Supplementary Figure 1. IFN-γ induces TRC dormancy. a, IFN-γ induced dormancy of various tumor type TRCs, including H22 (murine hepatocarcinoma) and CT26 (murine colon cancer). Bar, 50 µm. **b**, B16 cells were seeded in soft 3D fibrin gels for 3 days, and then treated with different doses of IFN-γ for the following 2 days (d2) or 4 days (d4). The relative colony size was calculated by comparing the colony size in groups with that in the PBS (d2) group, which was set to 1. The colony size is presented. Bar, 50 µm. **c,** 2×10^5 H22 hepatocellular carcinoma cells were i.p. injected into BALB/c mice (n=6 per group). 24 hours later, mice were peritoneally treated with PBS or IFN-γ (20 µg/day) for 3 days. H22 cells were isolated for cell cycle analysis. **d,** mice with 3×3 mm OVA-B16 melanoma were adoptively transferred with OVA-specific CD8^{+} T cells once per two days for twice. Some mice were pretreated with anti-IFN-γ antibody (250 µg/day) once

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per two days for twice. The CD133^{high} tumor cells were sorted by FACS from tumor and cell cycle analysis was performed. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m. (Student's t-test).
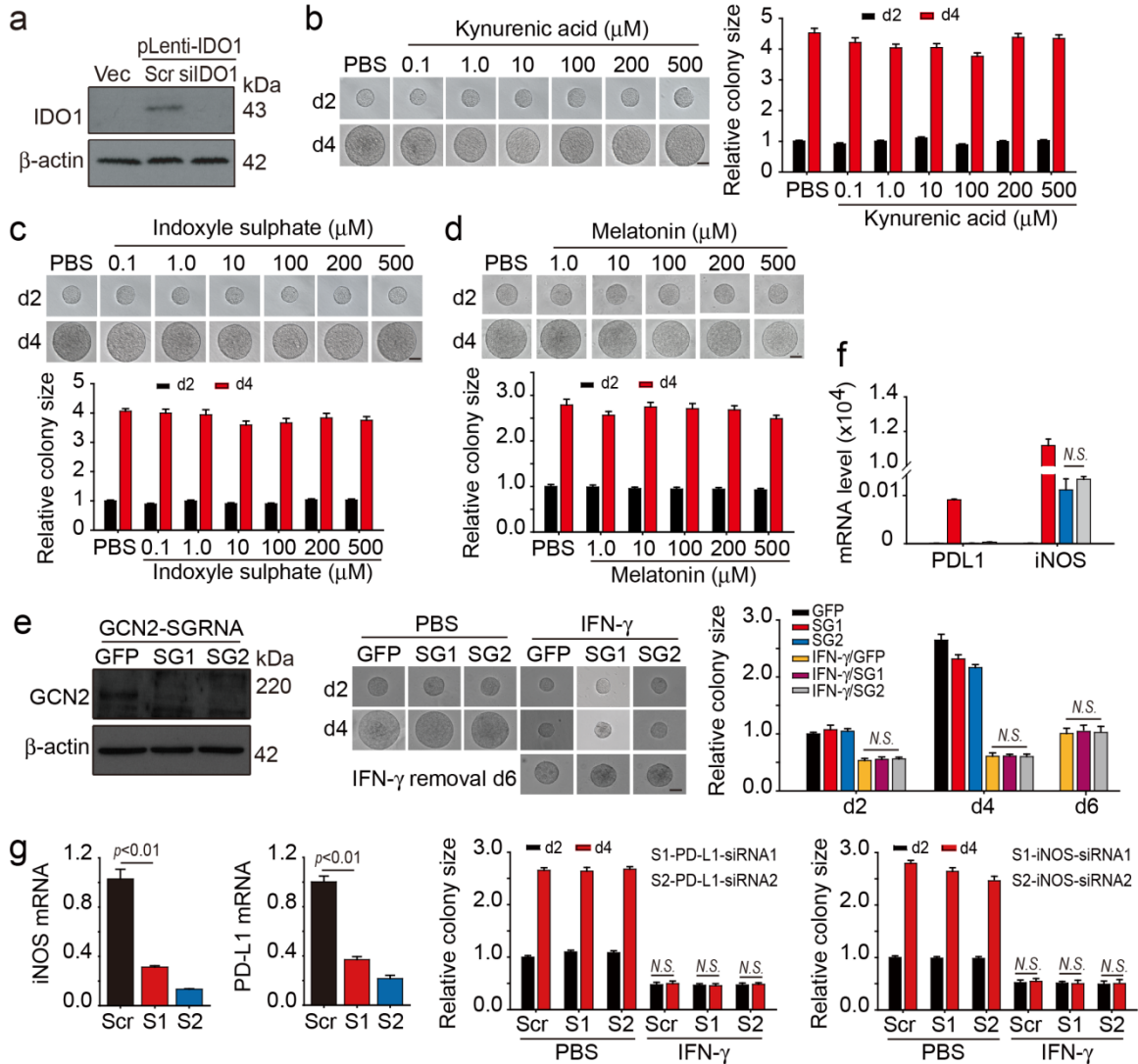
Supplementary Figure 2. IDO-AhR cascade was involved in TRC dormancy. a, Western blot analysis of IDO1 from Vec-B16 cells, IDO1 overexpressing B16 cells or IDO1-B16 cells transfected with siIDO1. **b, c and d**, B16 cells were seeded in soft 3D fibrin gels for 2 days, and then treated with different doses of kynurenic acid (b), indoxyle sulphate (c) or melatonin (d) for additional 2 days (d2) or 4 days (d4). The relative colony size was calculated by comparing the colony size in groups with that in PBS (d2) group, which was set to 1. Bar, 50 μm. **e,** GCN2-SGGFP-B16 cells, GCN2-SGRNA1-B16 cells or GCN2-SGRNA2-B16 cells were cultured in the soft 3D fibrin gels

for 2 days. Then, cells were treated with IFN-γ (100 ng/ml) for the indicated days. Western blot analysis shows the efficiency of stably knocking down GCN2. The colony size was presented photographically and graphically. The relative colony size was calculated by comparing the colony size in groups with that in GFP (d2) group, which was set to 1. Bar, 50 µm. **f,** Real-time PCR analysis of the expression of PD-L1 and iNOS in control B16 cells and B16 TRCs in the presence or absence of IFN-γ. **g,** B16 cells were transfected with PD-L1 siRNA, iNOS siRNA or scramble siRNA and then seeded in 3D fibrin gels and cultured for the indicated days. Real-time PCR analyzed the efficiency of PD-L1 and iNOS knock-down (left). The colony size is presented graphically (right). The relative colony size was calculated by comparing the colony size in groups with that in Scr (d2) group, which was set to 1. Bar, 50 µm. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m., *N.S.*, no significant difference (Student's t-test).
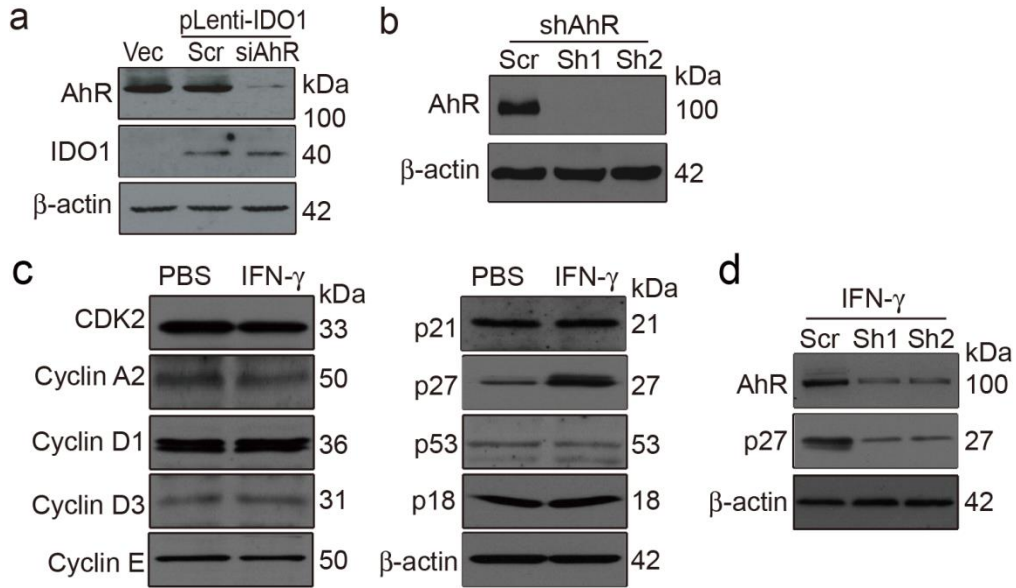
Supplementary Figure 3. AhR-p27 pathway participates in regulating TRC dormancy. a, Western blot analysis of AhR and IDO1 from Vec-B16 cells, IDO1 overexpressing B16 cells or IDO1-B16 cells transfected with siAhR. **b**, Western blot analysis shows the efficiency of stably knocking down AhR. **c,** B16 TRCs were treated with IFN-γ (100 ng/ml) for 72h. The TRCs were lysated and performed western blot analysis. **d,** Western blot analysis of AhR and p27 in AhR-Sramble B16 TRCs, AhR-Sh1 B16 TRCs and AhR-Sh2 B16 TRCs treated with IFN-γ for 72h. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m., *N.S.*, no significant difference (Student's t-test).
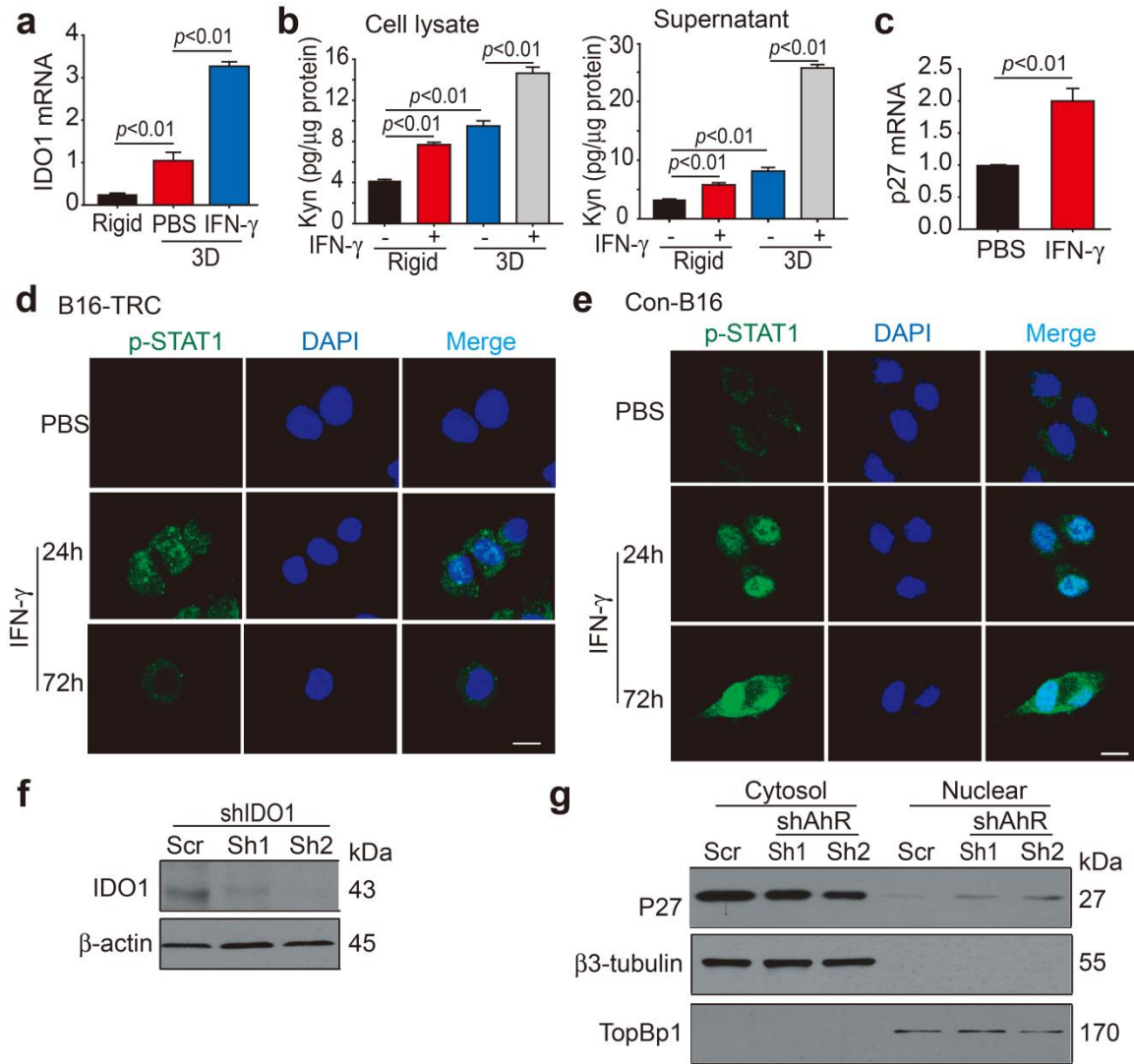
Supplementary Figure 4. IFN-γ activated both IDO-Kyn-AhR pathway and STAT1 signaling. a, the expression of IDO1 in control B16 cells, B16 TRCs or IFN-γ-treated B16 TRCs was determined by real time PCR. **b**, B16 cells, cultured on rigid plastic or in soft 3D fibrin gels, were treated with 100 ng/ml IFN-γ for 2 days. The Kyn levels in cell lysate or culture medium were determined. **c**, B16 TRCs were treated with IFN-γ (100 ng/ml) for 3 days. The expression of p27 was determined by real time PCR. **d, e,** B16 TRCs and control B16 cells (rigid plastic) were treated with IFN-γ (100 ng/ml) for 24h or 72h. Translocation of phosphorylated STAT1 into the nucleus was determined by

immunostaining with anti-p-STAT1 antibody (green) and DAPI (blue). The images are representative of three independent experiments. Bar, 10 µm. **f,** The knocking down efficiency of IDO1 is shown by western blot analysis. **g,** B16 TRCs transfected with scrambled shRNA or AhR shRNAs (Sh1 and Sh2) were treated with IFN-γ (100 ng/ml) for 72h. The cytoplasmic and nuclear fractions were isolated for p27 detection by western blot. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m..
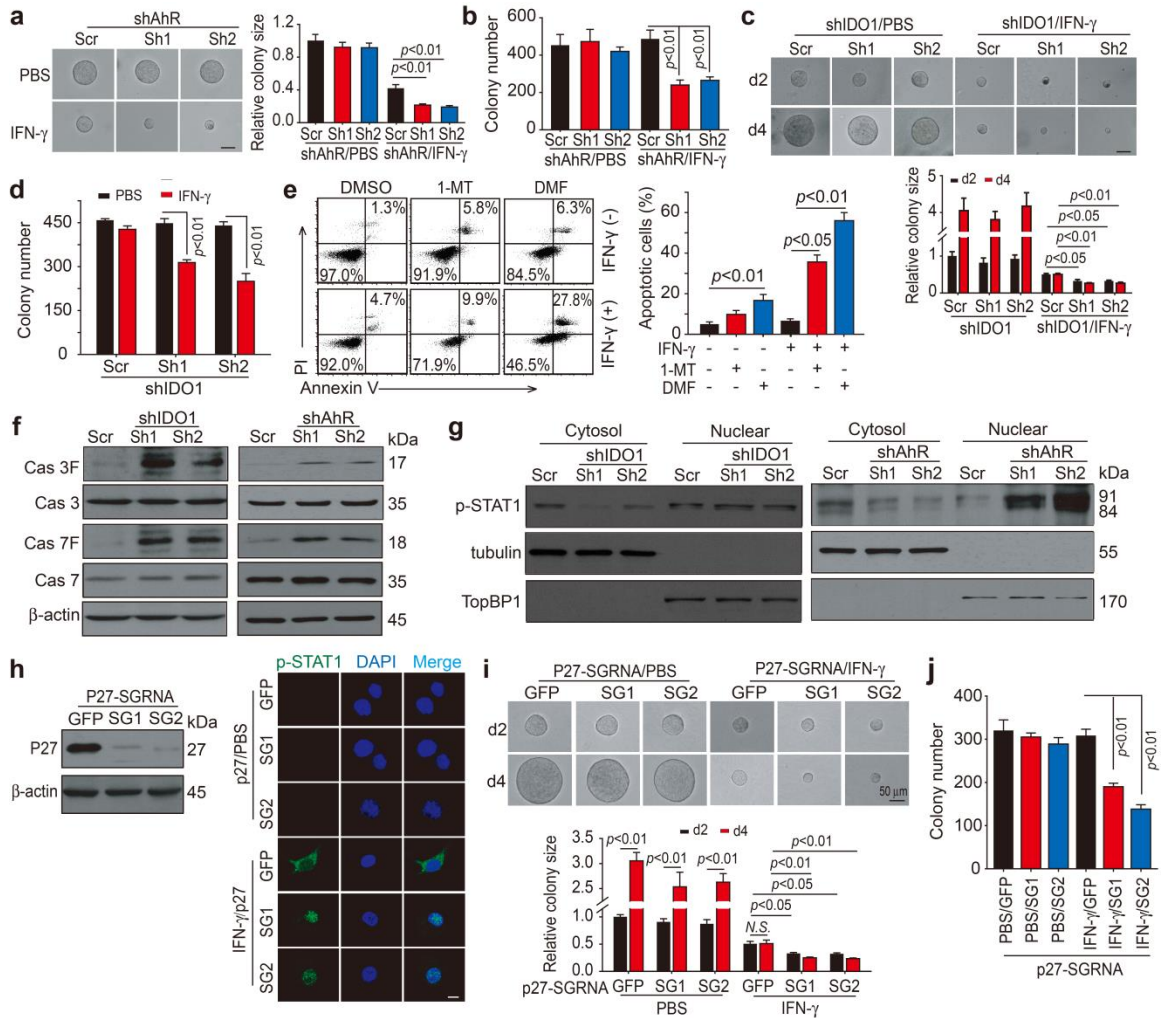
Supplementary Figure 5. Switching IDO-Kyn-AhR cascade to STAT1 signaling targets dormant TRC *in vitro*. a, b, Scr-B16 TRCs, shAhR-Sh1-B16 TRCs, and shAhR-Sh2-B16 TRCs were treated with IFN-γ (100 ng/ml) for 72h. The colony size was presented photographically and graphically (a) and conlony number was counted (b). Bar, 50 μm. **c, d,** Scr-B16 TRCs, shIDO1-Sh1-B16 TRCs, shIDO1-Sh2-B16 TRCs were treated with IFN-γ (100 ng/ml) for 72h. The colony size was presented (c) and conlony number was counted (d). The relative colony size was calculated by comparing the colony size in groups with that in the ShIDO1-Scr (d2) group, which was set to 1. Bar, 50 μm. **e,** B16 TRCs were treated with IFN-γ (100 ng/ml) in the presence or absence of 1-

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MT or DMF for 72h. Cell were stained with Annexin V and PI and the amount of cells undergoing apoptosis was analyzed by flow cytometry. **f,** Scr-B16 TRCs, shIDO1-Sh1-B16 TRCs, shIDO1-Sh2-B16 TRCs (left) or Scr-B16 TRCs, shAhR-Sh1-B16 TRCs, shAhR-Sh2-B16 TRCs (right) were treated with IFN-γ (100 ng/ml) for 72h. Caspases 3 and 7 and their cleaved forms (Cas 3F and Cas 7F) were analyzed by western blot. **g,** The same treatment as in c or a, but the cytoplasmic and nuclear fractions were isolated and analyzed by western blot. β3-tubulin and TopBP1 were used as controls. **h,** p27-SGGFP-B16 TRCs, p27-SGRNA1-B16 TRCs or p27-SGRNA2-B16 TRCs were treated with IFN-γ (100 ng/ml) for 72h. The silencing efficiency was determined by western blot (left). The localization of p-STAT1 was analyzed by immunofluorescent staining (right). Bar, 10 µm. **i, j,** p27-SGGFP-B16 cells, p27-SGRNA1-B16 cells or p27-SGRNA2-B16 cells were cultured in the soft 3D fibrin gels for 2 days. Then, cells were treated with IFN-γ (100 ng/ml) for the indicated days. The colony size was presented photographically and graphically (i) and the colony number was counted (j). The relative colony size was calculated by comparing the colony size in groups with that in the ShAhR-Scr group (a), ShIDO1-Scr (d2) group (c) or GFP/PBS (d2) group (i), which was set to 1. Bar, 50 µm. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m., *N.S.*, no significant difference (Student's t-test).
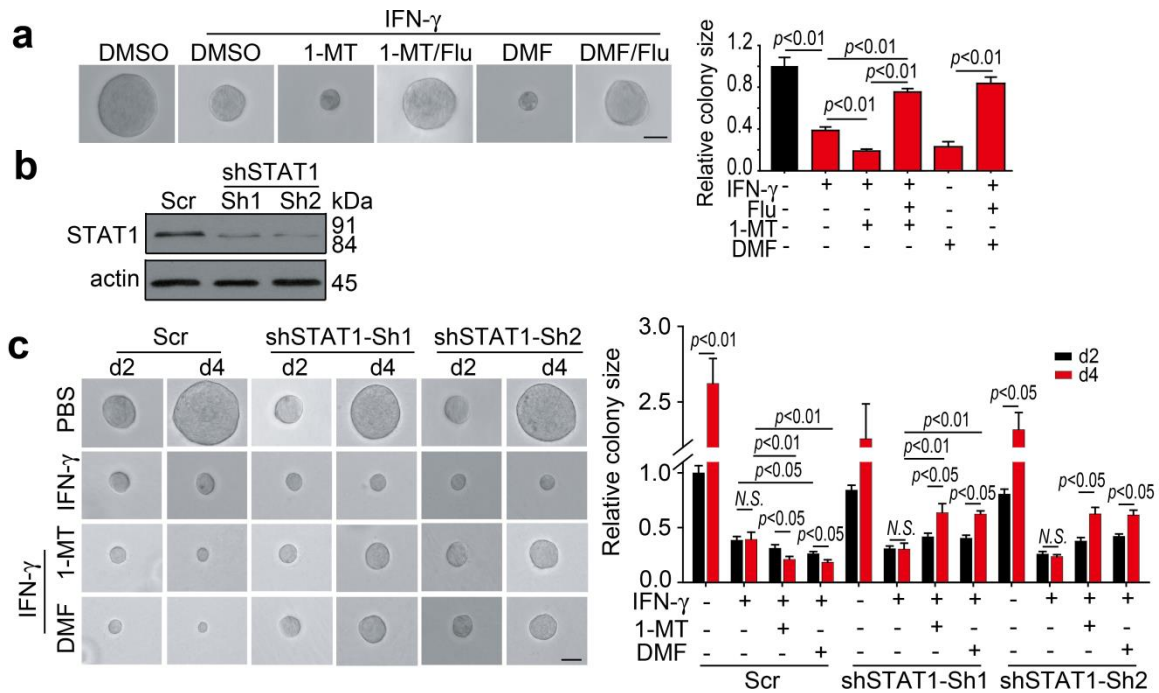
Supplementary Figure 6. STAT1 inhibition breaks IFN-γ-induced TRC dormancy. a, B16 TRCs were treated with DMSO control, IFN-γ (100 ng/ml), IFN-γ/1-MT (0.2 mM), IFN-γ/1-MT/Flu (1 μM), IFN-γ/ DMF (20 μM) or IFN-γ/1-MT/Flu for 72h. The colony size was presented. The relative colony size was calculated by comparing the colony size in groups with that in the DMSO group, which was set to 1. Bar, 50 μm. **b, c,** B16 cells were stably transfected with STAT1 shRNAs or scrambled shRNA. The silencing efficiency was determined by western blot (b). Cells were seeded in 3D soft fibrin gels and then treated with IFN-γ (100 ng/ml) in the presence or absence of 1-MT (0.2 mM) or DMF (20 μM). The colony size was presented (c). The relative colony size was calculated by comparing the colony size in groups with that in the Scr-PBS (d2) group, which was set to 1. Bar, 50 μm. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m., *N.S.*, no significant difference (Student's t-test).
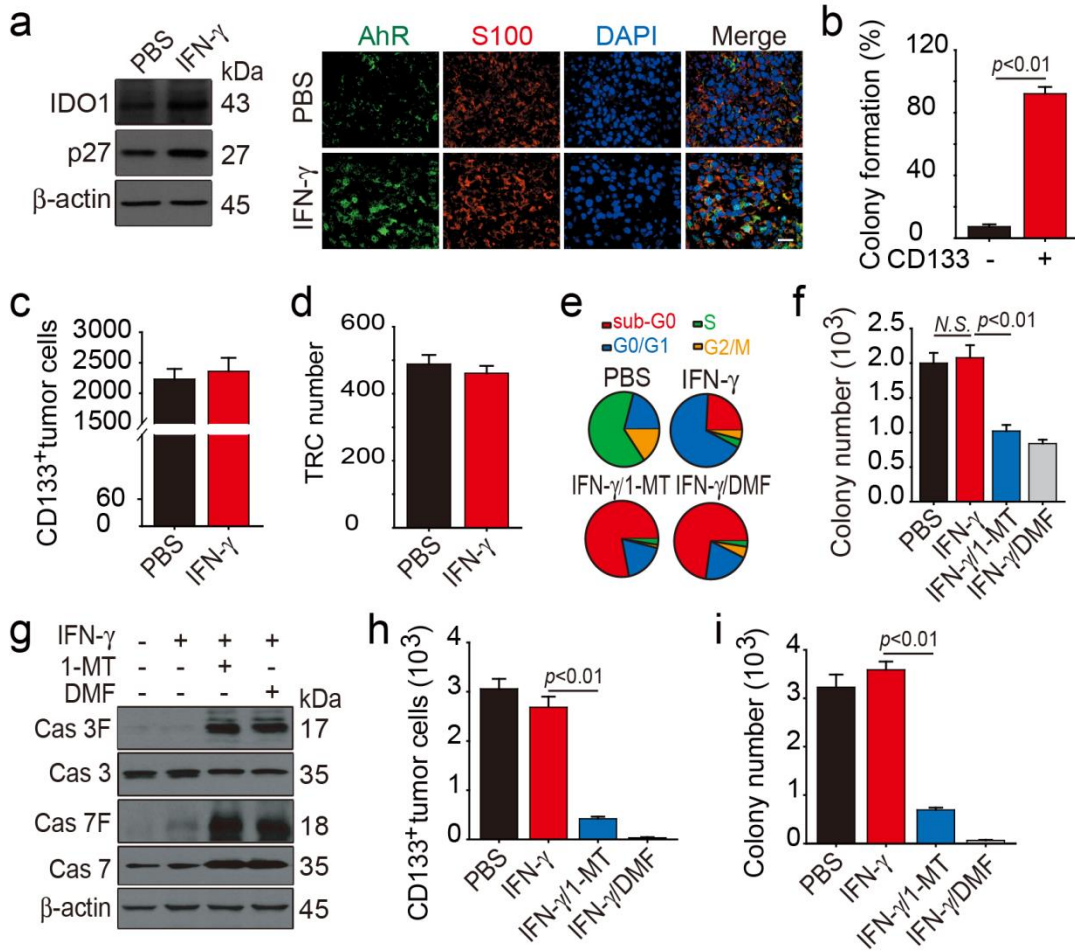
Supplementary Figure 7. Combining IFN-γ and an IDO1 or AhR inhibitor abrogates dormant TRC *in vivo*. a, C57BL/6 mice with 5×5 mm H22 hepatocarcinoma were intratumorally treated with 20 µg IFN-γ once daily for 3 days (n=6 per group). Isolated primary tumor cells from a part of tumor tissue were analyzed by western blot with anti-IDO1, p27 and β-actin antibody, respectively (left). Another part of tumor tissue was immunostained with anti-AhR (green), S100β (red) and DAPI (blue), and observed under confocal microscopy (right). Bar, 20 µm. **b,** C57BL/6 mice with 5×5 mm B16 melanoma were intratumorally treated with 10 µg IFN-γ once every day for 3 days (n=6 per group). CD133^{high} or CD133^{-} tumor cells were sorted by flow cytometry and seeded in the soft 3D fibrin gels for 4 days. The colony number was counted. **c and d**, as

the above (c), CD133^{high} tumor cells were counted by flow cytometry (d, n=6 per group). Then, the sorted same number of CD133^{high} tumor cells was seeded in soft 3D fibrin gels for 4 days. The colony number was counted (e). **e-g,** 2×10^5 H22 hepatocarcinoma cells were i.p. injected into BALB/c mice (n=6 per group). 24 hours larer, mice were intraperitoneally treated with PBS, IFN-γ, IFN-γ/1-MT (5 mg/ml, 3-4 ml/mice/day) or IFN-γ/DMF (10 mg/kg, every two days, i.g.) for 3 days. H22 cells in the peritoneal cavity were collected for cell cycle analysis (e), or total H22 cells were seeded in soft 3D fibrin gels for 4 days. The colony number was counted (f). Isolated H22 tumor cells were used to analyze caspases 3 and 7 and their cleaved forms by western blot (g). **h and i,** C57BL/6 mice were s.c. injected with 5×10^4 B16 TRCs (n=8 per group). Three days later, mice were treated with IFN-γ (intratumoral injection of 20 µg/day, once every two days) for 20 days, and then treated with either 1-MT or DMF for another 20 days. CD133$^+$ tumor cells were sorted by FACS from the whole tumor and counted (h). On the other hand, the tumor cells were seeded in 3D fibrin gels for 4 days and the colony number were counted (i). The data represent mean ± s.e.m., , *N.S.*, no significant difference (Student's t-test).
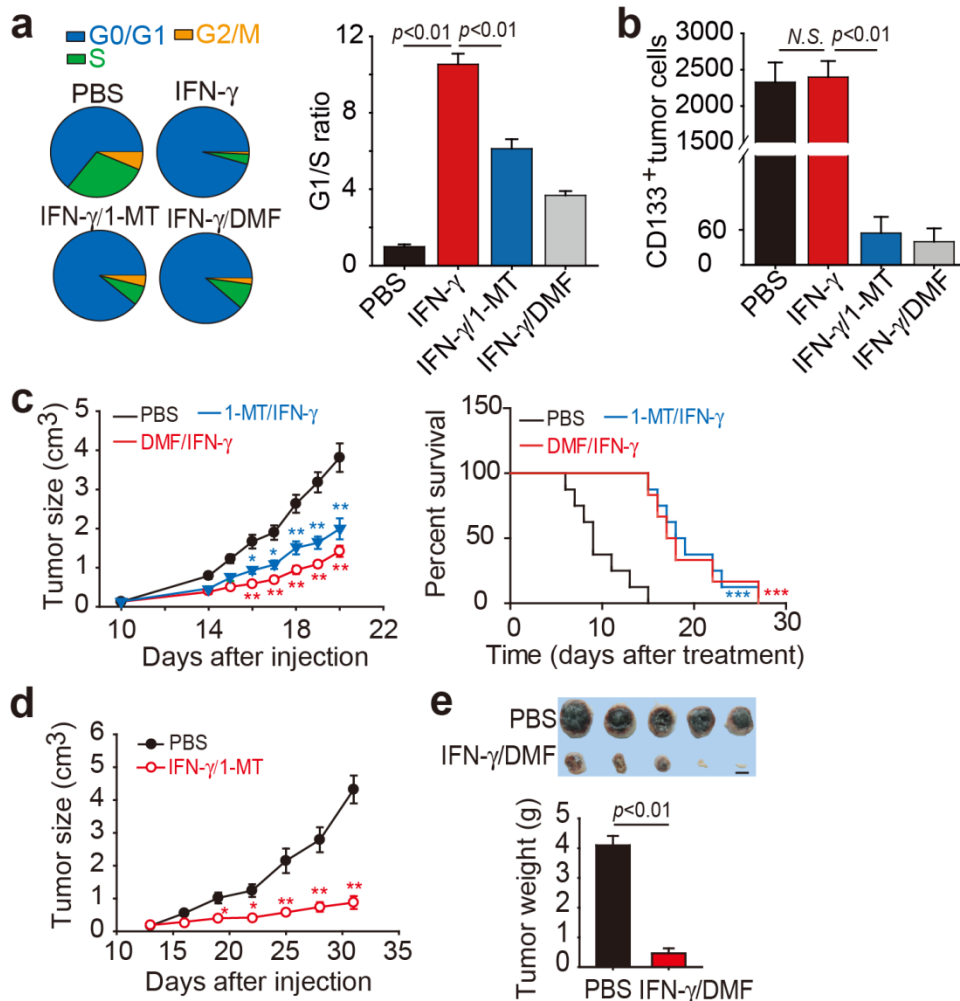
Supplementary Figure 8. Combining IFN-γ and an IDO or AhR inhibitor represses tumor growth and prolongs the survival of mice. a, Three days after injection of 1×10^5 B16 cells, C57BL/6 mice were treated with IFN-γ (intratumoral injection of 20 µg/day, once every two days), 1-MT (5 mg/ml in drinking water, 3-4 ml/mouse/day), IFN-γ /1-MT, DMF (intragastric injection of 10 mg/kg, once per two days) or IFN-γ/DMF for 10 days (n=6 per group). CD133^{high} tumor cells were sorted from tumor by FACS and performed cell cycle analysis. The data represent mean ± s.e.m.. **b,** The same as a, but CD133^{high} tumor cells were counted (n=6 per group). **c,** mice bearing large B16 melanoma (7×7 mm) were treated with IFN-γ/1-MT or IFN-γ/DMF for one week (n=10

per group). The tumor growth was measured (left) and long term survival was analyzed (right). **d**, 2×10^5 H22 hepatocarcinoma cells were s.c. injected to BALB/c mice (n=10 per group). When tumor size reached 7×7 mm, mice were treated with IFN-γ and 1-MT for one week. The tumor growth was measured. **e**, BALB/c mice (n=5) with 7×7 mm H22 hepatocarcinoma were treated with IFN-γ and DMF for 10 days. Mice were sacrificed and tumor weight was measured. Bar, 1 cm. The data represent mean ± s.e.m., *P<0.05, **P<0.01, ***P<0.001 *vs* PBS group (Student's t-test or Kaplan–Meier analysis).
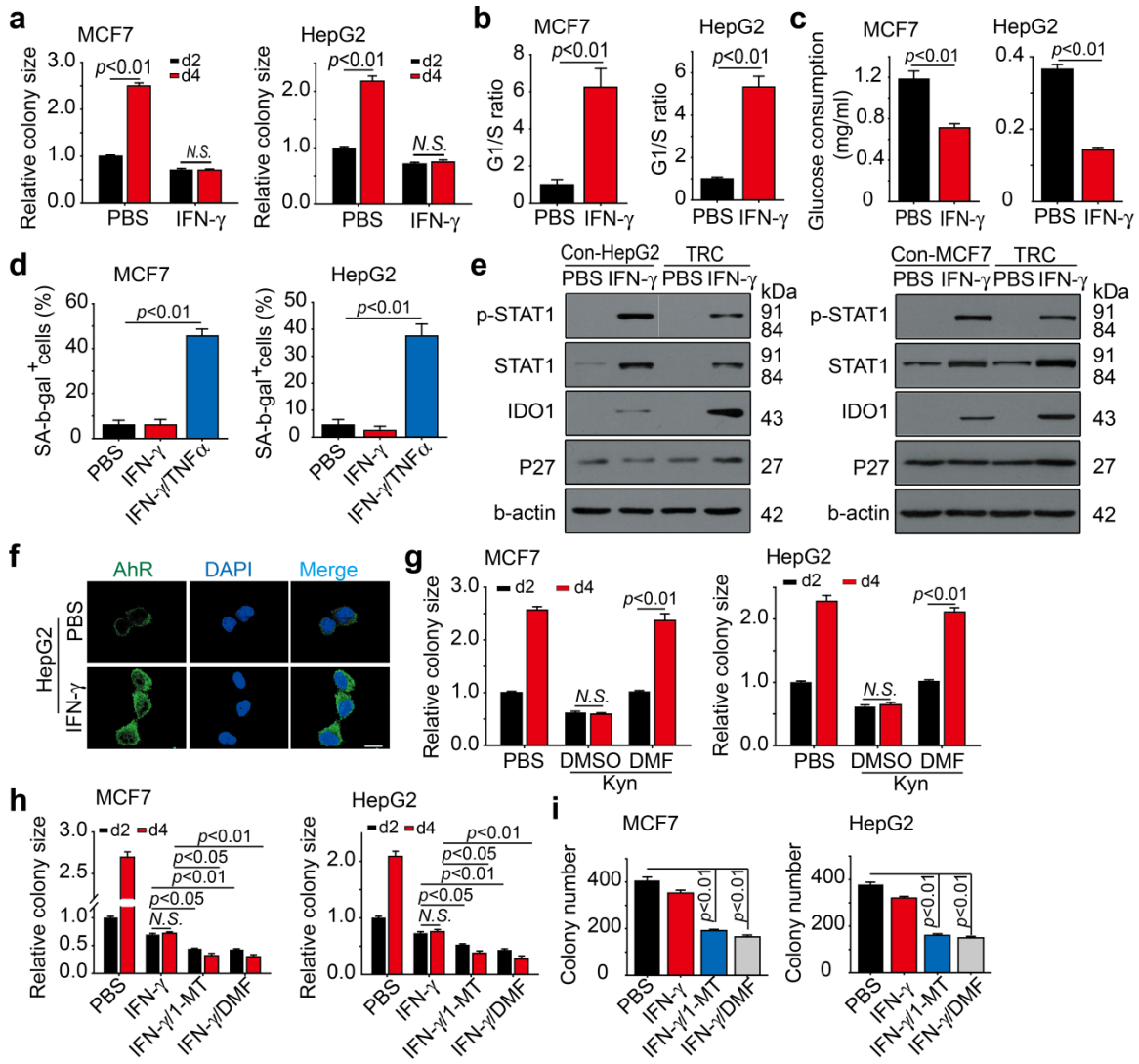
Supplementary Figure 9. Dormant human TRCs by IFN-γ are also abrogated by blocking IDO1-AhR pathway. a, MCF7 or HepG2 cells were cultured in soft 3D fibrin gels for 2 days and then treated with IFN-γ (150 ng/ml) for the indicated days. The data represent mean ± s.e.m.. **b-d**, MCF7 or HepG2 TRCs treated with IFN-γ (150 ng/ml) for 3 days were subjected to cell cycle analysis (b), glucose consumption assay (c) or SA-β gal staining (d). **e**, HepG2 or MCF7 cells grown in rigid plate or soft 3D gels were treated with IFN-γ (150 ng/ml) for 3 days and then subjected to western blot analysis incubated with anti-phospho-STAT1, STAT1, IDO1, p27 and β-actin antibody, respectively. **f**,

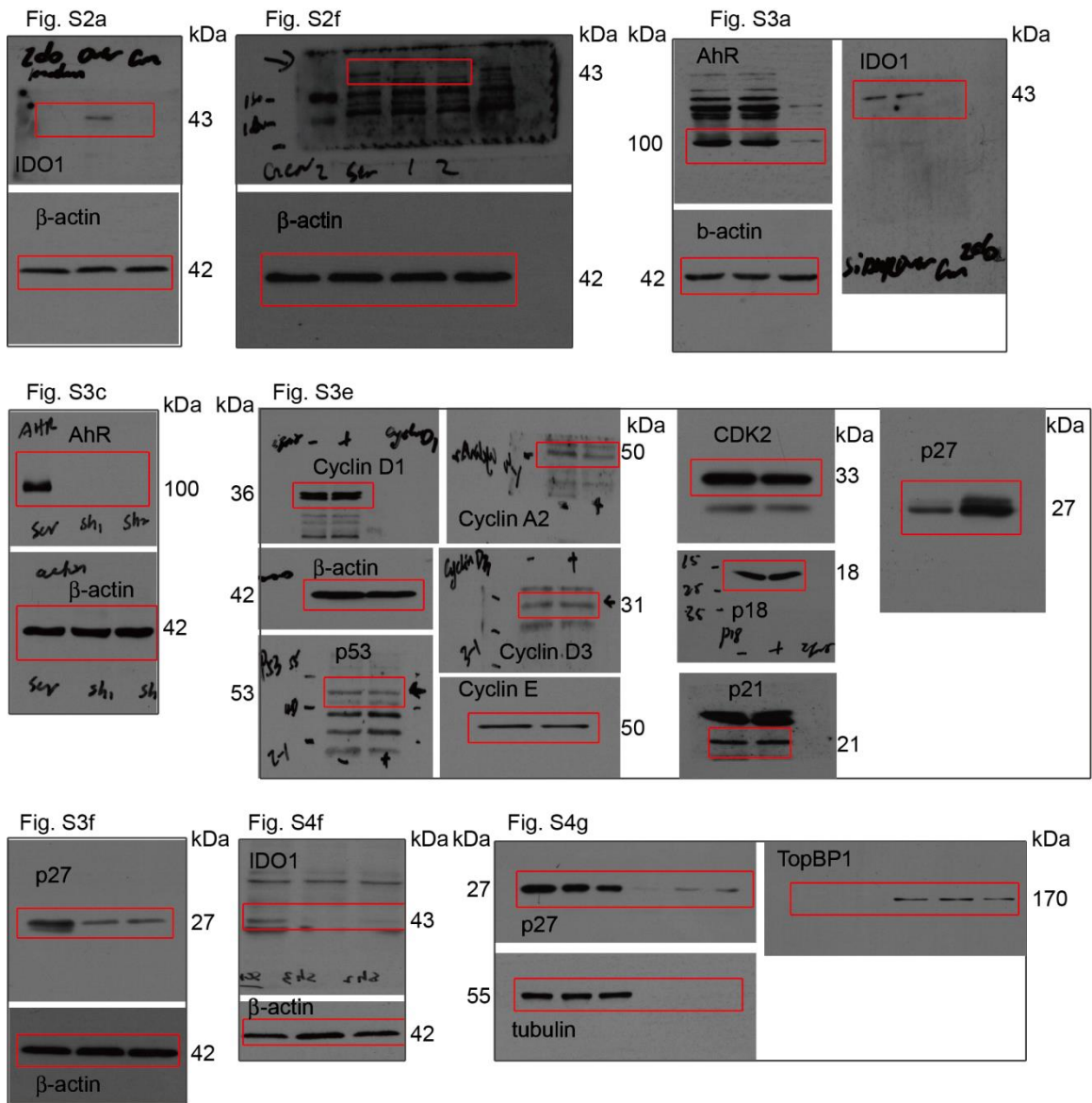HepG2 TRCs treated with IFN-γ (150 ng/ml) were immunostained with anti-AhR antibody (green) and DAPI (blue), and observed under confocal microscopy. Bar, 10 µm. **g**, MCF7 or HepG2 TRCs were treated with Kyn (150 µM) or Kyn + DMF (20 µM) for 48h. The colony size was quantified. **h, i**, HepG2 or MCF7 cells were treated with IFN-γ (150 ng/ml) in the presence or absence of 1-MT (0.2 mM) or DMF (20 µM) for 3 days. The colony size was quantified (h) and colony number was counted (i). The relative colony size in this figure was calculated by comparing the colony size in other groups with the colony size in the PBS (d2) group, which was set to 1. Data shown are representative of three independent experiments and error bars represent mean ± s.e.m., *N.S.*, no significant difference (Student's t-test).
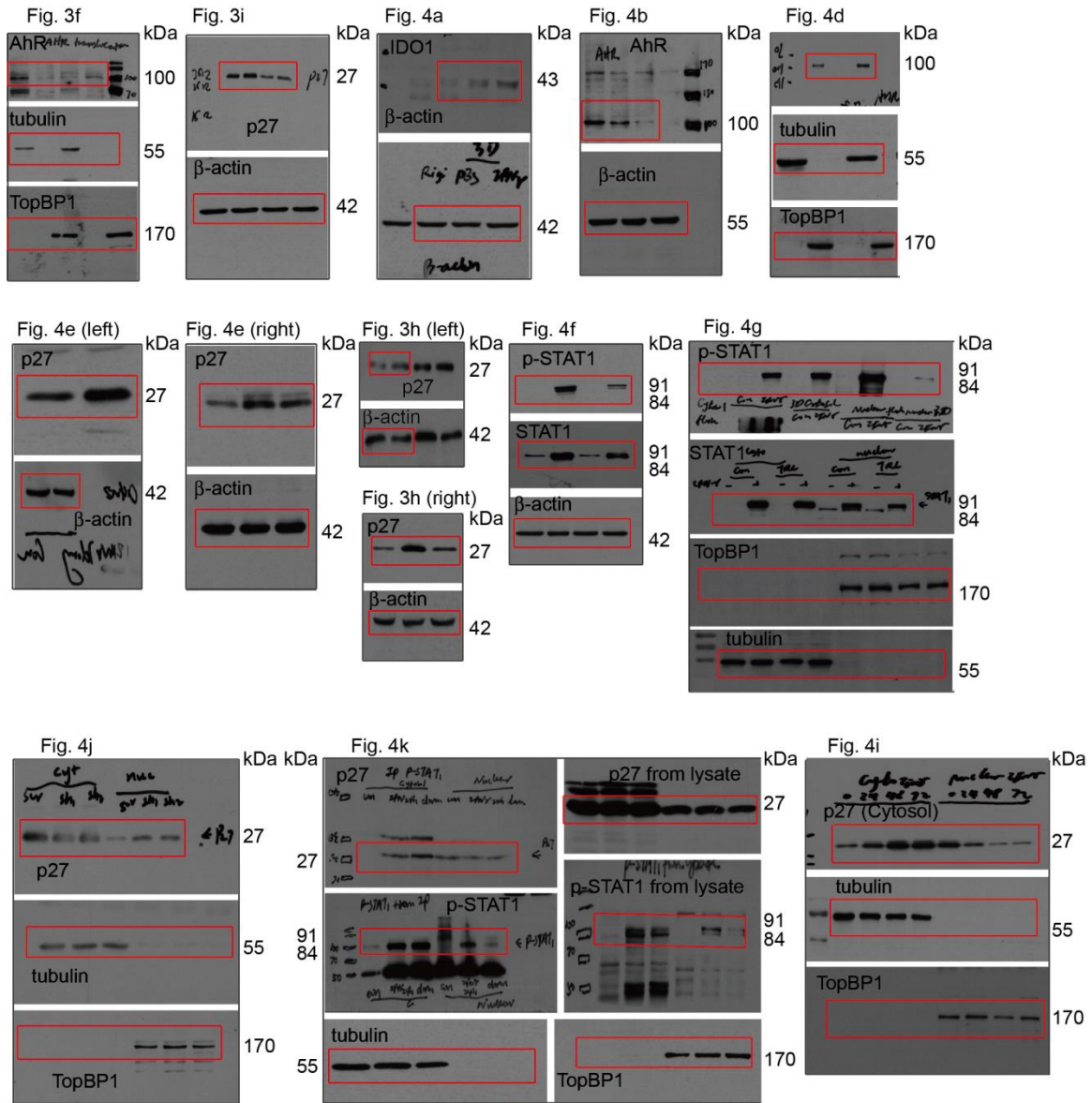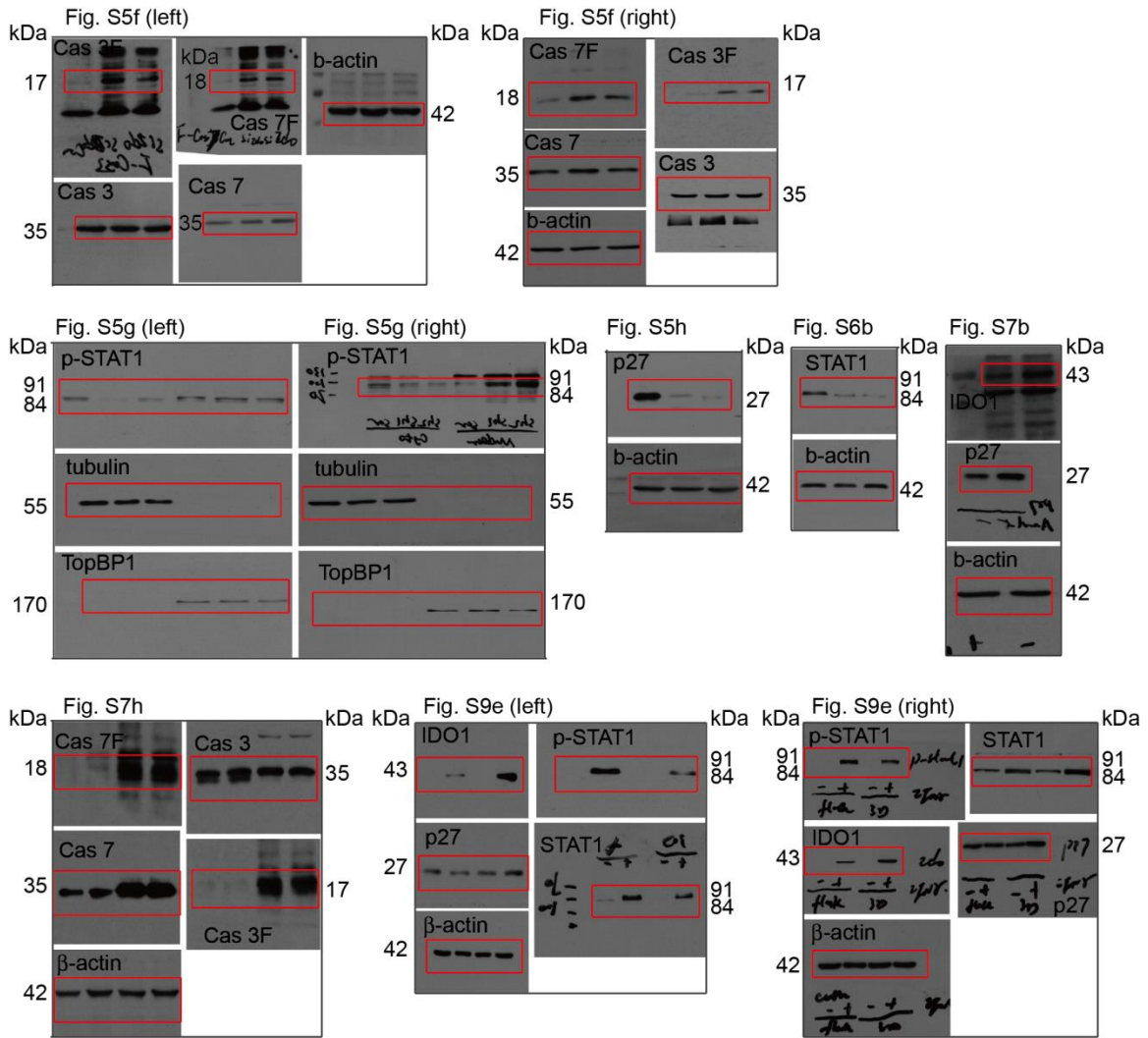
Supplementary Figure 10. Uncropped images of immunoblots for figure 3, 4. Red boxes show approximate image used for presentation.
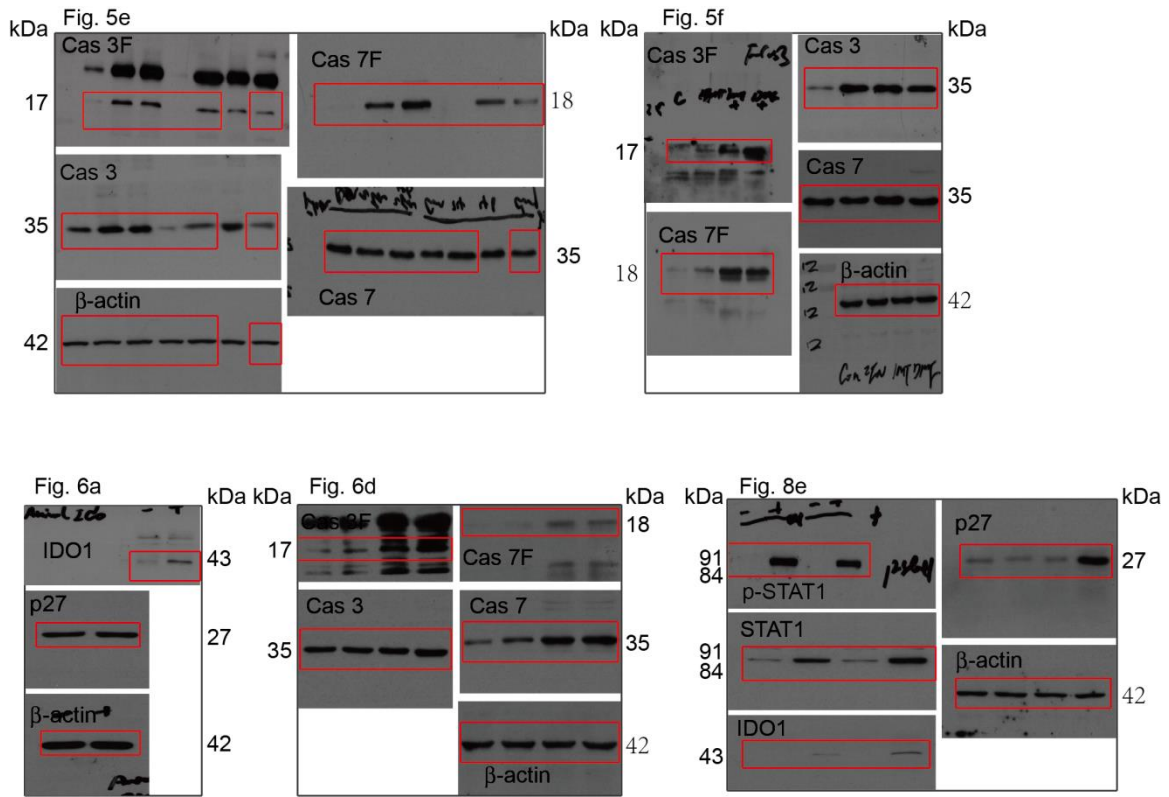
Supplementary Figure 11. Uncropped images of immunoblots for figure 5, 6, 8.

Supplementary Figure 12. Uncropped images of immunoblots for supplementary figure 2, 3, 4.

Fig. S5f (left)

kDa
Cas 3F
17

kDa
18
Cas 7F

b-actin
42

kDa kDa

Cas 3
35

Cas 7
35

Fig. S5f (right)

kDa
Cas 7F
18

Cas 3F
kDa
17

Cas 7
35

Cas 3
kDa
35

b-actin
42

Fig. S5g (left)

kDa
p-STAT1
91
84

tubulin
55

TopBP1
170

Fig. S5g (right)

p-STAT1
kDa
91
84

tubulin
55

TopBP1
170

Fig. S5h

kDa kDa
p27
27

b-actin
42

Fig. S6b

STAT1
kDa kDa
91
84

b-actin
42

Fig. S7b

kDa
43
IDO1

p27
27

b-actin
42

Fig. S7h

kDa
Cas 7F
18

Cas 3
35

Cas 7
35

Cas 3F
17

β-actin
42

kDa kDa

Fig. S9e (left)

IDO1
43

p-STAT1
91
84

p27
27

STAT1
91
84

β-actin
42

kDa kDa

Fig. S9e (right)

p-STAT1
91
84

STAT1
91
84

IDO1
43

27
p27

β-actin
42

kDa

Supplementary Figure 13. Uncropped images of immunoblots for supplementary figure 5, 6, 7, 9.