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LETTER

REPLY TO PENG AND ZHAO:

Loss of endocytic protein TOM1 in Alzheimer's disease

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We described a reduction of target of Myb1 (TOM1) protein levels by Western blot in the postmortem hippocampus of subjects with Alzheimer's disease (AD) versus nondemented subjects (1), validating similar findings by an independent research group in a separate human cohort (2). Based on single-cell transcriptomic data (3), Peng and Zhao (4) conclude that TOM1 levels are, contrariwise to our findings, higher in AD. Although we do not disagree with their hypothesis that TOM1 expression could be up-regulated in AD, at least at early disease stages, precautions should be taken when comparing our findings to theirs. First, we determined the protein levels in the hippocampus whereas the RNAseq was performed in the prefrontal cortex. Discrepancies could therefore be related to differential patterns of expression in distinct brain regions, as well as the poor association between RNA and protein levels. Another explanation is the methodology applied by Peng and Zhao (4) to interpret the transcriptomic data. In the original study, comparison of gene expression in cells isolated from subjects with AD versus nondemented subjects has demonstrated that TOM1 is not among the 1,031 unique differentially expressed genes (DEGs). Due to the numerous challenges of single-cell transcriptomic studies, it is not surprising that only a small fraction of highly expressing genes could be differentially detected (5). Although excitatory neurons from the nonpathology group show slightly higher differential expression values of TOM1 versus those from early- and late-pathology groups (IndModel.adj.pvals 1.01E-07 and 6.14E-23, respectively), these differences did not reach the overall criteria of significance (DEGs.Ind.Model and DEGs.Ind.Mix.models) (Tables 1–3).

In their analysis, Peng and Zhao (4) also describe that TOM1 expression is higher in microglia from patients with AD versus controls. This conclusion seems to be based solely on the IndModel.FC since IndModel.adj.pvals are clearly not significant. Peng and Zhao (4) also do not take into consideration other cell types when discussing TOM1 levels, including inhibitory neurons, astrocytes, oligodendrocytes, and oligodendrocyte progenitor cells. TOM1 levels are not significantly altered in these cells; however, when IndModel.FC is used to assess changes in gene expression, it shows reductions in TOM1 levels in most cells in subjects with early and late AD versus controls. By extrapolating this analysis, one could suggest that expression of TOM1 in individual cell types is differentially altered by AD and its overall levels would depend on the sum of individual cellular changes. As the bulk RNAseq data in the single-cell transcriptomic study were not directly accessible, we determined the overall TOM1 levels using the normalized bulk data from the Mayo Clinic Pilot RNAseq study (AMP-AD: syn3157268) (6). The Mayo Clinic study was performed in the temporal cortex of subjects with AD and non-AD controls and quantification of TOM1 expression demonstrated an overall reduction in AD (Fig. 1). Whether changes in RNA levels in individual cell populations or brain regions translate to changes in protein levels still needs further investigation. Considering the important role of TOM1 in regulating endocytic processes that counterbalance proinflammatory responses and β-amyloid (Aβ) deposition (1, 2), more studies are clearly needed to better address the levels and role of TOM1 in AD.

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The authors declare no competing interest.

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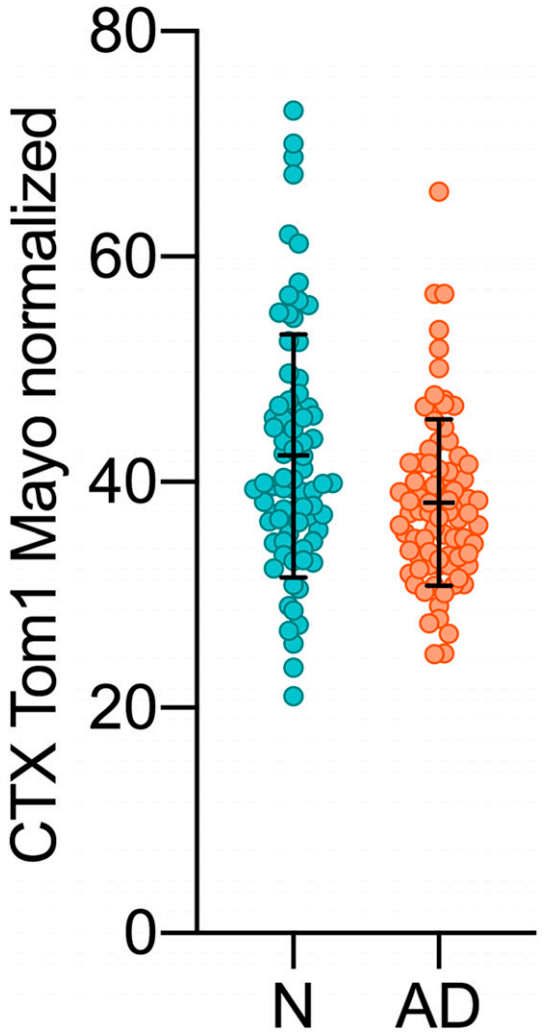

Fig. 1. Quantification of TOM1 expression in the temporal cortex of AD and non-AD controls. N, non-AD controls; AD, Alzheimer's disease.

Table 1. Differential expression of TOM1 between no-pathology and pathology groups

Cell type	IndModel.adj.pval	No.pathology.mean	Pathology.mean	IndModel.FC	MixedModel.z	MixedModel.p	DEGs.Ind.Model	DEGs.Ind. Mix.models
EX	3.00E-17	0.128926005	0.144562165	0.165146717	2.026028278	0.042761887	False	False
IN	0.015006292	0.085603478	0.088948236	0.055296583	0.449591041	0.653005349	False	False
AST	0.374592502	0.057867685	0.04303492	−0.427250122	−0.787603423	0.430928712	False	False
Oli	0.451636534	0.032320558	0.028495137	−0.18173637	−1.551603317	0.120757169	False	False
Opc	0.982386698	0.048697314	0.045452903	−0.099469773	0.757447002	0.448782106	False	False
Mic	0.854448758	0.035923584	0.038418993	0.09688839	0.522761051	0.601140547	False	False

EX, excitatory neurons; IN, inhibitory neurons; AST, astrocytes; Oli, oligodendrocytes; Opc, oligodendrocyte precursor cells; Mic, microglia.

Table 2. Differential expression of TOM1 between no-pathology and early-pathology groups

Cell type	IndModel.adj.pval	No.pathology.mean	Early.pathology.mean	IndModel.FC	MixedModel.z	MixedModel.p	DEGs.Ind.Model	DEGs.Ind. Mix.models
EX	6.14E-23	0.128393338	0.146853039	0.193802782	1.80129363	0.071656611	False	False
IN	1.59E-06	0.083380531	0.082797952	−0.010115485	−0.149499593	0.881159431	False	False
AST	0.393241093	0.057524363	0.043917183	−0.389387572	−1.013670654	0.310739931	False	False
Oli	0.281710458	0.031353627	0.027925276	−0.167060773	−1.758587131	0.07864766	False	False
Opc	0.835254702	0.047857848	0.044720057	−0.097833498	0.441953455	0.658522888	False	False
Mic	0.979582704	0.035452366	0.042145693	0.249503325	0.592315396	0.553639408	False	False

EX, excitatory neurons; IN, inhibitory neurons; AST, astrocytes; Oli, oligodendrocytes; Opc, oligodendrocyte precursor cells; Mic, microglia.

Table 3. Differential expression of TOM1 between early-pathology and late-pathology groups

Cell type	IndModel.adj.pval	Late.pathology. mean	Early.pathology. mean	IndModel.FC	MixedModel.z	MixedModel.p	DEGs.Ind.Model	DEGs.Ind. Mix.models
EX	1.01E-07	0.09445273	0.100376788	–0.087761279	0.544891865	0.585827892	False	False
IN	1.24E-07	0.072740517	0.064444927	0.174692386	0.712095737	0.476405494	False	False
AST	0.976687979	0.039483977	0.043085957	–0.125950428	0.404941407	0.685520581	False	False
Oli	0.28765617	0.02858149	0.029365221	–0.039027361	0.82582097	0.408905657	False	False
Opc	0.629135398	0.044360541	0.044510058	–0.004854422	0.501957966	0.615697089	False	False
Mic	0.89908377	0.034652334	0.044636471	–0.365270416	0.157557825	0.874805239	False	False

EX, excitatory neurons; IN, inhibitory neurons; AST, astrocytes; Oli, oligodendrocytes; Opc, oligodendrocyte precursor cells; Mic, microglia.

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