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Repurposing trazodone for Alzheimer's disease to modulate soluble ST2 levels and alleviate Alzheimer's pathology

Daniel Y. K. Wong[a,b], Wing-Yu Fu[a,b], Hyebin Uhm[a,b], Yuanbing Jiang[a,b], Yuki C. C. Yip[a], Vincent C. T. Mok[c], Timothy C. Y. Kwok[d], Li Ouyang[a], Amy K. Y. Fu[a,b,e,f], and Nancy Y. Ip[a,b,e,f,1]

Affiliations are included on p. 10.

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Alzheimer's disease (AD) is a multifactorial disorder involving various pathological mechanisms, such as amyloidosis, immune dysfunctions, and synaptic impairments, which are important therapeutic targets. Repurposing drugs to target these mechanisms offers a promising approach to reduce the costs and duration of drug development. Genetic studies underscore the critical role of microglial clearance of amyloid-beta (Aβ) in AD pathogenesis. Specifically, soluble ST2 (sST2)—one of the two major isoforms of the ST2 protein encoded by the IL1RL1 (interleukin-1 receptor-like 1) gene—acts as a decoy receptor isoform that interferes with IL-33/ST2 signaling and has been identified as a disease-modifying factor that impairs microglial Aβ clearance functions. In this study, we investigated drug repurposing opportunities to modulate sST2 levels and alleviate AD pathologies. Unbiased screening of commonly used medications in AD patients, followed by validation in model systems, identified trazodone—an antidepressant used to treat major depressive disorder—as a leading negative regulator of sST2. Trazodone primarily suppresses sST2 expression through its antagonistic effects on adrenergic signaling. In the APP/PS1 transgenic mouse model of AD, trazodone treatment enhanced microglial interaction with Aβ and alleviated Aβ pathology. Furthermore, trazodone reduced neurodegeneration and rescued synaptic deficits in APP/PS1 mice. Comprehensive molecular profiling of APP/PS1 mouse brains showed that trazodone restored the expression of synaptic proteins critical for synaptic integrity and plasticity. Overall, these findings demonstrate that trazodone is a promising repurposing candidate for AD that targets underlying immune dysfunctions and synaptic impairment.

drug screening | disease-modifying factor | interleukin-33 | microglia | synaptic function

Significance

Drug repurposing offers a cost-effective strategy for accelerating therapeutic development. This study identifies trazodone, an FDA-approved antidepressant, as a promising therapeutic candidate for Alzheimer's disease (AD). We show that trazodone use in patients with AD is associated with decreased levels of soluble ST2 (sST2), a known disease-modifying factor in AD. In the APP/PS1 transgenic mouse model of AD, trazodone treatment enhances microglial interactions with amyloid-beta (Aβ) and alleviates Aβ pathology. Additionally, trazodone rescues synaptic deficits and restores the expression of synaptic proteins in APP/PS1 mice. These findings demonstrate the therapeutic potential of repurposing trazodone to target immune and synaptic dysfunctions in AD, providing a therapeutic avenue for this debilitating condition.

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder primarily affecting the elderly. The incidence of AD is projected to rise rapidly owing to global population aging (1). AD is characterized by extracellular deposition of amyloid-beta (Aβ) plaques, intracellular formation of neurofibrillary tau tangles, neuroinflammation, synaptic dysfunction, and neuronal loss, leading to cognitive decline (2). Major advancements in AD treatment have been made through the approval of anti-amyloid antibody therapies (i.e., lecanemab and donanemab), which facilitate Aβ clearance and slow cognitive decline (3, 4); these advancements pave the way for future therapies that target the underlying pathology of AD for clinically meaningful outcomes. AD encompasses multiple pathological mechanisms, including amyloidosis, immune dysfunctions, synaptic impairments, and neuronal death (5), which are important targets for drug development. While drug development is a resource-intensive process that lasts 10 to 25 y with an average cost exceeding 500 million USD (6, 7), most drug development efforts have ended in failure due to safety issues or limited clinical efficacy (8). In this context, repurposing drugs with established safety profiles and known pharmacokinetics can mitigate safety risks, reduce cost, and accelerate drug development (9). Therefore, repurposing drugs to target the underlying pathological mechanisms of AD represents a promising strategy for the disease treatment.

Drug targets supported by genetic evidence are more likely to be involved in disease causal pathways, increasing the likelihood of success in clinical trials (10, 11). Genetic studies highlight the importance of microglial clearance of Aβ in AD pathogenesis (12). Microglial surface receptors, such as TREM2, CD33, and ST2 [encoded by the *IL1RL1* gene and serving as the receptor for interleukin-33 (IL-33)] (13). While historically named as "suppression of tumorigenicity 2" or "serum stimulation 2", ST2 plays an important role in regulating microglial activation states, governing microglial Aβ

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[1]To whom correspondence may be addressed. Email: boip@ust.hk.

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clearance (14–17). In particular, the activation of ST2 signaling by IL-33 drives microglia toward beneficial functions in AD, involving directed migration toward Aβ plaques and subsequent phagocytic clearance (17–20). IL-33/ST2 signaling is dysregulated in patients with AD, as indicated by decreased levels of IL-33 and elevated levels of soluble ST2 (sST2), a decoy receptor of the IL-33/ST2 signaling pathway (18, 21). Genetic variants that negatively regulate sST2 are associated with reduced AD risk, lower amyloid deposition, greater brain volumes, and better cognitive functions (18). Moreover, genetic causal inference analysis indicates that lower plasma sST2 levels are causally associated with reduced AD risk (18). Furthermore, functional studies in transgenic mouse models of AD demonstrate that elevated sST2 levels impair microglial Aβ clearance, resulting in more severe Aβ pathology (18). In addition, IL-33/ST2 signaling plays a role in regulating synaptic functions, including synaptic plasticity and memory (22). These findings collectively underscore the therapeutic potential of targeting sST2 to address various pathological mechanisms underlying AD.

In this study, we identified trazodone as a candidate repurposing agent for AD that negatively regulates sST2 and ameliorates AD pathologies. Comprehensive screening of common medications used by AD patients prioritized trazodone, an antidepressant indicated for the treatment of major depressive disorder, as the leading candidate associated with lower plasma sST2 levels. In vitro and in vivo experiments confirmed that trazodone negatively regulates sST2 expression, primarily through its antagonistic effects on adrenergic receptor signaling. In the APP/PS1 transgenic mouse model of AD, trazodone treatment increased microglia interactions with Aβ, alleviated Aβ pathology, reduced neurodegeneration, and rescued synaptic deficits. Moreover, unbiased molecular profiling revealed that trazodone promotes synapse stability, synaptic protein translation, and chemical synaptic transmission in the hippocampus. Together, our findings demonstrate the therapeutic potential of repurposing trazodone for AD treatment.

Results

Trazodone Usage Is Associated with Decreased Plasma sST2 Levels in Alzheimer's Disease Patients. To perform unbiased screening for FDA-approved drugs that modulate sST2 levels, we examined the relationship between medication use and plasma sST2 concentrations in patients with AD from the Hong Kong Chinese cohort (n = 459 individuals with AD). The medication records showed that the AD cohort used 293 different types of medication, including 28 medications being taken by more than 5% of the cohort (i.e., more than 22 patients with AD taking the medication). Linear regression analysis between plasma sST2 levels and the 28 commonly used medications, adjusting for age and sex, revealed three medications associated with plasma sST2 levels in patients with AD ($P < 0.05$), with trazodone being the top candidate associated with decreased plasma sST2 levels (β = – 1.801, P = 0.006; Dataset S1). Further examination of the plasma sST2 levels across healthy controls (HCs, n = 341), trazodone nonusers with AD (n = 430), and trazodone users with AD (n = 29) revealed that plasma sST2 levels were higher in nonusers with AD compared to HCs (β = 1.376, P = 5.75E – 4; Fig. 1*A* and Dataset S2), corroborating our previous findings (18) in an expanded dataset. Plasma sST2 levels in trazodone users with AD were lower than those in nonusers with AD (β = –1.716, P = 0.008) and comparable to those in HCs (β = – 0.340, P = 0.631; Fig. 1*A* and Dataset S2). Overall, these findings indicate that trazodone usage is associated with lower plasma sST2 levels in patients with AD.

Trazodone Treatment Downregulates sST2 and Ameliorates Amyloid Pathology in APP/PS1 Transgenic Mice. Next, we examined whether trazodone treatment modulates sST2 levels and affects AD-like pathologies in the APP/PS1 transgenic mouse model of AD. We orally administered trazodone (10 mg/kg body weight per day) or water to 12 to 14-mo-old APP/PS1 mice, for 2 wk and examined their circulating sST2 levels. Concordant with our human data, trazodone treatment decreased the serum sST2 levels in APP/PS1 mice compared to the untreated controls (Fig. 1 *B* and *C*), indicating that trazodone downregulates sST2 levels in vivo.

Our previous study shows that sST2 exacerbates Aβ pathology by inhibiting IL-33/ST2 signaling in microglia, impairing their response to Aβ (18). Therefore, we examined the effect of trazodone treatment on Aβ pathology and microglia–Aβ interaction in APP/PS1 mice. Trazodone treatment decreased the cortical Aβ plaque burden in APP/PS1 mice (Fig. 1 *D* and *E*). In particular, Aβ plaques in trazodone-treated APP/PS1 mice were smaller than those in untreated APP/PS1 mice (Fig. 1*F*), suggesting that the reduction in Aβ burden is largely due to decreased Aβ plaque size. Similarly, Aβ burden was significantly decreased in the hippocampi of trazodone-treated APP/PS1 mice (*SI Appendix,* Fig. S1).

Given that IL-33 signaling regulates microglial interactions with Aβ (17, 19, 20), we examined the characteristics of microglia in the cortices of trazodone-treated APP/PS1 mice. Trazodone treatment increased the number of microglia associated with Aβ plaques in the cortices of APP/PS1 mice compared to the untreated controls (Fig. 1 *G* and *H*). In addition, the area of Aβ plaques covered by microglia was significantly larger in trazodone-treated APP/PS1 mice than in the controls (Fig. 1 *G* and *I*), indicating that trazodone enhances microglial migration toward Aβ plaques. These results suggest that trazodone treatment alleviates Aβ burden and enhances microglia–Aβ plaque interaction.

Trazodone Treatment Alleviates Neurodegeneration in APP/PS1 Transgenic Mice. Axonal degeneration is a prevalent histological feature observed near amyloid plaques (23). Therefore, we examined the effect of trazodone on neuronal phenotypes in APP/PS1 mice. Trazodone treatment reduced the number and area of abnormal axonal swellings in the vicinity of Aβ plaques (Fig. 2 *A*–*C*), indicating that trazodone treatment ameliorates Aβ-associated axonal dystrophy in APP/PS1 mice. We further examined the effect of trazodone on neuronal density in the cortex and hippocampus in APP/PS1 mice. While neuronal density in the cortex was significantly lower in untreated APP/PS1 mice compared to wild-type (WT) mice, trazodone treatment reduced neuronal loss in APP/PS1 mice (Fig. 2 *D* and *E*). The protective effect of trazodone was most pronounced in cortical layer 5 (Fig. 2 *D* and *F* and *SI Appendix*, Fig. S2), an area particularly susceptible to dysfunction in AD (24). Concordantly, trazodone treatment reduced neuronal loss in the CA1 region of the hippocampus in APP/PS1 mice (Fig. 2 *G* and *H*). Together, these findings suggest that trazodone alleviates neuronal damage and loss in the cortex and hippocampus in APP/PS1 mice.

Trazodone Treatment Restores the Expression of Synaptic Genes in APP/PS1 Transgenic mice. We subsequently investigated the effects of trazodone on brain molecular phenotypes through transcriptomic profiling of the cortices of trazodone-treated APP/PS1 mice. Trazodone treatment resulted in the differential expression of 1,345 genes (false discovery rate (*FDR*)-adjusted $P < 0.05$], including 842 upregulated and 503 downregulated genes (Fig. 3*A* and Dataset S3). Gene Ontology (GO) enrichment analysis revealed that the upregulated genes were enriched in

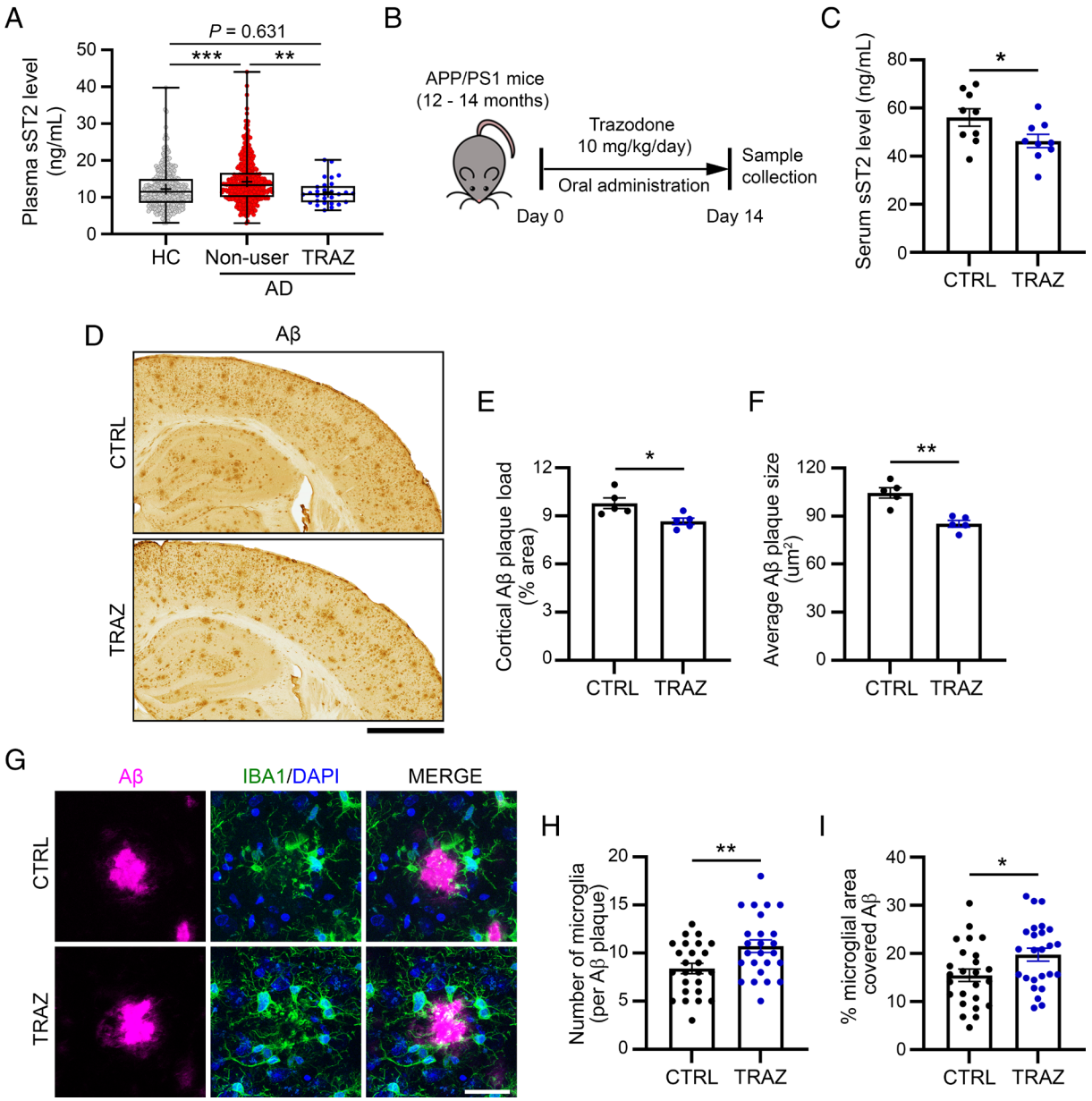

Fig. 1. Trazodone treatment reduces circulating sST2 and alleviates amyloid pathology. (*A*) Quantification of plasma sST2 levels stratified by trazodone use among participants: healthy controls (HC, n = 341), AD patients not taking trazodone (nonusers, n = 430), and AD patients taking trazodone (TRAZ, n = 29) from the Hong Kong Chinese cohort. $^{**}P < 0.01$, $^{***}P < 0.001$, linear regression analysis adjusting for age and sex. (*B*) Schematic diagram of experimental design. (*C*) Serum sST2 levels are significantly decreased in trazodone-treated APP/PS1 mice (n = 9 for each condition, $^{*}P < 0.05$, unpaired two-tailed Student's *t* test). (*D–F*) Amelioration of Aβ burden in the cerebral cortices of trazodone-treated APP/PS1 mice (TRAZ) compared to control APP/PS1 mice (CTRL). (*D*) Representative images of Aβ plaques labeled with D54D2 Aβ antibody in the cortices of APP/PS1 mice. (Scale bar, 100 μm). (*E*) Quantification of Aβ plaques in the mouse cortices, calculated as the total area of Aβ plaques divided by the total area of the cortex. (*F*) Quantification of average Aβ plaque size in the mouse cortices, calculated as the average area of individual Aβ plaques (CTRL and TRAZ: n = 5 for each condition, $^{*}P < 0.05$, $^{**}P < 0.01$, unpaired two-tailed Student's *t* test). (*G–I*) Trazodone increases microglial interaction with Aβ plaques. (*G*) Representative images showing IBA1^{+} microglia associated with methoxy-X04-labeled Aβ plaques. (Scale bar, 20 μm). Quantification of the number of IBA1^{+} microglia associated with Aβ plaques (*H*) and percentage of the surface area of methoxy-X04-labeled Aβ plaques in contact with IBA1^{+} microglia (*I*) (n = 30 Aβ plaques from 5 mice for each condition; Data are mean ± SEM, $^{*}P < 0.05$, $^{**}P < 0.01$, unpaired two-tailed Student's *t* test).

neuronal and synaptic pathways, including neuronal projection development (e.g., *Mapt*, *Map1a*, and *Dnm2*), chemical synaptic transmission (e.g., *Stx1a*, *Stx4a*, and *Grin2d*), and synaptic plasticity (e.g., *Npas4*, *Neurod2*, and *Fxr2*; Fig. 3*B*). Meanwhile, the downregulated genes were enriched in cellular response to zinc ion (e.g., *Mt1* and *Mt2*; Fig. 3*B*); of note, excess zinc is linked to neuronal damage (25, 26). Furthermore, the neuronal and synaptic genes upregulated in trazodone-treated APP/PS1 mice exhibited concerted downregulation in untreated APP/PS1 mice compared to WT mice (Fig. 3*C*), indicating that trazodone treatment restored the expression of neuronal and synaptic genes in APP/PS1 mice. Corroborating this notion, the transcriptomic changes in trazodone-treated APP/PS1 mice compared to untreated APP/PS1 mice were inversely correlated with the transcriptomic changes in untreated APP/PS1 mice compared to WT mice ($P < 0.0001$; Fig. 3*D*).

Trazodone Treatment Rescues Excitatory Synapse Loss and Rescues Synaptic Impairments in the Hippocampus of APP/PS1 Transgenic Mice. We subsequently examined whether trazodone modulates synaptic functions in APP/PS1 mice, particularly in the hippocampal CA1 region, which plays an

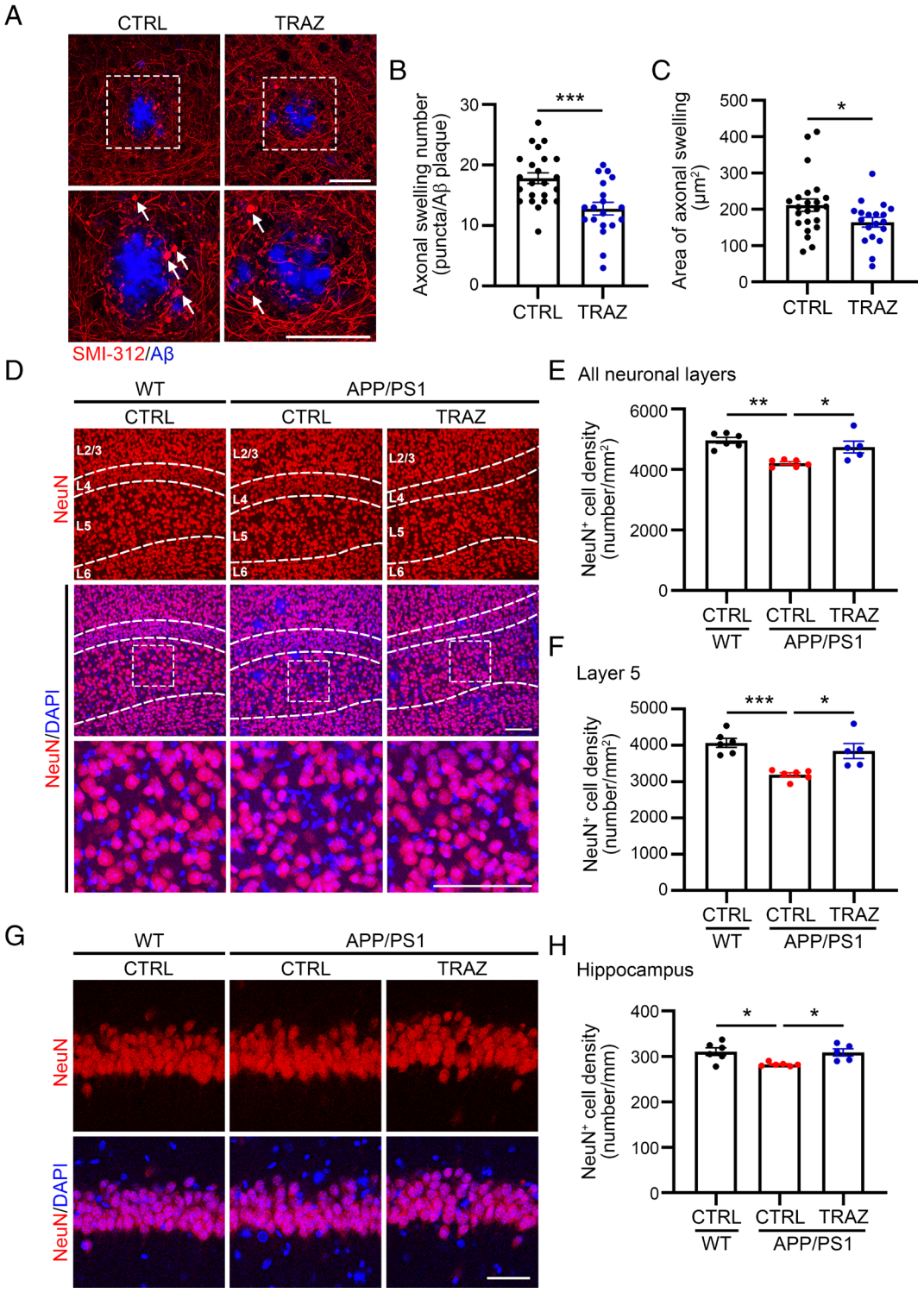

Fig. 2. Trazodone treatment mitigates neurodegeneration in APP/PS1 mice. (*A–C*) Decrease in axonal dystrophy in the cerebral cortices of trazodone-treated APP/PS1 mice (TRAZ) compared to untreated control mice (CTRL). (*A*) Representative images showing SMI-312-labeled axonal swellings and methoxy-X04-labeled Aβ plaques. (Scale bar, 100 μm.) White dashed boxes outline areas of high magnification shown in the lower panels, and white arrows denote abnormal axonal swellings. Quantification of the number (*B*) and total area (*C*) of axonal swellings around Aβ plaques (n = 19 to 23 Aβ plaques from 5 to 6 mice, $*P < 0.05$, $***P < 0.001$, unpaired two-tailed Student's *t* test). (*D–F*) Trazodone alleviates neuronal loss in the cerebral cortex of APP/PS1 mice. (*D*) Representative images showing NeuN$^+$ neurons in the mouse cortices. (Scale bar, 100 μm.) White dashed lines outline different neuronal layers in the cerebral cortex. White dashed boxes outline areas of layer 5 at high magnification shown in the lowest panels. Quantification of NeuN$^+$ neuron density across all layers of mouse cortices (*E*) and specifically in layer 5 of mouse cortices (*F*). (*G* and *H*) Trazodone alleviates neuronal loss in the hippocampal CA1 region of APP/PS1 mice. Representative images (*G*) (Scale bar, 50 μm) and quantification of NeuN$^+$ neurons in the mouse CA1 region (*H*), calculated as the number of NeuN$^+$ neurons divided by the length of the CA1 region (WT CTRL: n = 6, APP/PS1 CTRL: n = 6, APP/PS1 TRAZ: n = 5; *D–H*, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, one-way ANOVA with Tukey's multiple comparison test). Data are mean ± SEM.

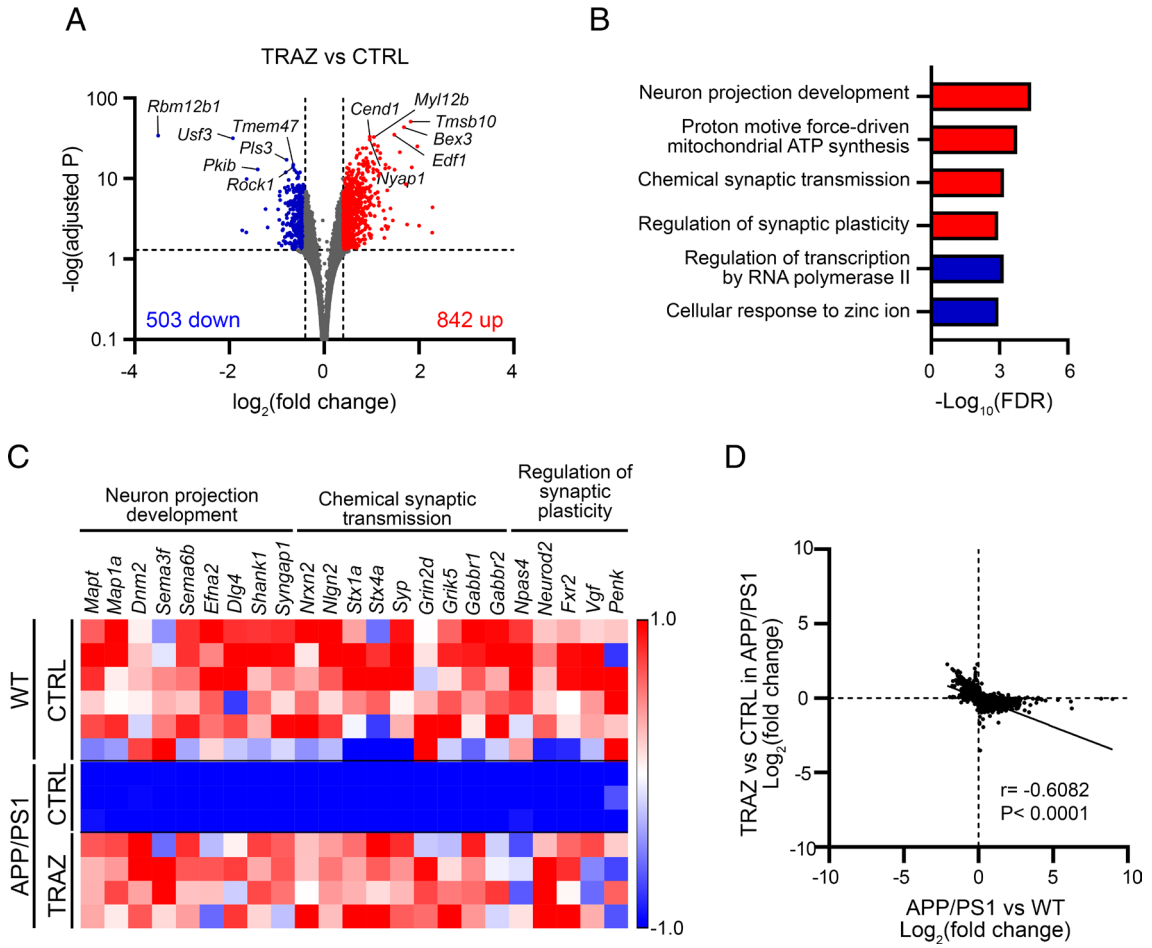

Fig. 3. Trazodone treatment restores molecular phenotypes associated with synaptic functions in APP/PS1 mouse cortices. (*A*) Volcano plot showing differentially expressed genes (DEGs) in the cerebral cortices of trazodone (TRAZ)-treated APP/PS1 mice compared to untreated control (CTRL), with 842 genes upregulated and 503 downregulated [DEGs defined as adjusted $P < 0.05$, $\log_2$(fold change) >0.4 or <−0.4]. (*B*) Bar graph depicting Gene Ontology (GO) enriched pathways related to upregulated and downregulated DEGs between APP/PS1 TRAZ and APP/PS1 CTRL cortices, with FDR indicated. (*C*) Heatmap displaying selected DEGs and their associated pathways across WT CTRL (n = 6), APP/PS1 CTRL (n = 3), and APP/PS1 TRAZ (n = 4) mouse cortices. (*D*) Correlation analysis of the cortical transcriptome profile comparing APP/PS1 TRAZ to APP/PS1 CTRL mice and APP/PS1 CTRL to WT CTRL mice, showing a significant correlation ($r = -0.6082$, $P < 0.0001$, Pearson correlation analysis).

important role in learning and memory (27, 28). Accordingly, we first examined the effects of trazodone on the excitatory synapse density in the hippocampal CA1 region in APP/PS1 mice. While trazodone treatment did not alter the densities of presynaptic marker VGLUT1 or postsynaptic marker PSD-95, it increased the colocalization of these synaptic markers (Fig. 4 *A* and *B* and *SI Appendix*, Fig. S3), suggesting that trazodone rescued the excitatory synapse loss in the hippocampal CA1 region in AD. Concordantly, trazodone rescued the impairment in hippocampal synaptic plasticity in APP/PS1 mice, as indicated by long-term potentiation (LTP) in the Schaffer collateral–CA1 pathway (Fig. 4 *C* and *D*). These findings indicate that trazodone promotes synapse stability and ameliorates synaptic dysfunctions in APP/PS1 mice.

To understand the molecular basis of the effects of trazodone on synaptic phenotypes, we performed untargeted proteomic analysis of the hippocampal synaptic membranes in APP/PS1 mice. Trazodone treatment resulted in the differential expression of 1,494 proteins (*FDR*-adjusted $P < 0.05$), including 742 upregulated and 752 downregulated proteins (Fig. 4*E* and Dataset S4). Synapse-focused GO analysis (SynGO) (29) revealed that the top upregulated pathways included synapse assembly (e.g., LRRTM4 and SEMA4D), protein translation at synapses (e.g., RPL12 and RPL18), structural support by postsynaptic cytoskeleton (e.g., INA and NEFL), and chemical synaptic transmission (e.g., VGF and NCAM1) (Fig. 4*F*). Meanwhile, downregulated pathways included ion channel activity (e.g., GABRA2 and GABRB2) and proton loading to synaptic vesicles (e.g., ATP6V0D1 and ATP6V1D) (Fig. 4*F*). Global comparison of proteomic profiles revealed that proteomic changes in the synaptic membranes of trazodone-treated APP/PS1 mice compared to untreated APP/PS1 mice were inversely correlated with the proteomic changes in the synaptic membranes of untreated APP/PS1 mice compared to WT mice ($P < 0.0001$; Fig. 4*G*). This restorative change was evident in synapse assembly, translation, and postsynaptic cytoskeleton proteins, which were downregulated in untreated APP/PS1 mice compared to WT mice, but were restored after trazodone treatment (Fig. 4*H*), suggesting that trazodone treatment ameliorates synaptic impairments related to synaptic structure and protein synthesis in APP/PS1 mice. Interestingly, trazodone also distinctly regulated synaptic proteins with similar expression profiles between WT and untreated APP/PS1 mice; proteins involved in modulation of chemical synaptic transmission were upregulated, while those related to ion channel activity and synaptic vesicle proton loading were downregulated (Fig. 4*H*).

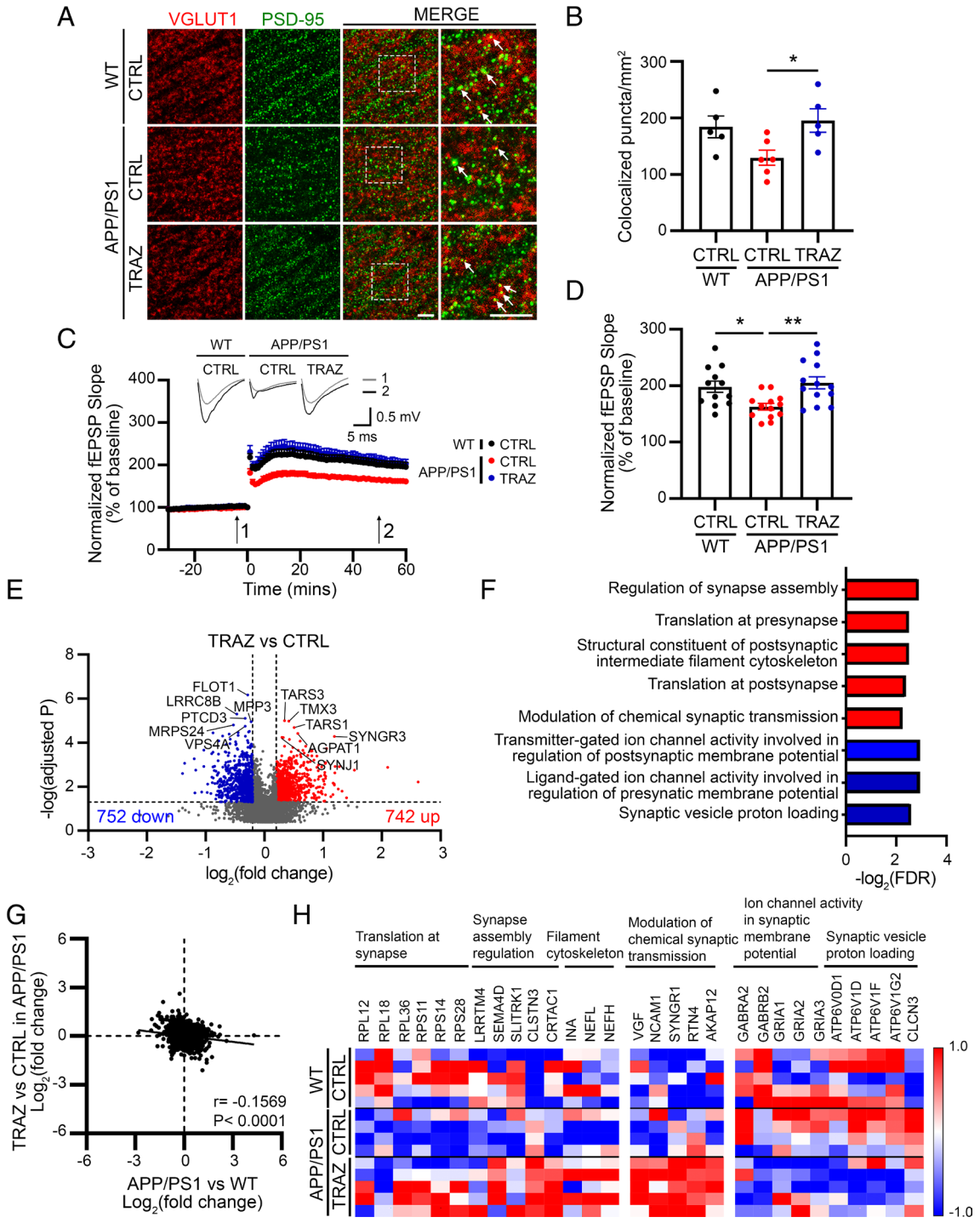

Fig. 4. Trazodone treatment ameliorates hippocampal synaptic dysfunction in APP/PS1 mice. (*A* and *B*) Trazodone increases excitatory synapses in hippocampal CA1 neurons in APP/PS1 mice (*A*) Representative images of VGLUT1 and PSD-95 puncta (Scale bar, 5 μm), with white dashed boxes indicating magnified areas on the *Right*; white arrows denote VGLUT1$^+$ PSD-95$^+$ puncta. (*B*) Quantification of colocalized puncta density, defined as the number of VGLUT1$^+$ PSD-95$^+$ puncta per total area of the hippocampus [control wild-type mice (WT CTRL): n = 5, control APP/PS1 mice (APP CTRL): n = 6, trazodone-treated APP/PS1 mice (APP TRAZ): n = 5; *P < 0.05, one-way ANOVA with Tukey's multiple comparison test]. (*C* and *D*) Trazodone restores LTP deficits at the Schaffer collateral pathway in APP/PS1 mice. LTP induction via high-frequency stimulation in the hippocampal CA1 region from trazodone-treated APP/PS1 mice. (*C*) Average fEPSP slopes normalized to baseline LTP induction. Trace recordings 5 min before 1) and 50 min after 2) LTP induction (arrows) are shown. (*D*) Quantification of mean fEPSP slopes during the last 10 min post–LTP induction (n = 12 to 13 slices from 5 to 6 mice, *P < 0.05, **P < 0.01, one-way ANOVA with Tukey's multiple comparison test). Data are mean ± SEM. (*E*–*H*) Proteomic profiling of hippocampal synaptic membrane proteins. (*E*) Volcano plot displaying differentially expressed proteins (DEPs) in the hippocampal synaptic membrane fraction of APP/PS1 TRAZ versus APP/PS1 CTRL mice, with 742 proteins upregulated and 752 downregulated [DEPs defined as adjusted P < 0.05, $\log_2$(fold change) >0.2 or <−0.2]. (*F*) Bar graph illustrating SynGO enriched pathways related to upregulated and downregulated synaptic DEPs in the hippocampal synaptic membrane fractions. (*G*) Correlation analysis of the hippocampal synaptic membrane proteome profile comparing APP/PS1 TRAZ to APP/PS1 CTRL mice and APP/PS1 CTRL to WT CTRL mice, showing a significant correlation (r = −0.1569, P < 0.0001, Pearson correlation analysis). (*H*) Heatmap of selected DEPs and their associated pathways in the hippocampal synaptic membrane fractions of WT CTRL (n = 5), APP/PS1 CTRL (n = 4), and APP/PS1 TRAZ (n = 5) mice.

Trazodone Negatively Regulates sST2 Expression in Human Endothelial Cells. Given the beneficial effects of trazodone against AD-like pathologies in vivo, we investigated the mechanism by which trazodone regulates sST2 in human cell systems. As brain endothelial cells serve as the primary source of sST2 (18), we treated primary human cerebral microvascular endothelial cells (hCMEC/D3) with different concentrations of trazodone. Notably, treatment with trazodone at 10 μM reduced the release of sST2 proteins from hCMEC/D3 cells by 35%, without affecting sST2 transcript levels (Fig. 5 *A* and *B*). In contrast, at 30 μM trazodone, a reduction in protein release of sST2 was again observed, accompanied by a 15% decrease in transcript

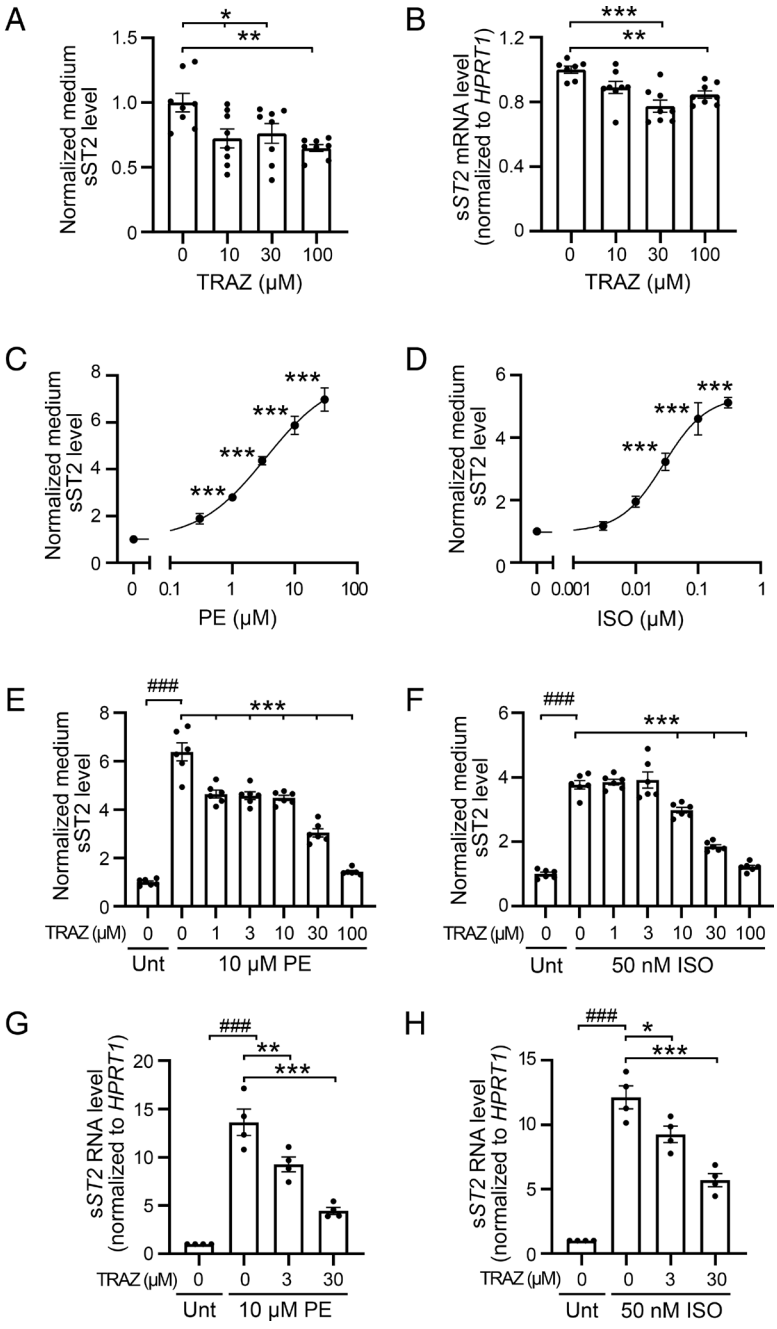

Fig. 5. Trazodone treatment suppresses adrenergic signaling-regulated expression and release of sST2 in human endothelial cell lines. (*A*) Quantification of medium sST2 levels in the culture media of hCMEC/D3 cells following trazodone treatment (TRAZ) at various concentrations for 24 h, normalized to sST2 levels at 0 μM (n = 8, $^{*}P < 0.05$, $^{**}P < 0.01$, one-way ANOVA with Dunnett's multiple comparison test). (*B*) Quantification of s*ST2* mRNA expression levels in hCMEC/D3 cells treated with TRAZ at different concentrations for 6 h, normalized to sST2 expression levels at 0 μM (vehicle-treated control) (n = 8, $^{**}P < 0.01$, $^{***}P < 0.001$, one-way ANOVA with Dunnett's multiple comparison test). (*C* and *D*) Quantification of medium sST2 levels in hCMEC/D3 cells treated with phenylephrine (PE, *C*) or isoproterenol (ISO, *D*) at various concentrations for 24 h, normalized to sST2 levels in vehicle-treated control (n = 6, $^{***}P < 0.001$, one-way ANOVA with Dunnett's multiple comparison test). (*E* and *F*) Quantification of medium sST2 levels in hCMEC/D3 cells pretreated with different concentrations of TRAZ for 1 h, followed by treatment with 10 μM PE (*E*) or 50 nM ISO (*F*), normalized to sST2 levels in vehicle-treated controls (n = 6, $^{\#\#\#}P < 0.001$ comparing PE- or ISO-treated cells to untreated cells, $^{***}P < 0.001$ comparing cells pretreated with TRAZ followed by PE or ISO to PE- or ISO-treated cells, one-way ANOVA with Dunnett's multiple comparison test). (*G* and *H*) s*ST2* mRNA expression levels in hCMEC/D3 cells pretreated with TRAZ at various concentrations for 1 h, followed by treatment with 10 μM PE (*G*) or 50 nM ISO (*H*), normalized to s*ST2* expression levels in vehicle-treated control (n = 4, $^{\#\#\#}P < 0.001$ comparing PE- or ISO-treated cells to vehicle-treated control, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ comparing cells pretreated with TRAZ followed by PE or ISO to PE- or ISO-treated cells, one-way ANOVA with Dunnett's multiple comparison test). Data are mean ± SEM.

levels (Fig. 5 *A* and *B*). These findings suggested that trazodone has a stronger effect on regulating sST2 protein release than sST2 transcript levels.

Given that trazodone is an antagonist for various G protein–coupled receptors (GPCRs), including serotonin (5-HT2), adrenergic, and histamine receptors (30), we examined whether trazodone downregulates sST2 levels by modulating GPCR signaling pathways. To this end, we treated hCMEC/D3 cells with 5 GPCR agonists: a histamine H1 receptor agonist (2-[3-trifluoromethylphenyl]histamine, TFMP), a histamine H2 receptor agonist (amthamine, AM), a 5-HT2 receptor agonist (2,5-dimethoxy-4-iodoamphetamine, DOI), an α_1-adrenergic receptor agonist (phenylephrine, PE), and a β-adrenergic receptor agonist (isoproterenol, ISO). While TFMP, AM, and DOI treatments did not affect sST2 levels (*SI Appendix*, Fig. S4), the adrenergic agonists PE and ISO increased the release of sST2 proteins in a dose-dependent manner (Fig. 5 *C* and *D*), indicating that adrenergic signaling activation upregulates sST2 expression in human endothelial cells. Moreover, pretreatment of hCMEC/D3 cells with trazodone reduced the release of sST2 proteins induced by PE and ISO in a dose-dependent manner (Fig. 5 *E* and *F*), suggesting that trazodone regulates adrenergic signaling to reduce the release of sST2 proteins. Concordant with the changes in sST2 protein release, PE and ISO upregulated s*ST2* transcript levels in hCMEC/D3 cells, which were negatively regulated by trazodone pretreatment (Fig. 5 *G* and *H*). Overall, these findings indicate that trazodone negatively regulates sST2 protein release by antagonizing adrenergic signaling in human endothelial cells.

Discussion

The biology of AD involves various pathological mechanisms that can serve as important therapeutic targets. Targeting these mechanisms through drug repurposing can accelerate and reduce the cost of drug development. In this study, we identify trazodone, an FDA-approved antidepressant, as a potential drug that can be repurposed for AD. Comprehensive drug screening in AD patients and validation in model systems demonstrate that trazodone negatively regulates sST2, a disease-modifying factor in AD that impairs microglial clearance of Aβ and exacerbates AD pathologies. In AD transgenic mice, trazodone treatment enhances microglial interaction with Aβ, alleviates Aβ pathology, and reduces neuronal loss. Furthermore, trazodone restores the expression of synaptic proteins in the hippocampus and rescues impairments in synaptic plasticity. Notably, while trazodone treatment has shown beneficial outcomes in other mouse models of neurodegeneration, such as tauopathy and prion disease (31, 32), our study demonstrates its effectiveness in mitigating Aβ-related AD pathology. These findings collectively underscore the therapeutic potential of repurposing trazodone to target multiple AD pathologies. Repurposing approved drugs with well-characterized dosage, safety, and tolerability profiles can substantially accelerate the drug development process by mitigating safety concerns and reducing costs and timelines (9). As such, our unbiased screening of common medications in AD patients has identified trazodone as a promising candidate for drug repurposing for AD.

Trazodone is an FDA-approved medication recognized for its ability to inhibit serotonin reuptake, primarily indicated for major depressive disorder at doses of 150 to 600 mg/day (30). Notably, at lower doses of 25 to 100 mg per day, trazodone exhibits sedative effects and is frequently used off-label to help manage these symptoms and improve sleep quality in Alzheimer's patients experiencing sundown syndrome.(33–35). Pharmacokinetic modeling predicts maximum brain trazodone concentrations of 7.6 μM at a 300-mg antidepressant dose and 2.3 μM at a 30-mg insomnia dose (36). Our study shows that trazodone ranks among the top 28 commonly used medications in AD patients, supporting its safety and tolerability in these patients. Importantly, trazodone treatment enhances microglial response to Aβ and repairs synaptic dysfunctions in AD transgenic mice, showcasing its therapeutic potential in targeting the pathological mechanisms underlying AD, including immune dysfunctions and synaptic deficits.

What are the molecular mechanisms that underlie the effects of trazodone on AD pathology? Trazodone negatively regulates sST2, which inhibits IL-33/ST2 signaling in microglia, impairing their cellular state transition toward AD-protective functions, including microglial chemotaxis toward Aβ plaques and subsequent phagocytic clearance of Aβ (17–20). Here, we show that trazodone treatment enhances microglial interaction with Aβ plaques and ameliorates Aβ pathology in 12 to 14-mo-old APP/PS1 mice, a stage characterized by considerable Aβ accumulation in the brain. Specifically, we show that trazodone increases microglial coverage of Aβ plaques and alleviates neuronal injury. Previous studies show that microglial coverage of Aβ plays an important neuroprotective role in AD by reducing Aβ toxicity to surrounding neurons (37), suggesting that trazodone promotes neuroprotective functions in microglia in AD. Interestingly, we observed that trazodone rescues synaptic functions in AD transgenic mice, corroborating previous findings that IL-33/ST2 signaling mediates synaptic plasticity (22). Because of the potential confounding effects of trazodone's sedative properties, we did not assess cognitive function in trazodone-treated APP/PS1 transgenic mice. Nevertheless, our molecular and phenotypic analyses offer compelling evidence for the neuroprotective role of trazodone in the context of AD. Further studies should investigate the effects of trazodone on younger AD transgenic mice, particularly at the stages associated with initial (i.e., 3 to 4 mo old) and intermediate (i.e., 6 to 8 mo old) deposition of Aβ. Such findings may help ascertain whether trazodone treatment can delay or attenuate the progression of AD pathology, thereby expanding the window for effective drug delivery.

Vascular endothelial cells are the primary cellular source of sST2 in humans, releasing it in response to inflammatory signals, which is relevant in the context of AD (18). Although the cellular sources of sST2 in mice are less defined, peripheral cells like mast cells and T cells are suggested to contribute to circulating sST2 levels (18) Notably, our observation of reduced circulating sST2 in trazodone-treated APP/PS1 mice aligns with clinical findings of decreased plasma sST2 levels in AD patients treated with trazodone. This connection underscores the therapeutic potential of trazodone in addressing key pathological mechanisms of AD.

Our in vitro experiments show that trazodone negatively regulates sST2 expression by inhibiting α_1- and β-adrenergic receptor signaling in human endothelial cells, suggesting that modulation of adrenergic signaling is a key mechanism of trazodone. Indeed, previous studies suggest the involvement of adrenergic signaling in AD pathophysiology. Specifically, the plasma and cerebrospinal fluid levels of the adrenergic ligand, noradrenaline, are elevated in AD patients and linked to increased synaptic dysfunctions (38, 39). Moreover, inhibition of α_1-adrenergic signaling ameliorates memory impairments in AD transgenic mice (40–42). Therefore, it is of interest to investigate whether sST2 is involved in the neuroprotective effects due to the inhibition of adrenergic

signaling. Furthermore, our results show that trazodone suppresses the β-adrenergic–mediated increase of sST2 despite low receptor affinity (43), suggesting possible indirect downstream effects that require further investigation. While our study focuses on the effects of adrenergic inhibition on brain endothelial cells, it is important to note that adrenergic receptors are expressed by several brain cell populations, including neurons and astrocytes (44). Therefore, further investigation is needed to examine the cell-type-dependent effects of adrenergic inhibition in AD.

Beyond adrenergic signaling, synaptic membrane proteome analysis reveals distinct regulation patterns. Specifically, trazodone restores pathways downregulated in APP/PS1 mice to WT levels while also bidirectionally regulating pathways that show similar expression in both WT and APP/PS1 mice. These differential effects suggest that trazodone may act on multiple receptors beyond adrenergic receptors, including histamine H1 and serotonin receptors, which warrants future receptor-specific studies.

Epidemiological studies report mixed results regarding the association between trazodone use and cognitive performance (35, 45) but suggest no association between trazodone and dementia risk (46). However, as trazodone is prescribed to individuals with neurological disorders, including major depressive disorder and sleep disorder, such associations may be confounded by indication. Therefore, randomized controlled trials are essential to fully understand the neuroprotective effects of trazodone. As with any sedative medications, trazodone carries the risk of side effects, including headaches, dizziness, and somnolence (47), which may impact medication adherence. This should be carefully considered when evaluating the opportunities for repurposing trazodone. Notably, trazodone is well tolerated at insomnia-targeting doses of 25 to 100 mg/day with few adverse effects (48), which may increase compliance among clinical trial participants taking trazodone. Of note, an ongoing pilot phase IV clinical trial (NCT05209035) is examining the effects of trazodone in individuals with comorbid mild cognitive impairment and sleep apnea (49). Overall, trazodone's potential therapeutic benefits in AD warrant further research.

In summary, drug repurposing is a powerful approach to accelerating therapeutic development. Our study highlights trazodone, an FDA-approved antidepressant, as a promising candidate for repurposing for AD treatment. Trazodone negatively regulates sST2, enhances microglial–Aβ interactions, alleviates Aβ pathology, and rescues synaptic deficits in AD transgenic mice. Our findings collectively highlight the potential of trazodone to target immune and synaptic dysfunctions in AD, offering a therapeutic approach for AD treatment.

Materials and Methods

For details regarding the methods and materials, please refer to *SI Appendix, Materials and Methods*.

Participant Recruitment and Assessment of the Hong Kong Chinese Cohort. The recruitment of participants from the Hong Kong Chinese cohort was approved by the Human Research Ethics Committee of the Hong Kong University of Science and Technology (HKUST; HREP-2023-0179), the Human Participants Research Panel of the HKUST (CRP#180), and the Clinical Research & Ethical Committees of the Joint Chinese University of Hong Kong–New Territories Eastern Cluster for the Prince of Wales Hospital (CREC ref. no. 2015.461). Written informed consent was obtained from all participants or the legal guardians of participants with advanced dementia prior to enrollment.

Mice. C57BL/6 and APPswe/PS1dE9 mice were housed in the Laboratory Animal Facility at HKUST. Experiments were conducted in accordance with guidelines and regulations provided by the Animal Ethics Committee of HKUST.

In Vivo Administration of Trazodone in Mice and Tissue Collection. Mice received trazodone by oral gavage for 14 consecutive days. Blood and forebrains were collected for downstream experiments.

hCMEC/D3 Cell Line. hCMEC/D3 was obtained from Cedarlane Laboratories and cultured according to the provided protocol.

Drug Treatment of Endothelial Cells and Collection of Conditioned Media. Drugs were treated in hCMEC/D3 cells, and cell media were collected after drug treatment.

Measurement of sST2 Protein Levels. The plasma levels of sST2 in 800 individuals from the Hong Kong Chinese cohort, the levels of sST2 secreted by the hCMEC/D3 cell line, and the serum level of sST2 in mice were measured.

RNA Preparation from Frozen Mouse Cerebral Cortices and Endothelial Cells. RNA was extracted from frozen mouse cerebral cortices.

Quantitative Real Time PCR (RT-qPCR). Extracted RNA was converted into full-length complementary DNA (cDNA) and RT-qPCR was conducted.

Bulk RNA Sequencing Analysis. We conducted bulk RNA sequencing analysis on mouse cortices.

Isolation of Synaptic membranes with Enriched Postsynaptic Densities. Synaptic membrane fractions were isolated from mouse hippocampi as previously described with some modifications (50).

Mass Spectrometry and Analysis of Synaptic Membrane Fraction. The samples were analyzed using the TimsTOF Pro mass spectrometer (Bruker Daltonics) coupled with an Evosep One LC system (Evosep). Captured data were processed using Spectronaut (version 19.6.250122.62635, Biognosys AG) for a directDIA search with the UniProt Mouse database (downloaded on 26 March 2023).

Immunohistochemistry and Image Quantification. We used antibodies for Aβ, IBA1, PSD-95, VGLUT1, NeuN, and neurofilament for immunostaining.

Electrophysiology. LTP was recorded as previously described (51).

Statistical Analysis. The data presented herein are expressed as the arithmetic mean ± SEM. Statistical analyses were performed using two-tailed unpaired Student's *t* test or one-way ANOVA with a post hoc Tukey's test or Dunnett's test in GraphPad Prism (version 9.0.2) or linear regression analysis using the lmrob() function in the robustbase R package (version 0.99.6). For correlation analysis, Pearson's correlation analysis in GraphPad Prism was used to determine r and *P* values. The specific statistical test used is denoted in the figure legends. Graphical representations of data were generated using GraphPad Prism or Morpheus.

Data, Materials, and Software Availability. The cortical transcriptome data are deposited in Gene Expression Omnibus (GEO) under the accession number (GSE314159) (52), and the synaptic proteome data is deposited to the ProteomeXchange Consortium via the PRIDE (53) partner repository with the dataset identifier PXD071776 (54). The associations between plasma sST2 levels and commonly used medications in AD patients from the Hong Kong Chinese cohort are provided in Dataset S1. The association between plasma sST2 levels and clinical diagnosis stratified by trazodone usage is provided in Dataset S2. The differentially expressed genes in the cortex between trazodone-treated and untreated APP/PS1 mice are provided in Dataset S3. The differentially expressed proteins in the hippocampal synaptic membrane between trazodone-treated and untreated APP/PS1 mice are provided in Dataset S4. Regarding Hong Kong Chinese Cohort, the consent forms signed by participants state that the research content will be kept private under the supervision of the hospital and research team. As such, individual data will only be made available and shared in formal collaboration. Any applications for data sharing and project collaboration can be made to HKUST at sklneurosci@ust.hk, where a review panel hosted at HKUST will process and review the applications. Previously published data were used for this work (18).

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Author affiliations: [a]Division of Life Science, State Key Laboratory of Nervous System Disorders, Daniel and Mayce Yu Molecular Neuroscience Center, The Hong Kong University of Science and Technology, Hong Kong Special Administrative Region, China; [b]InnoHK Hong Kong Center for Neurodegenerative Diseases, Hong Kong Special Administrative Region, China; [c]Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, Therese Pei Fong Chow Research Centre for Prevention of Dementia, Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; [d]Therese Pei Fong Chow Research Centre for Prevention of Dementia, Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; [e]Guangdong Provincial Key Laboratory of Brain Science, Disease and Drug Development, HKUST Shenzhen Research Institute, Shenzhen-Hong Kong Institute of Brain Science, Shenzhen, Guangdong 518057, China; and [f]Shenzhen Institutes of Advanced Technology-Hong Kong University of Science and Technology Joint Laboratory for Brain Science, Shenzhen, Guangdong 518055, China

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