
Supplementary information

Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy

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Supplementary Information

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Extended Data Video 1. CD3 and Iba1 staining in hippocampus of TE4 mice

Iba1 (red) and CD3 (green) staining in 9.5-month TE4 mice with tau-pathology in dentate gyrus (DG). Scale bar=10µm.

Extended Data Video 2. CD11c, CD8 and Iba1 staining in hippocampus of TE4 mice

Iba1 (blue), CD11c (red) and CD8 (green) staining in 9.5-month TE4 mice with tau pathology in DG. Scale bar=15µm.

Supplementary Table 1. Single cell immune sequencing sample information

ID	Age (months)	Sex	Genetics	Genetic background	Brain regions for sequencing	Total cell number	Microglia cell number	Median genes per microglia	T cell number	Median genes per T cell	Number of Mice
1	9.5	M	E4-Replicate1	BL6	CD45 ^{Total} Cortex and Hippocampus	22248	20547	2091	489	2044	10
2	9.5	M	E4-Replicate2	BL6	CD45 ^{Total} Cortex and Hippocampus	4640	4107	1466	198	1762	5
3	9.5	M	A/PE4	BL6	CD45 ^{Total} Cortex and Hippocampus	9869	9216	2019	263	3044	5
4	9.5	M	TE4-Replicate1	BL6	CD45 ^{Total} Cortex and Hippocampus	8570	7210	2913	745	2111	5
5	9.5	M	TE4-Replicate2	BL6	CD45 ^{Total} Cortex and Hippocampus	6305	4915	1470	700	1782	5
6	9.5	M	E4-Replicate1	BL6	CD45 ^{high} Cortex and Hippocampus	9489	501	2158	3396	1897	10
7	9.5	M	E4-Replicate2	BL6	CD45 ^{high} Cortex and Hippocampus	6019	544	2029	2251	1498	5
8	9.5	M	A/PE4	BL6	CD45 ^{high} Cortex and Hippocampus	7161	1352	2822	2300	1748	5
9	9.5	M	TE4-Replicate1	BL6	CD45 ^{high} Cortex and Hippocampus	6741	292	2060	4587	2352	5
10	9.5	M	TE4-Replicate2	BL6	CD45 ^{high} Cortex and Hippocampus	11364	1765	2322	5602	1740	5
11	9.5	M	E4-Replicate1	BL6	CD45 ^{Total} Meninges	27042	950	1718	1600	1708	10
12	9.5	M	E4-Replicate2	BL6	CD45 ^{Total} Meninges	13554	1358	2030	1279	1298	5

13	9.5	M	A/PE4	BL6	CD45 ^{Total} Meninges	11197	593	1786	468	1517	5
14	9.5	M	TE4- Replicate1	BL6	CD45 ^{Total} Meninges	14314	80	2886	1497	1953	5
15	9.5	M	TE4- Replicate2	BL6	CD45 ^{Total} Meninges	10741	653	1658	1053	1380	5
16	9.5	M	TE4-Ctrl (IgG)	BL6	CD45 ^{Total} Cortex and Hippocampus	12572	11310	2068	335	1779	5
17	9.5	M	TE4- α T	BL6	CD45 ^{Total} Cortex and Hippocampus	15080	14009	1974	74	1605	5

Supplementary Table 2. Alzheimer's disease patient sample information

ID	Age	Sex	ApoE isoform	Braak Score	Postmortem interval (PMI)
1	70	F	E4/E4	I	2
2	78	M	E2/E2	I	1.66
3	81	F	E4/E4	II	3
4	80	F	E4/E4	VI	1.33
5	68	F	E2/E2	VI	3.08
6	80	M	E3/E3	VI	2.16
7	83	M	E4/E4	VI	2.83
8	89	F	E3/E3	VI	2.7
9	90	F	E3/E3	VI	2.53
10	89	F	E4/E4	VI	2.5

Supplementary Table 3. Immune cell number of each cluster in brain parenchyma and meninges

CD45^{Total} immune cell number per cluster in brain parenchyma (Fig. 1f)

Cluster	Genotype	Replica	Total cell number	Cell number/Cluster	Percentage (%)
0 Microglia	E4	Rep1	22248	20547	92.4
0 Microglia	E4	Rep2	4640	4107	88.5
0 Microglia	A/PE4	Rep1	9869	9216	93.4
0 Microglia	TE4	Rep1	8570	7210	84.1
0 Microglia	TE4	Rep2	6305	4915	78.0
1 T cells	E4	Rep1	22248	489	2.2
1 T cells	E4	Rep2	4640	198	4.3
1 T cells	A/PE4	Rep1	9869	263	2.7
1 T cells	TE4	Rep1	8570	745	8.7
1 T cells	TE4	Rep2	6305	700	11.1
2 Proliferating cells	E4	Rep1	22248	226	1.0
2 Proliferating cells	E4	Rep2	4640	74	1.6
2 Proliferating cells	A/PE4	Rep1	9869	145	1.5
2 Proliferating cells	TE4	Rep1	8570	114	1.3
2 Proliferating cells	TE4	Rep2	6305	244	3.9
3 Neutrophils	E4	Rep1	22248	349	1.6
3 Neutrophils	E4	Rep2	4640	54	1.2
3 Neutrophils	A/PE4	Rep1	9869	101	1.0
3 Neutrophils	TE4	Rep1	8570	118	1.4
3 Neutrophils	TE4	Rep2	6305	149	2.4
4 B cells	E4	Rep1	22248	207	0.9
4 B cells	E4	Rep2	4640	84	1.8
4 B cells	A/PE4	Rep1	9869	32	0.3
4 B cells	TE4	Rep1	8570	64	0.7
4 B cells	TE4	Rep2	6305	57	0.9

5 DCs	E4	Rep1	22248	126	0.6
5 DCs	E4	Rep2	4640	37	0.8
5 DCs	A/PE4	Rep1	9869	28	0.3
5 DCs	TE4	Rep1	8570	93	1.1
5 DCs	TE4	Rep2	6305	116	1.8
6 NKs	E4	Rep1	22248	97	0.4
6 NKs	E4	Rep2	4640	21	0.5
6 NKs	A/PE4	Rep1	9869	14	0.1
6 NKs	TE4	Rep1	8570	76	0.9
6 NKs	TE4	Rep2	6305	55	0.9
7 Macrophages Fn1+	E4	Rep1	22248	92	0.4
7 Macrophages Fn1 ⁺	E4	Rep2	4640	19	0.4
7 Macrophages Fn1 ⁺	A/PE4	Rep1	9869	14	0.1
7 Macrophages Fn1 ⁺	TE4	Rep1	8570	37	0.4
7 Macrophages Fn1 ⁺	TE4	Rep2	6305	20	0.3
8 $\gamma\delta$ T cells	E4	Rep1	22248	19	0.1
8 $\gamma\delta$ T cells	E4	Rep2	4640	18	0.4
8 $\gamma\delta$ T cells	A/PE4	Rep1	9869	26	0.3
8 $\gamma\delta$ T cells	TE4	Rep1	8570	54	0.6
8 $\gamma\delta$ T cells	TE4	Rep2	6305	34	0.5
9 Macrophages	E4	Rep1	22248	57	0.3
9 Macrophages	E4	Rep2	4640	19	0.4
9 Macrophages	A/PE4	Rep1	9869	22	0.2
9 Macrophages	TE4	Rep1	8570	31	0.4
9 Macrophages	TE4	Rep2	6305	5	0.1
10 ILCs	E4	Rep1	22248	33	0.1
10 ILCs	E4	Rep2	4640	4	0.1
10 ILCs	A/PE4	Rep1	9869	7	0.1
10 ILCs	TE4	Rep1	8570	24	0.3
10 ILCs	TE4	Rep2	6305	9	0.1

11 Mast cells	E4	Rep1	22248	6	0.0
11 Mast cells	E4	Rep2	4640	5	0.1
11 Mast cells	A/PE4	Rep1	9869	1	0.0
11 Mast cells	TE4	Rep1	8570	4	0.0
11 Mast cells	TE4	Rep2	6305	1	0.0

CD45^{Total} immune cell number per cluster in meninges (Fig. 1h)

Cluster	Genotype	Replica	Total cell number	Cell number/Cluster	Percentage (%)
0 Neutrophils	E4	Rep1	27042	10165	37.6
0 Neutrophils	E4	Rep2	13554	5061	37.3
0 Neutrophils	A/PE4	Rep1	11197	3963	35.4
0 Neutrophils	TE4	Rep1	14314	5923	41.4
0 Neutrophils	TE4	Rep2	10741	4059	37.8
1 B cells	E4	Rep1	27042	6590	24.4
1 B cells	E4	Rep2	13554	1632	12.0
1 B cells	A/PE4	Rep1	11197	3237	28.9
1 B cells	TE4	Rep1	14314	2394	16.7
1 B cells	TE4	Rep2	10741	1977	18.4
2 Proliferating cells	E4	Rep1	27042	3392	12.5
2 Proliferating cells	E4	Rep2	13554	1327	9.8
2 Proliferating cells	A/PE4	Rep1	11197	1336	11.9
2 Proliferating cells	TE4	Rep1	14314	1337	9.3
2 Proliferating cells	TE4	Rep2	10741	1252	11.7
3 T cells	E4	Rep1	27042	1600	5.9
3 T cells	E4	Rep2	13554	1279	9.4
3 T cells	A/PE4	Rep1	11197	468	4.2
3 T cells	TE4	Rep1	14314	1497	10.5

3 T cells	TE4	Rep2	10741	1053	9.8
4 Macrophages Fn1 ⁺	E4	Rep1	27042	1701	6.3
4 Macrophages Fn1 ⁺	E4	Rep2	13554	916	6.8
4 Macrophages Fn1 ⁺	A/PE4	Rep1	11197	635	5.7
4 Macrophages Fn1 ⁺	TE4	Rep1	14314	959	6.7
4 Macrophages Fn1 ⁺	TE4	Rep2	10741	570	5.3
5 DCs	E4	Rep1	27042	1308	4.8
5 DCs	E4	Rep2	13554	997	7.4
5 DCs	A/PE4	Rep1	11197	574	5.1
5 DCs	TE4	Rep1	14314	1132	7.9
5 DCs	TE4	Rep2	10741	518	4.8
6 Microglia	E4	Rep1	27042	950	3.5
6 Microglia	E4	Rep2	13554	1358	10.0
6 Microglia	A/PE4	Rep1	11197	593	5.3
6 Microglia	TE4	Rep1	14314	80	0.6
6 Microglia	TE4	Rep2	10741	653	6.1
7 NKs	E4	Rep1	27042	427	1.6
7 NKs	E4	Rep2	13554	307	2.3
7 NKs	A/PE4	Rep1	11197	122	1.1
7 NKs	TE4	Rep1	14314	385	2.7
7 NKs	TE4	Rep2	10741	197	1.8
8 Macrophages	E4	Rep1	27042	489	1.8
8 Macrophages	E4	Rep2	13554	299	2.2
8 Macrophages	A/PE4	Rep1	11197	107	1.0
8 Macrophages	TE4	Rep1	14314	293	2.0
8 Macrophages	TE4	Rep2	10741	232	2.2
9 ILCs	E4	Rep1	27042	240	0.9
9 ILCs	E4	Rep2	13554	176	1.3
9 ILCs	A/PE4	Rep1	11197	96	0.9
9 ILCs	TE4	Rep1	14314	159	1.1

9 ILCs	TE4	Rep2	10741	104	1.0
10 Mast cells	E4	Rep1	27042	134	0.5
10 Mast cells	E4	Rep2	13554	95	0.7
10 Mast cells	A/PE4	Rep1	11197	48	0.4
10 Mast cells	TE4	Rep1	14314	82	0.6
10 Mast cells	TE4	Rep2	10741	77	0.7
11 $\gamma\delta$ T cells	E4	Rep1	27042	46	0.2
11 $\gamma\delta$ T cells	E4	Rep2	13554	107	0.8
11 $\gamma\delta$ T cells	A/PE4	Rep1	11197	18	0.2
11 $\gamma\delta$ T cells	TE4	Rep1	14314	73	0.5
11 $\gamma\delta$ T cells	TE4	Rep2	10741	49	0.5

T cell number per cluster in brain parenchyma and meninges (Fig. 3b)

Cluster	Region	Total cell number	Cell number/Cluster	Percentage (%)
0 CD8 ⁺ Xcl1 ⁺	Parenchyma	18565	3594	19.4
0 CD8 ⁺ Xcl1 ⁺	meninges	5040	457	9.1
1 CD8 ⁺ Tox ⁺ Pdcd1 ⁺	Parenchyma	18565	2607	14.0
1 CD8 ⁺ Tox ⁺ Pdcd1 ⁺	meninges	5040	537	10.7
2 CD8 ⁺ Ly6c ⁺	Parenchyma	18565	2422	13.0
2 CD8 ⁺ Ly6c ⁺	meninges	5040	548	10.9
3 CD8 ⁺ Isg15 ⁺	Parenchyma	18565	1635	8.8
3 CD8 ⁺ Isg15 ⁺	meninges	5040	303	6.0
4 CD4 ⁺ Folr4 ⁺ Slamf6 ⁺	Parenchyma	18565	1096	5.9
4 CD4 ⁺ Folr4 ⁺ Slamf6 ⁺	meninges	5040	724	14.4
5 Il17 ⁺	Parenchyma	18565	1283	6.9
5 Il17 ⁺	meninges	5040	302	6.0
6 Il4 ⁺	Parenchyma	18565	1112	6.0
6 Il4 ⁺	meninges	5040	274	5.4
7 Cd4 ⁺ Cd40lg ⁺	Parenchyma	18565	923	5.0
7 Cd4 ⁺ Cd40lg ⁺	meninges	5040	341	6.8
8 Cd8 ⁺ Egr1 ⁺	Parenchyma	18565	992	5.3
8 Cd8 ⁺ Egr1 ⁺	meninges	5040	13	0.3
9 Cd8 ⁺ Cd7 ⁺ Gzmb ⁺	Parenchyma	18565	1003	5.4
9 Cd8 ⁺ Cd7 ⁺ Gzmb ⁺	meninges	5040	233	4.6
10 Cd8 ⁺ Cd11c ⁺ Klre1 ⁺	Parenchyma	18565	820	4.4
10 Cd8 ⁺ Cd11c ⁺ Klre1 ⁺	meninges	5040	154	3.1
11 Cd8 ⁺ Ccr7 ⁺ Sell ⁺	Parenchyma	18565	255	1.4
11 Cd8 ⁺ Ccr7 ⁺ Sell ⁺	meninges	5040	464	9.2
12 Cd8 ⁺ Cx3cr1 ⁺ Gzma ⁺	Parenchyma	18565	220	1.2
12 Cd8 ⁺ Cx3cr1 ⁺ Gzma ⁺	meninges	5040	353	7.0

13 Cd4 ⁺ Foxp3 ⁺	Parenchyma	18565	286	1.5
13 Cd4 ⁺ Foxp3 ⁺	meninges	5040	287	5.7
14 Cd4 ⁺ Bcl3 ⁺ Relb ⁺	Parenchyma	18565	317	1.7
14 Cd4 ⁺ Bcl3 ⁺ Relb ⁺	meninges	5040	50	1.0

CD4⁺ T cell number per cluster in brain parenchyma (Fig. 3d)

Cluster	Replica	Total cell number	Cell number/Cluster
0 Egr1 ⁺	Rep1	2319	319
0 Egr1 ⁺	Rep2	2319	229
1 Nkg7 ⁺ Ccl5 ⁺	Rep1	2319	171
1 Nkg7 ⁺ Ccl5 ⁺	Rep2	2319	95
2 Rpl ⁺	Rep1	2319	409
2 Rpl ⁺	Rep2	2319	284
3 Slamf6 ⁺ Klf2 ⁺	Rep1	2319	185
3 Slamf6 ⁺ Klf2 ⁺	Rep2	2319	174
4 Cxcr6 ⁺ Ccr8 ⁺	Rep1	2319	111
4 Cxcr6 ⁺ Ccr8 ⁺	Rep2	2319	86
5 Foxp3 ⁺	Rep1	2319	103
5 Foxp3 ⁺	Rep2	2319	153

CD8⁺ T cell number per cluster in brain parenchyma (Fig. 3g)

Cluster	Replica	Total cell number	Cell number/Cluster
0 Rpl ⁺	Rep1	9447	1526
0 Rpl ⁺	Rep2	9447	1444
1 Tox ⁺ Pdcd1 ⁺	Rep1	9447	932
1 Tox ⁺ Pdcd1 ⁺	Rep2	9447	829
2 Ly6c ⁺	Rep1	9447	510
2 Ly6c ⁺	Rep2	9447	457
3 Isg15 ⁺	Rep1	9447	898
3 Isg15 ⁺	Rep2	9447	750
4 Hobit ⁺ Cd40lg ⁺	Rep1	9447	342
4 Hobit ⁺ Cd40lg ⁺	Rep2	9447	167
5 Egr1 ⁺	Rep1	9447	403
5 Egr1 ⁺	Rep2	9447	304
6 Cd11c ⁺ Klre1 ⁺	Rep1	9447	221
6 Cd11c ⁺ Klre1 ⁺	Rep2	9447	100
7 Ccr7 ⁺ Sell ⁺	Rep1	9447	135
7 Ccr7 ⁺ Sell ⁺	Rep2	9447	77
8 Bcl3 ⁺ Relb ⁺	Rep1	9447	122
8 Bcl3 ⁺ Relb ⁺	Rep2	9447	114
9 Cx3cr1 ⁺ Gzma ⁺	Rep1	9447	88
9 Cx3cr1 ⁺ Gzma ⁺	Rep2	9447	28

Microglia number per cluster in brain parenchyma (Fig. 4a)

Cluster	Genotype	Replica	Total cell number	Cell number/Cluster	Percentage (%)
0 Homeostatic microglia	E4	Rep1	16951	16265	96.0
0 Homeostatic microglia	E4	Rep2	2901	2702	93.1
0 Homeostatic microglia	A/PE4	Rep1	7502	6072	80.9
0 Homeostatic microglia	TE4	Rep1	6210	4566	73.5
0 Homeostatic microglia	TE4	Rep2	3341	2061	61.7
1 APOE ⁺ microglia	E4	Rep1	16951	455	2.7
1 APOE ⁺ microglia	E4	Rep2	2901	162	5.6
1 APOE ⁺ microglia	A/PE4	Rep1	7502	1206	16.1
1 APOE ⁺ microglia	TE4	Rep1	6210	1267	20.4
1 APOE ⁺ microglia	TE4	Rep2	3341	1137	34.0
2 IFN-activated microglia	E4	Rep1	16951	231	1.4
2 IFN-activated microglia	E4	Rep2	2901	37	1.3
2 IFN-activated microglia	A/PE4	Rep1	7502	224	3.0
2 IFN-activated microglia	TE4	Rep1	6210	377	6.1
2 IFN-activated microglia	TE4	Rep2	3341	143	4.3