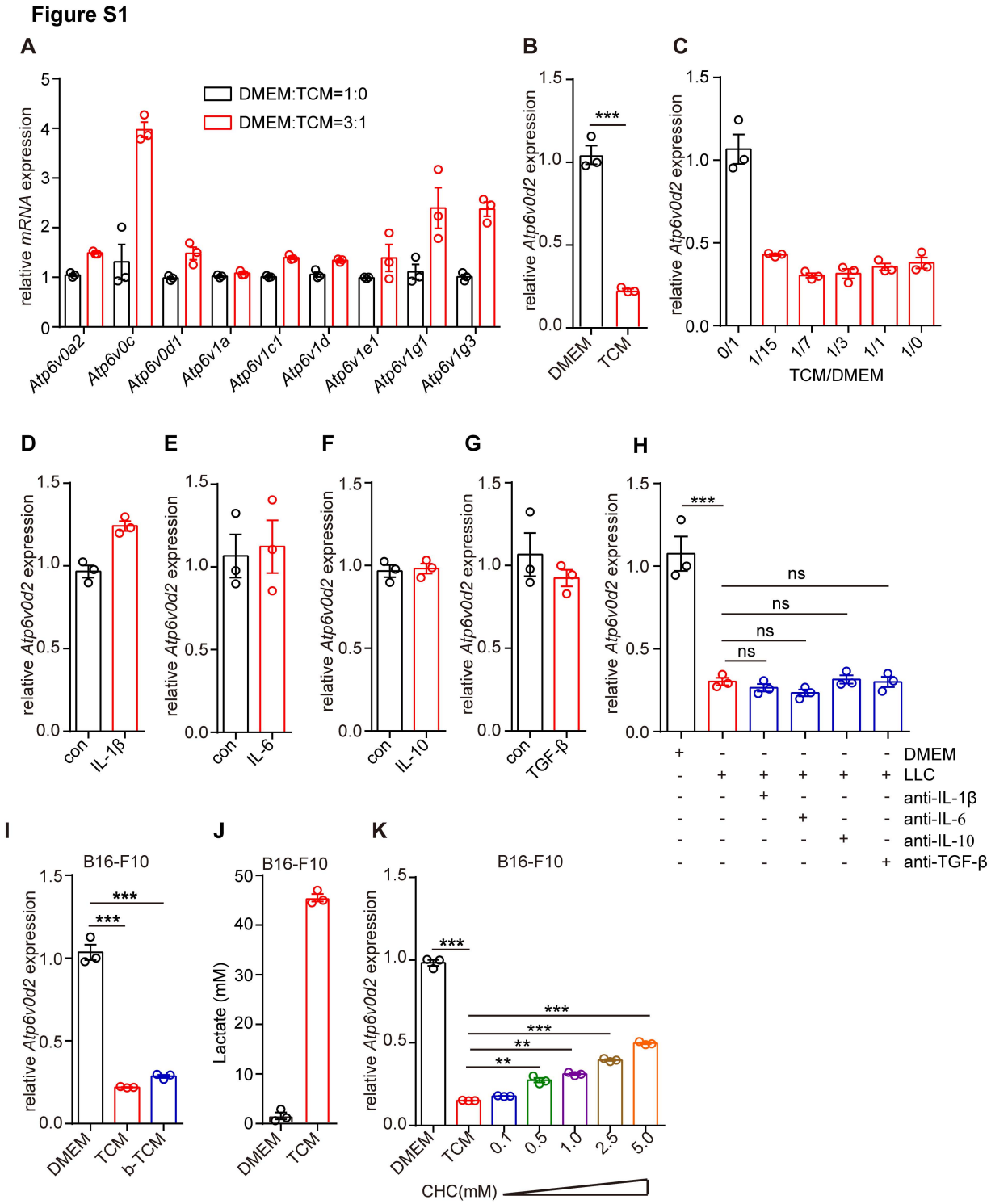
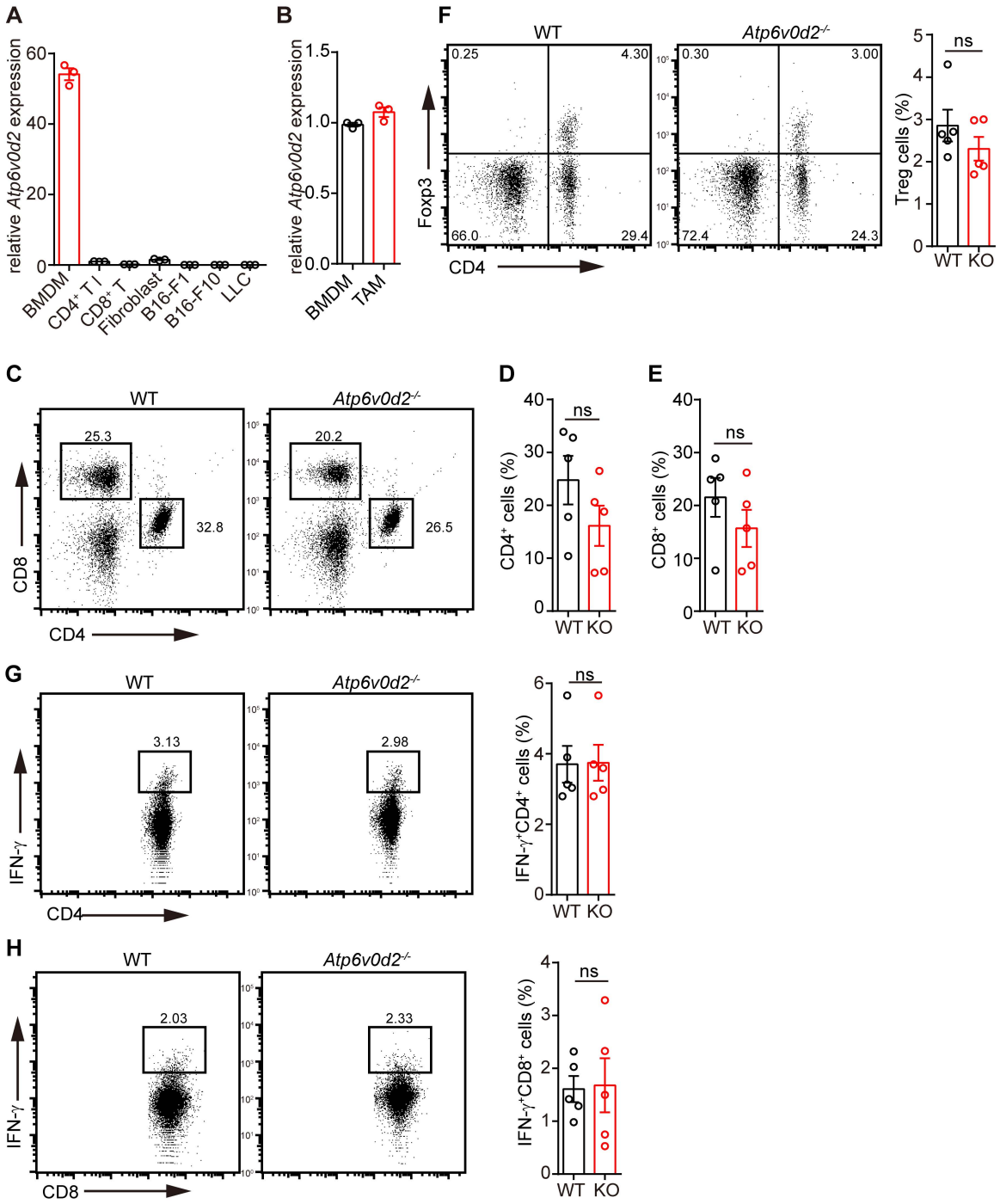


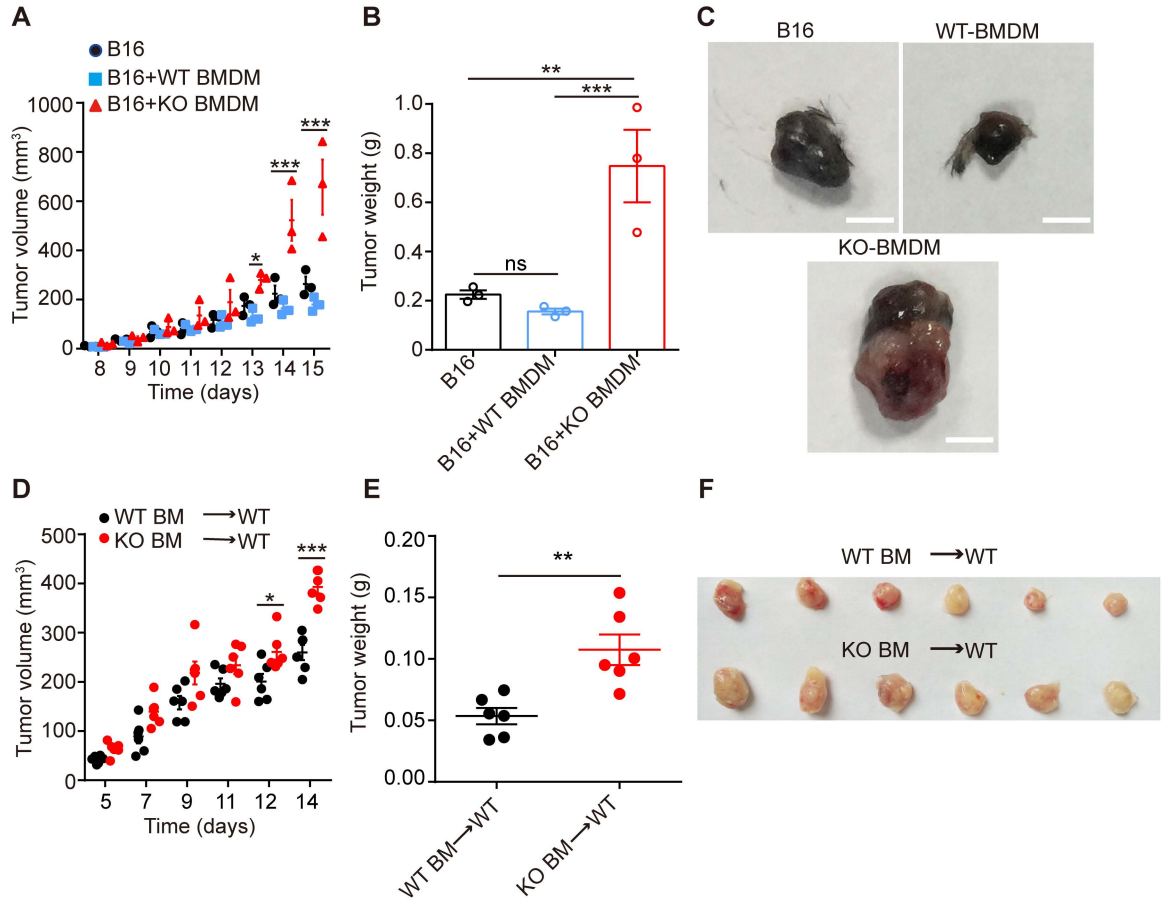
Supplementary Figure 1. TCM but not cytokines presented in tumors inhibits Atp6v0d2 expression.(**A**) Expression of different V-ATPase subunits were determined by q-PCR in BMDMs cultured with complete DMEM or stimulated with DMEM:LLC-TCM (3:1) for 6h. (**B**-**K**, except **J**) *Atp6v0d2* mRNA expression was determined by q-PCR. (**B** and **C**) BMDMs stimulated with B16-F10-TCM (**B**) or a concentration gradient of B16-F10-TCM (**C**) for 6h. (**D**-**G**) Expression of *Atp6v0d2* mRNA was determined by q-PCR in BMDMs stimulated with IL-1β (**D**), IL-6 (**E**), IL-10 (**F**) and TGF-β (**G**) for 6h. (**H**) BMDMs were stimulated with LLC-TCM or with the addition of different neutralization antibodies (10 ng/ml) for 6h. (**I**) BMDMs were stimulated with B16-F10-TCM or boiled B16-F10 TCM for 6h. (**J**) Lactate concentration in the B16-F10-TCM was determined. (**K**) BMDMs stimulated with B16-F10-TCM alone or with the addition of different doses of CHC for 6h. Data are representative of two independent experiments. Data are are assessed by Student *t* test (**A**, **B**, **D**-**G**) or one-way ANOVA with Turkey's test (**C**, **H**, **I**, **K**).mean±SEM. $^{**}p < 0.01$,$^{***}p < 0.001$.

Fiugre S2



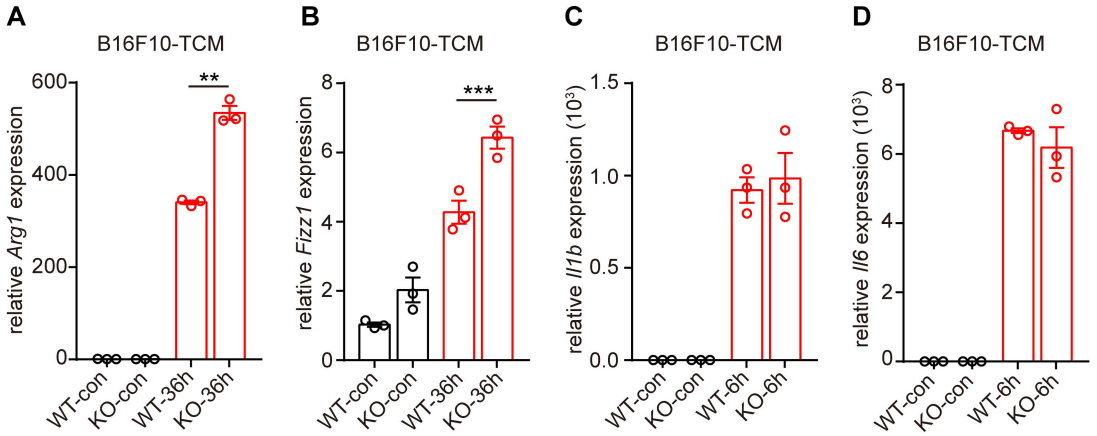
Supplementary Figure 2. Deficiency of Atp6v0d2 does not affect T cell functions within tumor. (**A**) q-PCR analysis of *Atp6v0d2* expression in BMDMs, CD4⁺T cell, CD8⁺ T cell, fibroblast, B16-F1, B16-F10 and LLC cells. (**B**) The expression of *Atp6v0d2* in BMDMs and TAMs from tumor-bearing WT mice isolated with CD11b magnetic beads was analyzed by q-PCR. (**C**-**H**) WT and *Atp6v0d2*$^{-/-}$ mice were injected *s.c.* with 5×10^5 LLC cells. On day 15 post-inoculation, mice were sacrificed (n=5). (**C**-**E**) Representative flow cytometric plot showing T cells fractions in LLC tumor tissues (**C**), comparisons of the percentages of CD4⁺ (**D**) and CD8⁺ (**E**) in LLC tumors between WT and *Atp6v0d2*$^{-/-}$ mice. (**F**-**H**) Representative dot plots showing percentages of Foxp3⁺CD4⁺ T cells (**F**), IFN-γ⁺CD4⁺ T cells (**G**), IFN-γ⁺ CD8⁺ T cells (**H**) in the tumor tissues. Right, cumulative results for the staining at left. Data Student *t* test and are representative of two independent experiments.

Figure S3



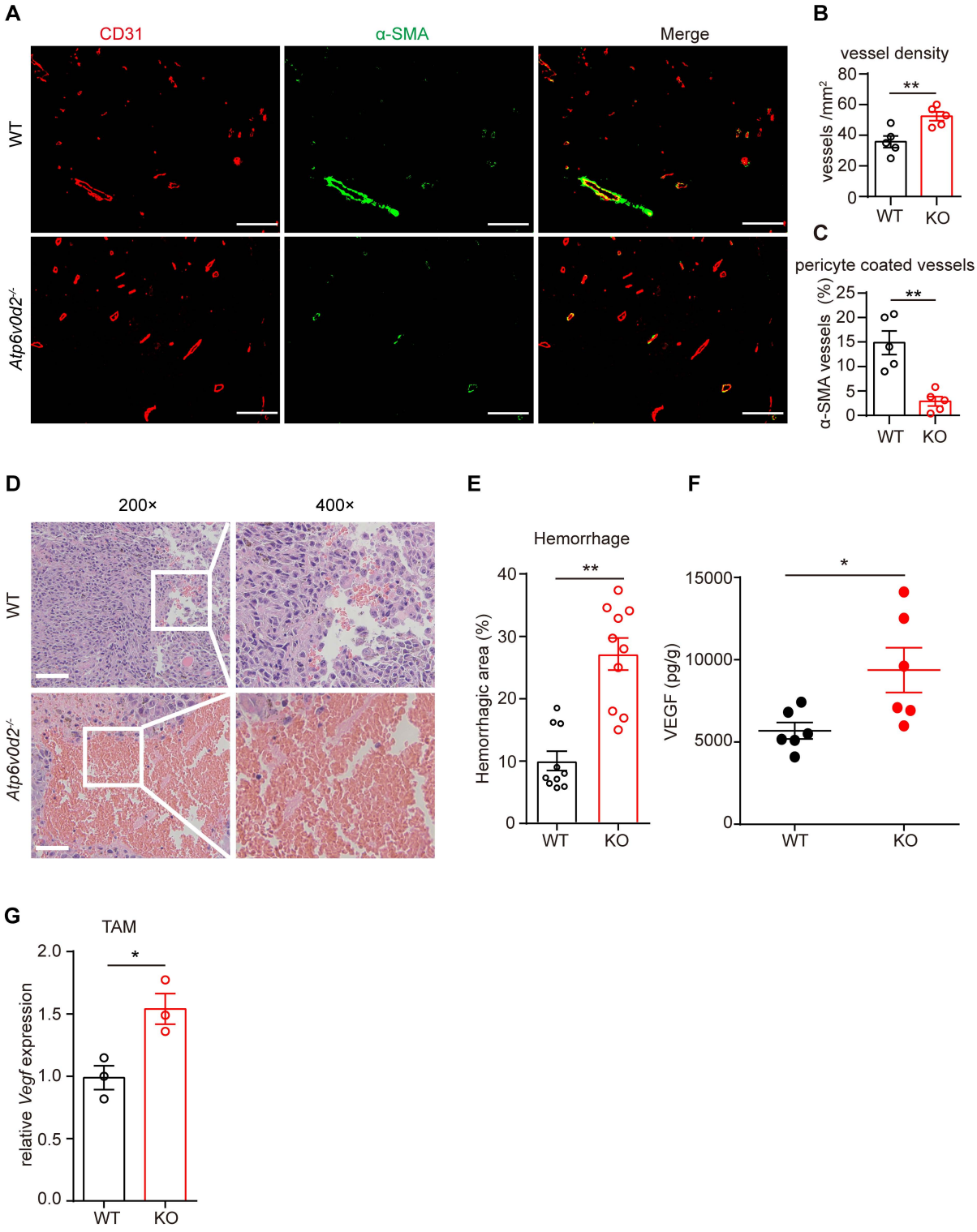
Supplementary Figure 3. Atp6v0d2-deficient BMDMs and bone marrows promote tumor growth. (**A**-**C**) *Atp6v0d2*$^{-/-}$ mice were challenged *s.c.* with 5×10^5 B16-F10 cells alone, or plus with 2×10^5 either WT BMDMs or *Atp6v0d2*$^{-/-}$ BMDMs (n=3). Tumor size was measured every 2 days (**A**). Tumor mass was determined at day 15 after inoculation (**B**). Representative images of tumor were presented (**C**). (**D**-**F**) WT mice were irradiated with 7Gy and reconstituted with either WT or *Atp6v0d2*$^{-/-}$ BM (n=6). After 4 weeks, mice were injected *s.c.* with 5×10^5 LLC cells, tumor growth rate (**D**) , tumor weight (**E**) and images of excised tumor (**F**). Data were assessed by one-way ANOVA with Turkey's test (**A**, **B**) or Student's t test (**D**, **E**). mean±SEM. *p < 0.05, **p < 0.01, ***p < 0.001. Scale bars: 5 mm

Fiugre S4



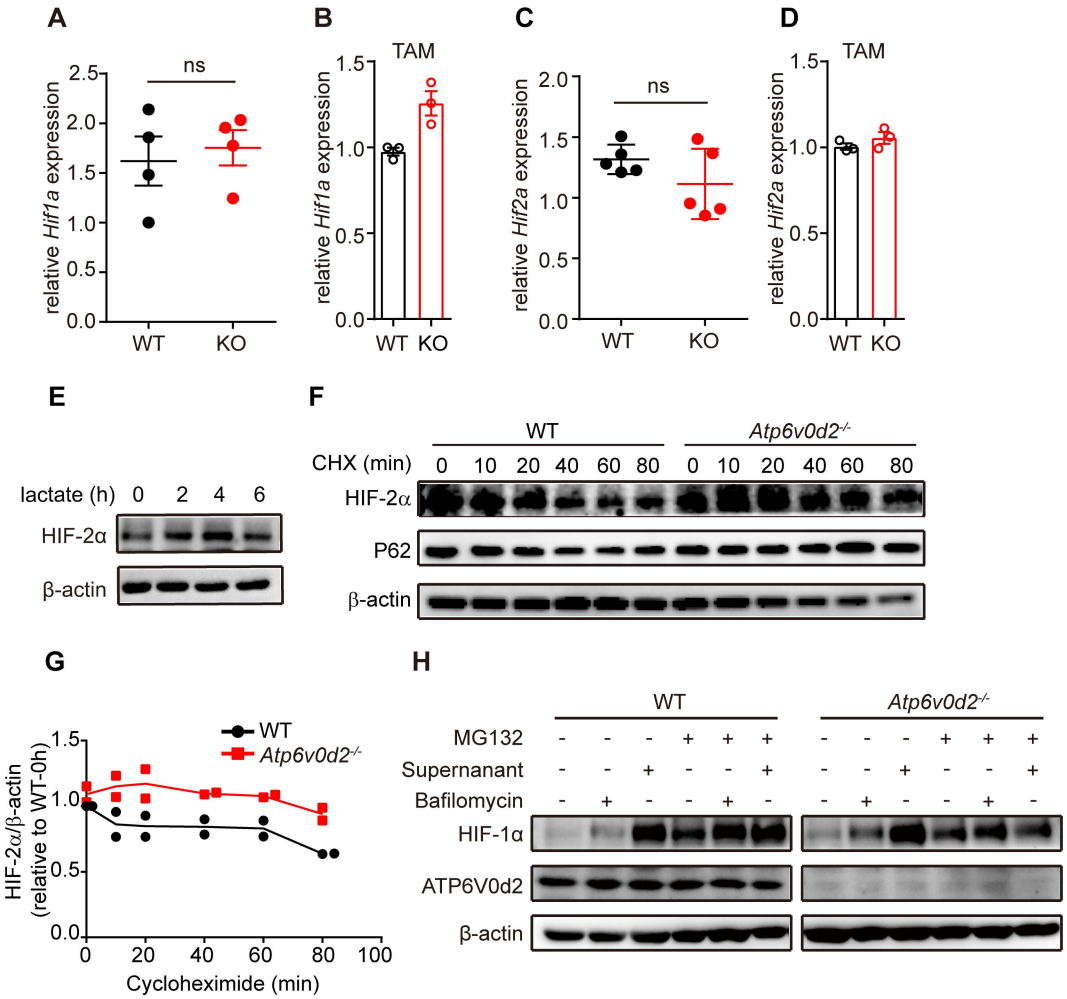
Supplementary Figure 4. Deletion of Atp6v0d2 leads to enhanced protumoral-related gene expression. (**A** and **B**) Expression analysis by q-PCR of *Arg1* (**A**) and *Fizz1* (**B**) in WT and *Atp6v0d2*$^{-/-}$ BMDMs stimulated with B16-F10-conditioned medium for 36h. (**C** and **D**) Expression of *Il1b* (**C**) and *Il6* (**D**) in WT and *Atp6v0d2*$^{-/-}$ BMDMs stimulated with B16-F10-conditioned medium for 6h. Data are assessed by student *t* test and representative representative of three independent experiments. mean±SEM. $^{**}p < 0.01$, $^{***}p < 0.001$.

Figure S5



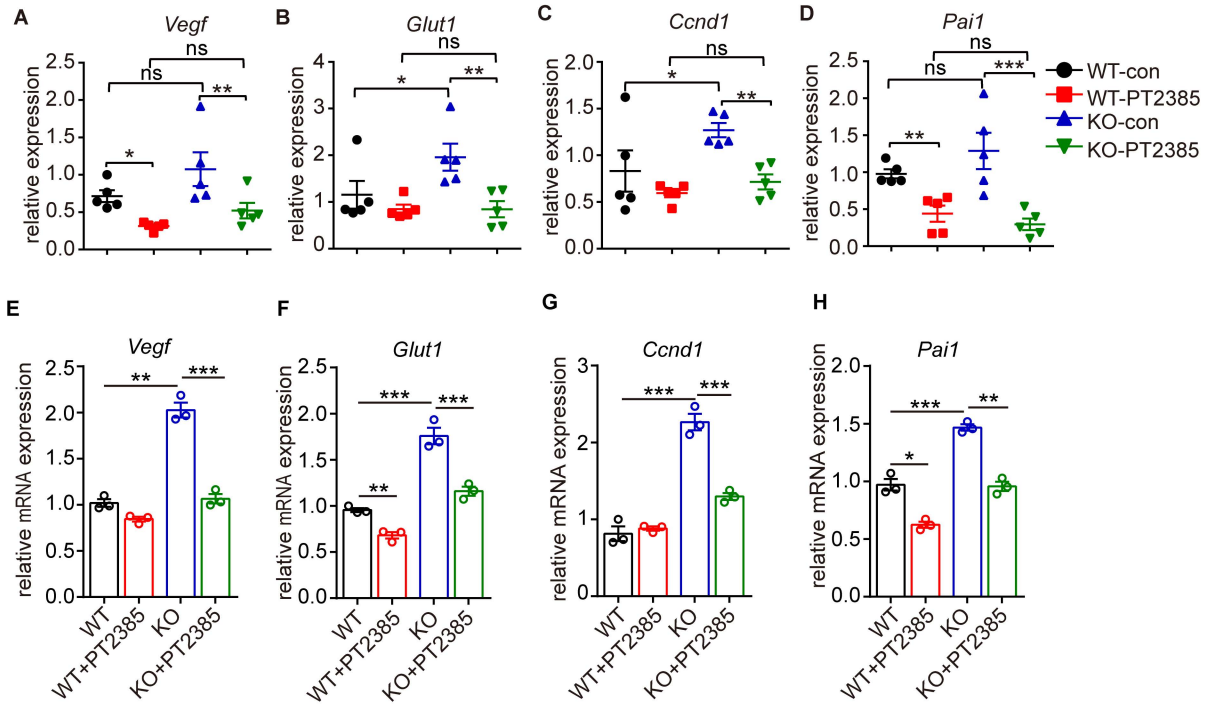
Supplementary Figure 5. *Atp6v0d2*-deficient mice have enhanced angiogenesis. (**A**-**G**) WT and *Atp6v0d2*$^{-/-}$ mice were injected *s.c.* with 2×10^5 B16-F10 cells. On day 15 post-inoculation, mice were sacrificed. (**A**-**C**) Double immunostaining for CD31 (red) and α-SMA (green) vessels in tumor tissues isolated from WT and *Atp6v0d2*$^{-/-}$ mice (**A**), quantifications of the percentage CD31$^+$ vessels (**B**), and α-SMA$^+$CD31$^+$ vessels (**C**) (n=5). Bars in all tissue section panels were 100 μm. (**D** and **E**) H&E staining (200×, 400×) showing hemorrhaging in B16 tumors tissues isolated from WT and *Atp6v0d2*$^{-/-}$ mice (**D**). Comparison of hemorrhagic area (% of tumor area) was shown in (**E**). (**F**) The levels of VEGF were determined in tumor tissues from WT and *Atp6v0d2*$^{-/-}$ mice by ELISA. (**G**) The mRNA of *Vegf* was determined in TAMs isolated from WT and *Atp6v0d2*$^{-/-}$ tumor bearing mice. Data are assessed by student *t* test and representative of two independent experiments. mean±SEM. *p < 0.05, **p < 0.01.

Figure S6



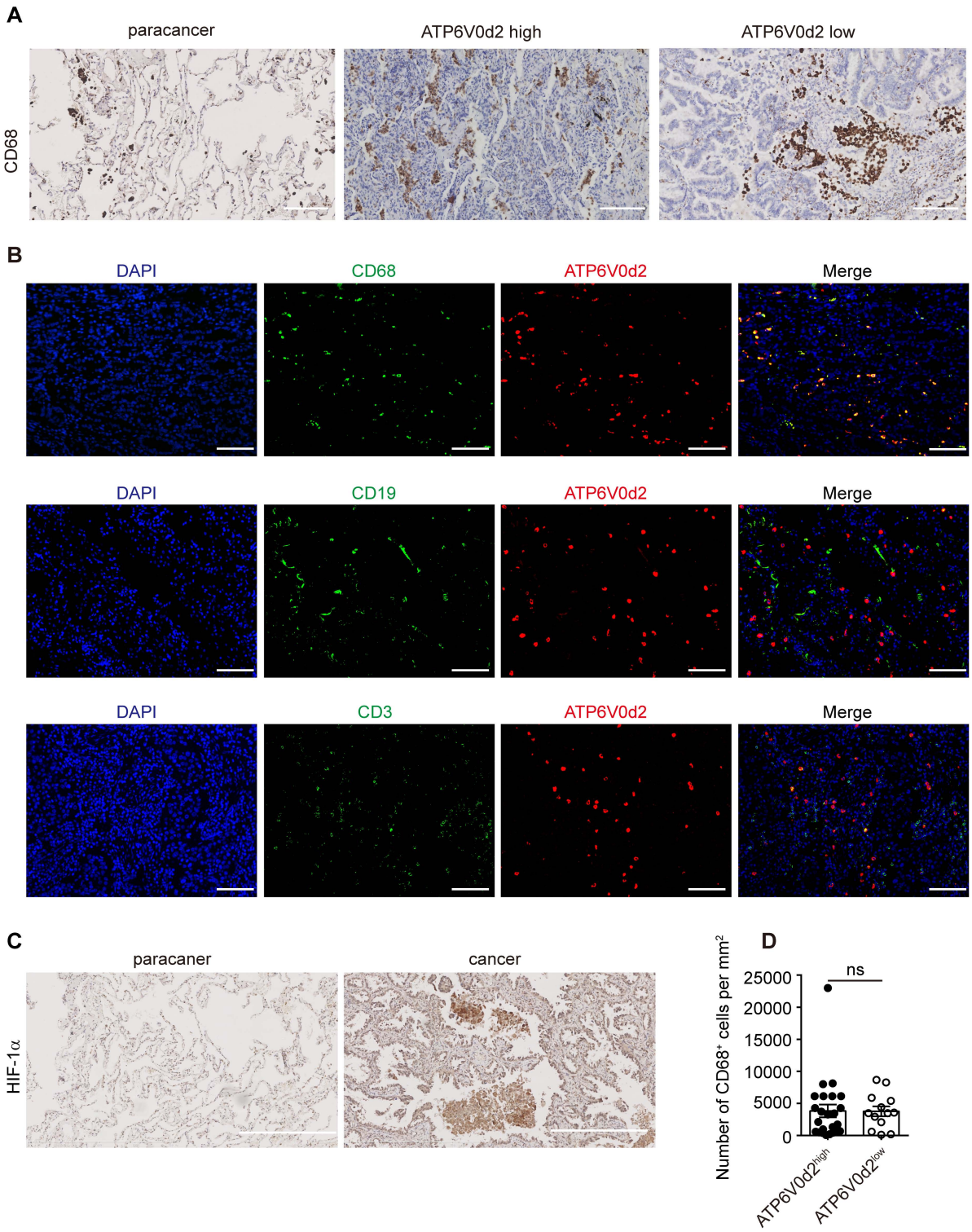
Supplementary Figure 6. ATP6V0d2 does not regulate HIF-1α stability. (**A** and **B**) *Hif1a* mRNA expression in LLC-tumor tissues (**A**) and TAMs (**B**) from WT and *Atp6v0d2*$^{-/-}$ mice. (**C** and **D**) *Hif2a* mRNA expression in LLC-tumor tissues (**C**) and TAMs (**D**) from WT and *Atp6v0d2*$^{-/-}$ mice. (**E**) Immunoblotting of HIF-2α on WT and *Atp6v0d2*$^{-/-}$ BMDMs that were stimulated with lactate (40mM) for the indicated times. (**F** and **G**) Immunoblotting of HIF-2α and P62 expression in WT and *Atp6v0d2*$^{-/-}$ BMDMs incubated with cycloheximide (100μg/ml) for indicated times (**F**) and band intensities were plotted (**G**). (**H**) Immunoblotting of HIF-1α expression in WT and *Atp6v0d2*$^{-/-}$ BMDMs stimulated with Bafilomycin (100nM), LLC-TCM, MG132 (20μM), MG132 together with Bafilomycin, or MG132 in addition to LLC-TCM for 6h. Data are assessed by Student *t* test and representative of two (**A-D, F-G**) or three (**E**, **H**) independent experiments.

Figure S7



Supplementary Figure 7. PT2385 inhibits HIF-2α target genes in macrophages. (**A**-**D**) q-PCR analysis of HIF-2α target genes *Vegf* (**A**), *Glut1* (**B**), *Ccnd1* (**C**), *Pai1* (**D**) in the tumor tissues of the WT and *Atp6v0d2*$^{-/-}$ mice treated with vehicle or PT2385. (**E**-**H**) q-PCR of HIF-2α target genes *Vegf* (**E**), *Glut1* (**F**), *Ccnd1* (**G**) and *Pai1* (**H**) in WT and *Atp6v0d2*$^{-/-}$ BMDMs stimulated with LLC-TCM for 6h with or without PT2385 (10mM). PT2385 was added 18h prior to the TCM stimulation. Experiments were repeated for two times. Data are assessed by two-way ANOVA with Turkey's test and presented as Mean±SEM, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Figure S8



Supplementary Figure 8. ATP6V0d2 is specifically expressed in macrophages in human primary lung cancers. (**A**) Immunohistochemistry(IHC) analysis of CD68 in the lung sections of adjacent non-tumorous lungs or tumor tissues isolated from two lung adenocarcinoma patients with differential ATP6V0d2 expression. (**B**) Immunofluorescence staining of human primary lung adenocarcinoma tissues with DAPI (blue), anti-CD68 (green), anti-CD20 (green), anti-CD3 (green), and anti-ATP6V0d2 (red) (n=3). (**C**) A representative image of IHC staining the HIF-1α in the lung sections of adjacent non-tumorous or tumor tissues of human adenocarcinoma patients. (**D**) Quantification of numbers of $CD68^+$ TAMs in 5 areas of each patients were determined manually in two groups of lung adenocarcinoma patients with high ATP6V0d2 expression (n=24, IRS>3) and low ATP6V0d2 expression (n=13, IRS<3). Scale bars, (A and C) 200μm; B 100μm.

Supplemental Table 1

Oligonucleotides		
m. *Atp6v0d2* qPCR Forward primer TGCGGCAGGCTCTATCCAGAGG	This paper	N/A
m. *Atp6v0d2* qPCR Reverse primer CCACTGCCACCGACAGCGTC	This paper	N/A
m. *Atp6v0a2* qPCR Forward primer GTGGAGTTTGAGCCCACGTA	This paper	N/A
m. *Atp6v0a2* qPCR Reverse primer AGGCCAGAAACGAATCCCAG	This paper	N/A
m. *Atp6v0c* qPCR Forward primer TTGGCTAGAACTTCTTTCAC	This paper	N/A
m. *Atp6v0c* qPCR Reverse primer CACGGAGATGAGGAAGAAGC	This paper	N/A
m. *Atp6v0d1* qPCR Forward primer CTGTGCCGAAAGAGTTGA	This paper	N/A
m. *Atp6v0d1* qPCR Reverse primer AGAGCAGGACCTTGATGAG	This paper	N/A
m. *Atp6v1a* qPCR Forward primer GCCCACACTGTAGAACTTGAGAT	This paper	N/A
m. *Atp6v1a* qPCR Reverse primer TGCACTTAGGACCAGGCACA	This paper	N/A
m. *Atp6v1c1* qPCR Forward primer ATCCAGTTTAGCCAGTTC	This paper	N/A
m. *Atp6v1c1* qPCR Reverse primer CAATAATCTTGCCGTCTC	This paper	N/A
m. *Atp6v1d* qPCR Forward primer GCTTCCCTGCAGACTTCCTT	This paper	N/A
m. *Atp6v1d* qPCR Reverse primer TAGGCAAGGGTGCGTTCAAT	This paper	N/A
m. *Atp6v1e1* qPCR Forward primer TGGTAACGGGTCGTATCT	This paper	N/A
m. *Atp6v1e1* qPCR Reverse primer ATCAAGCAAGGCTCAAAG	This paper	N/A
m. *Atp6v1g1* qPCR Forward primer GCGGTTCTTTTGACGGTGG	This paper	N/A
m. *Atp6v1g1* qPCR Reverse primer ACGGCCTAAGTCAACTGCTC	This paper	N/A
m. *Atp6v1g3* qPCR Forward primer AGAGCCACCTCTCGGATGAA	This paper	N/A
m. *Atp6v1g3* qPCR Reverse primer CGCACACCATGCTCAATAGC	This paper	N/A
m. *Vegf* qPCR Forward primer GCCGAAGCTCTCCACGATTT	This paper	N/A

m. *Vegf* qPCR Reverse primer ATTGGGGGAGCATTTGGGTT	This paper	N/A
m. *Glut-1* qPCR Forward primer CAATGGCGGCGGTCCTATAA	This paper	N/A
m. *Glut-1* qPCR Reverse primer CCCTGACGCACTTAAGACCC	This paper	N/A
m. *Pai-1* qPCR Forward primer GTGATAGATCTGGCCTGAAGCA	This paper	N/A
m. *Pai-1* qPCR Reverse primer TCTGAATGTATTTGGGTGACTCTGT	This paper	N/A
m. *Ccnd-1* qPCR Forward primer CCGGCCTCTGGCTAAACAAG	This paper	N/A
m. *Ccnd-1* qPCR Reverse primer CGCAGGCTTGACTCCAGAAG	This paper	N/A
m. *IL-1β* qPCR Forward primer ACCTTCCAGGATGAGGACATGA	This paper	N/A
m. *IL-1β* qPCR Reverse primer CTAATGGGAACGTCACACACCA	This paper	N/A
m. *IL-6* qPCR Forward primer GTTCTCTGGGAAATCGTGGA	This paper	N/A
m. *IL-6* qPCR Reverse primer TGTACTCCAGGTAGCTATGG	This paper	N/A
m. *Hif-1α* qPCR Forward primer TCCAAGGAGCCTTAACCTGTC	This paper	N/A
m. *Hif-1α* qPCR Reverse primer GCGTATGTCAGAAAGTTGGC	This paper	N/A
m. *Hif-2α* qPCR Forward primer CACTGGCCCATGTCTTCCAT	This paper	N/A
m. *Hif-2α* qPCR Reverse primer GTGTTGGATCTGCCTCCCAT	This paper	N/A
m. *Arg-1* qPCR Forward primer CGTGGGTCCAACACCCTTAT	This paper	N/A
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m. *Fizz-1* qPCR Forward primer CAAGACTATGAACAGATGGGCCT	This paper	N/A
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m. *Mrc-1* qPCR Forward primer ATGGATTGCCCTGAACAGCA	This paper	N/A
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m. *β-actin* qPCR Forward primer TCTGAATGTATTTGGGTGACTCTGT	This paper	N/A

m. *β-actin* qPCR Reverse primer AACGCAGCTCAGTAACAGTCC	This paper	N/A
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