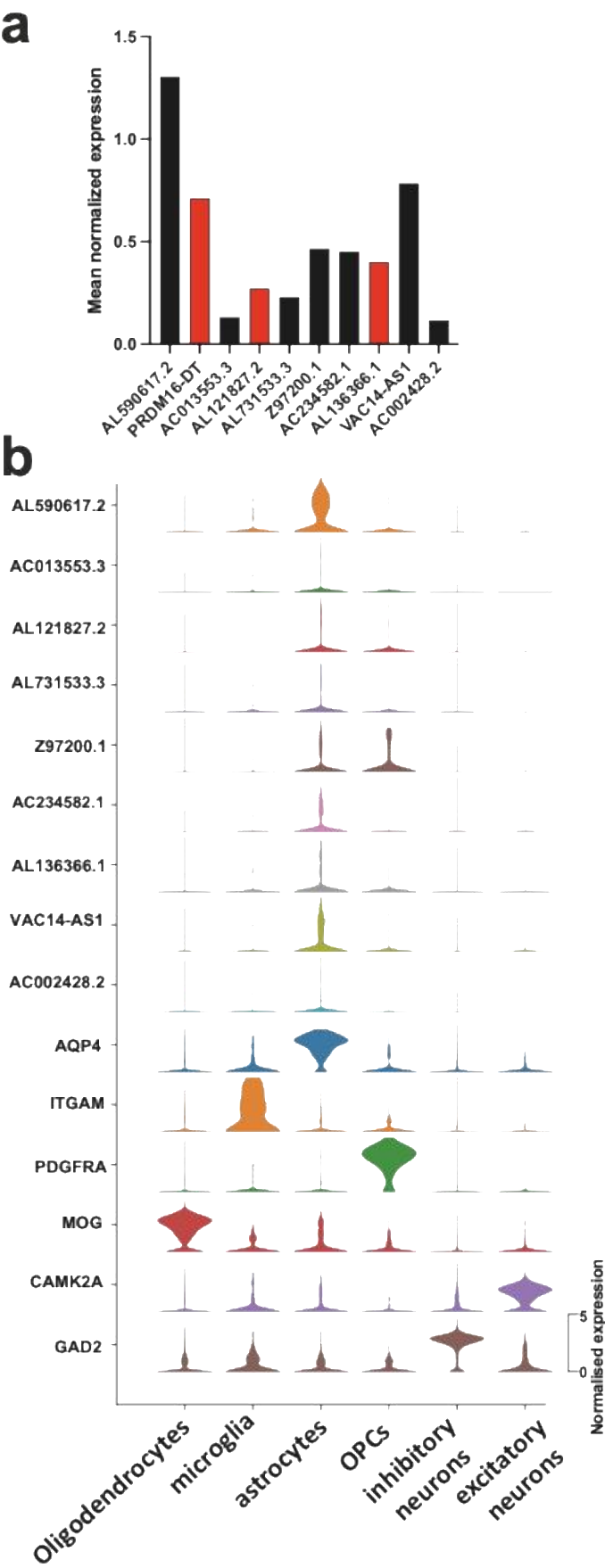


Supplemental Figures



Supplemental Figure 1 (Fig. S1).

a. Bar chart depicting the mean normalized expression of the lncRNA enriched in astrocytes as shown in Fig 1C. The data shows the expression in astrocytes. Note that lncRNAs *AL590617.2*, *VAC14-AS1* and *PRDM16-DT* show the highest expression levels when compared to the other lncRNAs. **b.** Violin plots showing the normalized expression of the lncRNAs depicted in panel A (except *PRMD16-DT* which is shown in Fig. 1D). Note the expression in astrocytes characterized by the marker gene *AQP4*.

Supplemental Figure 2 (Fig. S2)

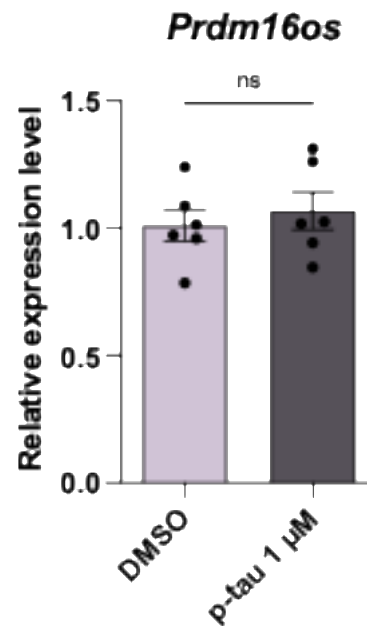


Fig. S2: Bar plot showing *Prdm16os* expression in mouse astrocytes after treatment with tau fibrils compared to the corresponding vehicle control. (ns = not significant, unpaired t-Test). *Prdm16os* expression was normalized to *18S*. Error bars indicate SEM.

Supplemental Figure 3 (Fig. S3)

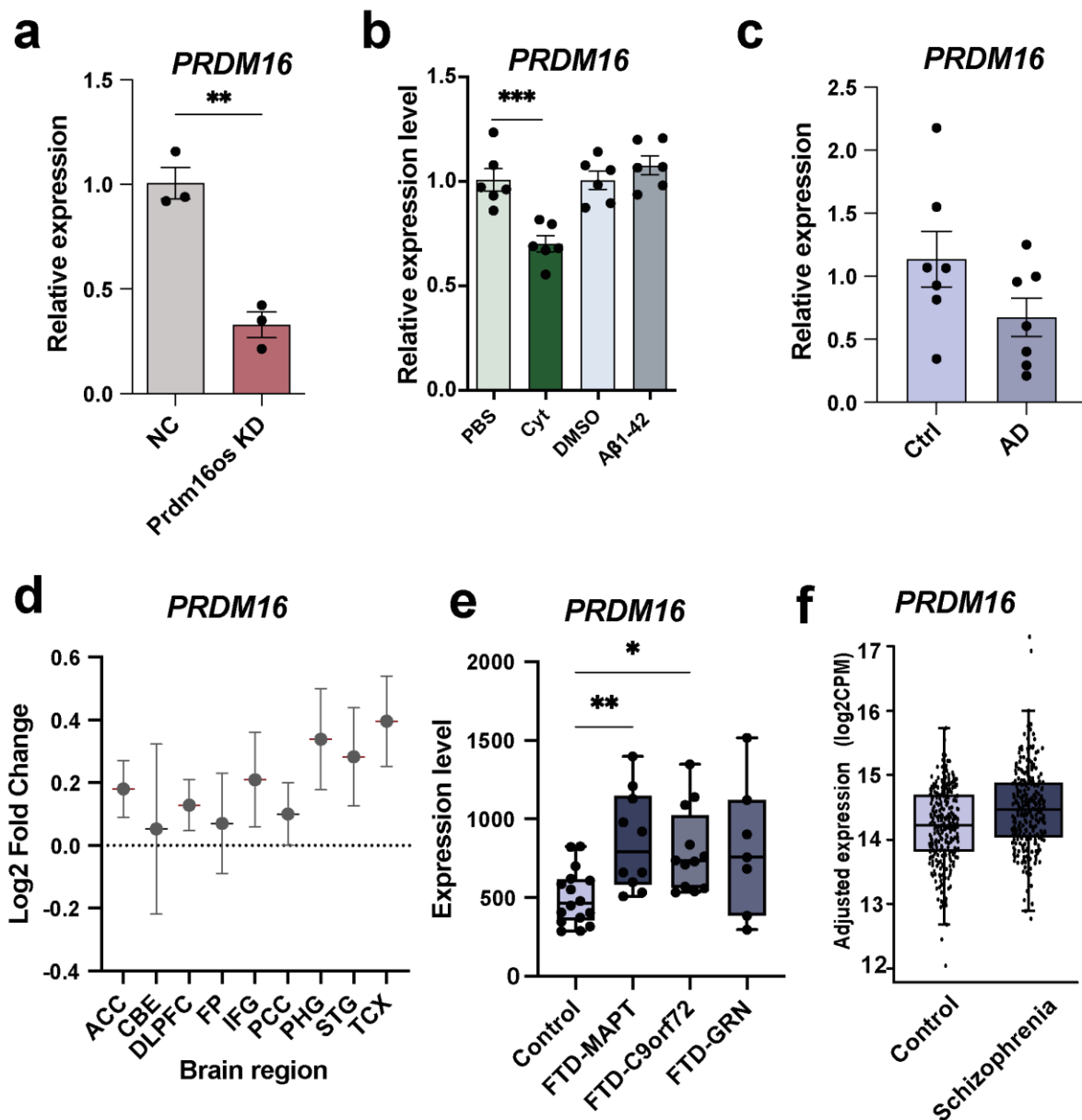


Fig. S3: *Prdm16* expression in reactive astrocytes and disease. **a.** Bar chart showing the expression of *Prdm16* after the KD of *Prdm16*os in primary astrocytes (** $P < 0.01$, unpaired t-test). **b.** Bar plot showing *Prdm16* expression in mouse astrocytes after treatment with a 3 cytokine cocktail (Cyt) and A β 1-42 treatment compared to the corresponding vehicle controls. (*** $P < 0.0001$, unpaired t-Test). **c.** Bar chart showing qPCR data on the expression of *PRDM16* in postmortem brain samples (prefrontal cortex, BA9) from control ($n = 7$) and AD patients ($n = 7$) (not significant, unpaired t-Test). **d.** Log2 Fold changes of *PRDM16* expression in different brain regions in AD patients compared to controls based on data from the Agora database (<https://agora.adknowledgeportal.org/>). (* $P < 0.05$). **e.** Bar chart showing the expression of *PRDM16* in postmortem tissue samples (frontal lobe) of FTD patients with MAPT ($n = 10$), C9ORF72 ($n = 8$) or GRN ($n = 6$) mutations compared to non-demented controls (NDC,

n = 13). Data were obtained from the RiMOD database [34] [35]. **F.** Bar chart showing the expression of *PRDM16* in postmortem brain tissue of controls (n = 279) compared to schizophrenia patients (n = 258) obtained from a study by Wu et al. [36].

Supplemental Figure 4 (Fig. S4)

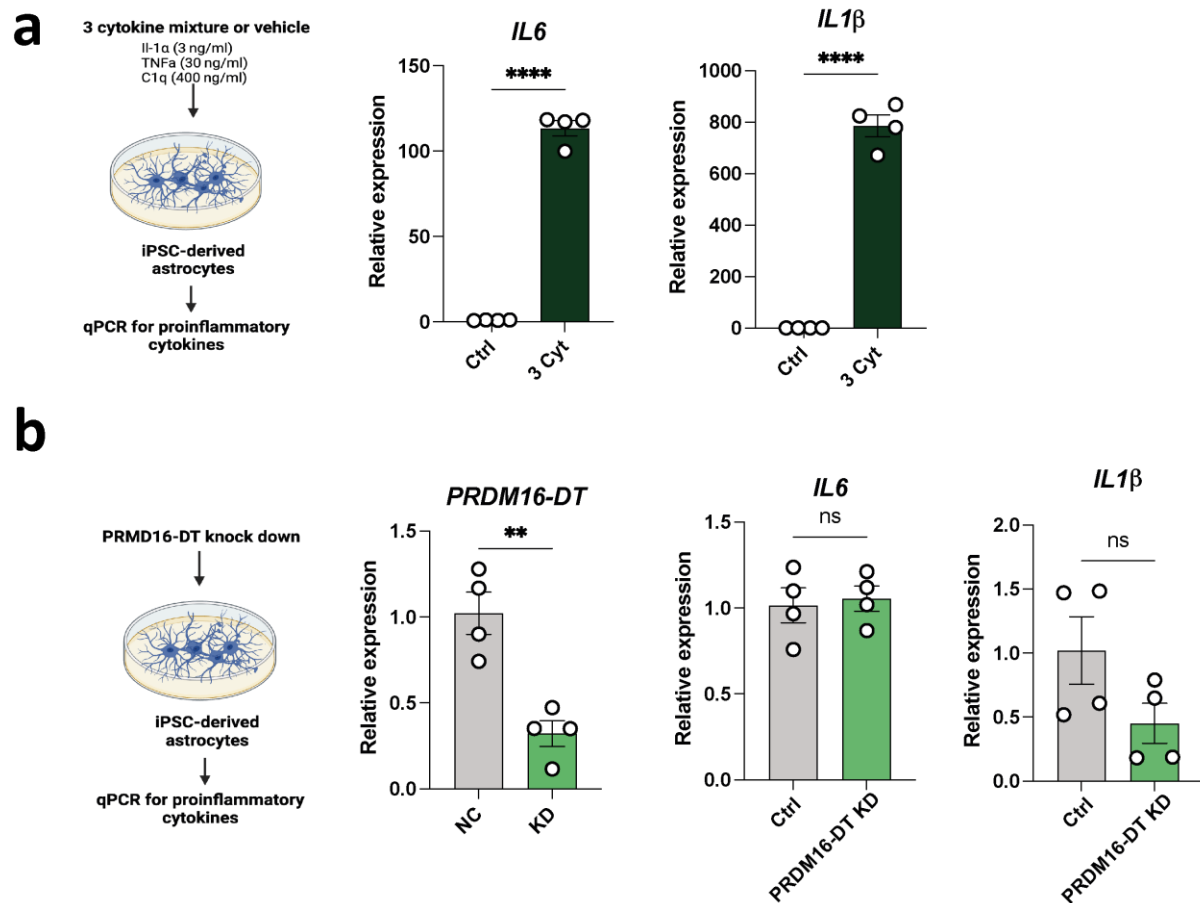


Figure S4: The knockdown of *PRDM16-DT* does not induce a pro-inflammatory phenotype in human iPSC-derived astrocytes. **a.** Scheme showing the experimental approach to stimulate human iPSC-derived astrocytes and the expression levels of pro-inflammatory cytokines after treatment with the 3 cytokine cocktail. **b.** Treatment scheme of *PRDM16-DT* KD in human iPSC-derived astrocytes followed by qPCR for IL6 and IL1b. KD: knockdown, NC: negative control. Statistical significance was assessed by a Student's unpaired t test; ** $P < 0.01$, **** $P < 0.0001$, ns = not significant. Gene expression was normalized to *18S* for *PRDM16-DT* or *GAPDH* for protein-coding genes.