

treatment in PPs and MLNs. Quantitative RT-PCR verifying upregulation of miRNA-217 in MLNs and downregulation of mir-217 in PPs, and upregulation of miRNA-141-3p expression in both MLNs and PPs in DSS-induced mice treated with FAAH-II. Data are expressed as mean  $\pm$  S.E.M. Statistical significance was calculated using the Student's t test. \*P< 0.05 in DSS+Vehicle vs. DSS+FAAH-II treated group.

**Supplementary Figure 1.** FAAH-II treatment reduces systemic pro-inflammatory cytokines and increases anti-inflammatory cytokines. After mice were sacrificed, serum levels of IL-6, IL-1 $\beta$ , MCP-1, RANTES, KC, G-CSF, IL-2, IL-3 and IL-10 were determined by a Bio-Rad ELISA multiplex kit capable of detecting >10 pg/ml of these analytes. The data presented are the mean concentrations of these cytokines  $\pm$  in three separate experiments. Asterisks (\*) indicate statistically significant differences (p< 0.01) between DSS+ vehicle and FAAH-II-treated groups.

**Supplementary Figure 2.** FAAH-II treatment alters the expression of miRNAs from both MLNs and PPs. FAAH-II induced miRNAs alterations in absolute fold-change in expression of 403 miRNAs tested by Affymetrix microarray analysis of DSS+ FAAH-II compared with DSS+vehicle. A few miRNAs that were > 1.5 fold up- or downregulated are highlighted and were chosen for verification by further RT-PCR analysis. A principal component analysis plot was constructed with a fold-change of 1.5 defined as upregulated and a fold-change of less than 1.5 defined as downregulated.

**Supplementary Figure 3.** Pathway analysis using Ingenuity software after FAAH-II treatment of colitis in PPs. Relationships of miRNAs with ~1.5-fold-increased or -decreased expression with FAAH-II treatment, for which mapping information was available on Ingenuity, were plotted. The known immunomodulatory miRNAs interacting with known targets of interest are

shown. miRNAs in dark red are upregulated > 1.5 folds, pink < 1.5 fold, and green downregulated.

**Supplementary Figure 4.** Pathway analysis in the MLNs miRNAs using Ingenuity software after FAAH-II treatment after DSS induced colitis. We plotted miRNAs with ~1.5-fold-increased or -decreased expression after FAHH-II treatment, for which mapping information was available on Ingenuity. Relationships between the miRNAs expression and their potential targets with known immune functions are shown. miRs in red are upregulated; those in green are downregulated.