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Corrigendum: Comprehensive expression analysis with cell-type-specific transcriptome in ALS-linked mutant SOD1 mice: Revisiting the active role of glial cells in disease

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transcriptome, amyotrophic lateral sclerosis, microarray, neurodegeneration, astrocytes, microglia, superoxide dismutase 1 (SOD1), lipids/lipoproteins

A corrigendum on

Comprehensive expression analysis with cell-type-specific transcriptome in ALS-linked mutant SOD1 mice: Revisiting the active role of glial cells in disease

by Yamashita, H., Komine, O., Fujimori-Tonou, N., and Yamanaka, K. (2023). *Front. Cell. Neurosci.* 16:1045647. doi: 10.3389/fncel.2022.1045647

In the published article, there was an error in Figure 2 as published. The fourth column heading in Figure 2B was falsely written as "Spinal cord (G93A)." The correct column heading is "Spinal cord (G37R)." The corrected Figure 2 appears below.

In the published article, there was an error in Figure 3 as published. The *Tnfrs12a* values shown in Figure 3 are different from the data in 207 DEGs. The corrected Figure 3 appears below.

In the published article, there was an error in Figure 5 and text as published. The fold change of *Abca1* in the spinal cords of $SOD1^{G85R}$ mice shown in Figure 5 is 2.0, but this is a rounded value, which was 1.9779. *Abca1* is not included in Table S5, which shows the list of 207 DEGs with more than strict 2-fold change, although the 1.9779-fold change of $SOD1^{G85R}$ mice is statistically significant as well as the 3.3-fold changes in the spinal cords of $SOD1^{G37R}$ and $SOD1^{G93A}$ mice. The corrected Figure 5 appears below.

A correction has been made to Results and discussion, Predicted pathomechanism among different cell types in SOD1-ALS mice related to TREM2, apolipoprotein E, and lipoproteins, Astrocytic changes. This sentence previously stated:

"*Abca1* was found in the 207 DEGs and was abundant in astrocytes and upregulated in P120 $SOD1^{G93A}$ astrocytes."

The corrected sentence appears below:

"*Abca1* was abundant in astrocytes and upregulated in P120 $SOD1^{G93A}$ astrocytes."

In the published article, there was an error in Supplementary Table 5. Fold changes and *p*-value of three SOD1 mutant mice in Aspg, Casp12, Psmb8, Ctsd, Ctsc, Ctsh, Ctsl, Ctss, and Ctsz (214^{th} to 222^{nd} rows in uncollapsed sheet, columns H to M) were shifted one line by a handling error. The Supplementary Table 5 has been updated.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

Publisher's note

A

PANTHER Protein Class	REFLIST (21997)	Input (207)	Expected	Fold Enrichment	*p*-value	FDR
Integrin	29	4	0.27	14.66	0.000243	0.00798
⇒ Cell adhesion molecule	306	10	2.88	3.47	0.000802	0.0226
Basic leucine zipper transcription factor	43	5	0.4	12.36	0.0000829	0.00327
Glycosidase	41	4	0.39	10.37	0.000811	0.02
Immunoglobulin receptor superfamily	284	12	2.67	4.49	0.0000234	0.00115
⇒ Defense / immunity protein	901	23	8.48	2.71	0.0000187	0.00123
Protease inhibitor	175	7	1.65	4.25	0.00164	0.0358

B

Gene Symbol	Spinal cord (G93A)		Spinal cord (G85R)		Spinal cord (G37R)		Integrated transcriptome (A.U.)					MG (F.C)	Astrocytes (F.C.)		Gene Title
	F.C.	*p*-value	F.C.	*p*-value	F.C.	*p*-value	Motor Neuron	Neuron	Astrocytes	Microglia	Oligodendrocyte	G93A-P90	G93A-P90	G93A-P120	
Cebpa	4.1	0.000194	2.3	0.004248	3.8	0.000319	19	46	213	3045	9	1.2	1.8	1.1	CCAAT/enhancer binding protein (C/EBP), alpha
Cebpb	3.3	0.001392	2.0	0.008924	2.3	0.000314	963	167	295	3247	25	0.9	1.5	4.3	CCAAT/enhancer binding protein (C/EBP), beta
Cebpd	10.8	0.000369	6.5	0.003752	9.2	0.000054	353	120	3458	4436	22	0.6	3.2	9.1	CCAAT/enhancer binding protein (C/EBP), delta
Irf8	5.4	0.000109	3.1	0.006585	4.1	0.000080	24	21	17	3892	18	1.4	2.9	3.7	interferon regulatory factor 8

C

207 Differentially expressed genes (207 DEGs)		
	Microglia-enriched	**121 genes**
	Astrocyte-enriched	**16 genes**
	Motor neuron-enriched	**3 genes**
	Neuron-enriched	**3 genes**
	Oligodendrocyte-enriched	**2 genes**
	Unclassified	**62 genes**

FIGURE 2
Enrichment analysis using the 207 DEGs and classification of each of the 207 DEGs by cell types with high expression. **(A)** Enrichment analysis using the 207 DEGs as an input. The first column shows the name of the PANTHER classification category. The second column shows the number of genes in the reference list that map to this particular PANTHER classification category. The total number of genes in the reference list is 21,997. The third column shows the observed number of genes in our input list that map to this PANTHER classification category. The fourth column shows the expected value, which is the number of genes we would expect in our list for this PANTHER category, based on the reference list. The fifth column shows the fold enrichment, which is the ratio of the value of column 3 (input: observed number) over that of column 4 (expected number). The sixth column shows the raw *p*-values. The seventh column shows the *q*-value (adjusted *p*-value, reflecting the false discovery rate) as calculated by the Benjamini-Hochberg procedure. *Cell adhesion molecule* is in the parent category of integrin, so it is shown in the row below. Similarly, *defense/immunity protein* is the parent category of *immunoglobulin receptor superfamily*. Therefore, they are indicated with arrows. **(B)** Representative transcription factors in the 207 DEGs. Three CCAAT/enhancer binding proteins and interferon regulatory factor 8 are shown. **(C)** All of the 207 DEGs were classified into cell types in which each gene is highly expressed; *Unclassified* are the genes that are not highly expressed in one particular cell type. MG, microglia.

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Enriched cell-type & Function	Gene Symbol	Spinal cord (F.C.)			Integrated transcriptome (A.U.)					MG (F.C.)	Astrocytes (F.C.)		Gene Title
		G93A	G85R	G37R	Motor Neurons	Neurons	Astro-cytes	Micro-glia	Oligoden drocytes	G93A-P90	G93A-P90	G93A-P120	
MN Receptor	Tnfrsf12a (Fn14)	3.8	2.3	2.8	1034	188	110	146	66	2.1	1.9	2.3	tumor necrosis factor receptor superfamily, member 12a
Ligand	Tnfsf12 (TWEAK) /Tnfsfm13	1.3	1.2	1.2	221	105	215	813	105	0.8	1.0	1.6	tumor necrosis factor superfamily,member12/ membrane-bound member 13
MN	Hspb1(Hsp25)	3.5	4.9	4.7	11847	314	828	836	198	1.5	1.3	4.8	heat shock protein 1
MN Ligand	Spp1 (Osteopontin)	2.4	2.0	2.8	16807	173	19	1509	6	16.8	0.7	0.8	secreted phosphoprotein 1
Receptor	Cd44	5.0	3.5	4.0	11	157	1175	5431	26	0.7	2.4	7.8	CD44 antigen
Receptor	Itgam (CD11b)	2.6	2.6	2.7	25	5	34	1159	30	1.2	2.2	0.6	integrin alpha M
Receptor	Itgb2(CD18)	8.6	6.0	10.3	32	79	33	10915	89	1.5	4.5	15.1	integrin beta 2
N Receptor	Met (HGF receptor)	3.2	3.2	3.3	7	1025	14	188	5	0.7	2.4	3.2	met proto-oncogene (Hepatocyte growth factor receptor)
Ligand	Hgf	1.4	1.6	7.5	21	11	208	176	11	1.3	2.4	0.4	hepatocyte growth factor
N	Sulf1	2.5	2.1	2.4	43	1455	181	59	20	0.4	3.0	4.2	sulfatase 1
N Ligand	Igf1	2.4	2.7	2.3	13	1887	158	128	5	10.9	0.6	2.8	insulin-like growth factor 1
N Ligand	Igf1	1.7	3.2	3.4	19	267	69	274	53	9.7	1.4	2.8	insulin-like growth factor 1
Receptor	Igf1r	0.9	0.9	1.0	338	626	1137	1020	266	0.7	0.7	1.0	insulin-like growth factor I receptor
OL	Plat	2.7	2.1	2.5	451	656	1399	81	19735	0.9	1.4	2.1	plasminogen activator, tissue
OL Ligand	Klk6	2.5	2.0	2.5	189	102	50	386	1670	1.1	1.4	3.5	kallikrein related-peptidase 6
Receptor	F2r (PAR-1)	0.9	0.9	1.1	946	1179	4736	1402	116	2.3	1.1	0.8	Proteinase-activated receptor 1
Receptor	F2rl1 (PAR-2)	0.8	1.6	3.8	6	53	10	9	14	1.0	0.8	1.4	Proteinase-activated receptor 2

FIGURE 3
Representative motor neuron-enriched genes, neuron-enriched genes, and oligodendrocyte-enriched genes in 207 DEGs were analyzed using the integrated transcriptome and $SOD1^{G93A}$ cell-type transcriptome. The 3rd to 5th columns show the fold changes in each gene expression in $SOD1^{G93A}$, $SOD1^{G85R}$, and $SOD1^{G37R}$ mouse spinal cords compared to control samples, respectively. Genes with dark gray backgrounds in the 3rd to 5th columns that indicate fold changes (F.C.) are not included in the 207 DEGs. The 6th to 10th columns show the integrated transcriptome. The 11th column shows the fold change in expression of each gene in P90 $SOD1^{G93A}$ microglia relative to control microglia. The 12th to 13th columns show the fold change in expression of each gene in $SOD1^{G93A}$ astrocytes (P90 or P120) relative to control astrocytes. MN, motor neurons; N, neurons; MG, microglia; OL, oligodendrocytes.

A

Function	Gene Symbol	Spinal cord (F.C.)			Integrated transcriptome (A.U.)					Microglia (F.C.)	Astrocytes (F.C.)		Gene Title
		G37R	G85R	G93A	Motor Neurons	Neurons	Astrocytes	Microglia	Oligodendrocytes	G93A-P90	G93A-P90	G93A-P120	
Transporter	Abca1	3.3	2.0	3.3	285	443	11313	6239	267	1.5	1.8	1.9	ATP-binding cassette, sub-family A, member 1
Apolipoproteins	Clu	1.7	1.9	2.1	7099	4736	40820	223	636	0.6	1.4	2.0	Clusterin (apolipoprotein J)
Apolipoproteins	Apoe	1.7	1.5	1.6	1216	1831	43262	22151	1115	2.2	2.2	7.0	apolipoprotein E
Receptor	Trem2	8.6	6.6	25.6	4	11	8	1659	15	3.0	12.8	7.7	triggering receptor expressed on myeloid cells 2
Receptor	Ldlr	0.6	0.9	0.6	2092	672	3108	1292	8837	1.4	0.7	0.4	low density lipoprotein receptor
Receptor	Lrp1	1.4	1.4	1.5	1172	1693	5922	2998	71	1.3	1.2	1.2	low density lipoprotein receptor-related protein 1

B

Molecules	Fold change (G93A-P120-Astrocytes)	Fold change (G93A-P90-Microglia)	Legend	
ApoE	7.0	2.2	Cholesterol (Chol)	LDLR
Clusterin	2.0	0.6	Lipoproteins	LDR1
ABCA1	1.9	1.5	ApoE + Chol	SOD1 aggregates
TREM2	7.7	3.0	Clusterin +Chol	Myelin debris

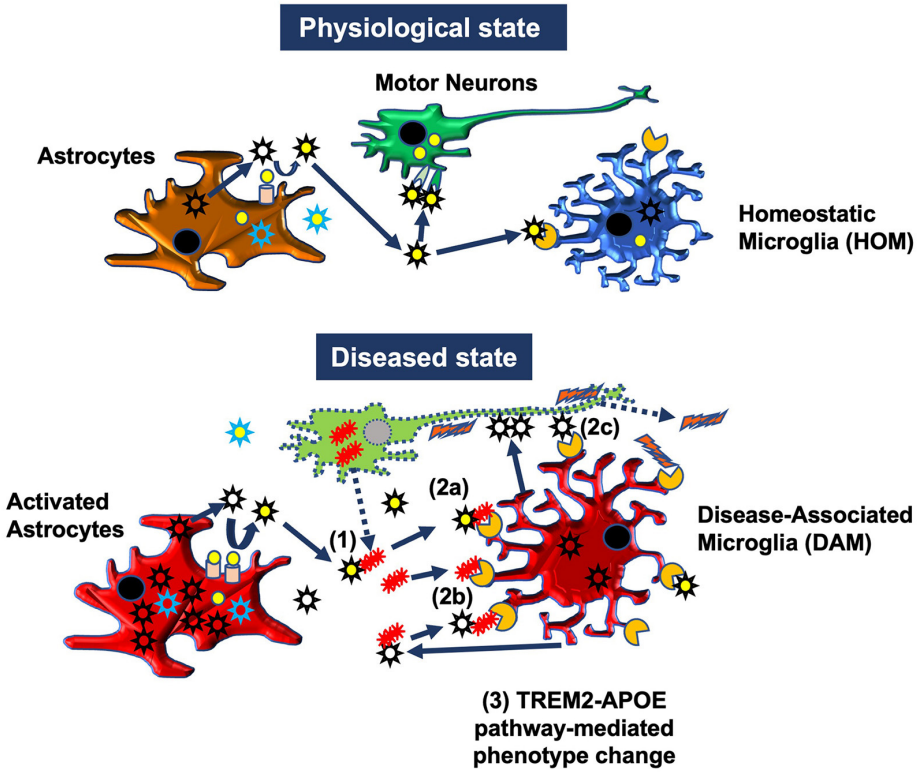

FIGURE 5
Model of the pathomechanism among different cell types in spinal cords of mutant SOD1 mice related to TREM2, apolipoprotein E, and lipoproteins. **(A)** Gene expression analysis of the relevant transporter *Abca1*, apolipoproteins *Apoe* and *Clu*, and receptors *Trem2, Ldlr*, and *Lrp1*, using integrated and $SOD1^{G93A}$ cell type transcriptomes. **(B)** Physiological state: cholesterol is transported from astrocytes to motor neurons and microglia *via* lipoproteins. Diseased state: (1) Mutant SOD1 aggregates are released from diseased motor neurons and bind to lipoproteins in the intercellular space. (2a) Microglia phagocytose SOD1 aggregate-lipoprotein complexes *via* TREM2. (2b) Microglia phagocytose SOD1 aggregates with or without ApoE *via* TREM2. (2c) Microglia phagocytose ApoE-bound motor neurons *via* TREM2. (3) TREM2-mediated phagocytosis changes the phenotype from HOM to DAM in microglia *via* ApoE signaling. Excessive DAM activation may contribute to exacerbation of ALS pathology.