

Figure S1

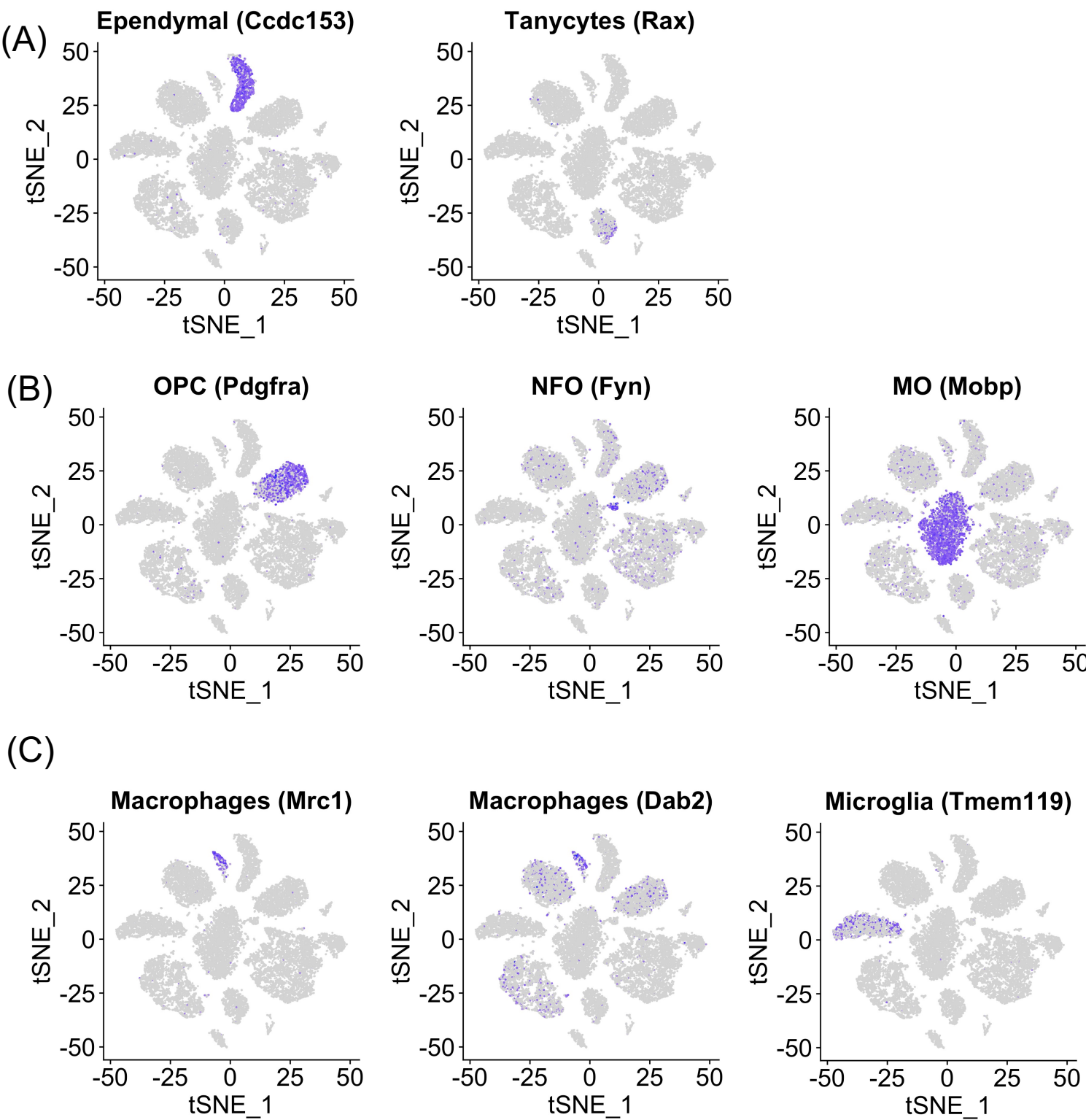


Figure S2

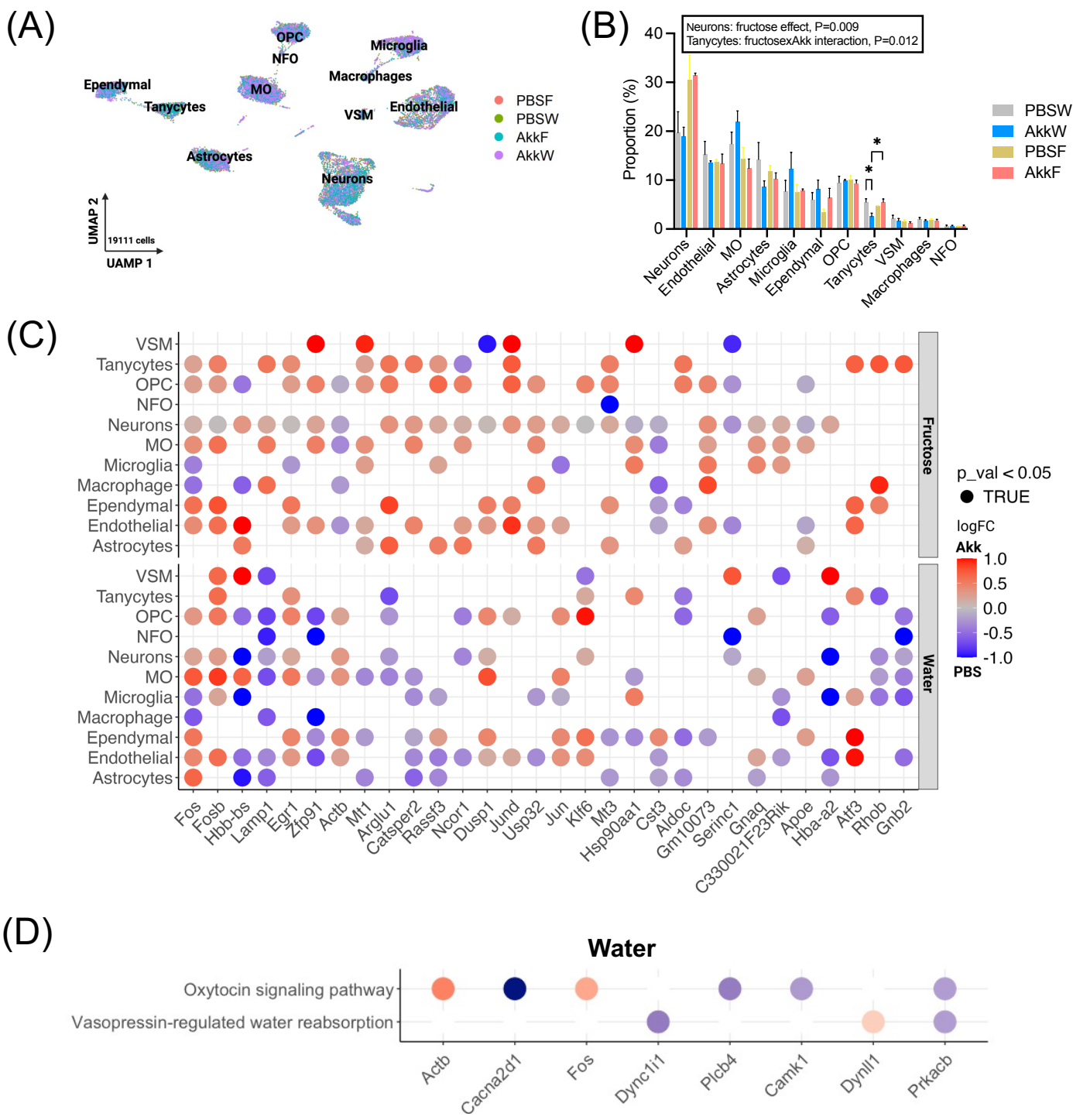
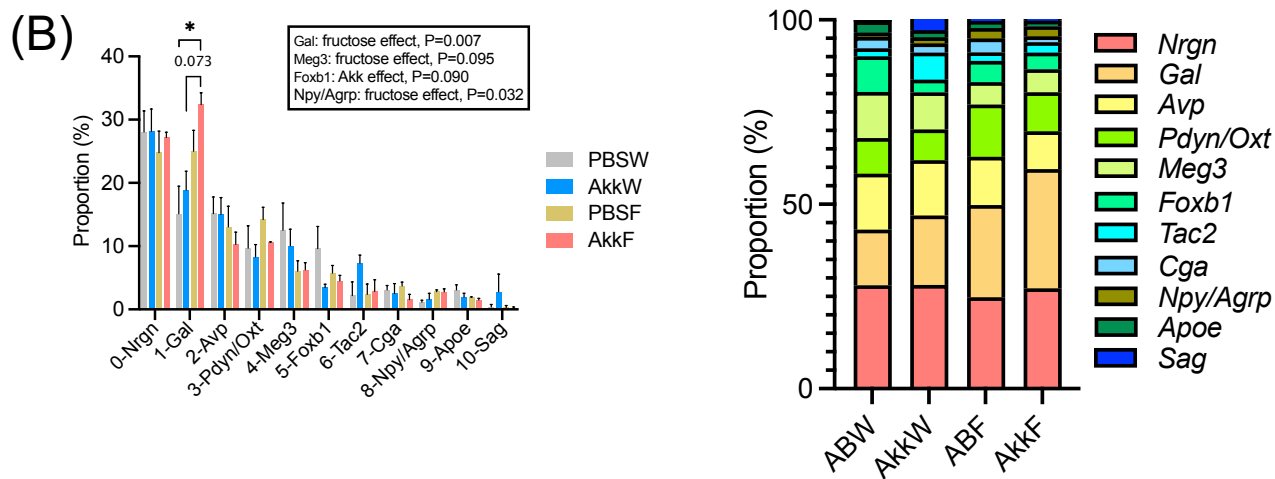
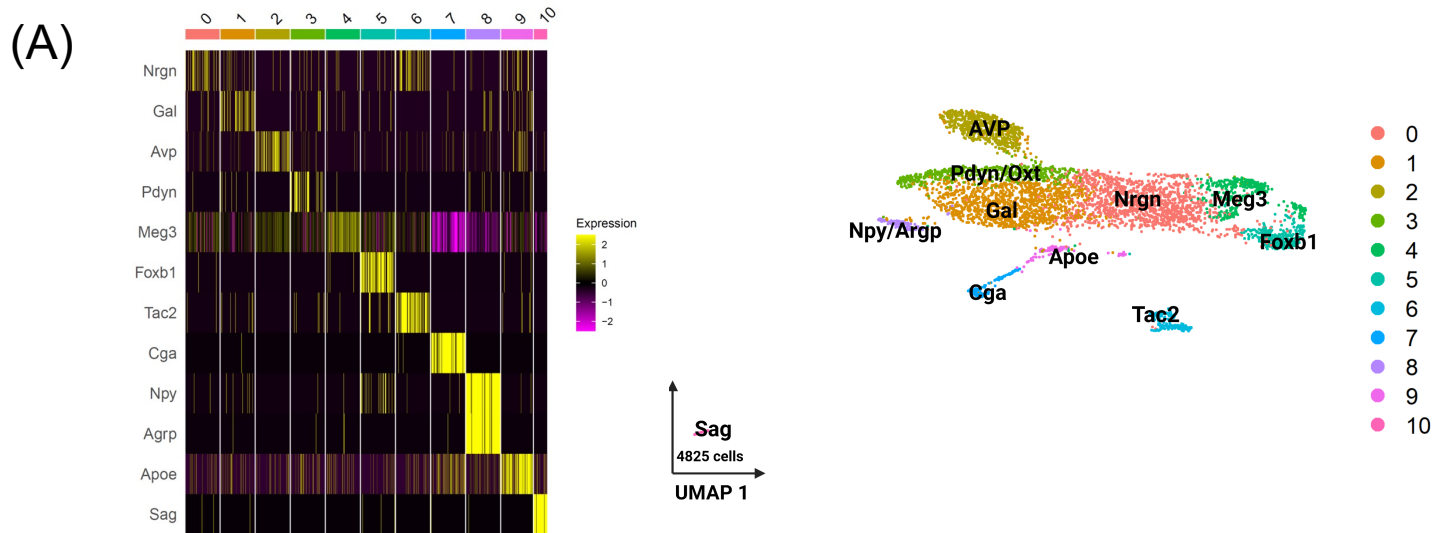


Figure S3



(A)

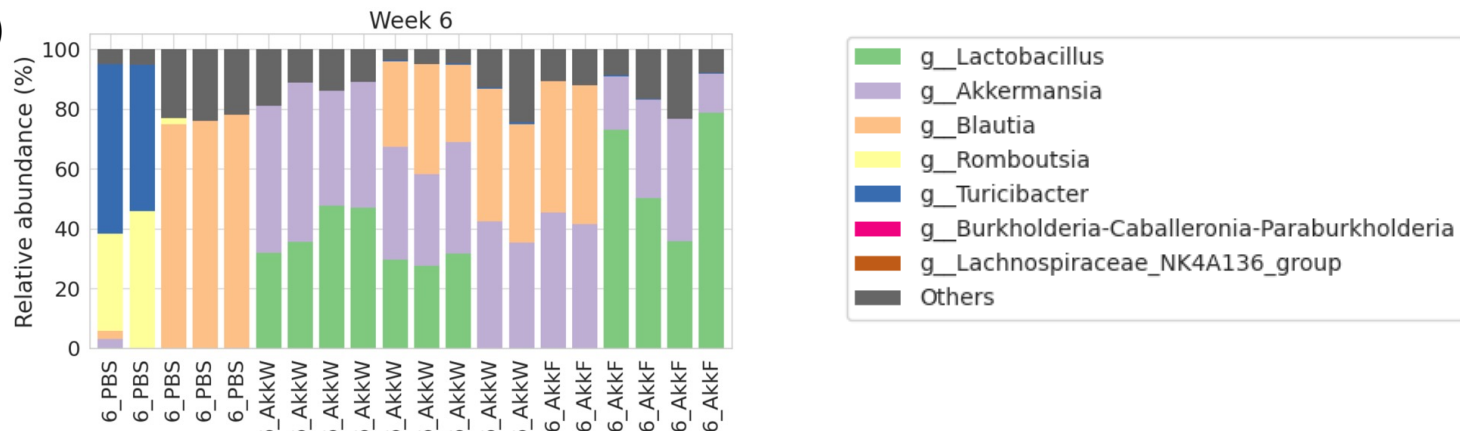


Figure S5

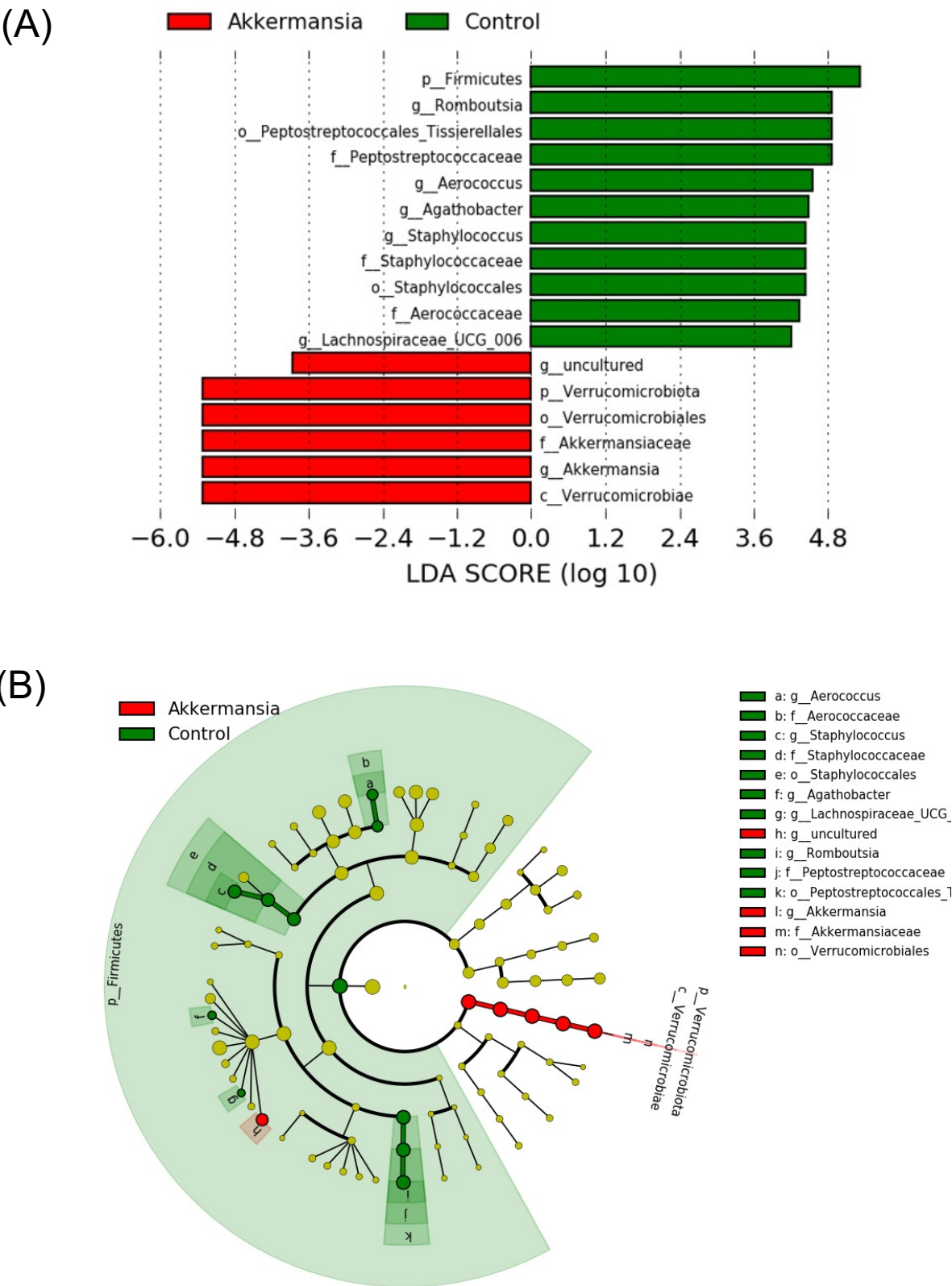


Figure S6

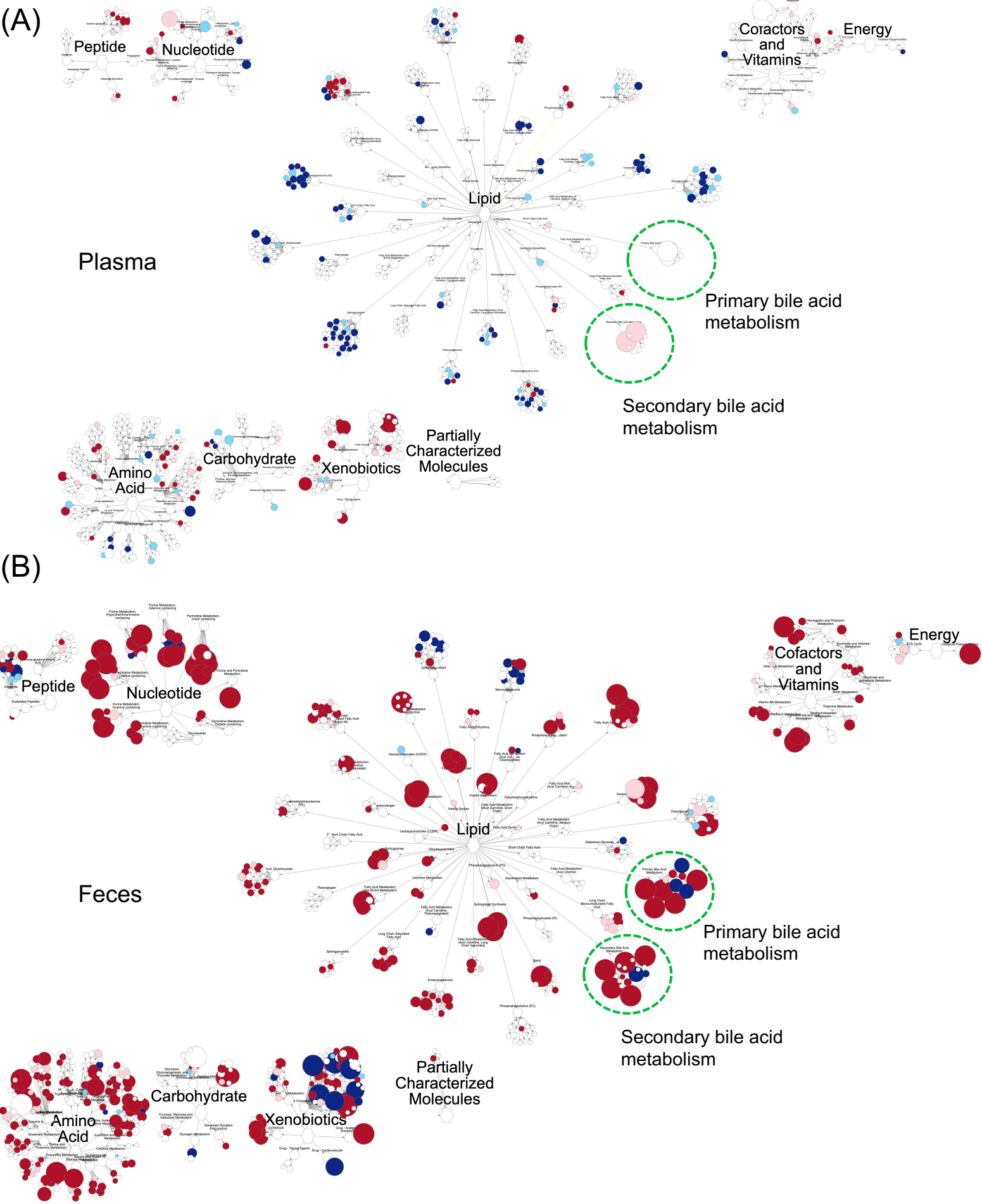


Figure S7

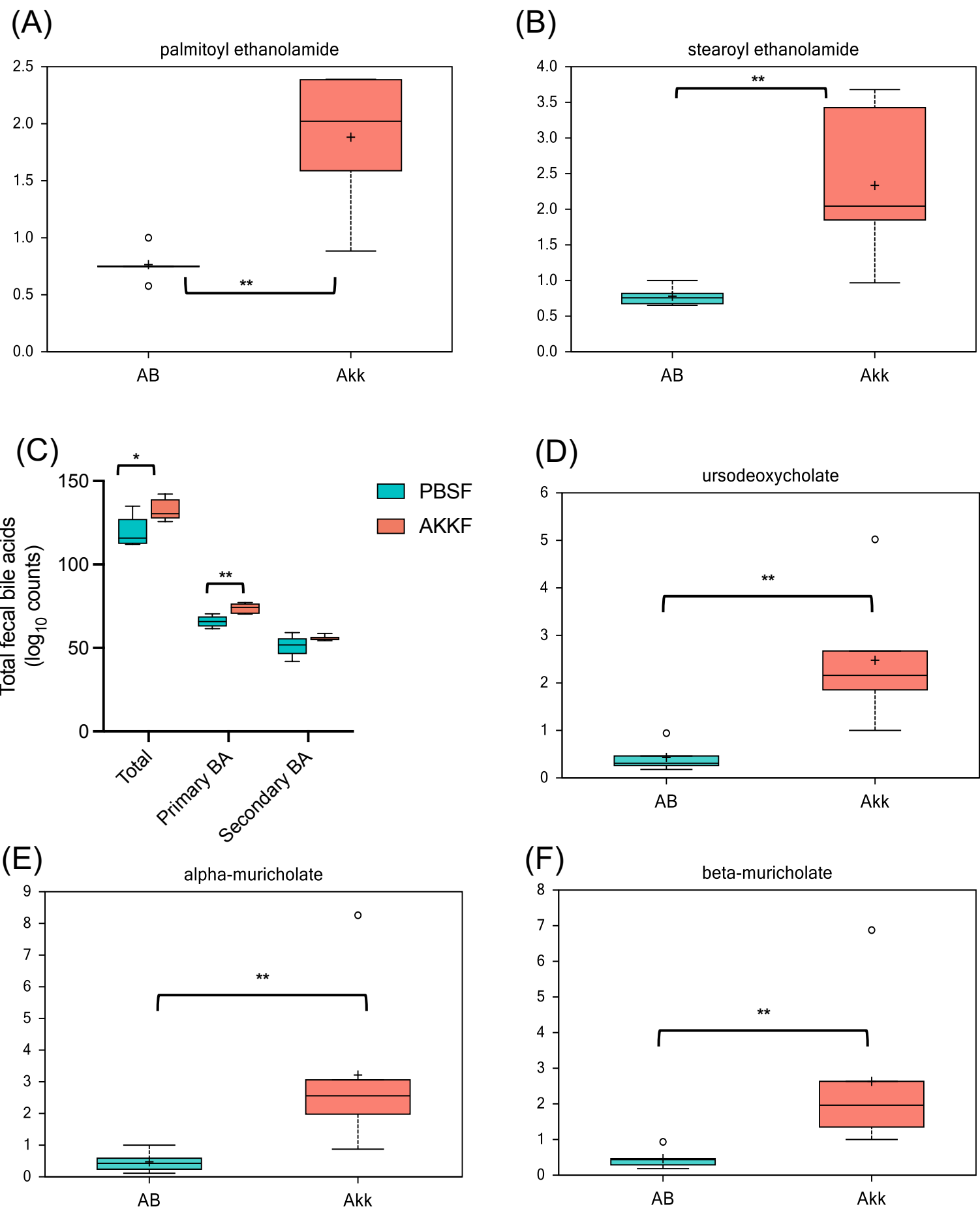
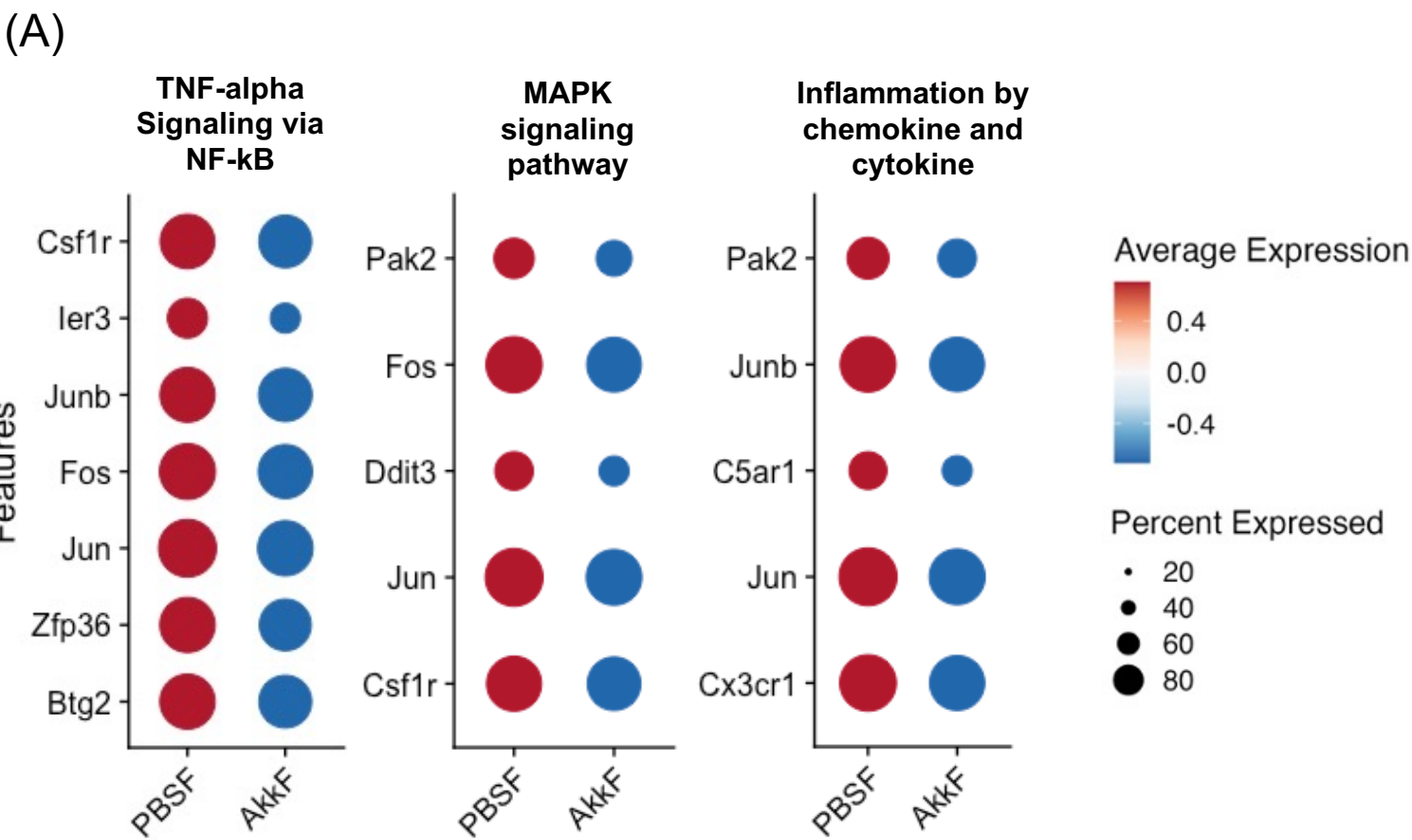


Figure S8



Supplemental Figure legends

Figure S1. Ependymal, oligodendrocyte and microglia were further differentiated into subtypes based on the marker gene expression. (A) Ependymal cells were divided into ependymal (*Ccdc153*) and tanycytes based on the expression of tanycyte specific genes (*Rax*). (B) Oligodendrocytes were separated into oligodendrocytes precursor cells (OPC; top marker *Pdgfra*), newly formed oligodendrocytes (NFO; top marker *Fyn*), and myelinating oligodendrocyte (MO; top marker *Mobp*). (C) Macrophages were determined based on the expression of *Mrc1* and *Dab2* gene. A microglia-specific marker gene (*Tmem119*) was used to identify microglia cells. All markers were obtained from Chen et al ³⁵, Romanov et al ³⁴, Hammond et al ³⁶, and Bennett et al ⁵⁰.

Figure S2. The effect of *A. muciniphila* on hypothalamus in scRNA-seq. (A) UMAP plot showing 11 cell types. (B) Cell type proportion. The P values of main factors (fructose, Akk) and interaction were determined by Two-way ANOVA with Tukey's post hoc test in each cell type. Sample size n = 3 per group. * p-val < 0.05. (C) The top 30 most altered DEGs by *A. muciniphila* across 11 cell types under fructose or water diet, that are ranked by logFC (fold change). (D) Dot plots depicting differentially regulated genes in oxytocin signaling pathway and vasopressin-regulated water reabsorption enriched in neuronal cell type under water condition.

Figure S3. The effect of *A. muciniphila* on neuronal subtypes in scRNA-seq. (A) Heatmap showing expression of marker gene that are uniquely expressed in neuronal subclusters and tSNE plot showing a total of 11 subtypes of neurons. (B) Neuronal subtype proportion. Proportions were analyzed using Two-way ANOVA to access the main effects of fructose and Akk and their interaction, followed by Tukey's post hoc test within each cell type. Sample size n = 3 per group. * p-val < 0.05.

Figure S4. Overall microbiome taxonomic profiles depicting changes in microbiome community structure. Taxa bar plots of fecal microbiota at (A) Week 0 (baseline). (B) Week 1 (after 1 week of antibiotic treatment). (C) Week 2 (after 1 week of *A. muciniphila* treatment). (D) Week 6 (after 5 weeks of *A. muciniphila* treatment and 4 weeks of fructose treatment).

Figure S5. LefSe results in a bar plot and a cladogram format. (A) Linear discriminant analysis (LDA) effect size (LEfSe) was used to identify taxa that discriminated between Akk and control (PBS) group at week 6 using standard parameters (p < 0.05, LDA score > 2.0). (B) Cladogram shows the significant taxa at all taxa levels (colored circles). Colors indicate the mouse group (red, green for Akkermansia, Control, respectively) with the highest mean of differential features for which significant differences between groups were found. Taxa (yellow) that do not show significant difference in abundance between groups are unlabeled. n = 5-9/group.

Supplemental Figure legends

Figure S6. Network representation of metabolites by known pathways. OEA is consistently upregulated (red) in both plasma (top) and fecal (bottom) samples. Overall bile acid pool sizes were increased in fecal samples but not in plasma samples. Metabolites of all 9 pathways altered by *A. muciniphila* under fructose in (A) plasma and (B) feces. Red and blue dots indicate metabolites increased and decreased at $p\text{-val} < 0.05$, respectively, in *A. muciniphila*-treated mice compared with controls under fructose. $n = 5\text{-}6/\text{group}$.

Figure S7. Box plot showing significantly increased fecal metabolites in the N-acylethanolamine (NAE) family and bile acids upon *A. muciniphila* treatment. Box plot showing the levels of fecal (A) Palmitoyl ethanolamide (B) stearoyl ethanolamide, (C) total bile acid pool size (D) ursodeoxycholate (E) alpha-muricholate and (F) beta-muricholate in the PBSF and AkkF groups. Levels are significantly higher in the Akk group. All these metabolites are directly or indirectly related to oleoylethanolamide (OEA) synthesis, suggesting a potential mechanism by which *A. muciniphila* modulates metabolic processes through NAE family and bile acid pathways. Statistical significance was determined by Welch's t-Test (* $q\text{-val} < 0.05$, ** $q\text{-val} < 0.01$)

Figure S8. *A. muciniphila* is associated with downregulation of genes involved in inflammatory signaling pathways. (A) Dot plots showing the expression of genes associated with inflammatory pathways in microglia cells. Under fructose (PBSF) conditions, we observed relatively strong inflammatory signals, including genes in TNF- α signaling via NF- κ B, MAPK signaling, and chemokine/cytokine pathways. In contrast, these signals were markedly reduced in the AkkF group, indicating that *A. muciniphila* supplementation alleviates fructose-induced inflammation.