Figure S1

A

Relative mRNA expression (fold)

□ Naive CD4
■ Freshly isolated nTreg
■ Expanded nTreg

Glut1 Glut3 HK2 GPI PFK1 TPI1 ENO1 PKM2 LDHα

B

Relative mRNA expression (fold)

□ Naive CD4
■ Freshly isolated nTreg
■ Expanded nTreg

HMGCR HMGCS1 SQLE IDI1 CPT-1 ACC1 FASN

C

**Metabolites in the glycomics**

Glucose

↓

Glucose-6-phosphate (G6P)

↓

Fructose-6-phosphate (F6P)

↓

Fructose-1,6-biphosphate (F-1.6-P)

↓

Dihydroxyacetone phosphate (DHAP) ↔ Glyceraldehyde 3-phosphate (G3P)

↓

1,3-Bisphosphoglycerate (1,3 BPG)

↓

3-phosphoglycerate (3-PG)

↓

2-phosphoglycerate (2-PG)

↓

Phosphoenolpyuvate (PEP)

↓

Lactate ← Pyruvate

↓

Acteyl-CoA → Oxaloacetate

Citrate → Isocitrate

↓

α-ketoglutarate (α-KG)

↓

Succinate

↓

Malate ← Fumarate

**Supplemental Figure S1, related to Figure 1.**

**Human Treg cells have heightened glucose and lipid metabolism**

**(A)** and **(B)** Both freshly purified and expanded nTreg cells have similar gene expression patterns of glucose transporters (Glut1 and Glut3) and the key enzymes in glycolysis (HK2, GPI, PFK1, TPI, ENO1, PKM2 and LDHα), cholesterol synthesis (HMGCR, HMGCS1, SQLE, and IDI1), as well as fatty acid oxidation (CPT-1) and synthesis (ACC1 and FASN). Fresh nTreg cells were directly purified from PBMCs of 4 healthy donors. Expanded nTreg cells were generated from nTreg cells stimulated with anti-CD3/anti-CD28 plus IL-2. Total RNA was isolated from each cell type and analyzed by real-time PCR. Expression levels of each gene were normalized to β-actin expression and adjusted to the levels in naïve CD4$^+$ cells (served as 1). Data shown are mean ± SD from four independent donors.

**(C)** Schematic diagram of the intermediate metabolites and molecules in glycolysis and TCA pathways measured with glycomics.

# Figure S2

## A



Glucose ⊣ Phloretin

Glut1 Glut3

Membrane

Glucose → HK2 → G-6-P

LND 2-DG 3-BrPA

GPI PFK1 TPI ENO1 PKM2

Pyruvate

LDHα → Lactate

TCA

Acetyl-CoA ⊣ CPT-1 ⊣ Etomoxir β-Oxidation ⊣ Citrate

Glycolysis

Mitochondrial respiration

TAG → Lipase → Fatty acids

Acetyl-CoA → ACC1 → FASN ⊣ Orlistat ⊣ C75

Simvastatin

25-HC

HMGCS1 HMGCR ⊣ Simvastatin IDI1 SQLE → Cholesterol

Lipid biosynthesis

## B

48 hours



Viable cells (%)

Medium, Phloretin, 2-DG, LND, 3-BrPA, Etomoxir, Orlistat, 25-HC, Simvastatin, Poly-G3, YC-1, 2-ME, Rapamycin, SB203580

## C



7-AAD / Annexin V

| Medium | Phloretin | 2-DG | LND | 3-BrPA |
|---|---|---|---|---|
| 1.2 / 6.2 | 1.4 / 5.9 | 1.2 / 6.2 | 1.6 / 6.3 | 1.6 / 6.1 |

| Etomoxir | Orlistat | 25-HC | Simvastatin | Poly-G3 |
|---|---|---|---|---|
| 1.5 / 6.5 | 1.4 / 5.9 | 1.9 / 5.8 | 1.4 / 7.2 | 1.8 / 6.4 |

| YC-1 | 2-ME | Rapamycin | SB203580 | unstaining |
|---|---|---|---|---|
| 1.7 / 6.7 | 1.2 / 6.2 | 4.6 / 13.3 | 0.7 / 4.6 | 0 / 0.3 |

## D

SA-β-Gal staining

Naive CD4

Naive CD4 T cells + nTreg-pretreated with



None, Phloretin, LND, 2-DG, 3-BrPA

nTreg, Etomoxir, C75, Orlistat, 25-HC, Simvastatin

**Supplemental Figure S2, related to Figure 1.**

**Both glycolysis and lipid metabolism are critical for Treg suppressive function**

**(A)** A schematic diagrams of glycolysis, mitochondrial respiration and lipid biosynthesis pathways. The key enzymes are shown in blue color, and the specific pharmaceutical inhibitors utilized in the experiments are shown in red color. **(B)** and **(C)** The pharmaceutical inhibitors and Poly-G3 with utilized concentrations in the experiments did not affect Treg cell viability or promote cell apoptosis. nTreg cells were treated with various inhibitors or Poly-G3 with the indicated concentrations (in Star Methods) for 48 hours. Treg viability and apoptosis treated with/without inhibitors were determined by the Typan blue staining (in B) and flow cytometry analysis after staining with annexin V and 7AAD, respectively (in C). **(D)** Inhibition of glycolysis and lipid metabolism significantly prevented Treg-induced responder T cell senescence. nTreg cells were pretreated with pharmacological inhibitors of glucose transporter, glycolysis and lipid metabolism for 48 hours, including phloretin (2 µM), 2-DG (1 mM), LND (125 µM), and 3-BrPA (30 µM), etomoxir (100 µM), C75 (5 µM), orlistat (10 µM), 25-HC (0.25 µg/ml), simvastatin (2 µM), respectively. Naïve CD4$^+$ T cells were then co-cultured with inhibitor-pretreated or untreated Treg cells (4:1) for 3 days. The treated naive CD4$^+$ T cells were purified by FACS and SA-β-Gal expression was determined. The morphological characteristics of SA-β-Gal positive T cells were identified with dark blue granules under light microscope. Scale bar, 25 µm.
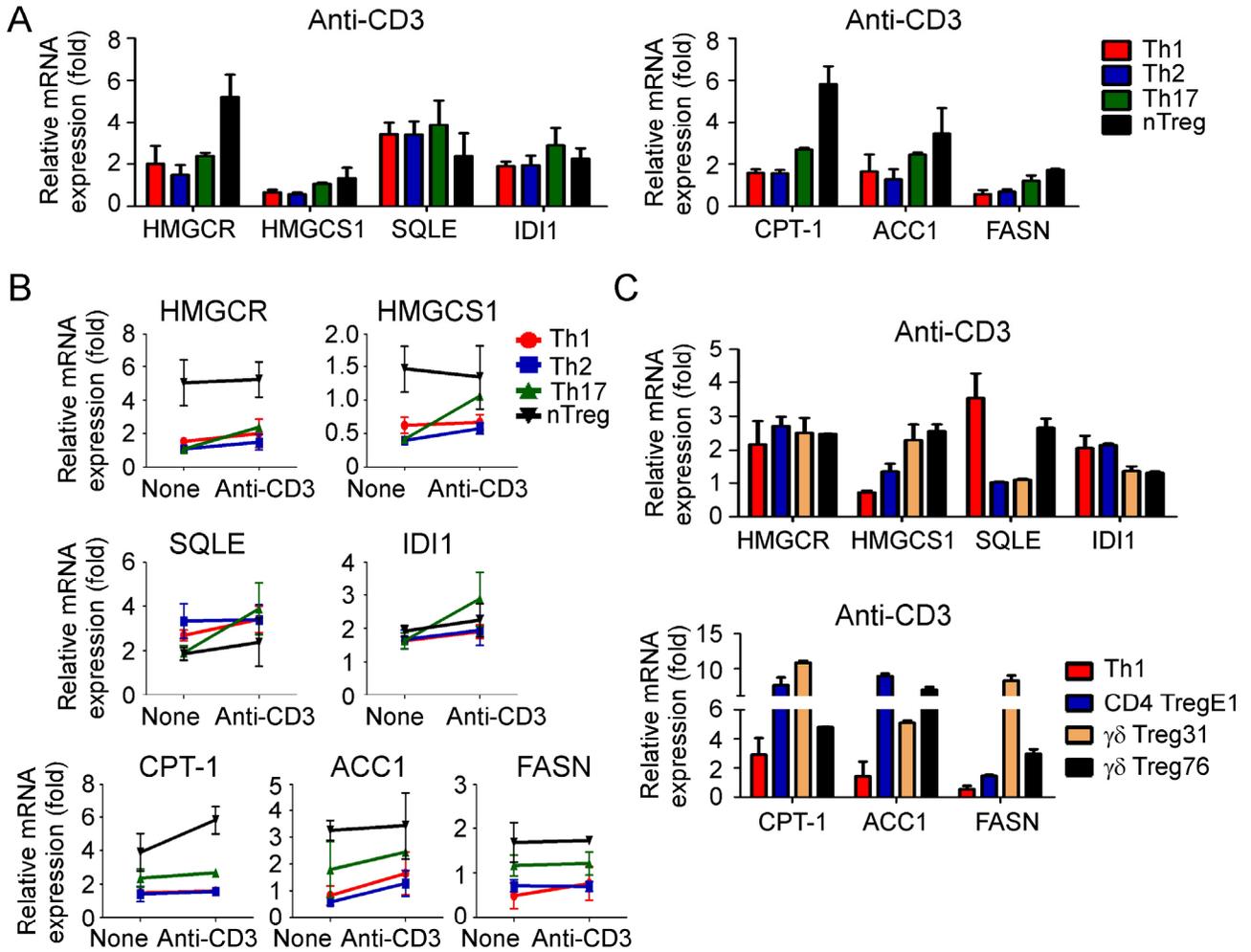
Figure S3

**Supplemental Figure S3, related to Figure 2.**

**TCR activation does not significantly promote gene expression levels of the key enzymes in lipid metabolism in Treg cells**

**(A)** and **(B)** Comparisons of gene expression levels of key enzymes involved in lipid metabolism in different T cell subsets before and after anti-CD3 stimulations. Anti-CD3 activated Treg cells display high enzyme gene expression of lipid metabolism compared with effector T cells, but activation does not induce increased gene expression levels.  T cells were stimulated with or without anti-CD3 for 8 hours and total RNA was isolated from each cell type and analyzed by real-time PCR. Expression levels of each gene were normalized to $\beta$-actin expression levels and adjusted to the levels in naïve CD4$^+$ T cells (served as 1). Data shown are mean ± SD from four independent healthy donors. **(C)** Activated tumor-derived CD4$^+$ Treg and $\gamma\delta$ Treg cells also have high gene expression levels of the key enzymes in lipid metabolism compared with those of activated Th1 cells. T cells were stimulated with or without anti-CD3 for 8 hours, and relative mRNA expression level of each gene was determined by real-time PCR, normalized to $\beta$-actin expression and then adjusted to the level in naïve CD4$^+$ T cells (set as 1). Data shown are mean ± SD from three independent experiments with similar results.

Figure S4

A

Glucose (mM)   0      2.8      5.5      11      25

Naive CD4

Naive CD8

B

Glut transporters

SLC2A1
SLC2A3
SLC2A4
SLC2A9
SLC2A11
SLC2A12
SLC2A14

-2  -1  0  1  2

C

CD4                              CD4
Glut1   DAPI   Merge        Glut3   DAPI   Merge

Medium

Poly-G3

Poly-T3
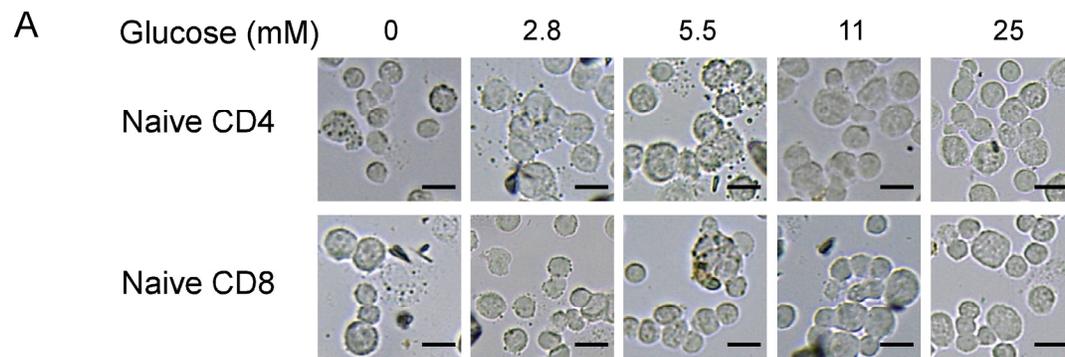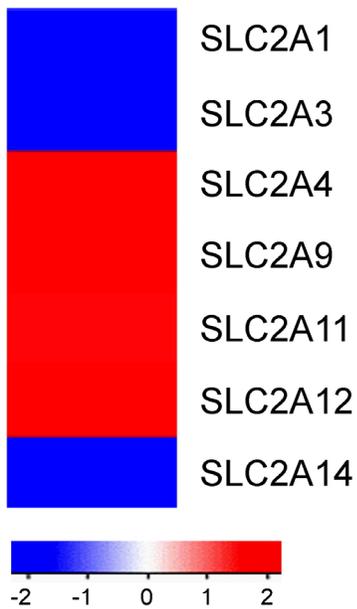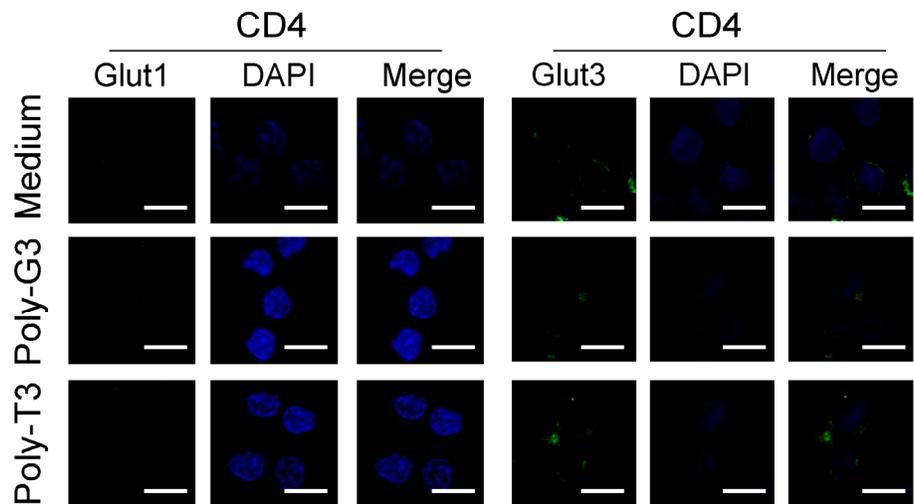
**Supplemental Figure S4, related to Figure 3 and Figure 4.**

**Poly-G3 treatment only affects Gluts in Treg cells but not in effector CD4$^+$ T cells**

**(A)** Significantly increased SA-$\beta$-Gal$^+$ T cell populations were induced in both naïve CD4$^+$ and CD8$^+$ T cells cultured in the medium with low concentrations of glucose. Anti-CD3-activated naïve T cells were cultured with different concentrations of glucose for 3 days. Normal medium with 11 mM glucose served as a control. SA-$\beta$-Gal expression in T cells was determined, and SA-$\beta$-Gal$^+$ T cells were identified with dark blue granules under light microscope. Scale bar, 25 $\mu$m. **(B)** Microarray analysis of glucose transporter genes expression in nTreg cells after treatment with Poly-G3 at 24 hours. Gene alterations were normalized to log$_2$ expression level. Human nTreg cells were isolated from PBMCs of five healthy donors and treated with Poly-G3 for different time points. Total RNA was purified and pooled, and transcriptome analyses of Treg cells were performed using the Illumina whole-genome Human HT-12 BeadChips. **(C)** Poly-G3 treatment did not induce protein expression and translocation changes of Glut1 and Glut3 in control CD4$^+$ T cells. Control CD4$^+$CD25$^-$ effector T cells were treated with Poly-G3 or Poly-T3 for 72 hours. Glut1 and Glut3 expression (green) was determined by an indirect immunofluorescence assay with a confocal microscopy. Scale bar, 25 $\mu$m.

Figure S5

A

**Medium** · **Poly-G3** · **Poly-T3**

nTreg

CD4 TregE1

γδ Treg31

CD4

B
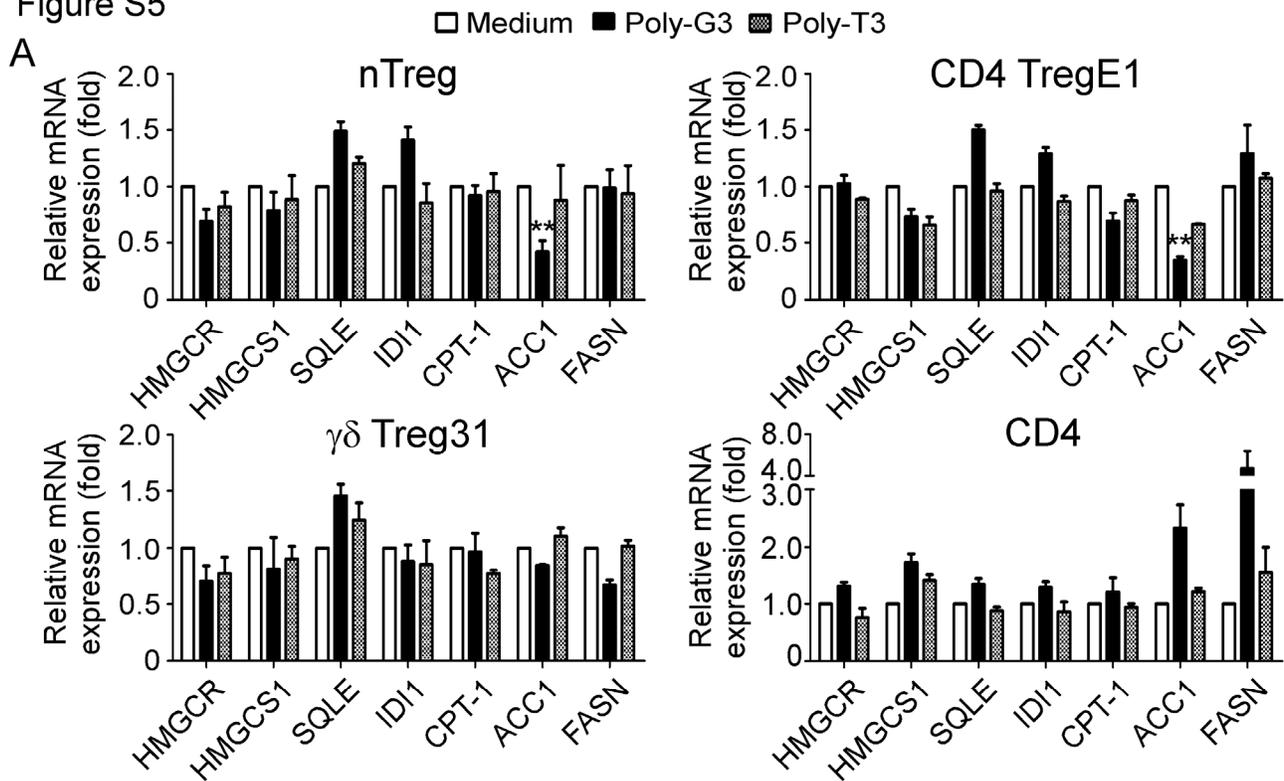
SA-β-Gal staining
Naive CD4 T cells + nTreg-pretreated with

Naive CD4

nTreg

None  Phloretin  LND  2-DG  3-BrPA  Etomoxir  C75  Orlistat  25-HC  Simvastatin

Medium

PolyG-3

C

D
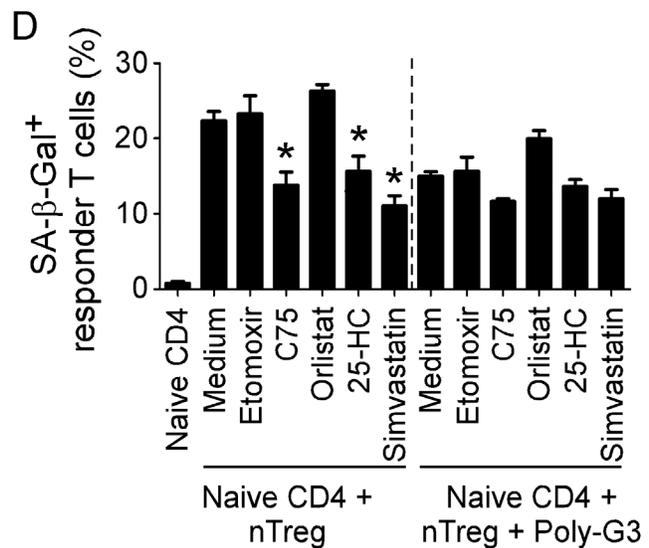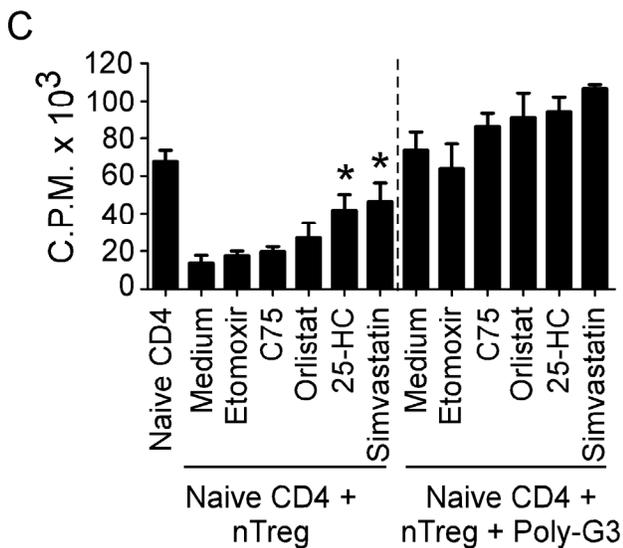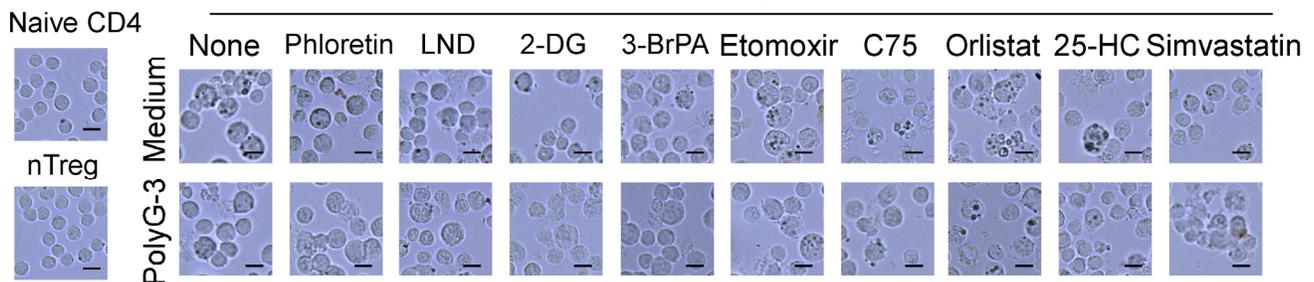
**Supplemental Figure S5, related to Figure 5.**

**TLR8 signaling does not affect lipid metabolism in Treg cells**

**(A)** Poly-G3 treatment has no obviously effect on lipogenic-related gene expression in both nTreg and tumor-derived Treg cells. Different types of human Treg cells and control effector CD4^{+} T cells were treated with or without Poly-G3 or Poly-T3 for 48 hours. Total RNA was isolated from the T cells and analyzed by real-time PCR. The expression levels of each gene were normalized to β-actin expression and adjusted to the levels in untreated T cells (medium, as 1). Data shown in nTreg and control CD4^{+} T cells are mean ± SD from four independent donors. Data for CD4 TregE1 and γδ Treg31 are average of three independent experiments. **p<0.01, compared with the medium only group. **(B)** Blockage of glycolysis rather than lipid metabolism in nTreg cells using specific pharmacological inhibitors dramatically enhanced the effects of Poly-G3-mediated reversal of Treg-induced responder T cell senescence. nTreg cells were pretreated with pharmacological inhibitors of glucose transporter, glycolysis and lipid metabolism for 48 hours, including phloretin (2 µM), 2-DG (1 mM), LND (125 µM), and 3-BrPA (30 µM), etomoxir (100 µM), C75 (5 µM), orlistat (10 µM), 25-HC (0.25 µg/ml), simvastatin (2 µM). Naïve CD4^{+} T cells were then co-cultured with inhibitor-pretreated or untreated Treg cells (4:1) for 3 days in the presence or absence of Poly-G3. SA-β-Gal expression in treated T cells was determined. The morphological characteristics of SA-β-Gal positive T cells were identified with dark blue granules under light microscope. Scale bar, 25 µm. **(C)** and **(D)** Blockage of lipid metabolism in nTreg cells using specific pharmacological inhibitors did not influence the effects of Poly-G3-mediated reversal of Treg suppression on the T cell proliferation and cell senescence induction. nTreg cells were pretreated with pharmacological inhibitors of lipid metabolism for 48 hours, including etomoxir (100 µM), C75 (5 µM), orlistat (10 µM), 25-HC (0.25 µg/ml) and simvastatin (2 µM). Naïve CD4^{+} T cells were then co-cultured with inhibitor-pretreated or untreated Tregs (10:1 for [3H]-thymidine incorporation assays and 4:1 for SA-β-Gal expression assays) for 3 days in the presence or absence of Poly-G3. Proliferation of co-cultured naïve T cells stimulated by anti-CD3 antibody was determined by [3H]-thymidine incorporation assays (in C), and SA-β-Gal expression in treated T cells

were determined (in D). Data shown are mean ± SD from representative of three independent experiments with similar results. *p<0.05, compared with the respective medium only group.

Figure S6
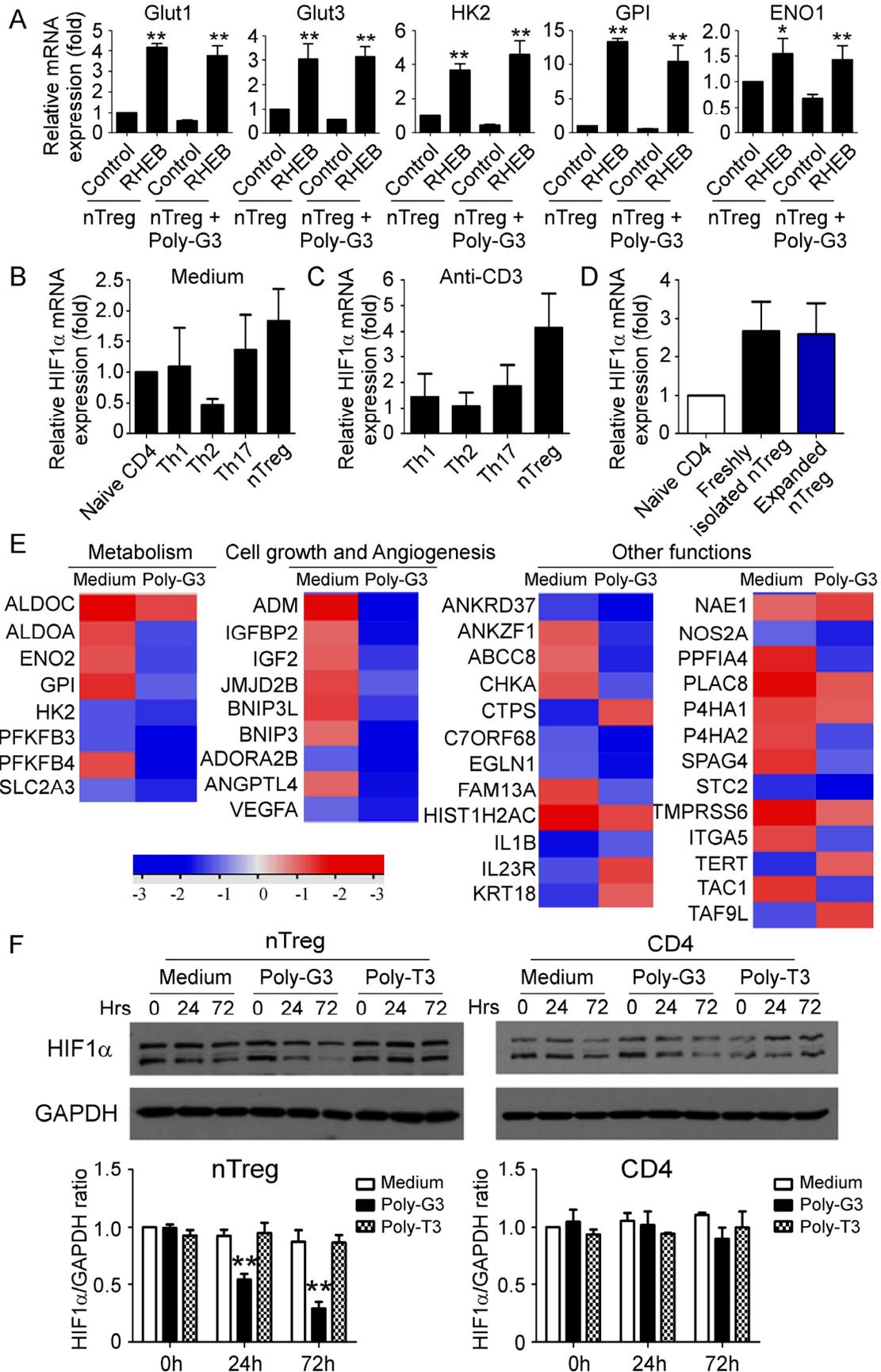
**Supplemental Figure S6, related to Figure 6.**

**mTOR-HIF1α signaling is involved in TLR8-induced reversal of Treg cell suppression**

**(A)** Activation of mTOR signaling with Retro-RHEB transfection enhanced Treg glucose metabolism and prevented Poly-G3-mediated down-regulation of gene expression of glucose metabolic enzymes. Anti-CD3 activated nTreg cells were infected with retrovirus carrying RHEB gene or control vector for 48 hours, and then were further cultured in the presence or absence of Poly-G3 (3 µg/ml) for 24 hours. Total RNA was isolated from the Treg cells and analyzed by real-time PCR. The expression levels of each gene were normalized to β-actin expression levels and adjusted to the levels in Treg cells transfected with control virus. Data shown are representative of average of three individual Treg cells ± SD. *p<0.05 and **p<0.01, compared with the respective control virus infected group. **(B)** and **(C)** Gene expression level of HIF1α in different T cell subsets stimulated with/without anti-CD3 antibody. Th1, Th2 and Th17 cells were polarized from naïve T cells purified from 4 individual healthy donors in the presence of related cytokine polarized conditions. nTreg cells were directly purified from PBMCs of healthy donors. Total RNA was isolated from each cell type and analyzed by real-time PCR. Expression level of HIF1α was normalized to β-actin expression and adjusted to the level in naïve CD4$^+$ T cells (served as 1). Data shown are mean ± SD from four independent donors. **(D)** Both freshly purified and expanded nTreg cells have higher expression levels of HIF1α than that of naïve T cells. Fresh nTreg cells were directly purified from PBMCs of 4 healthy donors. Expanded nTreg cells were expanded from nTreg cells stimulated with anti-CD3/anti-CD28 plus IL-2. Total RNA was isolated from each cell type and analyzed by real-time PCR. Expression levels of each gene were adjusted to the levels in naïve CD4$^+$ cells (served as 1). Data shown are mean ± SD from four independent donors. **(E)** Gene changes involved in the HIF1α signaling pathway were identified and analyzed in nTreg cells after treatment with or without Poly-G3 at 24 hours. Gene alterations were normalized to log$_2$ expression level. Human nTreg cells were isolated from PBMCs of five healthy donors and treated with Poly-G3 for different time points. Total RNA was purified and pooled, and transcriptome analyses of Treg cells were performed using the Illumina whole-genome Human HT-12

BeadChips. **(F)** Poly-G3 treatment down-regulated HIF1$\alpha$ protein expression in nTreg cells. nTreg cells and control effector CD4$^+$ T cells were treated with Poly-G3 or Poly-T3 for different times. The cell lysates were prepared for western blot analysis. The upper panel shows the western blot analysis results. The bottom panel shows HIF1$\alpha$ expression analyzed quantitatively and compared with GAPDH expression with a densitometer. Results shown in the histogram are mean ± SD from 3 independent experiments. **P< 0.01 compared with medium only group.

# Figure S7



A

CD8 T cells co-cultured with

- □ None
- ■ nTreg
- ■ nTreg + Poly-G3
- ■ nTreg + 2-DG
- ■ nTreg + 2-ME

B

CD8 T cells co-transferred with

- □ None
- ■ nTreg
- ■ nTreg + Poly-G3
- ■ nTreg + 2-DG
- ■ nTreg + 2-ME

C

Spleen

D

Spleen
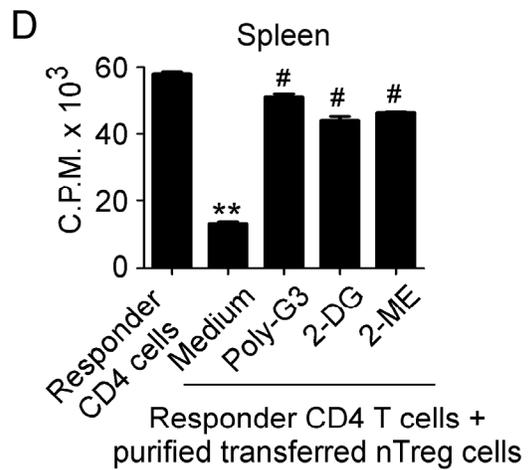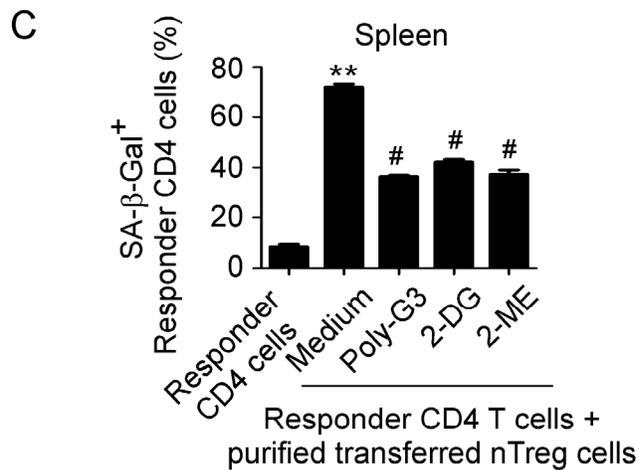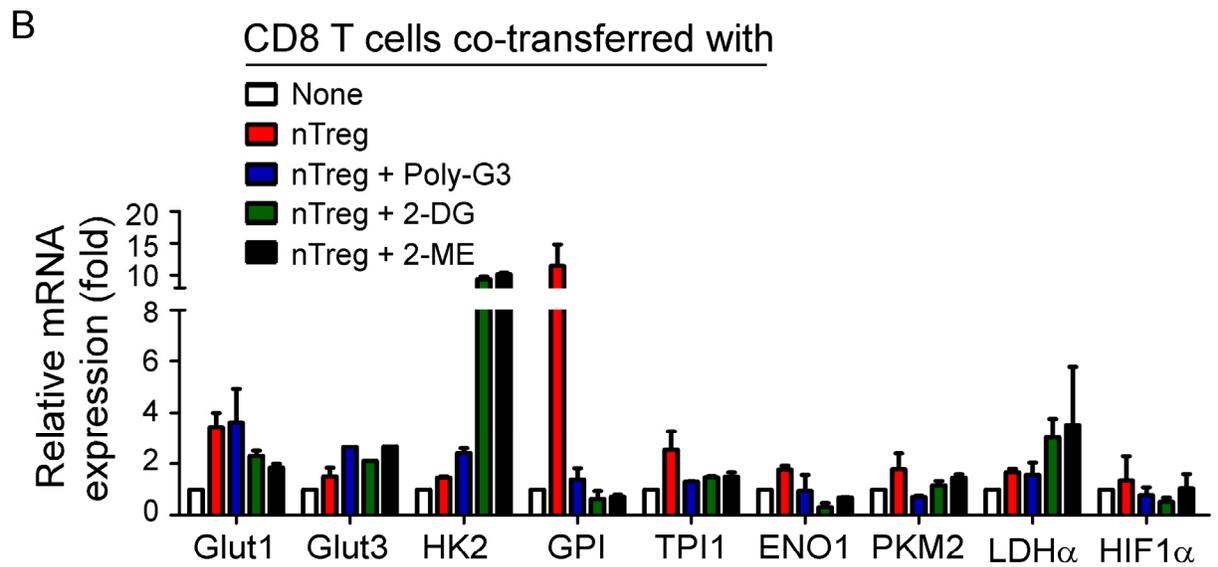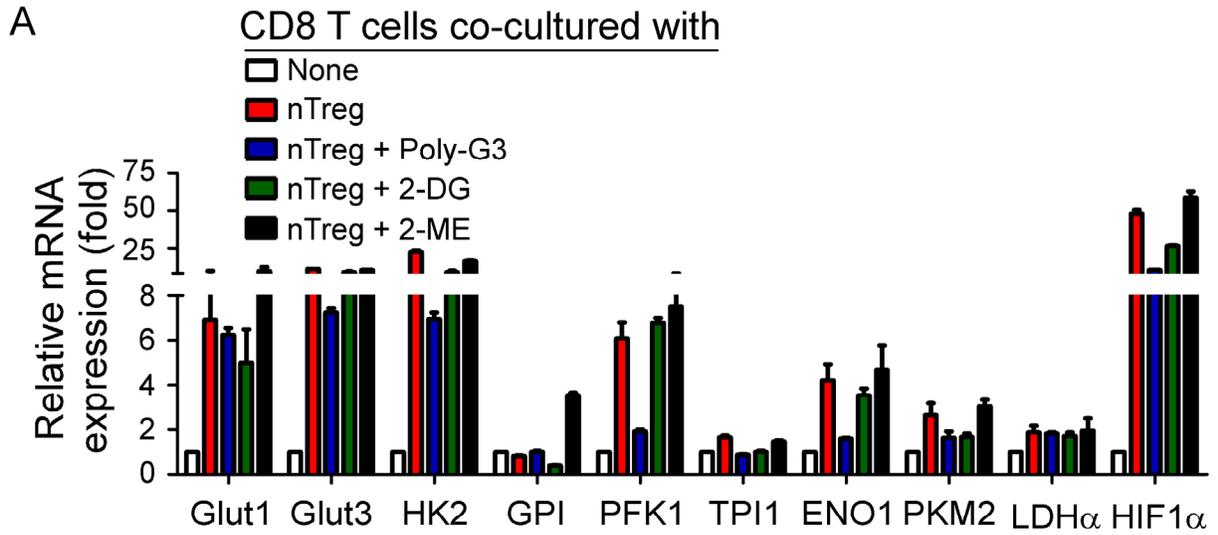
**Supplemental Figure S7, related to Figure 7.**

**Treatments with Poly-G3, 2-DG and 2-ME do not inhibit glucose metabolism in effector CD8$^+$ T cells *in vitro* and *in vivo***

**(A)**The relative gene expression levels of glucose transporters and glycolytic enzymes in CD8$^+$ T cells co-cultured with Treg cells *in vitro*. Naive CD8$^+$ T cells were incubated alone or co-cultured with nTreg cells at a ratio of 4:1 in anti-CD3 bound plates in the presence or absence of Poly-G3, 2-DG and 2-ME for 3 days. The co-cultured CD8$^+$ T cells were isolated by microbeads and analyzed for gene expression by real-time PCR. Total RNA was isolated from CD8$^+$ T cells, and expression levels of each gene were normalized to β-actin expression levels and adjusted to the levels in naïve CD8$^+$ T cells (served as 1). Data shown are mean ± SD from three independent experiments. **(B)** The relative gene expression levels of glucose transporters and glycolytic enzymes in CD8$^+$ T cells co-transferred with nTreg cells *in vivo* in NSG mice. Anti-CD3-preactivated naïve CD8$^+$ T cells (5 × 10$^6$/mouse) were adoptively co-transferred with nTreg cells (3 × 10$^6$/mouse) into NSG mice. The transferred human CD8$^+$ T cells were harvested and purified from spleens at 12 days post-injection. Expression levels of each gene were analyzed by real-time PCR as described in (A). **(C)** and **(D)** Treatments with Poly-G3 and inhibitors reversed the suppressive activities of purified Treg cells in 586mel tumor-bearing NSG mice. The experimental procedures were described in Figure 7E (n=5 mice per group).  Purified nTreg cells from spleens of different treatment groups were co-cultured with naive CD4$^+$ T cells (at the ratios of 1:10 for proliferation assays and 1:4 for SA-β-Gal expression assays) for 3 days. SA-β-Gal expression in treated naïve T cells was determined (in C) and proliferation of co-cultured naïve T cells was determined by [$^3$H]-thymidine incorporation assays (in D).  Data shown are mean ± SD from representative of 5 mice in each group. **p<0.01, compared with responder T cell only group, and $^\#$p<0.01, compared with Treg cells without Poly-G3 and inhibitor treatment groups.

**Supplemental Table S1, related to Figures 1, 2, 4, 5, 6, and 7, and the STAR Methods section.**
**Primers used for real-time quantitative RT-PCR**

| Genes | Primers |
|---|---|
| Glut1 Forward | ATTGGCTCCGGTATCGTCAAC |
| Glut1 Reverse | GCTCAGATAGGACATCCAGGGTA |
| Glut3 Forward | GCTCTCTGGGATCAATGCTGTGT |
| Glut3 Reverse | CTTCCTGCCCTTTCCACCAGA |
| HK2 Forward | AACAGCCTGGACGAGAGCAT |
| HK2 Reverse | GCCAACAATGAGGCCAACTT |
| GPI Forward | GATGGTAGCTCTCTGCAGCC |
| GPI Reverse | GCCATGGCGGGACTCTTG |
| PFK Forward | GGCAGCCATGCATAAAGACG |
| PFK Reverse | AAGCTTCCCCAGCTGTTCTC |
| TPI Forward | AGGCATGTCTTTGGGGAGTC |
| TPI Reverse | AGTCCTTCACGTTATCTGCGA |
| ENO1 Forward | CGCCTTAGCTAGGCAGGAAG |
| ENO1 Reverse | GGTGAACTTCTAGCCACTGGG |
| PKM2 Forward | ACGAGAACATCCTGTGGCTG |
| PKM2 Reverse | AGGAAGTCGGCACCTTTCTG |
| LDHα Forward | AGCTGTTCCACTTAAGGCCC |
| LDHα Reverse | TGGAACCAAAAGGAATCGGGA |
| CPT1 Forward | ATCAATCGGACTCTGGAAACGG |
| CPT1 Reverse | TCAGGGAGTAGCGCATGGT |
| ACC1 Forward | TCACACCTGAAGACCTTAAAGCC |
| ACC1 Reverse | AGCCCACACTGCTTGTACTG |
| FASN Forward | ACAGCGGGGAATGGGTACT |
| FASN Reverse | GACTGGTACAACGAGCGGAT |
| HMGCR Forward | GTGAGATCTGGAGGATCCAAGG |
| HMGCR Reverse | GATGGGAGGCCACAAAGAGG |
| HMGCS1 Forward | GTTGGCGGCTATAAAGCTGGT |
| HMGCS1 Reverse | CCTTCGGGCACAAGCG |
| SQLE Forward | TGACAATTCTCATCTGAGGTCCA |
| SQLE Reverse | TCCCAAAAGAAGAACACCTCGT |
| IDI1 Forward | CGGAGGCTGATCAGTGTTCTA |
| IDI1 Reverse | TGTTGCTTGTCGAGGTGGTT |
| HIF1α Forward | GAACGTCGAAAAGAAAAGTCTCG |
| HIF1α Reverse | CCTTATCAAGATGCGAACTCACA |
| β-actin Forward | TGGCACCCAGCACAATGAA |
| β-actin Reverse | CTAAGTCATAGTCCGCCTAGAAGCA |
| GAPDH Forward | AGCCGCATCTTCTTTTGCGTCG |
| GAPDH Reverse | GACCAGGCGCCCAATACG |

**Supplemental Table S2, related to Figures 3-6.**
**Alternations of genes in nTreg cells are ranked after treatment with Poly-G3 at 24 hour**

| Probe set ID | Gene symbol | Full gene name | Fold change (Poly-G3 *vs* Medium) |
|---|---|---|---|
| **CD and functional markers** | | | |
| 2190019 | CD160 | CD160 molecule | 1.34297 |
| 4830255 | CD26 (DPP4) | Dipeptidyl peptidase 4 | 1.25529 |
| 3170246 | PD273 (PDL2) | Programmed cell death 1 ligand 2 | 1.43555 |
| 4900239 | CD274 (PDL1) | CD274 molecule | 1.29254 |
| 1050482 | CD46 | CD46 molecule | 1.37847 |
| 5900575 | CD276(B7-H3) | CD276 molecule | -1.26798 |
| 2710575 | CD69 | CD69 molecule | -1.20991 |
| 4570368 | CD86 | CD86 molecule | -1.20608 |
| 5550341 | KLRC1 | Killer cell lectin like receptor C1 | -1.25172 |
| 4880193 | KLRG1 | Killer cell lectin like receptor G1 | -1.25257 |
| 20246 | LILRB1 | Leukocyte immunoglobulin like receptor B1 | -1.3391 |
| 1850523 | GZMB | Granzyme B | 1.28895 |
| 2370010 | GZMH | Granzyme H | 1.24362 |
| **Cytokines and their receptors** | | | |
| 2900093 | CSF1 | Colony stimulating factor 1 | 1.38392 |
| 5420477 | CSF3 | Colony stimulating factor 3 | 1.89076 |
| 630725 | IFNG | Interferon gamma | 1.6905 |
| 840685 | IL1B | Interleukin 1 beta | 1.56268 |
| 4830327 | IL5 | Interleukin 5 | 1.51066 |
| 6180093 | IL10 | Interleukin10 | 1.42656 |
| 1470091 | IL15 | Interleukin15 | 1.24714 |
| 4040201 | IL31 | Interleukin 31 | 1.46287 |
| 6330717 | IL33 | Interleukin 33 | 1.23208 |
| 6650722 | IL23R | Interleukin 23 receptor | 1.60484 |
| 150703 | IFNA4 | Interferon alpha 4 | -1.22687 |
| 460255 | IFNA5 | Interferon alpha 5 | -1.35947 |
| 5080615 | IL16 | Interleukin16 | -1.24492 |
| 6330070 | IL19 | Interleukin 19 | -1.32876 |
| 6450577 | IL21 | Interleukin 21 | -1.21126 |
| 730753 | IL22 | Interleukin 22 | -1.27481 |
| 7510753 | IL29 | Interleukin 29 | -1.65626 |
| 5910609 | IL4R | Interleukin 4 receptor | -1.25157 |
| 3830349 | IL7R | Interleukin 7 receptor | -1.3233 |
| 4490053 | IL10RA | Interleukin 10 receptor subunit alpha | -1.26315 |
| 2760148 | IL11RA | Interleukin 11 receptor subunit alpha | -1.3268 |
| 6580356 | IL15RA | Interleukin 15 receptor subunit alpha | -1.31561 |
| **Chemokine and their receptors** | | | |
| 4610364 | CCL7 | C-C motif chemokine ligand 7 | 1.97026 |
| 1230605 | CCL13 | C-C motif chemokine ligand 13 | 1.23628 |
| 780356 | CCL24 | C-C motif chemokine ligand 24 | 1.25165 |
| 7320176 | CCR1 | Chemokine (C-C motif) receptor 1 | 1.22457 |
| 2680753 | CCR10 | Chemokine (C-C motif) receptor 3 | 1.2786 |
| 6100162 | CXCL3 | C-X-C motif chemokine ligand 3 | 1.30332 |
| 6270553 | CXCL10 | C-X-C motif chemokine ligand 10 | 1.43906 |
| 2760240 | CXCL11 | C-X-C motif chemokine ligand 11 | 1.23813 |
| 4390202 | CXCR3 | C-X-C motif chemokine receptor 3 | 1.23285 |
| 460168 | XCL1 | X-C motif chemokine ligand 1 | 1.31592 |
| 1580138 | XCL2 | X-C motif chemokine ligand 2 | 1.27636 |
| 1300707 | XCR1 | X-C motif chemokine receptor 1 | 1.28653 |
| 1300296 | CCR2 | Chemokine (C-C motif) receptor 2 | -1.28425 |
| 4040195 | CCR3 | Chemokine (C-C motif) receptor 3 | -1.2565 |
| 60192 | CXCL6 | C-X-C motif chemokine ligand 6 | -1.56099 |
| 630521 | CX3CL1 | C-X3-C motif chemokine ligand 1 | -1.23595 |

**Supplemental Table S2 continued**

**TGFß pathway**

| | | | |
|---|---|---|---|
| 4290500 | BMPR1A | Bone morphogenetic protein receptor type 1A | 1.22292 |
| 1660296 | ID2 | Inhibitor of DNA binding 2, HLH protein | 1.36765 |
| 7570324 | ID3 | Inhibitor of DNA binding 3, HLH protein | 1.39592 |
| 7510195 | TGFB2 | Transforming growth factor beta 2 | 1.20034 |
| 2340082 | IFRD1 | Interferon related developmental regulator 1 | 1.29887 |
| 6550600 | MYC | MYC proto-oncogene | 1.25973 |
| 4810187 | STAT1 | Signal transducer and activator of transcription 1 | 1.23486 |
| 6130181 | BMP1 | Bone morphogenetic protein 1 | -1.50088 |
| 5490035 | BMP4 | Bone morphogenetic protein 4 | -1.23411 |
| 7570068 | EP300 | E1A binding protein p300 | -1.21791 |
| 4150446 | LTBP1 | Latent transforming growth factor beta binding protein 1 | -1.31258 |
| 580692 | ID1 | Lnhibitor of DNA binding 1, HLH protein | -1.23287 |
| 4060332 | IGF1 | Insulin like growth factor 1 | -1.23371 |
| 6840328 | SMAD3 | SMAD family member 3 | -1.24959 |
| 4220767 | SMAD7 | SMAD family member 7 | -1.492 |
| 840598 | SMURF1 | SMAD specific E3 ubiquitin protein ligase 1 | -1.26152 |
| 7330142 | TGFB1I1 | Transforming growth factor beta 1 induced transcript 1 | -1.25396 |
| 4210196 | TGIF1 | TGFB induced factor homeobox 1 | -1.41518 |
| 60131 | RBL1 | RB transcriptional corepressor like 1 | -1.41815 |

**TNF receptor superfamily**

| | | | |
|---|---|---|---|
| 2190255 | TNFRSF6B | TNF receptor superfamily member 6b | -1.33376 |
| 2120035 | TNFRSF8 | TNF receptor superfamily member 8 | -1.27397 |
| 1050762 | TNFRSF10A | NF receptor superfamily member 10a | -1.20746 |
| 830113 | TNFRSF10D | TNF receptor superfamily member 10d | -1.57843 |
| 1510240 | TNFRSF11A | TNF receptor superfamily member 11a | -1.29907 |
| 620484 | TNFRSF13B | TNF receptor superfamily member 13B | -1.24669 |

**Transcriptional Regulators**

| | | | |
|---|---|---|---|
| 7320372 | EOMES | Eomesodermin | 1.33112 |
| 20162 | FOXP1 | Forkhead box P1 | 1.21874 |
| 6760711 | MEF2A | Myocyte enhancer factor 2A | 1.20684 |
| 3140386 | NFATC3 | Nuclear factor of activated T-cells 3 | 1.22536 |
| 5260204 | NR4A1 | Nuclear receptor subfamily 4 group A member 1 | 1.30919 |
| 6020255 | EGR2 | Early growth response 2 | -1.20844 |
| 2630546 | FOXO3 | Forkhead box O3 | -1.31041 |
| 50053 | FOXP4 | Forkhead box P4 | -1.25736 |
| 6980370 | IRF4 | Interferon regulatory factor 4 | -1.34518 |
| 2760368 | IRF6 | Interferon regulatory factor 6 | -1.2138 |
| 6380164 | IRF7 | Interferon regulatory factor 7 | -1.28077 |
| 2100484 | STAT3 | Signal transducer and activator of transcription 4 | -1.34364 |
| 1850543 | TBX21 (T-bet) | T-box 21 | -1.3009 |
| 3120521 | NFATC4 | Nuclear factor of activated T-cells 4 | -1.4939 |
| 840348 | NR4A3 | Nuclear receptor subfamily 4 group A member 3 | -1.24167 |