**Supplementary Table 1. A list of names and targeting sequences of crRNAs used in screening for Mm apoE knock out.**

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| --- | --- |
| **crRNA name** | **Sequence** |
| Mm.Cas9.APOE.1-A | GAGGATCTACGCAACCGACT |
| Mm.Cas9.APOE.1-B | CAACGAGGTGCACACCATGC |
| Mm.Cas9.APOE.1-C | GAGGTGACAGATCAGCTCGA |
| Mm.Cas9.APOE.1-D | GACGCTGTCTGACCAGGTCC |
| Mm.Cas9.APOE.1-E | GGACACTATGACGGAAGTAA |
| Mm.Cas9.APOE.1-F | CTGGTGGAGCAAGGTCGCCA |
| Mm.Cas9.APOE.1-F | CTGGTGGAGCAAGGTCGCCA |

**Supplementary Table 2. A list of primers used for NGS of target regions in Mm ApoE to evaluate total editing and INDEL profile. Uppercase letters indicate target-specific annealing sequence in PCR1, and lowercase letters indicate sequence for incorporating P5 and P7 Illumina adapters to amplicon ends in PCR2.**

|  |  |
| --- | --- |
| **Primer name** | **Sequence** |
| NGS For 1 | acactctttccctacacgacgctcttccgatctAGACCCAAAAAGACTGTAGG |
| NGS Rev 1 | gtgactggagttcagacgtgtgctcttccgatctTGCCGAGGGTGAAAGAGCTG |
| NGS For 2 | acactctttccctacacgacgctcttccgatctGCCTTCATCTCCTTCCTGTG |
| NGS Rev 2 | gtgactggagttcagacgtgtgctcttccgatctCCTCTGTGCTCTGGCCCAGC |
| NGS For 3 | acactctttccctacacgacgctcttccgatctAGGCTGGGCAAAGAGGTGCA |
| NGS Rev 3 | gtgactggagttcagacgtgtgctcttccgatctCGCTTCTGCAGATCCTCGGC |
| NGS For 4 | acactctttccctacacgacgctcttccgatctTGCCGAGGATCTGCAGAAGC |
| NGS Rev 4 | gtgactggagttcagacgtgtgctcttccgatctGCCGCCCTCGGATGCGGTCA |

**Supplemental Figure legends:**

**Supplement Figure 1. ApoE has a repressive effect on T cell function and viability.** **(A)** T cells isolated from naïve mouse spleens were cultured in RPMI media, WT B16 conditioned media and apoE-/- B16 conditioned media for 48hr and the media was analyzed with ProcartaPlex multiplex immunoassay. Results show the production of pro-inflammatory cytokines and chemokines such as LIF, MIP-1α, TNFα, IL18, GM-CSF and IL-13 were suppressed while production of IL-6, RANTES and Gro-α KC were enhanced when T cells were cultured in WT B16 conditioned media. Remarkably, these effects were reversed by incubating T-cells with conditioned media from apoE-/- cells, similar to T-cells activated in control RPMI media alone. Results are expressed as mean score ±SD. \*p<0.05; \*\*p<0.005; \*\*\*p<0.001, determined by unpaired two-tailed Student’s t-test. **(B)** The effect of apoE agonist peptide COG133 on the viability of activated mouse T cells was tested by culturing the cells in the presence of the indicated concentrations of peptide for 48hr and cell death was quantified with flow cytometry using the APC-conjugated Sytox Red dead cell stain. T-cell viability decreases in a dose dependent fashion in the presence of COG133 ApoE agoist. The number in Quadrant 2 is the percentage of dead cells.

**Supplement Figure 2. Role of apoE on effector function of dendritic cells.** Mouse primary bone-marrow derived dendritic cells (DC) were cultured in the presence of conditioned medium (CM) from WT B16 and apoE-/- cells for 48hr with or without toll like receptor (TLR7/8) stimulation. Multiplex ELISA assay was used to detect cytokines and chemokines and results showed that WT B16 CM enhances the production of anti-inflammatory cytokine IL-10 while downregulating the production of proinflammatory cytokines IL1α, IL1β, MIP-1α and MIP-1β, IL28 and RANTES. This effect was reversed when DCs were cultured in apoE-/- cell CM.

**Supplement Figure 3.** **Dendritic cell function is modulated by apoE agonist COG133.**

Mouse bone-marrow derived dendritic cells (DC) were cultured in the presence of the indicated concentrations of apoE agonist COG133 for 48hr. COG133 increased the production of anti-inflammatory IL-10, GM-CSF, and chemokines MCP-1 and MCP-3 by TLR7/8 activated DC while decreasing the levels of proinflammatory cytokines IL-1α, IL-1β and IL-23 in a dose-dependent manner as determined by multiplex ELISA.

**Supplement Figure 4.** **Vaccination with immunogenic WT B16 tumor cells enhances splenocyte response which is dampened by the presence of apoE agonist COG 133.** Splenocytes from naïve mice (NS) as well as mice vaccinated with 104 WT B16 and 100µg/ml anti-CTLA4 antibody (VS) were co-cultured for 48 hr with either WT B16 cells or Myc-inhibited immunogenic B16 tumor cells in the presence of the indicated concentrations of apoE agonist COG133. Multiplex ELISA shows the suppressive effect of the apoE agonist in production of IFN, IL-6 and IL-18 in the cocultures with naïve splenocytes and this suppressive effect although diminished in vaccinated splenocytes is still observed.

**Supplement Figure 5.** **ApoE affects T cell function at least partially through lrp8 receptor pathway.** Splenocytes were isolated from vaccinated WT mice as well as lrp8-/- mice and cocultured for 48 hr with Myc-inhibited immunogenic B16 cells, in the presence of the indicated concentrations of apoE agonist COG133. Multiplex immunoassay shows a suppression of proinflammatory cytokines and chemokines IL-13, IL-4, IL22, IL18, MCP-1, RANTES and Gro-α in the cocultures with WT vaccinated splenocytes. However, this suppressive effect is diminished in lrp8-/- vaccinated splenocytes.