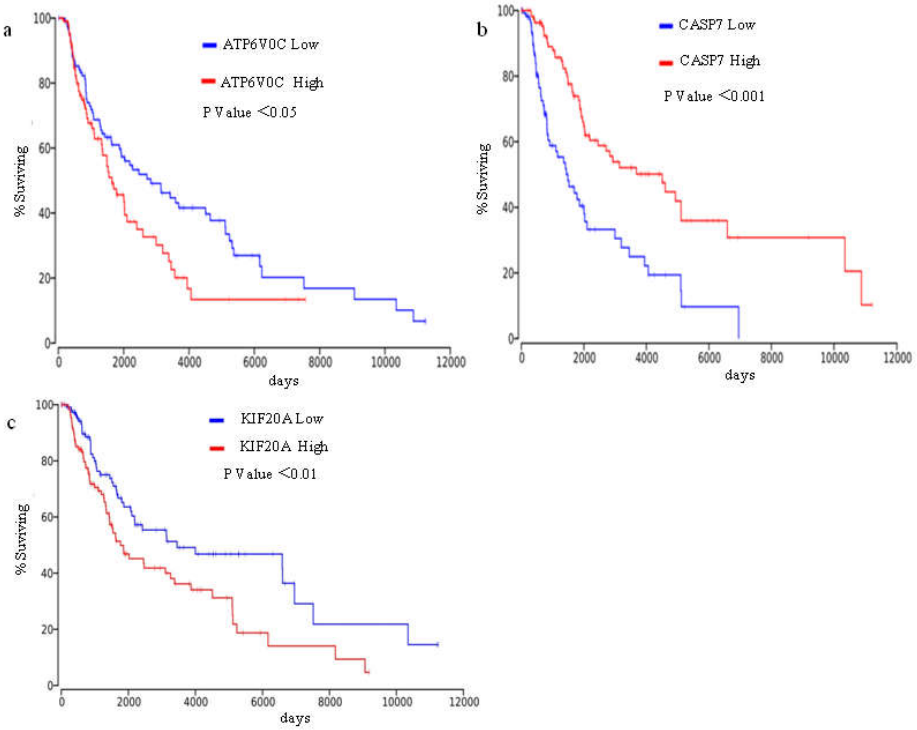


Protein identified	Up-regulated Protien	down-regulated protien
5696	101	71

Supplement4

Kaplan-Meier curves of ATP6V0C ,KIF20A and CASP7 in melanoma patients. (a) Kaplan-Meier curves of the survivalbetween ATP6V0C-high and ATP6V0C–lowmelanoma patients. (b) Kaplan-Meiercurves of CASP7 in melanoma patients. (c) Kaplan-Meiercurves of KIF20A in melanoma patients.

Supplement 4


a
ATP6V0C Low
ATP6V0C High
P Value <0.05
% Surviving
days
b
CASP7 Low
CASP7 High
P Value <0.001
% Surviving
days
c
KIF20A Low
KIF20A High
P Value <0.01
% Surviving
days