Supplementary material

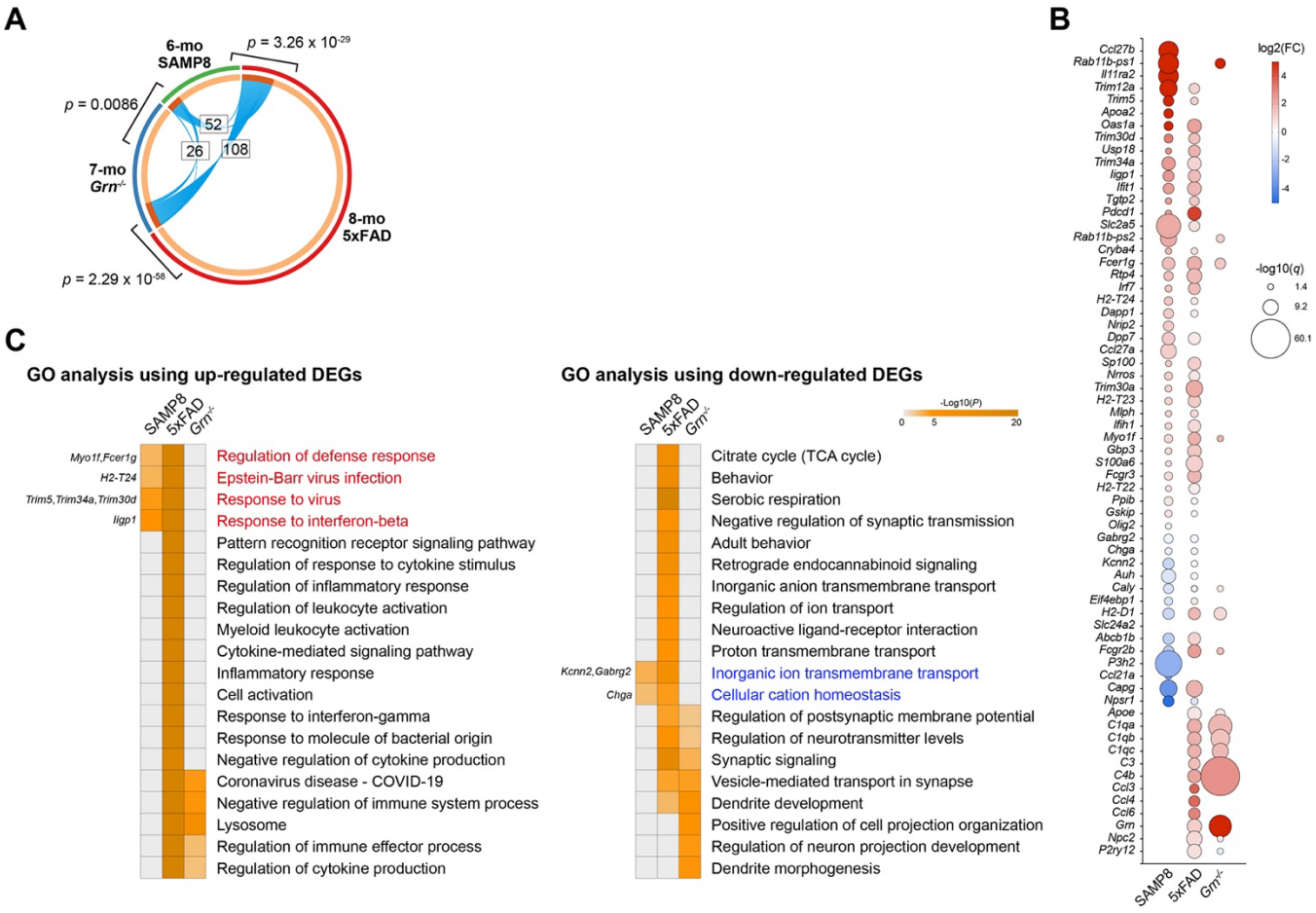

Fig. S1 Comparison of bulk RNA-seq analyses of various neurodegenerative disease model mice reveals specific aging process in SAMP8 mice. (**A**) Circle plot highlighting the shared DEGs among 6-month-old SAMP8 mice, 8-month-old 5×FAD mice, and 7-month-old *Grn*$^{-/-}$ mice. The numbers in boxes indicate the numbers of shared DEGs. Statistics uses hypergeometric tests. Transcriptome data were obtained from NCBI, NIH data sets of SRR13842813-SRR13842817 for 8-month-old 5×FAD mice, SRR13842823-SRR13842827 for 8-month-old wild-type mice in PRJNA706199, SRR5905580-SRR5905581 for 7-month-old *Grn*$^{-/-}$ mice, and SRR5905576-SRR5905577 for 7-month-old wild-type mice in PRJNA397327. Transcriptome analyses for SAMP8, 5×FAD, and *Grn*$^{-/-}$ mice included 383, 602, and 1954 DEGs, respectively. (**B**) Dot plot of characteristic shared DEGs by the hippocampi of SAMP8, 5×FAD, and *Grn*$^{-/-}$ mice with fold change and q-value. (**C**) Heatmap for multiple GO enrichment analysis using upregulated (left) and downregulated (right) DEGs in the hippocampi of SAMP8, 5×FAD, and *Grn*$^{-/-}$ mice.

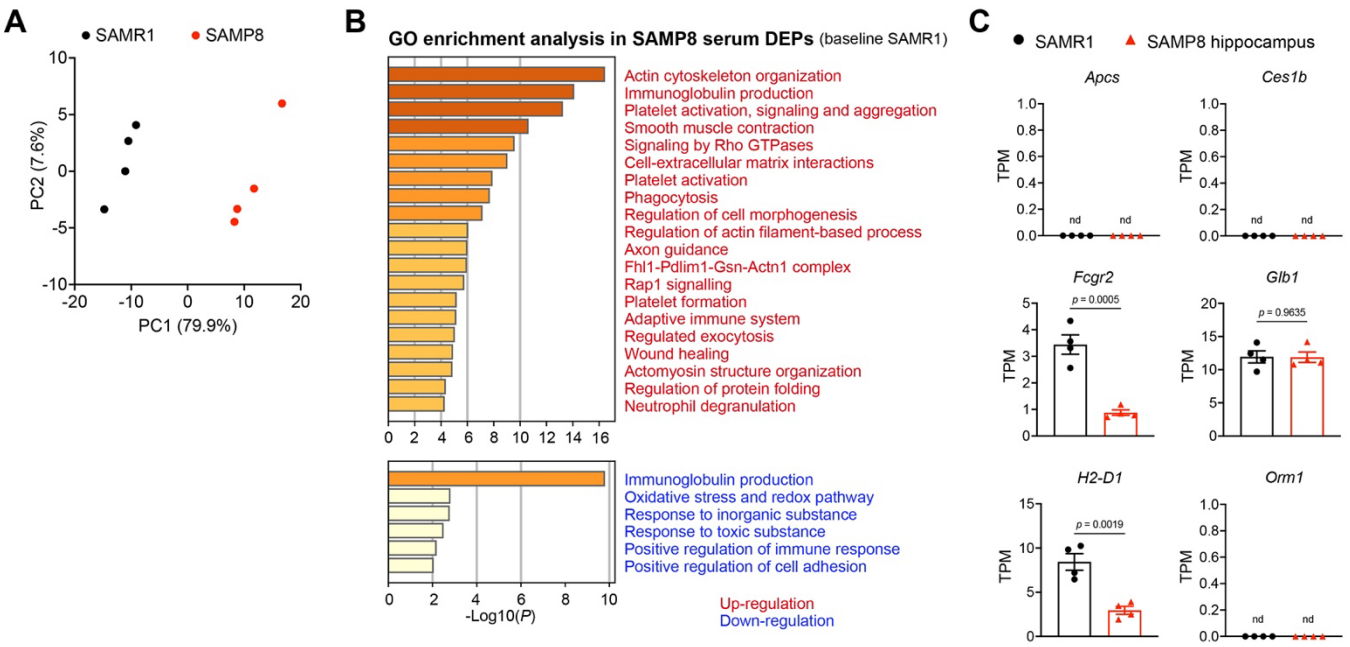

Fig. S2 Proteomic analysis using the sera of SAMP8 mice revealed immune system alteration. (**A**) PC analysis of detected peptides in the sera of control SAMR1 and SAMP8 mice. (**B**) Heatmap of GO enrichment analysis using upregulated (upper) and downregulated (bottom) DEPs in the sera of SAMP8 mice with control SAMR1 mice as baseline. (**C**) Transcripts per million of *Apcs*, *Ces1b*, *Fcgr2*, *Glb1*, *H2-D1*, and *Orm1* from bulk RNA-seq analysis using the hippocampi of SAMR1 and SAMP8 mice. Data represent mean ± SEM from the hippocampi of four mice, and dots indicate the results of each mouse. Statistic uses unpaired and two-tailed t test. nd, non-detected.

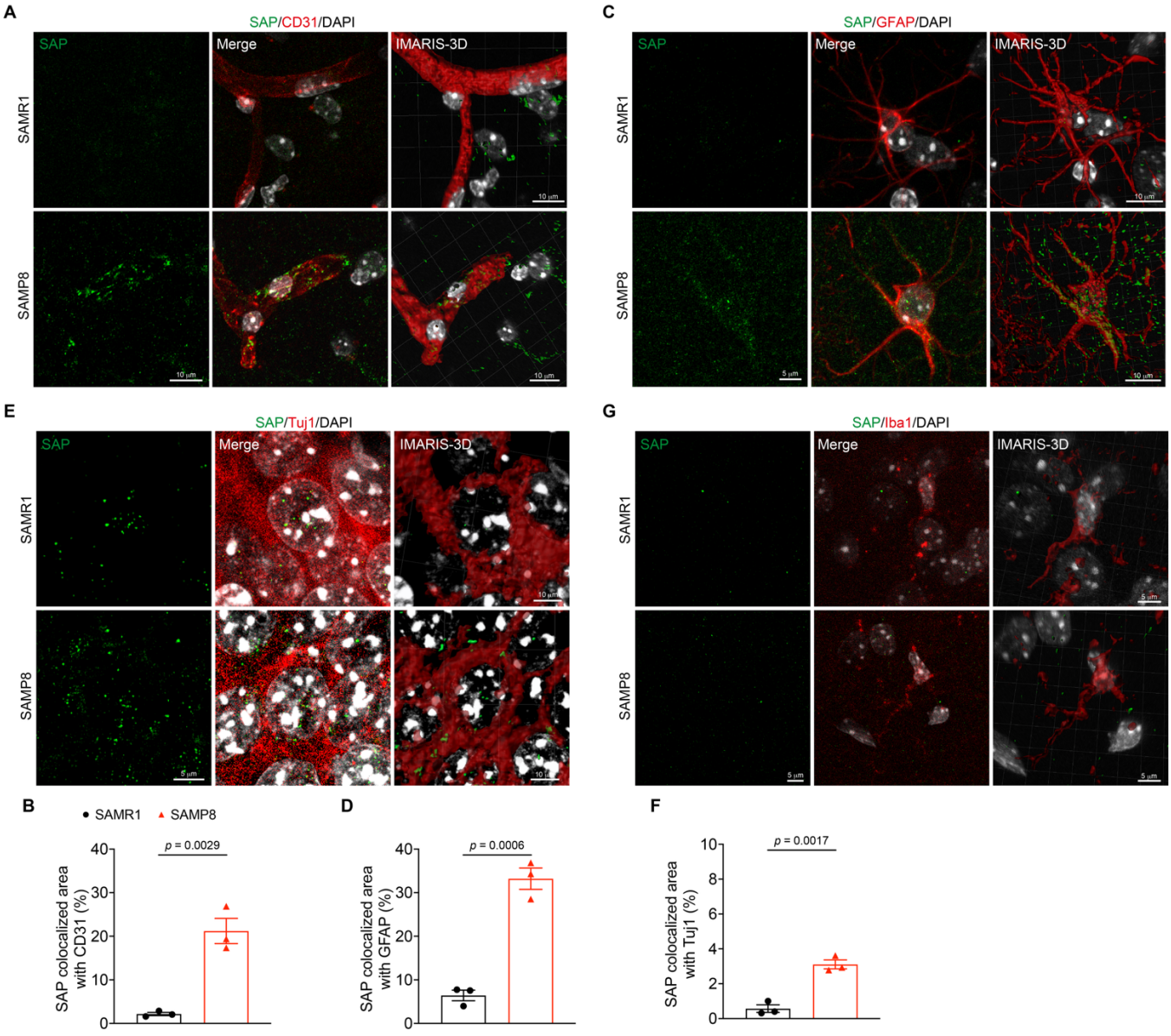

Fig. S3 Cell type-specific SAP localization in astrocytes and neurons of the hippocampus of SAMP8 mice. (**A, C, E, G**) Confocal and IMARIS-3D images of blood vessels (A), astrocytes (C), neurons (E), and microglia (G) stained with SAP (green), and CD31, GFAP, Tuj1, or Iba1 (red) as markers for endothelial cells, astrocytes, neurons, and microglia, respectively, in the hippocampi of 6-month-old SAMR1 and SAMP8 mice. (**B, D, F**) Colocalized area of SAP^+ area with $CD31^+$ (B), $GFAP^+$ (D), or $Tuj1^+$ (F) area in hippocampi of SAMR1 and SAMP8 mice. Data represent mean ± SEM, and dots indicate the results of each mouse. Statistic uses unpaired and two-tailed *t* test.

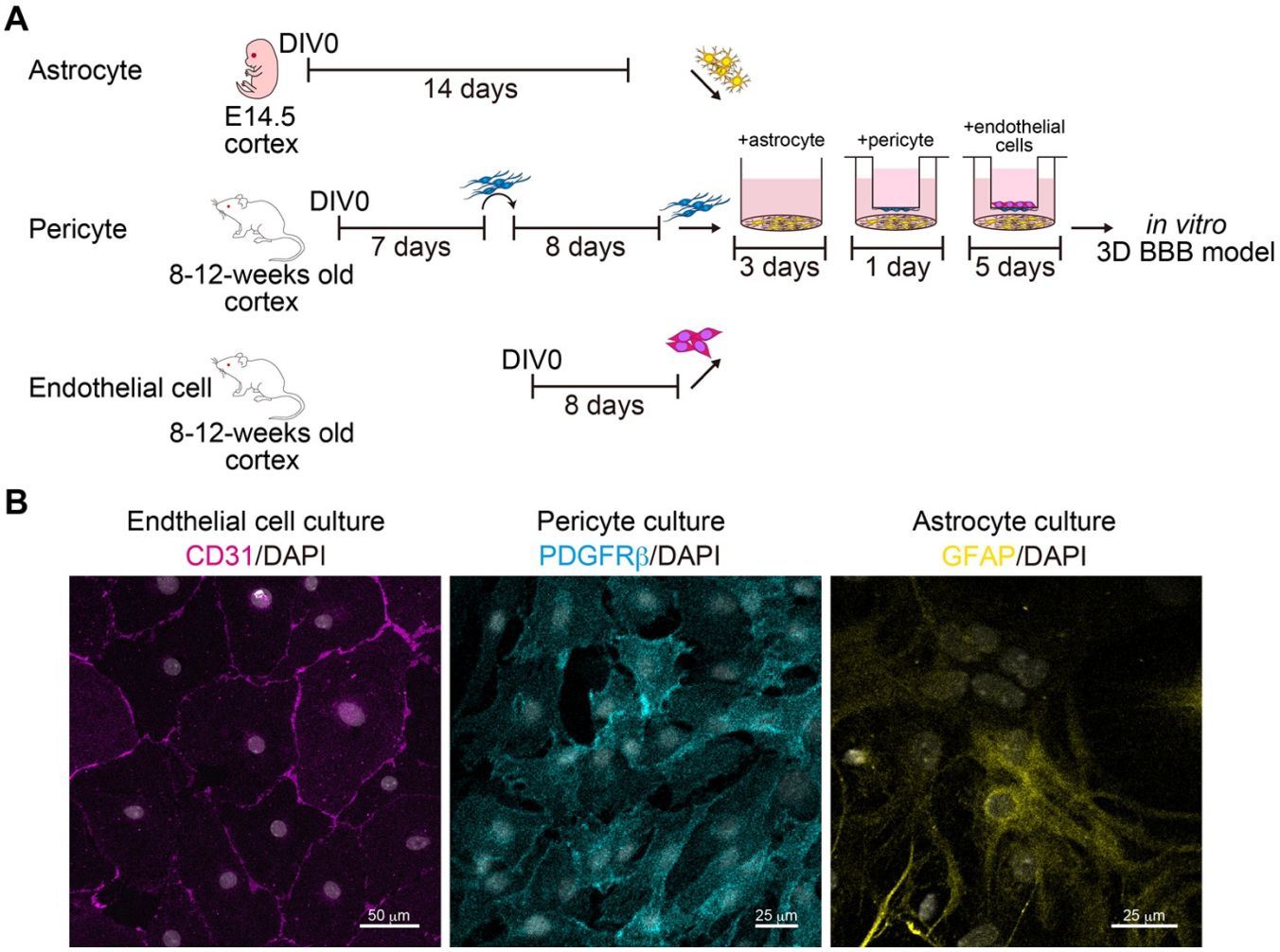

Fig. S4 *In vitro* 3D BBB model system. (**A**) Primary astrocytes, pericytes, and endothelial cells are combined in Boyden chamber-inserted 24-well plates. (**B**) Confocal images of primary endothelial cells (left panel), primary pericytes (middle panel), and primary astrocytes (right panel), stained with CD31, PDGFRβ, and GFAP, respectively.