Supplementary Table 1: Targeted gene expression profile in the corpus callosum following cuprizone
Related to figure 1

Targeted expression profile in the corpus callosum														
Gene symbol	**Fold expression to untreated controls**				***P*-Value (Student's t-test)**									
	5w	**6w**	**12w**	**+2w**	**Ctrl vs. 5w**	**Ctrl vs. 6w**	**Ctrl vs. 12w**	**Ctrl vs. +2w**	**5w vs. 6w**	**5w vs. 12w**	**5w vs. +2w**	**6w vs. 12w**	**6w vs. +2w**	**12w vs. +2w**
Hmgcr	0.18	0.29	0.59	0.77	0.00	0.01	0.05	0.37	0.04	0.01	0.01	0.04	0.03	0.05
Fdft1	0.27	0.36	0.56	0.92	0.00	0.00	0.05	0.91	0.08	0.04	0.02	0.18	0.03	0.04
Cyp51	0.19	0.15	0.44	0.79	0.01	0.01	0.05	0.10	0.69	0.03	0.08	0.07	0.13	0.90
Dhcr24	0.20	0.31	0.54	1.50	0.00	0.00	0.03	0.02	0.19	0.06	0.00	0.31	0.00	0.01
Ldlr	0.24	0.11	0.47	1.68	0.03	0.01	0.07	0.57	0.05	0.03	0.19	0.00	0.15	0.30
Vldlr	0.35	0.34	0.79	0.96	0.03	0.06	0.36	1.00	1.00	0.01	0.22	0.02	0.23	0.88
Apobr	3.20	5.32	5.00	10.40	0.05	0.00	0.02	0.15	0.03	0.12	0.33	0.96	0.48	0.48
Scarbl	1.26	0.63	0.24	0.79	0.99	0.13	0.01	0.87	0.89	0.66	0.96	0.01	0.81	0.22
Lrp1	1.12	1.79	1.07	8.88	0.96	0.47	0.55	0.00	0.74	1.00	0.01	0.57	0.00	0.00
Tspo	7.85	8.25	1.79	2.13	0.07	0.01	0.15	0.78	1.00	0.07	0.29	0.01	0.13	1.00
Pltp	1.33	0.85	1.27	2.12	0.40	0.91	0.09	0.04	0.38	1.00	0.15	0.49	0.00	0.14
Apoe	5.16	2.77	1.23	1.22	0.10	0.01	0.45	0.97	0.28	0.11	0.13	0.00	0.02	1.00
Clu	2.17	0.60	1.20	1.57	0.15	0.07	0.67	0.41	0.09	0.30	0.64	0.05	0.07	0.73
Apoa1	0.54	4.90	0.61	7.64	0.15	0.32	0.28	0.09	0.29	0.92	0.08	0.30	0.28	0.09
Lcat	0.12	0.70	0.03	1.36	0.00	0.12	0.00	0.23	0.02	0.04	0.02	0.01	0.14	0.02
Abca1	17.63	6.74	3.29	8.96	0.01	0.15	0.03	0.03	0.04	0.01	0.00	0.36	0.69	0.05
Abcg1	1.93	1.70	1.18	4.17	0.00	0.11	0.95	0.00	0.82	0.12	0.00	0.53	0.00	0.01
Abcg4	0.82	0.54	1.38	1.86	0.00	0.11	0.95	0.00	0.82	0.12	0.00	0.53	0.00	0.01
Soat1	0.86	2.24	0.82	0.87	0.99	0.09	0.16	0.21	0.36	1.00	1.00	0.09	0.05	0.98
Nceh1	1.18	5.70	2.23	0.86	0.58	0.03	0.27	0.65	0.04	0.45	0.50	0.14	0.02	0.22
Npc1	1.92	3.61	1.84	1.22	0.01	0.08	0.12	0.78	0.21	0.98	0.17	0.30	0.06	0.53
Npc2	5.43	3.95	2.30	6.89	0.02	0.02	0.12	0.03	0.46	0.14	0.64	0.13	0.17	0.08
Cyp46a1	0.14	0.22	0.59	1.42	0.00	0.00	0.08	0.42	0.14	0.09	0.03	0.09	0.03	0.12
Ch27a1	1.71	0.63	0.22	0.83	0.67	0.11	0.00	0.23	0.44	0.25	0.59	0.04	0.36	0.00
Ch25h	70.56	7.44	1.35	5.22	0.41	0.11	0.93	0.10	0.50	0.41	0.45	0.13	0.87	0.11

Supplementary Table 2: Targeted sterol gene expression profile in isolated cells of untreated mice

Related to figure 1

Targeted expression profile in isolated cells				
Gene symbol	**Mean expression ($2^{-\Delta CT}$)**			
	OL	**A**	**M**	**EC**
Hmgcr	0.00185131	0.00340585	0.00007785	0.00025608
Fdft1	0.00252692	0.00249386	0.00006067	0.00022896
Cyp51	0.00167273	0.00069921	0.00000911	0.00008611
Dhcr24	0.00657979	0.00438422	0.00001925	0.00025997
Ldlr	0.00007158	0.00021110	0.00000130	0.00003656
Vldlr	0.00387669	0.00031833	0.00000635	0.00002702
Scarbl	0.00004549	0.00010977	0.00007789	0.00001088
CD36	0.00000337	0.00000586	0.00002392	0.00049891
Lrp1	0.00008158	0.00003199	0.00008775	0.00006137
Tspo	0.00003135	0.00008258	0.00003689	0.00000030
Pltp	0.00426978	0.03506886	0.00195897	0.00004228
Apoe	0.00459414	0.01388507	0.00351643	0.00189860
Clu	0.00376362	0.00731472	0.00005575	0.00189860
Apod	0.13612923	0.00336636	0.00027997	0.00124774
Apoa1	0.00000149	0.00000301	0.00000699	0.00329111
Lcat	0.00022748	0.00059168	0.00012503	0.00005685
Abca1	0.00017157	0.00285070	0.00000841	0.05043125
Abcg1	0.00009913	0.00004952	0.00003859	0.00018880
Abcg4	0.00006157	0.00013694	0.00000052	0.00000194
Soat1	0.00000964	0.00001264	0.00022252	0.00000559
Nceh1	0.00002482	0.00020923	0.00012503	0.00031717
Npc1	0.00007943	0.00038931	0.00000112	0.00030702
Npc2	0.00583792	0.00696956	0.00047487	0.00071298
Cyp46a1	0.00000004	0.00000824	0.00000015	0.00000113
Cyp27a1	0.00000855	0.00007471	0.00000004	0.00000002
Ch25h	0.00000121	0.00001778	0.00002256	0.00000387

Supplementary Table 3: Targeted gene expression profile in isolated cells following cuprizone
Related to figure 1

Targeted expression profile in isolated cells																				
Gene symbol	**Fold expression (6w)**				**Fold expression (12+2w)**				***P*-Value (Student's t-test)**											
	OL	**A**	**M**	**EC**	**OL**	**A**	**M**	**EC**	**OL Ctrl vs. 6w**	**OL Ctrl vs. +2w**	**OL 6w vs. +2w**	**A Ctrl vs. 6w**	**A Ctrl vs. +2w**	**A 6w vs. +2w**	**M Ctrl vs. 6w**	**M Ctrl vs. +2w**	**M 6w vs. +2w**	**EC Ctrl vs. 6w**	**EC Ctrl vs. +2w**	**EC 6w vs. +2w**
Hmgcr	0.72	0.08	2.60	0.66	3.05	0.25	0.95	0.59	0.02	0.03	0.02	0.00	0.00	0.04	0.03	0.85	0.04	0.16	0.20	0.98
Fdft1	0.25	0.07	1.20	1.06	1.80	0.09	1.04	0.17	0.01	0.01	0.00	0.00	0.00	0.84	0.39	0.82	0.52	0.74	0.00	0.00
Cyp51	0.42	0.08	3.12	0.77	1.93	0.30	0.94	0.38	0.03	0.21	0.04	0.00	0.00	0.00	0.00	0.87	0.01	0.15	0.03	0.27
Dhcr24	0.28	0.05	0.21	1.06	2.64	0.05	0.17	0.22	0.00	0.05	0.02	0.02	0.02	0.81	0.02	0.00	0.73	0.34	0.09	0.02
Ldlr	0.37	0.03	3.29	0.03	5.10	0.12	0.97	0.06	0.04	0.05	0.02	0.00	0.00	0.07	0.12	0.93	0.08	0.00	0.00	0.80
Vldlr	0.34	0.44	4.16	1.02	0.59	0.19	0.78	0.13	0.03	0.17	0.22	0.02	0.01	0.01	0.03	0.43	0.05	0.65	0.04	0.08
Scarbl	0.61	0.72	1.16	0.22	0.97	0.43	0.94	0.49	0.27	0.97	0.53	0.31	0.02	0.36	0.36	0.73	0.61	0.00	0.01	0.09
CD36	6.64	8.16	4.79	0.00	4.25	1.56	2.46	NA	0.10	0.05	0.35	0.15	0.01	0.19	0.00	0.07	0.04	0.75	NA	NA
Lrp1	1.53	0.43	3.78	1.06	3.41	0.94	0.81	0.06	0.48	0.31	0.35	0.01	0.01	1.00	0.01	0.45	0.00	0.82	0.00	0.00
Tspo	1.98	1.16	1.12	4.66	4.51	1.17	2.65	2.58	0.42	0.15	0.16	0.68	0.68	1.00	0.40	0.09	0.09	0.01	0.15	0.25
Pltp	0.25	0.15	0.76	0.24	0.98	0.17	0.22	0.31	0.00	0.98	0.26	0.01	0.01	1.00	0.14	0.00	0.03	0.00	0.00	0.47
Apoe	7.95	7.56	44.36	20.46	5.41	0.52	19.92	0.31	0.00	0.02	0.29	0.01	0.01	1.00	0.01	0.00	0.06	0.00	0.86	0.00
Clu	0.71	2.57	2.95	1.11	3.01	0.28	0.19	0.29	0.15	0.33	0.25	0.01	0.01	1.00	0.22	0.05	0.15	0.70	0.06	0.03
Apod	0.44	0.43	0.22	0.78	0.62	0.25	0.39	0.93	0.06	0.00	0.33	0.43	0.43	1.00	0.03	0.03	0.04	0.16	0.70	0.32
Apoa1	1.12	0.71	0.25	0.00	2.60	4.51	0.72	0.58	0.69	0.01	0.02	0.00	0.00	1.00	0.13	0.09	0.25	0.01	0.21	0.10
Lcat	0.11	0.06	0.00	8.22	1.17	0.02	1.47	NA	0.00	0.56	0.03	0.00	0.00	1.00	0.01	0.41	0.07	0.03	NA	NA
Abca1	0.86	0.15	36.46	0.05	0.84	0.63	4.40	0.00	0.71	0.42	0.99	0.06	0.06	1.00	0.04	0.04	0.04	0.00	0.00	0.50
Abcg1	0.42	0.45	2.44	1.97	3.00	0.83	1.02	0.02	0.02	0.03	0.02	0.00	0.00	0.90	0.14	0.94	0.11	0.00	0.93	0.00
Abcg4	0.39	0.41	0.18	3.42	1.08	0.09	0.41	0.10	0.15	0.85	0.10	0.37	0.37	1.00	0.00	0.00	1.00	0.25	0.03	0.19
Soat1	0.37	0.85	5.08	1.67	0.91	0.55	0.94	0.82	0.02	0.73	0.01	0.05	0.05	1.00	0.01	0.85	0.00	0.05	0.53	0.02
Nceh1	3.20	2.81	19.38	0.51	0.70	0.80	3.28	0.36	0.06	0.03	0.03	0.00	0.00	1.00	0.01	0.05	0.03	0.09	0.06	0.69
Npc1	0.22	0.11	2.99	0.43	0.36	0.34	0.81	0.36	0.00	0.01	0.15	0.00	0.00	1.00	0.06	0.34	0.03	0.05	0.03	0.57
Npc2	0.86	2.16	3.41	0.95	2.06	2.17	1.48	0.31	0.45	0.01	0.02	0.00	0.00	1.00	0.03	0.03	0.03	0.82	0.10	0.14
Cyp46a1	0.46	0.12	4.02	0.00	0.95	0.29	1.09	0.04	0.16	0.90	0.15	0.65	0.65	1.00	0.07	0.96	0.06	0.03	0.05	0.93
Ch27a1	21.33	1.48	2.07	164.29	3.48	3.35	1.06	6.54	0.06	0.07	0.09	0.09	0.09	1.00	0.02	0.90	0.02	0.00	0.53	0.01
Ch25h	0.06	21.84	2.41	0.53	1.06	7.41	0.48	0.76	0.04	0.90	0.01	0.00	0.00	0.04	0.14	0.31	0.00	0.17	0.57	0.43

Supplementary Table 4: List of primer sequences, Related to figures 1-7

All primers used for expression analysis were intron-spanning.

Gene	**Sequence (5'-3'; forward - reverse)**
Hprt	TCCTCCTCAGACCGCTTTT - CCTGGTTCATCATCGCTAATC
Rplp0	GATGCCCAGGGAAGACAG - ACAATGAAGCATTTTGGATAATCA
Rps13	CGAAAGCACCTTGAGAGGAA -TTCCAATTAGGTGGGAGCAC
18S	AAATCAGTTATGGTTCCTTTGGTC - GCTCTAGAATTACCACAGTTATCCAA
Gapdh	CTACATGGTCTACATGTTCCAGTA - TGATGGCATGGACTGTGGTCAT
Car2	CAAGCACAACGGACCAGA - ATGAGCAGAGGCTGTAGG
Olig2	AGACCGAGCCAACACCAG - AAGCTCTCGAATGATCCTTCTTT
Plp1	TCAGTCTATTGCCTTCCCTAGC - AGCATTCCATGGGAGAACAC
Cspg4	TCATACAGAATGTTCCCAGCA - GCAGAGGAGGTCTTGGTGAA
Pdgfra	CTCTTGGAGATAGACTCCGTAG - ACTTCTCTTCCTGCGAATGG
Gfap	TGCTCCTGCTTCGAGTCCTT - CAAGAGGAACATCGTGGTAAAGA
Aqp4	TGGAGGATTGGGAGTCACC - TGAACACCAACTGGAAAGTGA
S100b	AACAACGAGCTCTCTCACTTCC - CTCCATCACTTTGTCCACCA
Aif1	TGTTTTTCTCCTCATACATCAGAATC - CCGAGGAGACGTTCAGCTAC
Lamp2	AAGGTGCAACCTTTTAATGTGAC - TGTCATCATCCAGCGAACAC
Hmgc1	GGACCGCTGCTATTCTGTCT - AGCCAAAATCATTCAGGGTAAA
Hmgcr	TGATTGGAGTTGGCACCAT - TGGCCAACACTGACATGC
Fdft1	CCAAACAGGACTGGGACAAG - GACGAGAAAGGCCAATTCC
Dhcr24	GGTCATGACGGACGACGTA - AGGGCTTGTAGTAACTGCCAAT
Cyp51	TTAGAACAGAAAGCAGTGTGTGG - TGCATCTATCAAGTAAATTCAGATCC
Mvk	CTCAAGGACGGGGTCTCC - GGCCCACTTGTTGATTGACT
Apoe	GACCCTGGAGGCTAAGGACT - AGAGCCTTCATCTTCGCAAT
Apod	ACGGAAACATCGAAGTGCTAA - TGGCTTCACCCTTTACTTGG
Clu	GCCATGGATGTCCAGCTC - CACACAGTGCGGTCATCTTC
Apoa1	TCAGGATGAAAGCTGTGGTG - TCATCTTGCTGCCATACGTG
Ldlr	GATGGCTATACCTACCCCTCAA - TGCTCATGCCACATCGTC
Vldlr	AAGTCAGTGTTCCCCCAAAA - TGCTGCCATCACTAAGAGCA
Apobr	TCACAGCAACTGGAATGAGG - GCTTCGAGAGAGGAGCACAC
Lrp1	ACCACCATCGTGGAAAATG - GTCCCAGCCACGGTGATA
Scarb1	GCCCATCATCTGCCAACT - TCCTGGGAGCCCTTTTTACT
Pltp	GCTTCTGAGGGCCACCTAC - TTCAGCTTCAGTGGGGAGTT
Abca1	CTGTTTCCCCCAACTTCTG - TCTGCTCCATCTCTGCTTTC
Abcg1	TCTTTGATGAGCCCACCAGT - GGGCCAGTCCTTTCATCA
Abcg4	TGATGTGCCCTTCCAGGT - CAAGGCTGAGAAGAGCAGGA
Srebp2	ACCTAGACCTCGCCAAAGGT - GCACGGATAAGCAGGTTTGT
Npc1	CCTTCGGGCCTCCATTG - TGTCACGGTTTCATTGTTGTAAGA
Npc2	CCGGTGAAGAATGAATACCC - TTCTTTTTGTCATCTTCAAGTTTCC
Cyp46a1	AACTTTGTCACCTTCTTCATTGC - CCATCACTGTGAATGCCAGA
Ch25h	TGCTACAACGGTTCGGAGC - AGAAGCCCACGTAAGTGATGAT
Cyp27a1	ATGGGATCTTCATCGCACA - CGTTTAAGGCATCCGTGTAGA
Tnf	TGCCTATGTCTCAGCCTCTTC - GAGGCCATTTGGGAACTTCT
Il1b	GCTACCAAACTGGATATAATCAGGA - CCAGGTAGCTATGGTACTCCAGAA
Il2	CGCAGAGGTCCAAGTTCATCT - CGCAGAGGTCCAAGTTCATCT
Il6	GCTACCAAACTGGATATAATCAGGA - CCAGGTAGCTATGGTACTCCAGAA
Ccl2	GCCTGCTGTTCACAGTTGC - CAGGTGAGTGGGGCGTTA
Cxcl10	GCTGCCGTCATTTTCTGC - TCTCACTGGCCCGTCATC
Ifng	TCAAGTGGCATAGATGTGGAAGAA - TGGCTCTGCAGGATTTTCATG
H2-DMb2 (MhcII)	GCGACGTGGGCGAGTACC - CATTCCGGAACCAGCGCA
Nos2	TGAACTTGAGCGAGGAGCA - TTCATGATAACGTTTCTGGCTCT
Csf2	GGGCGCCTTGAACATGAC - CGCATAGGTGGTAACTTGTGTTTC
Fcgr3a	TCACCATCACTGTCCAAGACC - ACTAGGGAGAAAGCAGTGTGGT
Il10	GGTTGCCAAGCCTTATCGGA - ACCTGCTCCACTGCCTTGCT
Il12	CCAGGTGTCTTAGCCAGTCC - GCAGTGCAGGAATAATGTTTCA
Tgfb1	TGGAGCAACATGTGGAACTC - CAGCAGCCGGTTACCAAG
Mrc1	AAGGAAAGTTCCCAGATGTACC - GCAAGCCAATGTACACGATG
Arg1	AAGGAAAGTTCCCAGATGTACC - GCAAGCCAATGTACACGATG
Nlrp3	TGCGTGTTCTCTGTATACCAC - GGCTTAGGTCCACACAGAAAG
Casp1	CCCACTGCTGATAGGGTGAC - GCATAGGTACATAAGAATGAACTGGA

Supplementary Table 5: Differentially expressed genes in SQS/McKO and ABC/McKO mutants during remyelination

Related to figure 2

Gene expression of SQS/McKO and ABC/McKO cuprizone corpus callosum samples over control				
Gene name and function	**Gene symbol**	**Fold expression**		***P*-value (Student's t-test)**
		SQS/McKO	**ABC/McKO**	
Carbonic Anhydrase 2	*Car2*	0.31	1.78	0.0005
Proteolipid protein 1	*Plp1*	0.47	0.38	0.3339
ATP binding cassette subfamily A member 1	*Abca1*	0.49	0.12	0.0132
ATP binding cassette subfamily G member 1	*Abcg1*	0.52	0.65	0.0184
Allograft Inflammatory Factor 1	*Aif1*	1.33	0.51	0.0002
Nitric oxide synthase 2	*Nos2*	2.20	0.44	0.0001
Fc Fragment Of IgG Receptor IIIa	*Fcgr3*	1.56	0.51	0.0014
Interleukin 12	*Il12*	1.61	0.66	0.0161
Arginase 1	*Arg1*	0.99	2.76	0.0235
Interleukin 10	*Il10*	0.16	5.74	0.0100

Supplementary Table 6: Upregulated genes in SQS/McKO during myelin disease
Related to figure 3

Targeted expression profile in SQS/McKO over control			
Gene name and function	**Gene symbol**	***P*-value (Student's t-test)**	**Fold expression**
Cuprizone, corpus callosum			
Allograft inflammatory factor 1	*Aif1*	0.008	2.89
Apolipoprotein B receptor	*Apobr*	0.013	2.21
Aquaporin 4	*Aqp4*	0.000	2.33
CC-chemokine ligand 2	*Ccl2*	0.001	2.30
Cholesterol 25-Hydroxylase	*Ch25h*	0.025	1.65
C-X-C motif chemokine 10	*Cxcl10*	0.010	1.67
Fc Fragment Of IgG Receptor IIIa	*Fcgr3a*	0.009	1.61
Interleukin 12A	*Il12a*	0.014	1.83
Interleukin 1 beta	*Il1b*	0.036	1.59
Interleukin 6	*Il6*	0.014	1.95
Lysosome-associated membrane protein 2	*Lamp2*	0.004	1.58
Low density lipoprotein-related protein 2	*Lrp2*	0.035	1.96
Nitric oxide synthase 2	*Nos2*	0.000	2.13
Platelet-derived growth factor receptor A	*Pdgfra*	0.006	1.47
Scavenger Receptor Class B Member 1	*Scarb1*	0.005	1.50
Tumor necrosis factor	*Tnf*	0.000	2.76
EAE, spinal cord			
CC-chemokine ligand 2	*Ccl2*	0.035	2.81
C-X-C motif chemokine 10	*Cxcl10*	0.038	2.80
Interleukin 12	*Il12*	0.022	3.09
Interleukin 1 beta	*Il1b*	0.030	2.09
Interleukin 2	*Il2*	0.037	5.16
Nitric oxide synthase 2	*Nos2*	0.000	2.00
Tumor necrosis factor	*Tnf*	0.043	1.68
Cuprizone, isolated CD11b+ cells			
Cholesterol 25-Hydroxylase	*Ch25h*	0.042	3.24
Colony Stimulating Factor 2	*Csf2*	0.010	4.50
C-X-C motif chemokine 10	*Cxcl10*	0.003	2.77
Interleukin 1 beta	*Il1b*	0.010	1.71
LDL receptor related protein 1	*Lrp1*	0.038	3.50
Nitric oxide synthase 2	*Nos2*	0.034	3.23
Tumor necrosis factor	*Tnf*	0.015	1.97
EAE, isolated CD11b+ cells			
Colony Stimulating Factor 2	*Csf2*	0.009	4.09
C-X-C motif chemokine 10	*Cxcl10*	0.007	3.13
Fc Fragment Of IgG Receptor IIIa	*Fcgr3a*	0.012	2.84
Interferon gamma	*Ifng*	0.008	3.68
Interleukin 1 beta	*Il1b*	0.045	1.95
Nitric oxide synthase 2	*Nos2*	0.029	6.09
Phospholipid-transferprotein	*Pltp*	0.031	7.30

Supplementary Table 7: Downregulated genes in SQS/McKO during myelin disease,
Related to figure 3

Targeted expression profile in SQS/McKO over control			
Gene name and function	**Gene symbol**	***P*-value (Student's t-test)**	**Fold expression**
Cuprizone, tissue			
ATP binding cassette subfamily A member 1	*Abca1*	0.003	0.53
ATP binding cassette subfamily G member 1	*Abcg1*	0.008	0.53
Apolipoprotein D	*Apod*	0.040	0.68
Apolipoprotein E	*Apoe*	0.008	0.58
Carbonic anhydrase II	*Car2*	0.000	0.29
Cholesterol 27-hydroxylase	*Cyp27a1*	0.047	0.74
Lanosterol 14 alpha-demethylase	*Cyp51*	0.000	0.59
24-dehydrocholesterol reductase	*Dhcr24*	0.002	0.63
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.003	0.49
Interleukin 10	*Il10*	0.004	0.14
Low density lipoprotein receptor	*Ldlr*	0.000	0.28
Mevalonate kinase	*Mvk*	0.000	0.65
Proteolipid protein 1	*Plp1*	0.000	0.47
Sterol regulatory element-binding protein-2	*Srebp2*	0.001	0.59
Transforming growth factor beta 1	*Tgfb1*	0.046	0.54
EAE, tissue			
ATP binding cassette subfamily A member 1	*Abca1*	0.003	0.52
Apolipoprotein E	*Apoe*	0.002	0.61
Cholesterol 27-hydroxylase	*Cyp27a1*	0.009	0.63
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.011	0.69
Glial fibrillary acidic protein	*Gfap*	0.034	0.75
Interferon gamma	*Ifng*	0.038	0.22
Interleukin 10	*Il10*	0.047	0.42
Low density lipoprotein receptor	*Ldlr*	0.048	0.53
Mevalonate kinase	*Mvk*	0.022	0.60
Transforming growth factor beta 1	*Tgfb1*	0.013	0.37
Very low density lipoprotein receptor	*Vldlr*	0.033	0.59
Cuprizone, isolated CD11b+ cells			
ATP binding cassette subfamily A member	*Abca1*	0.005	0.30
Apolipoprotein E	*Apoe*	0.014	0.37
Cholesterol 24-hydroxylase	*Cyp46a1*	0.010	0.12
Lanosterol 14 alpha-demethylase	*Cyp51*	0.029	0.55
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.000	0.01
Interleukin 2	*Il2*	0.022	0.14
Transforming growth factor beta 1	*Tgfb1*	0.033	0.27
EAE, isolated CD11b+ cells			
ATP binding cassette subfamily A member 1	*Abca1*	0.047	0.20
ATP binding cassette subfamily G member 1	*Abcg1*	0.027	0.41
Apolipoprotein E	*Apoe*	0.009	0.38
Cholesterol 25-hydroxylase	*Ch25h*	0.038	0.23
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.031	0.40
3-Hydroxy-3-methylgutaryl-CoA reductase	*Hmgcr*	0.000	0.44
Transforming growth factor beta 1	*Tgfb1*	0.001	0.05

Supplementary Table 8: Top 25 Gene Ontologies of cluster 2, Related to figure 4

	Gene Ontology	**Size**	**-log10 (FDR q-val)**
1	SRP-DEPENDENT COTRANSLATIONAL PROTEIN TARGETING TO MEMBRANE_GO:0006614	41	Inf
2	ESTABLISHMENT OF PROTEIN LOCALIZATION TO ENDOPLASMIC RETICULUM_GO:0072599	45	Inf
3	PROTEIN TARGETING TO MEMBRANE_GO:0006612	49	Inf
4	**REGULATION OF PLASMA LIPOPROTEIN PARTICLE LEVELS_GO:0097006**	20	Inf
5	VIRAL TRANSCRIPTION_GO:0019083	44	Inf
6	PROTEIN TARGETING TO ER_GO:0045047	44	Inf
7	PROTEIN LOCALIZATION TO ENDOPLASMIC RETICULUM_GO:0070972	48	Inf
8	COTRANSLATIONAL PROTEIN TARGETING TO MEMBRANE_GO:0006613	44	Inf
9	PROTEIN TARGETING_GO:0006605	68	Inf
10	NUCLEAR-TRANSCRIBED MRNA CATABOLIC PROCESS_GO:0000956	58	Inf
11	PROTEIN LOCALIZATION TO MEMBRANE_GO:0072657	84	Inf
12	TRANSLATION_GO:0006412	62	Inf
13	CYTOPLASMIC TRANSLATION_GO:0002181	17	3.9
14	INTERSPECIES INTERACTION BETWEEN ORGANISMS_GO:0044419	101	3.9
15	ESTABLISHMENT OF PROTEIN LOCALIZATION TO ORGANELLE_GO:0072594	81	3.9
16	RNA CATABOLIC PROCESS_GO:0006401	65	3.7
17	EXTRACELLULAR STRUCTURE ORGANIZATION_GO:0043062	46	3.7
18	REGULATED EXOCYTOSIS_GO:0045055	147	3.2
19	NEUTROPHIL DEGRANULATION_GO:0043312	119	3.2
20	**REGULATION OF LIPID LOCALIZATION_GO:1905952**	33	3.3
21	ORGANIC CYCLIC COMPOUND CATABOLIC PROCESS_GO:1901361	100	3.3
22	**REGULATION OF LIPID TRANSPORT_GO:0032368**	21	3.0
23	REGULATION OF ENDOTHELIAL CELL MIGRATION_GO:0010594	31	2.9
24	EXOCYTOSIS_GO:0006887	158	2.7
25	POSITIVE REGULATION OF EPITHELIAL CELL MIGRATION_GO:0010634	34	2.7

Supplementary Table 9: Mean expression level of candidate genes in immune cell clusters, Related to figure 4

	Cluster 1		Cluster 2		Cluster 3	
	Ctrl	**MS**	**Ctrl**	**MS**	**Ctrl**	**MS**
DHCR24	0.16	0.10	0.45	0.06	1.216	1.05
ABCA1	0.40	1.54	4.43	8.23	0.82	1.91
APOE	8.63	13.17	68.78	78.51	7.43	8.23
NR1H2	0.51	0.82	0.74	1.22	0.64	0.77
NR1H3	0.035	0.04	0.21	0.64	0.04	0.24

Supplementary Table 10: Patient characteristics

	Diagnosis	Sex	Age	ApoE genotype	Post mortem delay
Patient 1	Multiple sclerosis	m	47	33	7:15
Patient 2	Multiple sclerosis	m	61	N.A.	9:15
Patient 3	Multiple sclerosis	f	47	N.A.	8:35
Patient 4	Multiple sclerosis	m	51	33	11:00
Control 1	Non-demented control	m	49	N.A.	6:15
Control 2	Non-demented control	f	46	33	10:25
Control 3	Control with space-occupying process	m	58	N.A.	05:15

Supplementary Table 11: Differentially expressed genes in squalene treated EAE mice,
Related to Figure 6

Targeted expression profile of squalene treated EAE over control EAE			
Gene name and function	**Gene symbol**	***P*-value (Student's t-test)**	**Fold expression**
EAE (tissue): Upregulated genes			
ATP binding cassette subfamily A member 1	*Abca1*	0.018	3.39
ATP binding cassette subfamily G member 1	*Abcg1*	0.027	1.47
Apolipoprotein E	*Apoe*	0.000	1.67
Clusterin (Apolipoprotein J)	*Clu*	0.016	2.26
Lanosterol 14 alpha-demethylase	*Cyp51*	0.045	1.82
24-dehydrocholesterol reductase	*Dhcr24*	0.028	2.78
Fc Fragment Of IgG Receptor IIIa	*Fcgr3a*	0.004	2.58
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.009	1.96
3-Hydroxy-3-methylgutaryl-CoA reductase	*Hmgcr*	0.021	2.64
3-Hydroxy-3-Methylglutaryl-CoA Synthase 1	*Hmgcs1*	0.020	2.14
Interleukin 10	*Il10*	0.035	4.34
Low density lipoprotein receptor	*Ldlr*	0.038	2.24
Low density lipoprotein-related protein 1	*Lrp1*	0.041	2.28
Mevalonate kinase	*Mvk*	0.025	1.55
Phospholipid-transferprotein	*Pltp*	0.008	1.88
Transforming growth factor beta 1	*Tgfb1*	0.042	8.32
EAE (CD11b+ cells): Upregulated genes			
ATP binding cassette subfamily A member 1	*Abca1*	0.039	6.38
Apolipoprotein E	*Apoe*	0.040	2.89
Arginase 1	*Arg1*	0.004	5.97
Clusterin (Apolipoprotein J)	*Clu*	0.001	8.46
Farnesyl-diphosphate farnesyltransferase 1	*Fdft1*	0.001	12.44
Transforming growth factor beta 1	*Tgfb1*	0.002	18.26
EAE (tissue): Downregulated genes			
Colony Stimulating Factor 2	*Csf2*	0.014	0.53
Cholesterol 24-hydroxylase	*Cyp46a1*	0.019	0.73
Interferon gamma	*Ifng*	0.019	0.68
Interleukin 12A	*Il12a*	0.005	0.39
Nitric oxide synthase 2	*Nos2*	0.003	0.54
Tumor necrosis factor	*Tnf*	0.015	0.61
EAE (CD11b+ cells): Downregulated genes			
3-Hydroxy-3-Methylglutaryl-CoA Synthase 1	*Hmgcs1*	0.010	0.37
Cholesterol 25-hydroxylase	*Ch25h*	0.001	0.07
Tumor necrosis factor	*Tnf*	0.033	0.38
Interleukin 2	*Il2*	0.001	0.06
C-X-C motif chemokine 10	*Cxcl10*	0.018	0.34
Interferon gamma	*Ifng*	0.039	0.37
Nitric oxide synthase 2	*Nos2*	0.001	0.13
Colony Stimulating Factor 2	*Csf2*	0.031	0.32
Low density lipoprotein receptor	*Ldlr*	0.028	0.13
Scavenger Receptor Class B Member 1	*Scarb1*	0.046	0.13

Supplementary Table 12: Resource table

Reagent	Source	Identifier
Antibodies		
ABCA1	Santa Cruz	Cat#sc-58219
ACSA-2	Miltenyi biotec	Cat #130–097-679
CAII	S. Ghandour	N/A
CD11b	Biolegend	Cat # 101207
CD11b	Miltenyi biotec	Cat #130–093-636
CD31	Miltenyi biotec	Cat #130–091-935
CD3e	Biolegend	Cat # 100312
CD4	Becton Dickinson	Cat # 553730
CD45.2	Biolegend	Cat # 109814
CD8	Becton Dickinson	Cat # 100706
GAPDH	Enzo	Cat #ADI-CSA-335-E
GFAP	Chemicon	Cat #MAB3402
Iba1	Wako	Cat #019-19741
KiM1P	HJ Radzun	N/A
LAMP1	BD Pharmingen	Cat #09671D
MAC3	Pharmigen	Cat #01781D
MBP	Serotec	Cat #MCA 4095
O4	Miltenyi biotec	Cat #130–096-670
OLIG2	C. Stiles / J. Alberta	DF308
SMI31	Covance	Cat #SMI31P
Chemicals, Peptides and Recombinant proteins		
2′,7′-Dichlorofluorescein	Sigma-Aldrich	Cat #D6665
2′,7′-Dichlorofluorescein	Sigma-Aldrich	Cat #D6665
4-hydroxytamoxifen	Sigma-Aldrich	Cat #T176
Accustase	Innovative Cell Technologies	Cat #AT104-500
BC theta	Max-Planck-Institute (MPI-EM)	N.A.
Betaferon (IFNβ-1b)	BAYER	Cat #04674936
Cholesterol	HEW	Cat #60211
Corn oil	Sigma-Aldrich	Cat #C8267
Cuprizone	Sigma-Aldrich	Cat #14690
DMHCA	Avanti	Cat #700125P
Fluoromyelin	ThermoFisher Scientific	Cat #F34651
Lipopolysaccharides (LPS)	Sigma-Aldrich	Cat #L3012
Lymphocyte separation medium	PAA	Cat #LSM1077
Lysolecithin	Sigma-Aldrich	Cat #L4129
M. tuberculosis H37 Ra	BD	Cat #231141
MOG35-55	Max-Planck-Institute (MPI-EM)	N.A.
Monastral blue	Sigma-Aldrich	Cat #274011
PageRulerTM	ThermoFisher Scientific	Cat #26619
Pertussis toxin	Sigma-Aldrich	Cat #P7208
PhosSTOP™	Roche	Cat #4906845001
Squalene	Sigma-Aldrich	Cat #S3626
Tamoxifen	Sigma-Aldrich	Cat #T5648
Lipid depleted serum (LDS)	Biowest-bw	Cat #S181L-500
Cholesterol	HEW	Cat #60211

Desmosterol	Sigma-Aldrich	Cat #700060P
Lathosterol	Sigma-Aldrich	Cat #C3652
Lanosterol	Sigma-Aldrich	Cat #L5768
Critical Commercial Assays		
Adult Brain Dissociation Kit	Miltenyi biotec	Cat #130-107-677
DAB Substrate Kit	Zymomed	Cat #DAB057
LSAB®2 System-HRP	Dako	Cat #K0609
Ovation Pico WTA System V2	NuGEN	Cat #3302
RNeasy Mini Kit	Qiagen	Cat #74104
VECTASTAIN® Elite® ABC HRP Kit	VECTOR	Cat #PK-6100
Biological samples		
Human Brain tissue	Netherland Brain Bank	https://www.brainbank.nl/
Experimental Models: Organisms/Strains		
Plp1-CreERT2	Max-Planck-Institute (MPI-EM)	Leone, et al., 2003
NG2-CreERT2	Max-Planck-Institute (MPI-EM)	Huang, et al., 2014
GLAST-CreERT2	Max-Planck-Institute (MPI-EM)	Mori, et al., 2006
CX3CR1-CreERT2 (Line 1)	Max-Planck-Institute (MPI-EM)	Parkhurst, et al., 2013
CX3CR1-CreERT2 (Line 2)	Max-Planck-Institute (MPI-EM)	Yona, et al., 2013
SLCO1c1-CreERT2	Max-Planck-Institute (MPI-EM)	Ridder, et al., 2011
Aldh1l1-CreERT2	Max-Planck-Institute (MPI-EM)	Winchenbach et al., 2016
SQS$^{flox/flox}$	Max-Planck-Institute (MPI-EM)	Saher et al., 2005
Abca1$^{flox/flox}$	Max-Planck-Institute (MPI-EM)	Westerterp, et al., 2012
Abcg1 $^{flox/flox}$	Max-Planck-Institute (MPI-EM)	Westerterp, et al., 2012
MBP $^{flox/flox}$	Max-Planck-Institute (MPI-EM)	Meschkat et al., 2020
Rosa26-tdTomato	Max-Planck-Institute (MPI-EM)	Madisen, et al., 2010
ApoEKO (Apoe -/-)	Max-Planck-Institute (MPI-EM)	Piedrahita, et al., 1992
Experimental Models: Cell lines		
L929	N/A	Garcia-Agudo, et al., 2019
Oligonucleotides		
Primer, Table S1	This paper	N/A
Original source data		
GSE118257	https://www.ncbi.nlm.nih.gov	Jakel et al., 2019
GSE124335	https://www.ncbi.nlm.nih.gov	Masuda et al., 2019
Software and Algorithms		
Cellprofiler	McQuin, et al., 2018	www.cellprofiler.org
GraphPad Prism 6	GraphPad Software, Inc.	https://www.graphpad.com/
ImageJ (Fiji)	Schindelin, et al., 2012	https://imagej.nih.gov/ij/
InteractiVenn	Heberle, et al., 2015	http://www.interactivenn.net/
LAS X software	Leica-microsystems	https://www.leica-microsystems.com
R	This paper	https://www.r-statistik.de
R package ggplot2 v3.2.0	Wickham, 2009	https://cran.r-project.org
R package Seurat v3.1.0	Butler et al., 2018	https://satijalab.org
GSEA	Subramanian et al., 2005	http://software.broadinstitute.org/gsea/index.jsp
Cytoscape v3.7.1	Otasek, et al., 2019	https://cytoscape.org
ZEN 2012 blue edition	Zeiss	https://www.zeiss.de

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