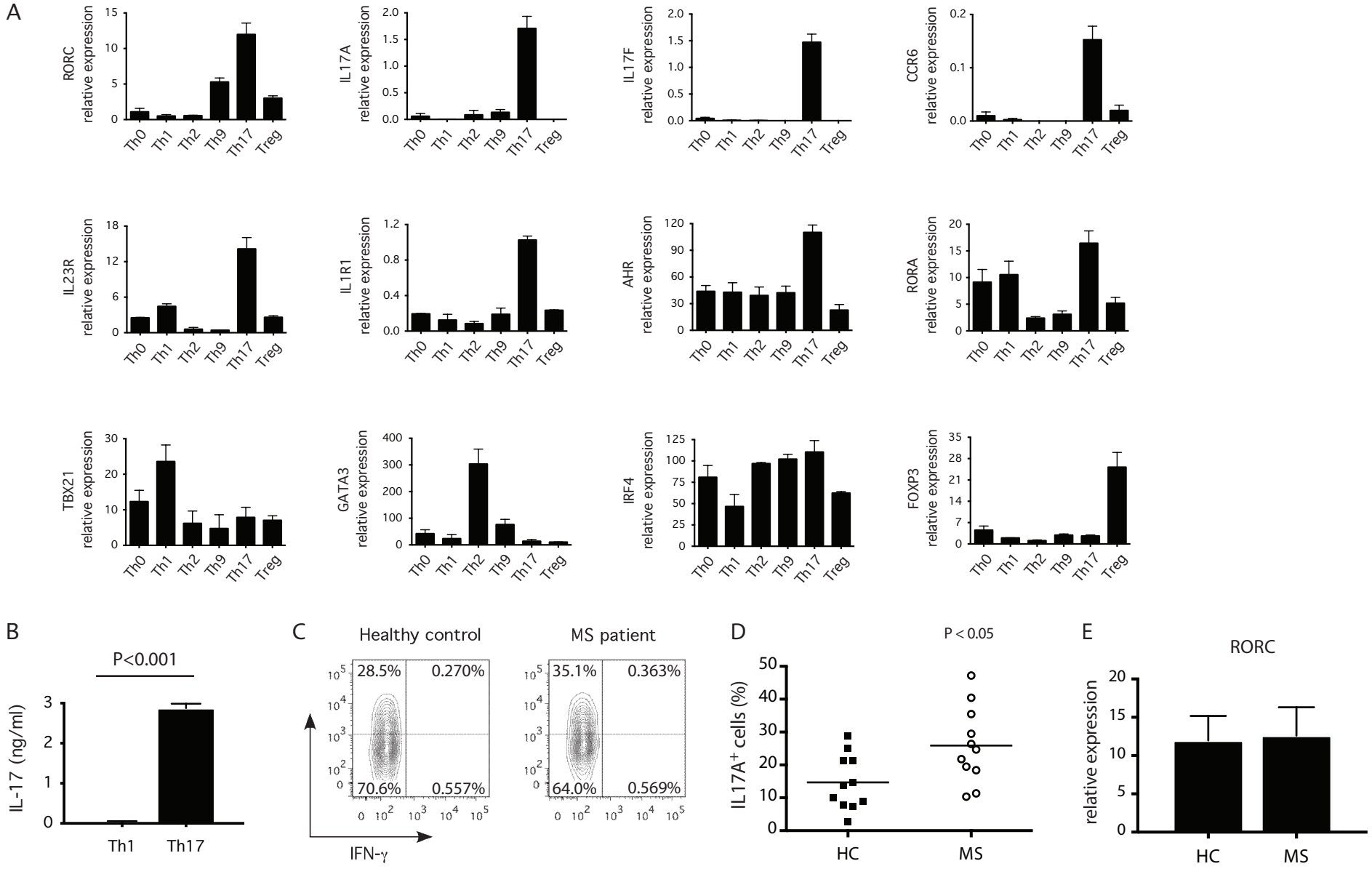
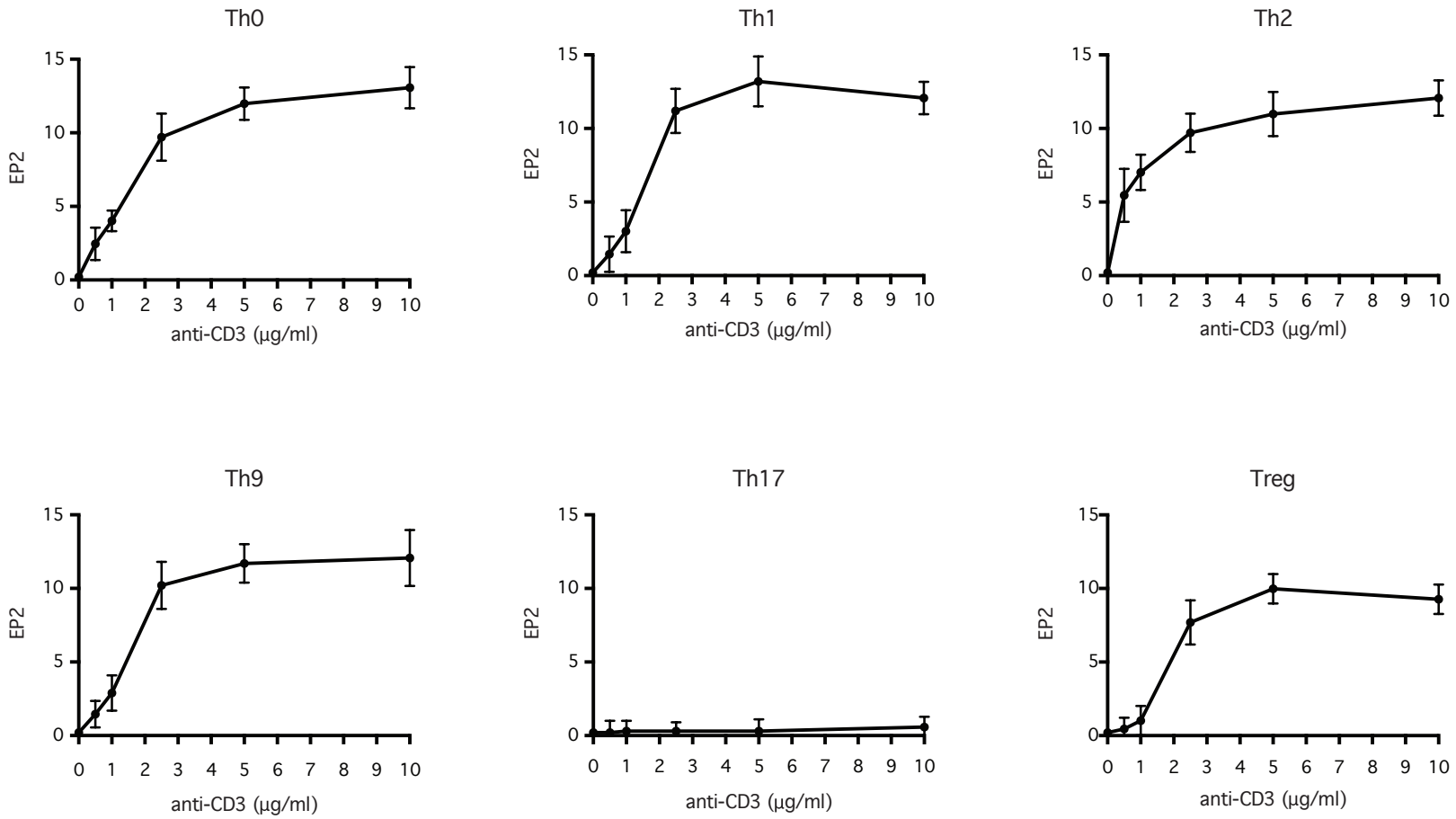


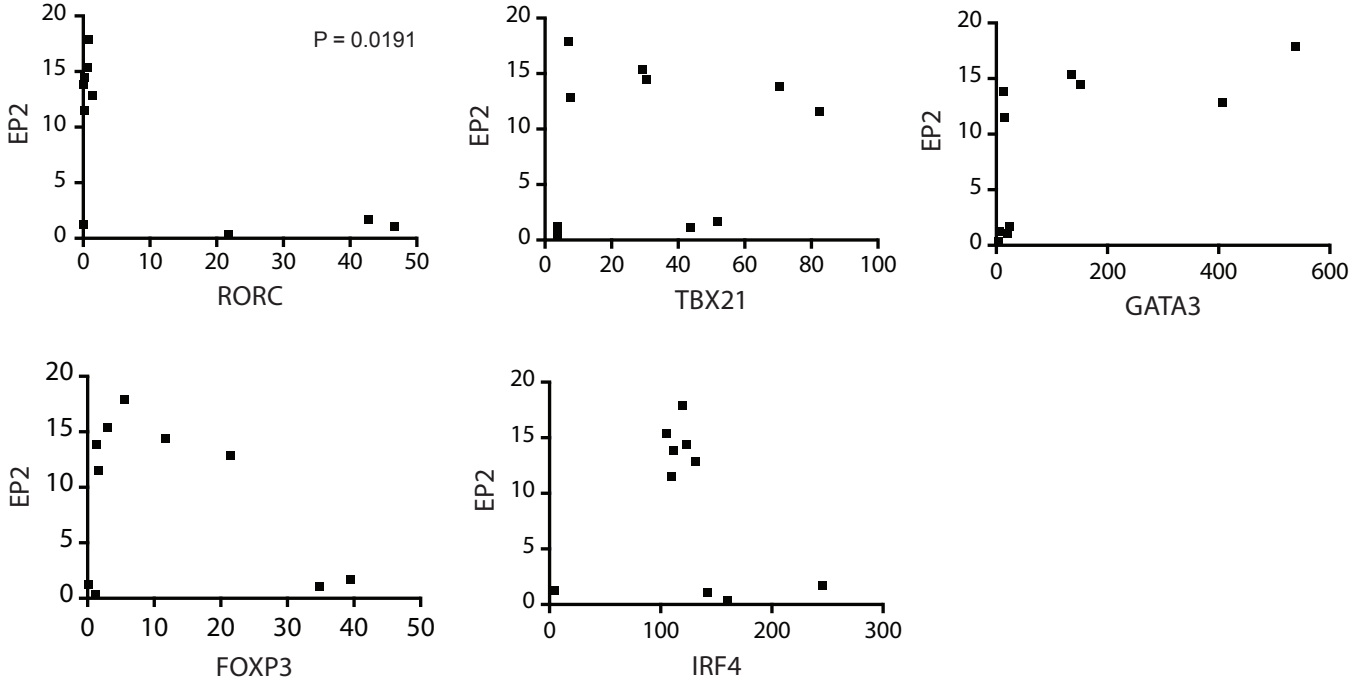
Supplemental Figure S1. Characterization of polarized CD4+ T cell subsets. (**A**) Expression of transcription factors, cytokines, and receptors was analyzed by RT-PCR in polarized CD4+ T cell subsets (mean±s.e.m. are shown; n=5). (**B**) IL-17 secretion by polarized Th17 cells and Th1 cells. (P was calculated by unpaired Student's t test; mean±s.e.m. are shown; n=5). (**C**) Representative experiment and cummulative results (**D**) of Th17 cell induction. Naïve CD4+ T cells were cultured for 7 days under Th17 skewing conditions and subsequently expanded for additional 4-5 days in the presence of anti-CD3, anti-CD28, and IL-23. IL-17 secretion was analyzed by flow cytometry after re-stimulation with PMA and ionomycin (n= 11). (**E**) RORC expression in Th17 cells from MS patients healthy controls (HC) (n=4). All P values in Fig. S1 were calculated by unpaired Student's t test.

Supplemental Figure S1



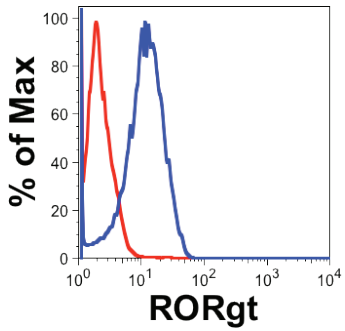
Supplemental Figure S2. Induction of EP2 in CD4+ cells. Naïve CD4+ T cells were differentiated into distinct CD4+ subsets in the presence of various concentrations of anti-CD3 antibodies, 1 μg/ml anti-CD28 antibodies, and the respective cytokines required for the induction of specific CD4+ subsets. EP2 expression was assessed by quantitative RT-PCR ((mean±s.e.m.: n=3).

Supplemental Figure S2



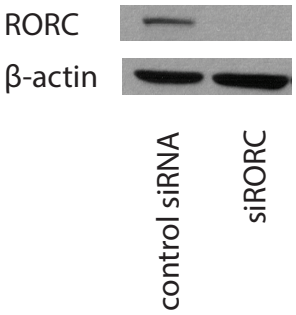
Supplemental Figure S3. Correlation between EP2 expression and transcription factors. Naïve CD4+ T cells from 2 healthy donors were differentiated into Th1, Th2, Th9, Th17, and Treg cells and analyzed for expression of EP2 and the transcription factors T-bet, GATA3, IRF4, RORC, and FOXP3. While expression of RORC and EP2 correlated negatively, no correlation between EP2 and other transcription factors was found. P values were calculated using unpaired student's t-test.

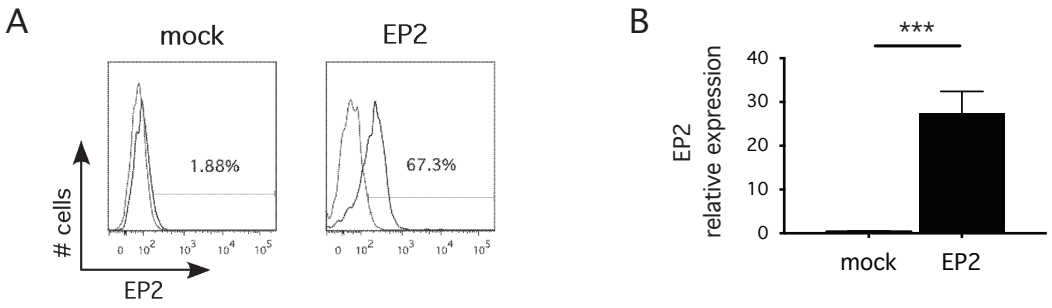
A



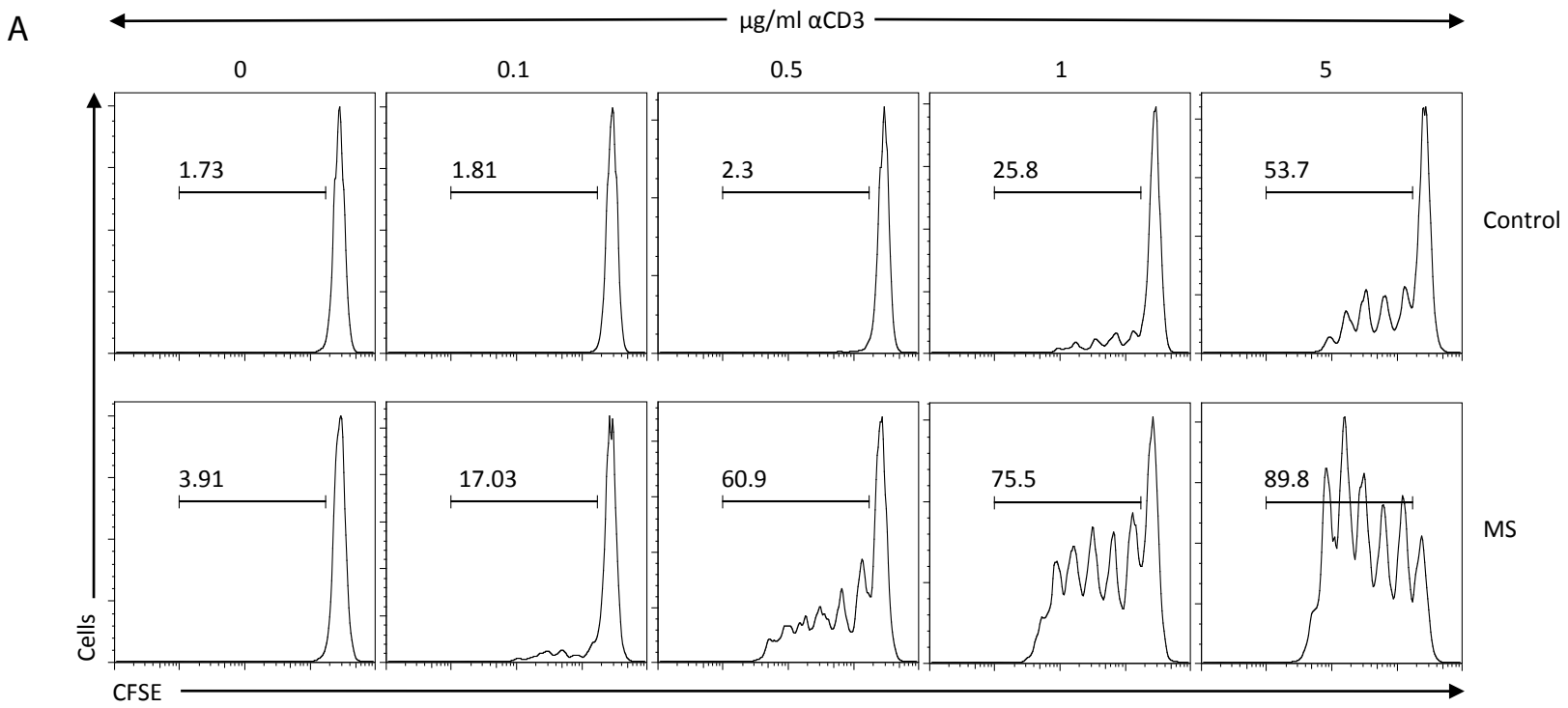
Supplemental Figure S4. RORγt expression in Rorc-/- knockout mice and RORC knockdown in human Th17 cells. (A) Flow cytometry analysis of RORγt in wildtype Th17 cells (blue line) and Rorc-/- Th17 cells (red line) from C57/BL6 mice. **(B)** siRNA knockdown of RORC in human Th17 cells.

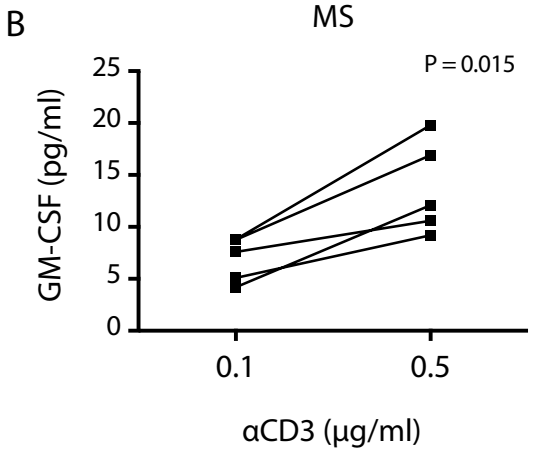
B





Supplemental Figure S5. EP2 over-expression induces a pathogenic genotype in Th17 cells. (**A**) EP2 was over-expressed in Th17 cells by gene transfer. Th17 cells were transfected with an EP2 expression plasmid or with a control plasmid. One representative example of flow cytometry analysis of EP2 expression is shown (dark grey line = EP2 specific antibodies; light grey line = isotype control). (**B**) RNA expression in Th17 cells after transduction.





Supplemental Figure S6. TCR signaling threshold in MS patients. (**A**) Representative example of CFSE-labeled CD4+ T cells from a healthy individual (upper row) and an untreated MS patient (lower row) stimulated with plate bound aCD3 at different doses. Proliferation of viable cells was measured at day 3 by CFSE dilution. (**B**) Correlation between TCR signaling strength and EP2 driven GM-CSF production by Th17 cells from MS patients. Cells were activated through EP2 in the Presence of different concentrations of αCD3. P value was calculated by unpaired student's t-test.

Supplemental Figure S6