Supplementary Appendix

The miR-17/106-p38 axis is a key regulator of the neurogenic-to-gliogenic transition in developing neural stem/progenitor cells

Hayato Naka-Kaneda, Shiho Nakamura, Mana Igarashi, Hisashi Aoi, Hiroaki Kanki, Jun Tsuyama, Shuichi Tsutsumi, Hiroyuki Aburatani, Takuya Shimazaki, and Hideyuki Okano

Supplementary Figures

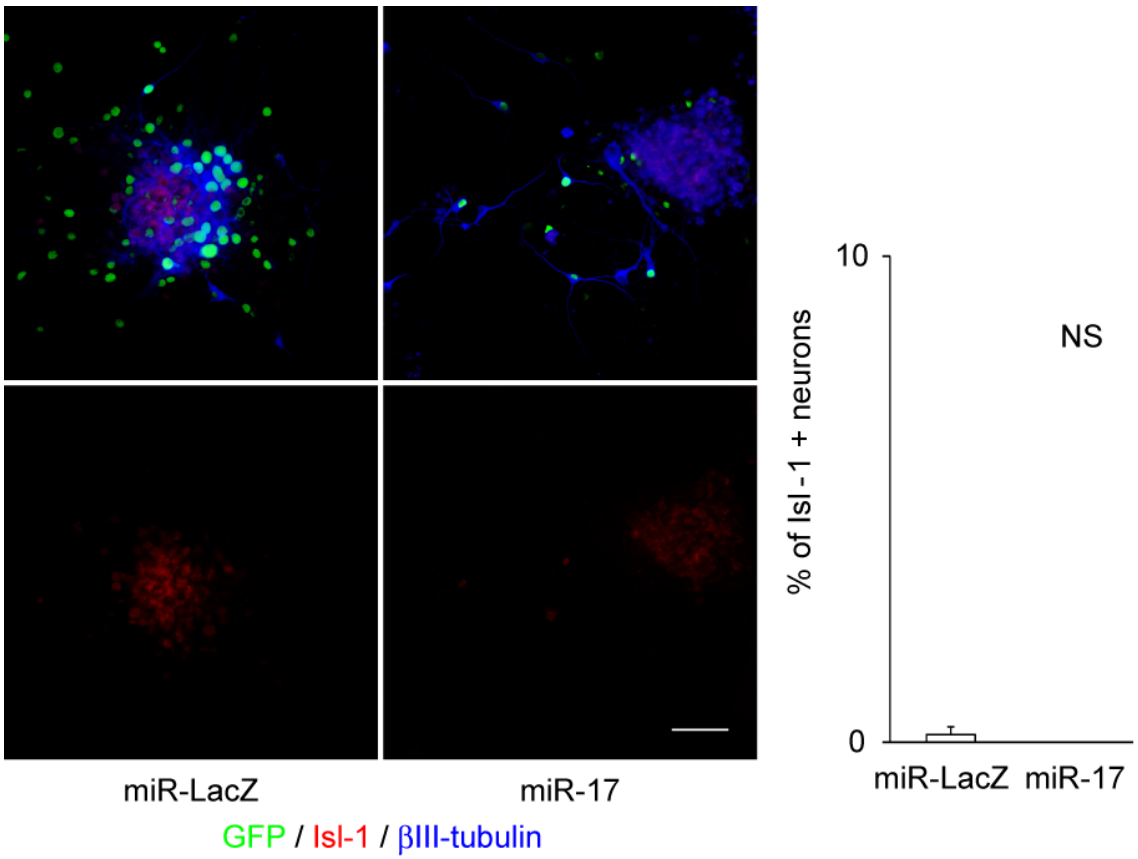

Fig. S1. MiR-17 OE does not increase production of Isl-1 + neurons. MiR-17-OE p2 neurospheres did not increase production of Isl-1+ neurons (n = 3). Scale bar: 50 □m. Results are shown as mean ± SEM. NS, p > 0.05.

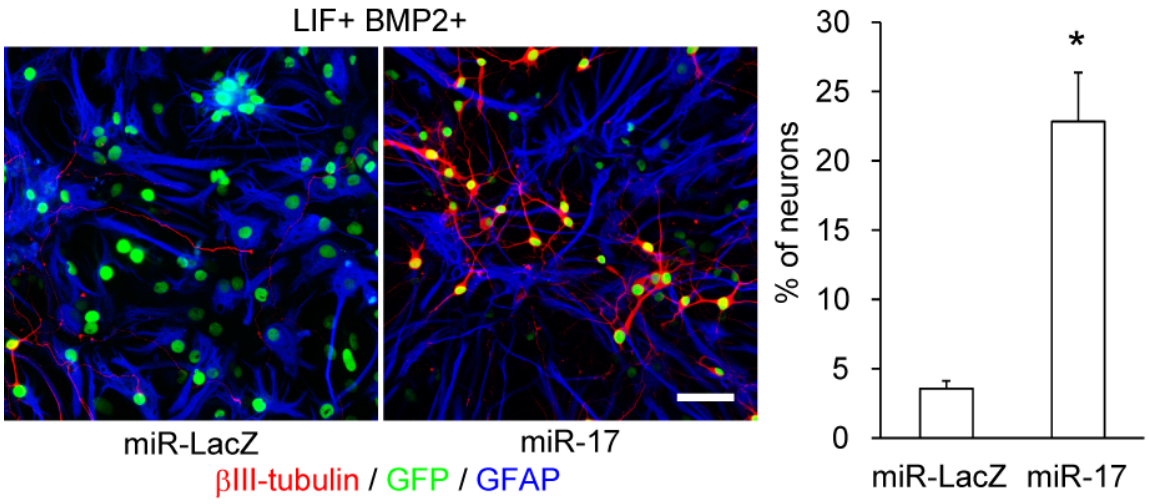

Fig. S2. Neurogenic effect of miR-17 OE in primary cultured neurospheres. The SVZ of the forebrain from P30 mice was dissociated and cultured for 1 week to form neurospheres, and then subjected to the differentiation assay. Cells were infected with lentivirus for miR-17 OE at the time of cell plating for neurosphere formation. Consistent with our results from the ESC-derived neurosphere assay, miR-17 OE in primary cultured neurospheres had a similar neurogenic effect. Scale bar: 50 □m. Results are shown as mean ± SEM. *p < 0.05.

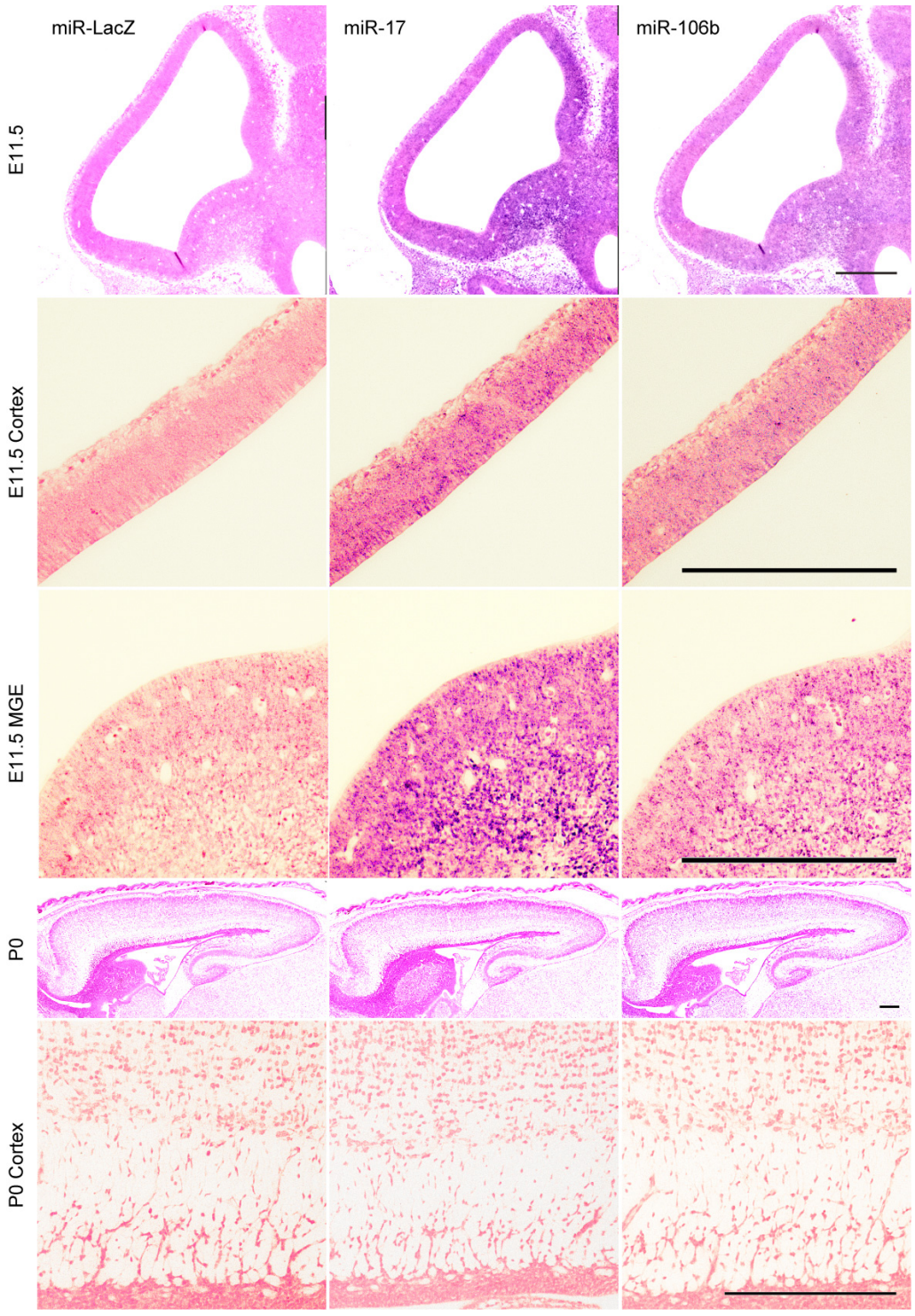

Fig. S3. Expression patterns of miR-17/106 in the developing mouse forebrain. Expression of miR-17 and miR-106b at E11.5 and P0 was determined by in situ hybridization with specific locked nucleic acid probes. MGE: medial ganglionic eminence. Scale bars: 300 □m.

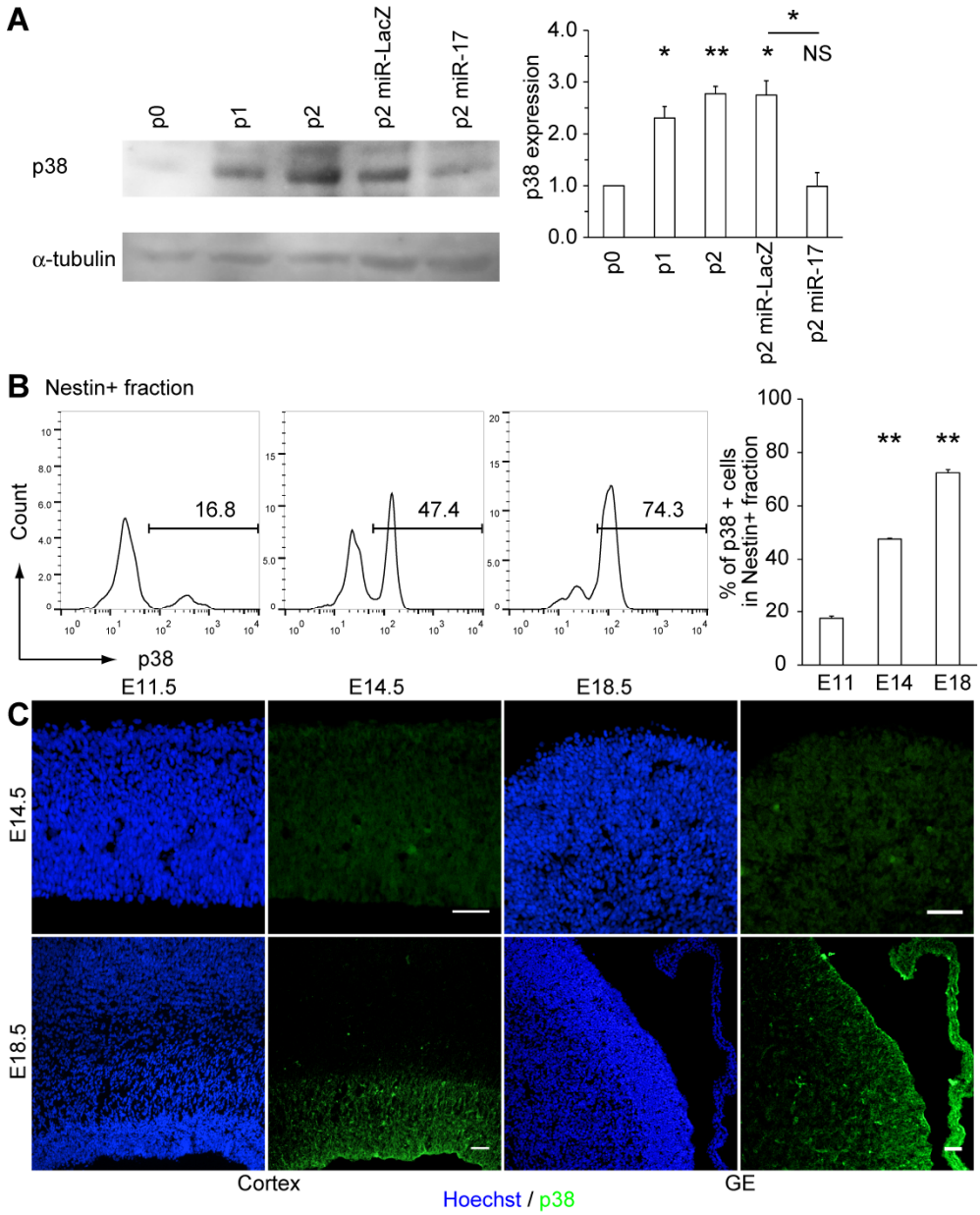

Fig. S4. Expression levels of p38 in neurospheres. (*A*) Expression levels of p38 in p0, p1, and p2 neurospheres were investigated by Western blotting with an anti-p38 antibody (Cell Signaling Technology 9212). MiR-17 repressed p38 expression at the p2 stage (n = 3). (*B*) The expression level of p38 in developing NSPCs was investigated by analyzing Nestin+ (anti-Nestin antibody, abcam ab6142) cell populations in the mouse forebrain at E11.5, E14.5, and E18.5. Consistent with the in vitro neurosphere study, the number of p38-expressing NSPCs increased with developmental age. (*C*) Immunohistochemistry of p38 expression with an anti-p38 antibody (Cell Signaling Technology 9218) in developing mouse cortex and ganglionic eminence (GE) at E14.5 and E18.5. Scale bars: 50 □m. Results are shown as mean ± SEM. NS, $p > 0.05$; *$p < 0.05$; **$p < 0.01$.

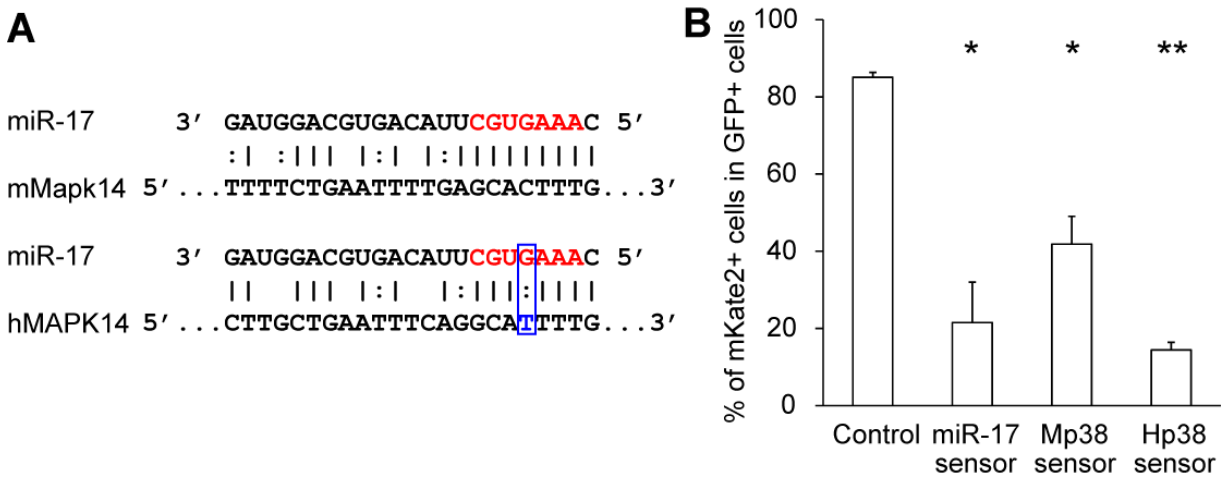

Fig. S5. MiR-17 binds the 3'UTR of p38 mRNA. (*A*) Schematic diagrams show the binding between miR-17 and its binding site in the 3'UTR of mouse p38 mRNA (mMapk14) and its human counterpart (hMAPK14). (*B*) A reporter assay was performed to detect any direct interaction between miR-17 and the 3'UTR of p38 mRNA. A control miR-17 antisense (miR-17 sensor), the miR-17 binding site in the 3'UTR of p38 mRNA (Mp38sensor; nt 2970–2992 of NM_011951), and its counterpart in the 3'UTR of human p38 mRNA (Hp38sensor; nt 3204–3226 of NM_001315) were cloned into a mammalian expression vector featuring an mKate2 reporter system. Expression vectors for miR-LacZ or miR-17, which were inserted in the 3'UTR of an EGFP reporter, were co-transfected with the Mp38sensor or Hp38sensor into HEK293 cells. After 3 days of culture, the expression levels of mKate2 in the cells were analyzed by fluorescence-activated cell sorting. Compared with miR-LacZ OE, miR-17 OE caused downregulation of mKate2 linked to the Mp38sensor and the Hp38sensor (n = 3). Results are shown as mean ± SEM. *$p < 0.05$ and **$p < 0.01$.

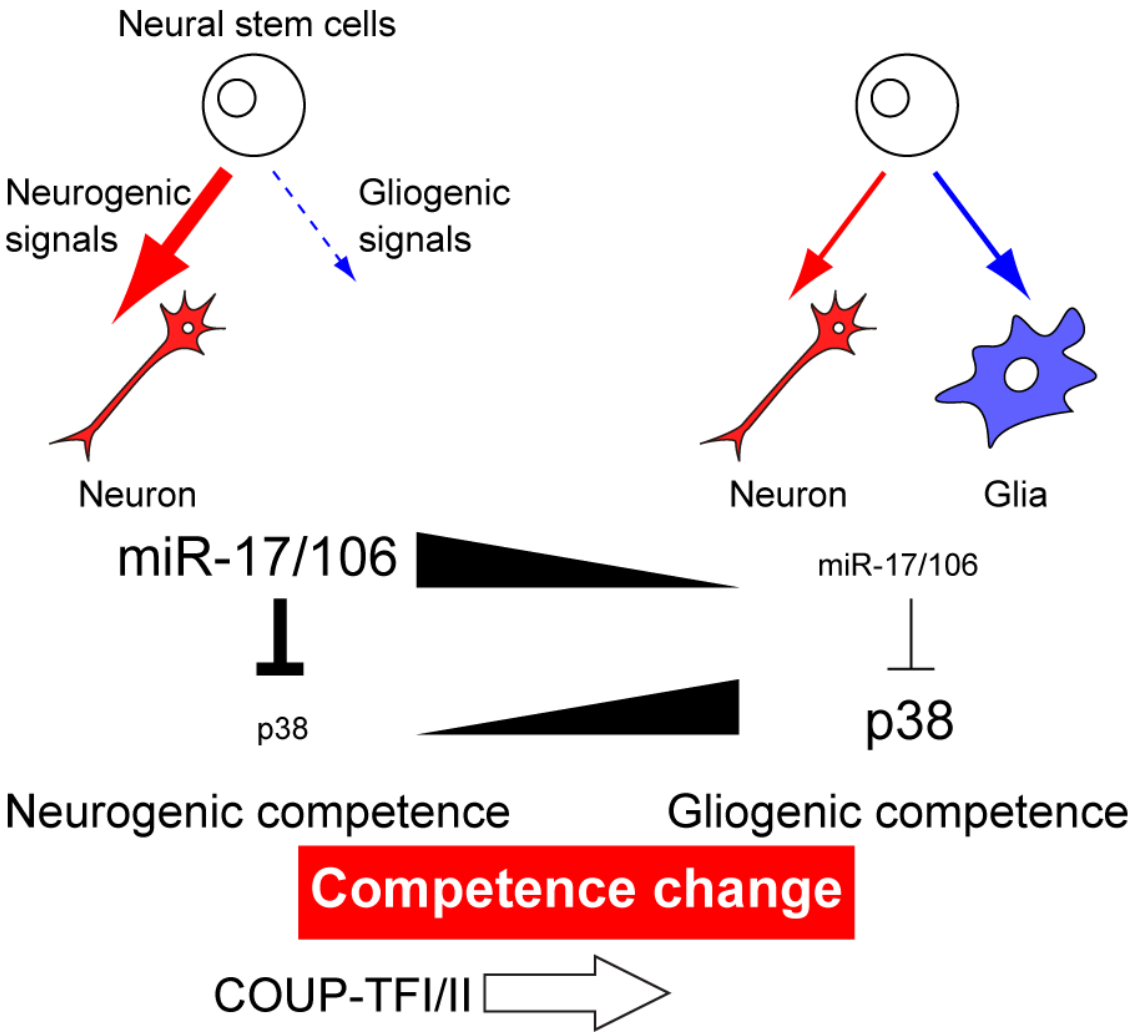

Fig. S6. Schematic diagram showing neurogenic-to-gliogenic NSPC competence transition. The expression of Coup-tfI/II triggers the competence transition in NSPCs and gliogenesis. Downregulation of miR-17/106 causes an increase in the level of p38 protein, which alters the responsiveness of NSPCs to extrinsic signals. NSPCs then promote gliogenic potency by responding to gliogenic cytokines.

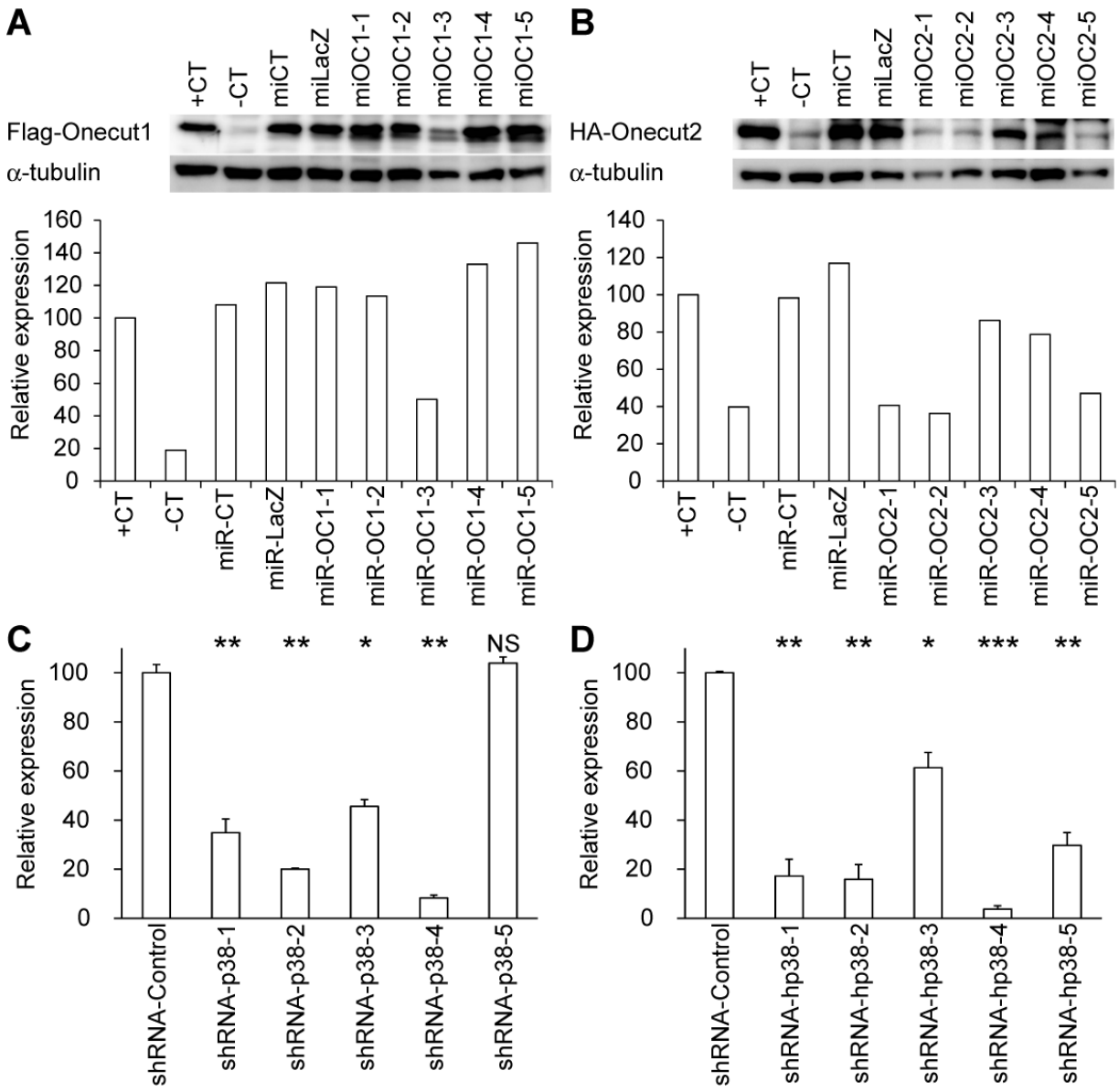

Fig. S7. Knockdown efficiencies of shRNAs and artificial miRNAs. We designed and constructed five shRNAs/miRNAs for each gene and investigated the knockdown efficiencies by Western blot analyses (*A* and *B*, n = 1) or fluorescence-activated cell sorting analyses with mKate2-fused cDNA (*C* and *D*, n = 3). The shRNA and miRNA that elicited the largest reduction in the expression of their target gene were used for experiments. CT, control; OC, Onecut. Results are shown as mean ± SEM. NS, $p > 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Supplementary Tables

Table S1. Candidate downstream effectors of Coup-tfs identified by the microarray analysis.

Gene symbol	Accession no.	Fold change (relative to p0-CT) p0-KD	p2-CT	p2-KD	p2-KD/p2-CT
Sim1	NM_011376	2.17	0.18	2.29	12.48
Nkx2-1	NM_009385	1.13	0.24	2.96	12.22
Rax	NM_013833	2.09	0.31	2.30	7.43
Zfp62	NM_009562	0.74	0.21	1.53	7.20
Hmx3	NM_008257	0.99	0.46	2.79	6.06
Vgll2	NM_153786	1.80	0.20	0.94	4.74
Dmrta1	NM_175647	2.12	0.26	1.16	4.42
Onecut2	NM_194268	0.82	0.16	0.70	4.32
Onecut1	NM_008262	0.73	0.18	0.76	4.27
Fezf2	NM_080433	1.39	0.18	0.75	4.07
Hmx2	NM_145998	0.91	0.32	1.30	4.01
Kbtbd8	NM_001008785	1.08	0.18	0.70	3.98
Zfp91	NM_053009	1.73	0.29	1.14	3.94
C77370	NM_001077354	0.81	0.19	0.75	3.91
Wdr54	NM_023790	1.24	0.39	1.47	3.77
Lhx5	NM_008499	0.98	0.32	1.19	3.72
Klhl29	XM_906219	0.86	0.31	1.11	3.64
1700045I19Rik	NR_003640	1.85	0.28	1.01	3.58
Wt1	NM_144783	1.81	0.22	0.74	3.37
D1Ertd471e	XM_001473525	1.02	0.21	0.69	3.29
Foxa1	NM_008259	0.91	0.25	0.81	3.24
Crhbp	NM_198408	0.79	0.30	0.95	3.18
Sp3	NM_001018042	1.61	0.33	1.03	3.11
Sim2	NM_011377	1.65	0.46	1.40	3.05
ENSMUSG00000046088	XM_001477677	2.58	0.26	0.80	3.05
Hdac9	NM_024124	0.81	0.38	1.13	2.97
Prdm16	NM_027504	1.13	0.18	0.51	2.86
Msx2	NM_013601	1.88	0.26	0.75	2.85
4932417H02Rik	NM_028898	0.97	0.25	0.69	2.82
Xist	NR_001463	1.22	0.35	0.95	2.71
Vax1	NM_009501	1.37	0.36	0.94	2.63
Tex14	NM_031386	1.89	0.45	1.17	2.62
Csrnp3	NM_153409	0.78	0.39	1.00	2.60
Npas1	NM_008718	1.32	0.31	0.80	2.54
Tbr1	NM_009322	1.20	0.32	0.81	2.52
Dmrtb1	XM_205469	0.76	0.30	0.75	2.49
Ddx51	NM_027156	0.92	0.36	0.88	2.47
Zfp750	NM_178763	1.99	0.22	0.55	2.47
Zfp652	NM_201609	1.09	0.26	0.63	2.40
Foxg1	NM_008241	1.36	0.22	0.52	2.39
Zfp462	NM_172867	0.74	0.30	0.71	2.33
Phf16	NM_199317	0.80	0.44	1.02	2.32
Cux2	NM_007804	0.84	0.24	0.56	2.32
Zmym4	NM_001114399	0.72	0.41	0.96	2.32
Bcl7a	NM_029850	0.91	0.38	0.88	2.31

Tle4	NM_011600	1.14	0.30	0.68	2.30
Rcor2	NM_054048	1.02	0.24	0.54	2.28
Atf7ip2	XM_148109	1.41	0.23	0.53	2.28
Zfp146	NM_011980	1.03	0.36	0.81	2.27
Bub3	NM_009774	1.56	0.34	0.78	2.27
Fbxl22	NM_175206	1.15	0.38	0.86	2.25
Htatip2	NM_016865	0.87	0.38	0.86	2.25
Satb1	NM_009122	0.89	0.32	0.71	2.23
Sall1	NM_021390	0.89	0.25	0.55	2.22
Nkx2-3	NM_008699	0.90	0.29	0.63	2.21
Rfx3	NM_011265	0.78	0.36	0.78	2.20
Onecut3	NM_139226	0.81	0.36	0.76	2.14
BC037703	NM_172295	1.18	0.29	0.61	2.14
Lass4	NM_026058	1.28	0.50	1.06	2.13
Zdbf2	XM_991644	1.01	0.45	0.95	2.13
D330045A20Rik	NM_175326	1.39	0.33	0.69	2.12
Dhx9	NM_007842	0.74	0.32	0.69	2.12
Sox11	NM_009234	0.74	0.31	0.65	2.11
Tcf7l2	NM_009333	0.99	0.41	0.87	2.10
Obfc2a	NM_028696	1.28	0.35	0.74	2.10
Uhmk1	NM_010633	1.41	0.42	0.88	2.08
Ovol1	NM_019935	1.05	0.39	0.81	2.08
Sox1	NM_009233	0.81	0.32	0.66	2.08
Arid4b	NM_194262	1.48	0.28	0.58	2.07
Magi3	NM_133853	0.85	0.47	0.98	2.07
Prdm1	NM_007548	1.50	0.28	0.56	2.02
Foxe1	NM_183298	1.77	0.35	0.71	2.01
Otud7a	NM_130880	0.72	0.36	0.72	2.00
Ccdc88c	NM_026681	1.02	0.32	0.65	2.00
Epha3	NM_010140	0.74	0.60	2.63	4.35
Gse1	NM_198671	0.71	0.56	1.66	2.98
Nuak2	NM_028778	0.84	0.47	0.84	1.80
Lrrc9	NM_001142728	0.86	0.55	0.92	1.69
Mkrn1	NM_018810	1.44	0.16	0.22	1.36
Maml3	NM_001004176	1.55	0.66	0.87	1.31
Nol7	NM_023554	1.22	0.79	0.72	0.92
Pspc1	NM_025682	1.48	1.05	0.93	0.89
Shc1	NM_001113331	1.25	2.40	1.67	0.70
Glis2	NM_031184	1.01	0.98	0.58	0.59
Rbbp7	NM_009031	1.25	1.33	0.70	0.53
Psap	NM_011179	1.04	3.70	1.73	0.47
Dpf3	NM_058212	1.30	6.32	2.63	0.42
Plekhm1	NM_183034	0.95	0.79	0.69	0.87
Rad51l1	NM_009014	1.17	0.74	0.55	0.75
Gm7968	XM_986599	-	-	-	-
Nhlh1	NM_010916	0.48	0.19	0.65	3.42
Nhlh2	NM_178777	0.45	0.12	0.38	3.23
Hist1h2ba	NM_175663	1.06	0.29	0.53	1.86
Hist1h2bm	NM_178200	1.01	0.25	0.48	1.91
Foxb1	NM_022378	0.99	0.12	0.37	3.22

Hist1h2bk	NM_175665	1.03	0.24	0.49	2.00
Bhlhb4	NM_080641	0.45	0.03	0.11	3.88
Bzw1	NM_025824	0.81	0.65	0.34	0.52
Nr2e1	NM_152229	0.61	0.31	0.52	1.70
Ybx1	NM_011732	1.07	0.47	0.54	1.16
Sp8	NM_177082	1.08	0.03	0.14	4.94
Myt1	NM_008665	0.42	0.43	1.29	3.02
Baz1a	XM_885873	0.77	0.23	0.38	1.67
Smarca4	NM_011417	0.90	0.43	0.44	1.02
Suhw2	NM_177475	1.32	0.35	0.55	1.58
Smarca5	NM_053124	0.94	0.44	0.49	1.13
Neurod1	NM_010894	0.52	0.22	1.24	5.60
Ezh2	NM_007971	0.98	0.17	0.22	1.32
Zfp652	NM_201609	1.09	0.26	0.63	2.40
Phf10	NM_024250	0.94	0.65	0.54	0.83
Actl6a	NM_019673	1.07	0.24	0.29	1.20
Baz1b	NM_011714	0.88	0.62	0.63	1.02
Foxa2	NM_010446	1.46	0.05	0.19	3.93
Sox5	NM_011444	1.44	0.85	1.07	1.26
SERPINE1	NM_008871	1.56	24.26	4.77	0.20
COL5A2	NM_007737	0.93	5.30	1.53	0.29
ARHGEF10	NM_172751	0.94	1.18	0.88	0.74
TGFB1I1	NM_009365	1.32	5.41	3.03	0.56
5430411K18Rik	NM_001195633	0.86	1.31	1.20	0.92
FYCO1	NM_148925	0.92	2.07	1.61	0.78
TXNIP	NM_001009935	1.02	4.78	4.41	0.92
REEP3	NM_178606	0.56	1.23	0.69	0.57
FBN1	NM_007993	0.89	4.25	1.41	0.33
CALD1	NM_145575	0.99	1.30	1.10	0.85
LIMK1	NM_010717	1.17	1.59	1.35	0.85
AKAP12	NM_031185	0.96	1.14	0.35	0.30
THBS1	NM_011580	1.11	2.63	2.18	0.83
LIMA1	NM_001113545	1.09	2.34	1.50	0.64
ITGA4	NM_010576	0.85	1.08	1.02	0.94
FMR1	NM_008031	1.13	0.89	0.81	0.91
FNDC3B	NM_173182	0.97	2.22	1.36	0.61
AXL	NM_009465	0.60	6.25	1.43	0.23
CIRBP	NM_007705	1.14	1.46	1.28	0.88
9430031J16Rik	NM_020864	1.35	0.90	1.66	1.84
PALLD	NM_016081	1.22	0.84	1.09	1.30
FBLN1	NM_006486	1.31	2.80	1.76	0.63
ACBD5	NM_145698	0.83	0.85	0.85	1.00
PKD2	NM_008861	0.99	1.73	1.03	0.59
PACS1	NM_018026	0.90	1.33	1.17	0.88
IRF9	NM_006084	0.89	1.73	1.20	0.69
CD46	NM_002389	0.96	2.26	1.71	0.75
STK38	NM_007271	0.97	0.65	0.60	0.92
SH3BP4	NM_014521	1.11	0.94	0.89	0.95
HIP1R	NM_003959	0.93	1.02	1.13	1.11
NAGK	NM_017567	0.97	2.82	2.10	0.74

ATL3	NM_015459	1.00	1.35	0.78	0.58
RAPGEF2	NM_014247	0.86	0.58	0.61	1.06
PLXNA4	NM_001105543	0.77	0.97	1.71	1.76
FLJ11151	NM_001099455	0.97	0.88	0.83	0.94
PLXNA2	NM_025179	0.61	0.69	0.92	1.34

CT: control (shRNA-Control); KD: knockdown of *Coup-tfs* (shRNA-*Coup-tfs*); p0: stage p0 neurospheres; p2: stage p2 neurospheres

Table S2. Nucleotide sequences of the cloned microRNAs.

Cloned microRNA	Cloned sequence	Length (bp)
miR-LacZ	TGGAGGCTTGCTGAAGGCTGTAtgctgAAATCGCTGATTTGTGTAGTCgttttggccactgactgacGACTAC ACATCAGCGATTTcaggACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCC	132
mmu-mir-21	ttggcattaagccccagcaaaccagagatgtttgctttgctttaaaccctgcctgagcacctcgtgcttgccc cctgtcgtggtcgtgacatcgcatggctgTaccaccttgtcggaTAGCTTATCAGACTGATGTTGActgttga atctcatggCAACAGCAGTCGATGGGCTGTCtgacattttggtatctttcatctgaccatccataGcaaatgt ttcattcaaacattacccagcatcatggtttgcagtcaaaaattgtggtccttatgtcttgtgagacttgga	292
mmu-miR-9	caccacgcgcgtccccatccgccgtcgagcgactcgagactacggaggtccaggcggtggccgggaggctgc gtggaagaggaggaggcggccaggaggcgggGttggttgttaTCTTTGGTTATCTAGCTGTATGAgtggtgtg gagtcttcATAAAGCTAGATAACCGAAAGTaaaaataaccccatacactgcgcagagggcctggaacgctggt agtggccgagctgcaggagggagagccgtgccaggcgtgcctggaggctggaggggctgggggggaggggga	289
mmu-miR-132	ccctgtgggttgcggtgggcgcaggccccgcagacactcgcgccaccccgccgcccgcggtgctgacgtcagc ctgcaagccccgccccgcgtctccaggGcaaccgtggctttcgattgttactgtgggaaccggaggTAACAG TCTACAGCCATGGTCGccccgcagcacgcccacgctccccaccactcccgagttctgccagcctgggtttggg cagatacagagcaagaggaggcggggcggcgacgcaacattcgatg	265
mmu-miR-195	aaggtgggacaggagacactggaaagagcccctctgcaacccccaggttgtctgataccagttatcaggaacc ctggtaatgagttctggccccacagagcaaagtagagtctttgttgcccacacccaactctcctggctcTAGC AGCACAGAAATATTGGCatggggaagtgagtctgccaatattggctgtgctgctccaggcagggtggtgagag ctactgagaaggggccaagccccgagggcgaagcagaggagagggaacggcagctggcagcaccatgttgaga gaatcttt	300
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mmu-miR-22	tagagccaggtttggatggcctctgggtcgctggccctgtcacccagctttcctgttttttttttttcctcccc ttccttttaggaacctgtgcctcccacaccctcacctggctgagccgcagtAGTTCTTCAGTGGCAAGCTTTA tgtcctgacccagctaAAGCTGCCAGTTGAAGAACTGTtgccctctgcccctggcttcgtggaggaagaggag aagcagcagctttgcctatcatccggaaggtgacagaactggggtgggaaggtctggacagctggggtgatgg ctttatggT	301
mmu-miR-128	tctttgatacgtagctgctttcattcttggactcttttgaaaagtttgcagcttctccttatgtgcttatatt ttacaataattggccttcttcctgagctgtTggattcggggccgtagcactgtctgagaggtttacatttcTC ACAGTGAACCGGTCTCTTTttcagctgcttcctgacttcttttttacttctttttgctttttttgctttttttt ctatgctatattaagatactaatatttgtttatattttccattgcctataat	271
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miR-382-485	cactcagcatccaatctgcctgcaggttggtggttggaaaccatagcccttggagaaatggaaggggccctttgtctgtcttgtctctgcttttctgtggTACTTGAAGAGAAGTTGTTCGTGGTGGATTCGCTTTACTTGTGACGAATCATTCACGGACAACACTTTTTTCAGTAccaaatgctacctctaaggatttcctggacatgatggcaacttgcagaaagatggcggttcagtcaagctggtagagaagccaagtatggatgtttggccacggacagtgtgcttgagctagctgtaagtcacctggtcgggttacctgagcatctgatccacctgtaggcctctcatcagtgggccgtgccaaccttggtgaggcagctgtggctctgcccccaagtatcagcttacaagactttgaaaagaggtcatcttccggaagagatgttggtgccagcaccattcAGGGTGTGTGACTGGTTGACCAGAGGGGCGTGCACTCTGTTCACCCTGTGGGCCACCTAGTCACCAACCCTcagcatcaattccactcaaagaagactttccagagatcctaccaagtttggggatatgtcaatggacttgatggctgtgcctgctcagtggaccaggatgaactgtggtcttaggggtgtatgtttacataagatgccatgaggcatccgtggtagctgctgcatcactgtcacagcctccttgaaatgttgacttcagatgtggacatgatgttgacttcccatgagggacctgaagtcccttctctcctgggtgtgtgactgaattgtactttactaagcatgtgcctgtgccttacttatctgatggatctatcttccagttgtctaacctcaatatcctgtctctacaggagagtctgtgagatgataccaacctctagaagcaggcatggttgtcccgacatcgccacactaccacaggagcttccagaatacattctcttcatggaaactgtggaaccacgccccctctggtccaggaggactaaccagattcaaggctatcaccatccccttcaGGTAAGTGTGCCTCGGGTGAGCATGCACTTAATGTAGGTGTATGTCACTCGGCTCGGCCCACTACCcaatgctgtcccaccccttcttcacaggacagtggaagcagccacctttcgagagagtcgatgtgttcttcaccagtgttcttcgccagtgatcatgtgtgatACTTGGAGAGAGGCTGGCCGTGATGAATTCGATTCATCTAAACGAGTCATACACGGCTCTCCTCTCTTCTAGTgtcaaactctgcctcagaggtcttctcaagccactactgttcccaaggtgggtttctggatggctaaacccatgtcaagtgcctttatccaattgtatat	1404
miR-409-410	gctcctcactgaatggggagttataatctctgaggggctccaggatggttcttctggaaactcagccatcggcctcgttctgagcatccgagcctctccgTGGTACTCGGAGAGAGGTTACCCGAGCAACTTTGCATCTGGAGGACGAATGTTGCTCGGTGAACCCCTTTTCGGTATCAaatccctccagggaggccacctcagggaagaccatggactcatctcgctctgGGGTATGGGACGGATGGTCGACCAGCTGGAAAGTAATTGTTTCTAATGTACTTCACCTGGTCCACTAGCCGTCGGTGCCCgctgcagcctgcgcccaggatgtcacagcctcagctcaacacctctgctGGTACTTGAAGGGAGATCGACCGTGTTATATTCGCTTGGCTGACTTCGAATAATACATGGTTGATCTTTTCTCAGTATCaacgctcagcttggagaagctcttggagttgcagcccctgtgggggtggggacagcatggtgcttctaggttgctgcctccgcggggaactgggctgggtggaacaggctgtgtgctgcctgtgtcaaccctactcaccatttatatgcaatccccccttcccccaggacagcttcaggtggtgattccagctccagggttgctgcggtcaacactGGGTACTTGAGGAGAGGTTGTCTGTGATGAGTTCGCTTTATTAATGACGAATATAACACAGATGGCCTGTTTTCAATACCAcctgccactccggtcactcggcagtacataccaggtgtcacaccactgcccggtaggtaaatgcatggactctgtatgacgcttgtcacccctcttcac	838

Table S3. Candidate direct targets of miR-17 identified by the proteomics analyses.

IPI	Gene symbol	Fold change (relative to p0-CT) p0-OE	p2-CT	p2-OE	p2-OE/p2-CT	p0-OE/p2-CT
IPI00409360.3	Acox1	1.32	9.29	3.77	0.41	0.14
IPI00120165.1	Crot	0.48	1.33	0.54	0.41	0.36
IPI00121833.3	Acaa1a	0.55	1.15	0.54	0.47	0.48
IPI00454049.4	Echs1	1.61	3.34	1.58	0.47	0.48
IPI00115607.3	Hadhb	0.77	2.42	1.22	0.51	0.32
IPI00889843.1	Abca1	1.19	1.87	0.95	0.51	0.64
IPI00877214.1	Peci	0.96	2.00	1.11	0.55	0.48
IPI00310567.2	Pon2	0.89	1.21	0.69	0.56	0.73
IPI00222935.3	Itgb8	1.07	1.66	0.95	0.57	0.64
IPI00228645.5	Pfn2	1.63	3.08	1.75	0.57	0.53
IPI00134680.2	Saal1	0.89	1.02	0.59	0.58	0.87
IPI00323114.3	Vldlr	2.15	6.67	3.87	0.58	0.32
IPI00387379.1	Decr1	0.91	2.23	1.32	0.59	0.41
IPI00828615.1	Lamp2	1.56	2.73	1.61	0.59	0.57
IPI00225337.5	Rbp1	0.74	1.69	1.04	0.61	0.44
IPI00315187.5	2400001E08Rik	1.14	1.57	0.96	0.61	0.72
IPI00122633.3	Acsf2	0.76	2.38	1.46	0.61	0.32
IPI00896710.1	Erbb2ip	1.21	1.54	0.97	0.63	0.79
IPI00627008.2	Ptprz1	1.84	5.11	3.28	0.64	0.36
IPI00222419.5	Cycs	0.70	2.56	1.64	0.64	0.28
IPI00117986.3	Slc12a9	2.61	5.25	3.40	0.65	0.50
IPI00113517.1	Ctsb	1.31	2.54	1.64	0.65	0.52
IPI00169862.1	Coq9	1.31	2.01	1.32	0.65	0.65
IPI00169916.11	Cltc	1.63	5.81	3.87	0.67	0.28
IPI00125035.1	Ak4	0.41	1.43	0.98	0.69	0.28
IPI00968403.1	Spna2	0.88	4.13	2.86	0.69	0.21
IPI00223875.1	Asrgl1	0.40	2.42	1.67	0.69	0.17
IPI00130118.1	Rab10	2.70	4.53	3.13	0.69	0.60
IPI00654420.1	Prosc	2.40	3.28	2.27	0.69	0.73
IPI00112346.1	Mapk14	2.86	3.16	2.19	0.69	0.90
IPI00458393.3	Atl3	1.39	1.66	1.17	0.70	0.84
IPI00755997.2	Golga2	1.45	2.03	1.46	0.72	0.71
IPI00228583.5	Mtpn	1.11	1.60	1.15	0.72	0.69
IPI00318841.4	Eef1g	0.82	3.84	2.81	0.73	0.21
IPI00648685.1	Ppp1r8	1.15	1.16	0.85	0.73	0.99
IPI00884460.1	Prkca	0.90	4.13	3.05	0.74	0.22
IPI00405742.6	Plxnb2	1.72	1.91	1.41	0.74	0.90
IPI00453582.2	Grsf1	0.98	1.12	0.83	0.74	0.88
IPI00119024.3	Arl6ip5	0.71	1.00	0.75	0.75	0.71
IPI00407499.1	Abat	1.56	7.59	5.70	0.75	0.21

Forty genes that encode mRNAs with complementary regions to the seed sequence of miR-17 were downregulated in miR-17-expressing neurospheres at the p2 stage. CT: control (miR-LacZ); OE: miR-17 overexpression; p0: stage p0 neurospheres; p2: stage p2 neurospheres; IPI: international protein index.

Table S4. Candidate downstream effectors of Coup-tfs identified by the microRNA array analyses (microRNAs whose expression levels were more than 2-fold higher in p2-CT neurospheres than in p0-CT neurospheres and less than 0.75-fold lower in p2-KD neurospheres than in p2-CT neurospheres).

	Fold change (relative to p0-CT)			
microRNA	p0-KD	p2-CT	p2-KD	p2-KD/p2-CT
mcmv-miR-m01-2	1.99	4.09	0.20	0.05
mghv-miR-M1-8	2.87	9.95	1.00	0.10
mmu-miR-34c*	2.33	2.07	0.40	0.19
mmu-miR-9*	0.76	2.79	0.72	0.26
mmu-miR-132	0.72	3.69	1.15	0.31
mmu-miR-190b	1.13	2.41	0.79	0.33
mmu-miR-302c*	1.00	3.06	1.00	0.33
mmu-miR-21	0.89	2.81	1.10	0.39
mmu-miR-195	1.02	3.90	1.52	0.39
mmu-miR-24-2*	0.59	4.96	1.96	0.40
mmu-miR-497	1.06	4.62	1.87	0.40
mmu-miR-222	2.15	3.89	1.63	0.42
mmu-miR-486	1.21	2.16	0.92	0.43
mmu-miR-133a	1.93	2.33	1.00	0.43
mmu-miR-22	0.76	3.22	1.46	0.45
mmu-miR-302b	1.51	2.06	0.96	0.46
mmu-miR-146b	0.87	3.26	1.55	0.48
mmu-miR-128	0.84	2.15	1.16	0.54
mmu-miR-22*	1.00	12.76	7.46	0.58
mmu-miR-29a	0.87	2.89	1.79	0.62
mmu-miR-676	0.85	2.78	1.76	0.63
mmu-miR-326	0.89	2.24	1.45	0.65
mghv-miR-M1-6	1.72	2.60	1.73	0.67
mmu-miR-138	0.93	2.29	1.59	0.69
mmu-miR-214	0.77	11.58	8.06	0.70

CT: control (shRNA-Control); KD: knockdown of *Coup-tfs* (shRNA-*Coup-tfs*); p0: stage p0 neurospheres; p2: stage p2 neurospheres.

Table S5. Candidate downstream effectors of Coup-tfs identified by the microRNA array analyses (microRNAs whose expression levels were less than 0.5-fold lower in p2-CT neurospheres than in p0-CT neurospheres and greater than 2-fold higher in p2-KD neurospheres than in p2-CT neurospheres).

	Fold change (relative to p0-CT)			
microRNA	p0-KD	p2-CT	p2-KD	p2-KD/p2-CT
mmu-miR-106b*	1.21	0.05	1.08	21.40
mmu-miR-224	1.30	0.11	1.59	13.80
mmu-miR-431*	1.02	0.11	1.17	10.18
mmu-miR-666-3p	1.20	0.25	1.71	6.76
mmu-miR-1193	1.23	0.20	1.31	6.64
mmu-miR-20a*	0.98	0.10	0.62	6.17
mmu-miR-18a*	1.33	0.09	0.52	5.52
mmu-miR-708	1.30	0.19	1.01	5.44
mmu-miR-452	0.97	0.09	0.48	5.11
mmu-miR-154*	0.98	0.32	1.56	4.83
mmu-miR-301b	1.01	0.07	0.31	4.56
mmu-miR-409-3p	1.06	0.25	0.96	3.79
mmu-miR-369-3p	0.76	0.27	1.02	3.71
mmu-miR-376c	0.88	0.31	1.11	3.58
mmu-miR-17*	1.01	0.18	0.65	3.58
mmu-miR-377	0.94	0.25	0.89	3.51
mmu-miR-124*	0.70	0.06	0.19	3.50
mmu-miR-18a	0.86	0.10	0.34	3.39
mmu-miR-25	1.04	0.23	0.77	3.29
mmu-miR-130b*	0.96	0.19	0.61	3.18
mmu-miR-543	0.97	0.33	1.03	3.12
mmu-miR-450b-5p	1.08	0.22	0.67	3.01
mmu-miR-301a	0.99	0.19	0.58	3.00
mmu-miR-431	1.01	0.20	0.59	2.98
mmu-miR-7a*	0.81	0.36	1.06	2.98
mmu-miR-92a	1.14	0.16	0.48	2.95
mmu-miR-411*	0.92	0.29	0.84	2.88
mmu-miR-181d	1.00	0.50	1.43	2.87
mmu-miR-744*	1.04	0.23	0.64	2.84
mmu-miR-541	0.79	0.24	0.68	2.79
mmu-miR-130b	0.94	0.13	0.37	2.77
mmu-miR-423-3p	1.83	0.25	0.69	2.74
mmu-miR-495	0.95	0.38	1.05	2.73
mmu-miR-20b	1.04	0.12	0.33	2.72
mmu-miR-337-3p	0.86	0.40	1.08	2.72
mmu-miR-20a	0.95	0.16	0.42	2.69
mmu-miR-106b	0.95	0.28	0.74	2.68
mmu-miR-135b	0.76	0.26	0.69	2.64
mmu-miR-335-3p	1.02	0.14	0.38	2.62
mmu-miR-299*	0.88	0.27	0.71	2.60
mmu-miR-93	0.92	0.28	0.72	2.60
mmu-miR-342-5p	1.00	0.42	1.08	2.58
mmu-miR-323-3p	0.96	0.50	1.26	2.53

mmu-miR-805	1.35	0.47	1.17	2.48
mmu-miR-380-3p	0.98	0.45	1.12	2.47
mmu-miR-433	0.92	0.45	1.09	2.42
mmu-miR-325	0.83	0.33	0.80	2.41
mmu-miR-466g	1.05	0.16	0.39	2.35
mmu-miR-540-5p	0.52	0.29	0.67	2.33
mmu-miR-379	0.83	0.49	1.14	2.32
mmu-miR-153	0.81	0.41	0.95	2.32
mmu-miR-17	0.96	0.18	0.41	2.28
mmu-miR-337-5p	0.95	0.50	1.12	2.26
mmu-miR-19a	0.82	0.15	0.33	2.25
mmu-miR-216a	0.85	0.13	0.29	2.24
mmu-miR-670	0.94	0.27	0.60	2.21
mmu-miR-298	0.94	0.38	0.84	2.20
mmu-miR-15b	0.92	0.27	0.58	2.20
mmu-miR-299	0.75	0.16	0.34	2.13
mmu-miR-329	0.89	0.49	1.04	2.10
mmu-miR-19b	0.89	0.22	0.47	2.10
mmu-miR-103	0.91	0.36	0.75	2.07
mmu-miR-196a	1.05	0.40	0.81	2.03
mmu-miR-744	0.99	0.48	0.96	2.03

CT: control (shRNA-Control); KD: knockdown of *Coup-tfs* (shRNA-*Coup-tfs*); p0: stage p0 neurospheres; p2: stage p2 neurospheres

Table S6. Nucleotide sequences used in the knockdown constructs.

Name	Sequence
shRNA-Control	ACTACCGTTGTTATAGGTGttcaagagaCACCTATAACAACGGTAGT
shRNA-*Coup-tfs*	GTCGAGCGGCAAGCACTACttcaagagaGTAGTGCTTGCCGCTCGAC
shRNA-p38	GGGCTGAAGTATATACATTCGgagaCGAATGTATATACTTCAGCCC
shRNA-hp38	GGCAGATCTGAACAACATTGTgagaACAATGTTGTTCAGATCTGCC
miR-LacZ	AAATCGCTGATTTGTGTAGTCgttttggccactgactgacGACTACACATCAGCGATTT
miR-Onecut1	AGAAGTTGCTGACAGTGCTCAgttttggccactgactgacTGAGCACTCAGCAACTTCT
miR-Onecut2	TGGTGTTGATCTCTTCCAGCTgttttggccactgactgacAGCTGGAAGATCAACACCA
TuD-miR-LacZ	catcaacGACTACACAAAgtatTCAGCGATTTcaagtattctggtcacagaatacaacGACTACACAAAgtatTCAGCGATTTcaag
TuD-miR-17/106	catcaacCTACCTGCACTGTaatcAAGCACTTTGcaagtattctggtcacagaatacaacCTACCTGCACTGTaatcAAGCACTTTGcaag
TuD-miR-17*	catcaacCTACAAGTGCCCaacaTCACTGCAGTcaagtattctggtcacagaatacaacCTACAAGTGCCCaacaTCACTGCAGTcaag
shRNA-p38-1	GCTGAATTGGATGCACTATAAgagaTTATAGTGCATCCAATTCAGC
shRNA-p38-2	GGTCACTGGAGGAATTCAATGgagaCATTGAATTCCTCCAGTGACC
shRNA-p38-3	GCAAGGTCACTGGAGGAATTCgagaGAATTCCTCCAGTGACCTTGC
shRNA-p38-5	GGCTCGGCACACTGATGATGAgagaTCATCATCAGTGTGCCGAGCC
shRNA-hp38-1	GGGCAGATCTGAACAACATTGgagaCAATGTTGTTCAGATCTGCCC
shRNA-hp38-2	GGTCTCTGGAGGAATTCAATGgagaCATTGAATTCCTCCAGAGACC
shRNA-hp38-3	GCAAGGTCTCTGGAGGAATTCgagaGAATTCCTCCAGAGACCTTGC
shRNA-hp38-5	GGCACACAGATGATGAAATGAgagaTCATTTCATCATCTGTGTGCC
miR-Onecut1-1	TGGTATTGATCTCTTCCATCTgttttggccactgactgacAGATGGAAGATCAATACCA
miR-Onecut1-2	TAGAGTTCGACGTTGGACGTCgttttggccactgactgacGACGTCCAGTCGAACTCTA
miR-Onecut1-4	CATTCAGGTGGGCATGAGGATgttttggccactgactgacATCCTCATCCACCTGAATG
miR-Onecut1-5	TTACTTCCATTGCTGACCTGCgttttggccactgactgacGCAGGTCAAATGGAAGTAA
miR-Onecut2-1	TTCCATTGTCAGCTCCGGGTTgttttggccactgactgacAACCCGGATGACAATGGAA
miR-Onecut2-3	TTTGCATGCTGCCAGGCGTAAgttttggccactgactgacTTACGCCTCAGCATGCAAA
miR-Onecut2-4	TGAAGATGGCGAAGAGTGTTCgttttggccactgactgacGAACACTCCGCCATCTTCA
miR-Onecut2-5	AGAAGTTACTGACAGTGGTCAgttttggccactgactgacTGACCACTCAGTAACTTCT

SI Materials and Methods

Identification of microRNA (miR)-17/106.

Of the 43,379 probes screened by the microarray analyses, the expression levels of 952 met three criteria: (1) more than 2-fold higher in p0 (p0-CT) neurospheres than in p2 neurospheres (p2-CT); (2) less than 0.5-fold lower in *Coup-tf*-knockdown (KD) p2 neurospheres (p2-KD) than in p0-CT neurospheres; and (3) more than 2-fold higher in p2-KD neurospheres than in p2-CT neurospheres. These candidate genes were then further restricted to transcriptional regulators by using the gene ontology annotation of the DAVID online program (http://david.abcc.ncifcrf.gov/home.jsp). These analyses reduced the total to 150 candidate genes. Sixteen of these candidate genes were eventually identified as direct targets of Coup-tfs by ChIP-seq analyses.

All 150 candidate genes (*SI Appendix*, Table S1) were cloned into lentivirus expression vectors and functionally screened by lentivirus-mediated overexpression (OE) in embryonic stem cell (ESC)-derived neurospheres. These screening procedures identified Onecut1/2 as a positive regulator of Isl-1-positive neuron production. No critical regulators of the neurogenic-to-gliogenic neural stem/progenitor cell (NSPC) transition were identified by this process.

The expression levels of different miRNAs were compared using miRNA arrays. Of the 674 miRNAs that were originally screened, the expression levels of 25 were more than 2-fold higher in p2-CT neurospheres than in p0-CT neurospheres and were less than 0.75-fold lower in p2-KD neurospheres than in p2-CT neurospheres (*SI Appendix*, Table S4). In addition, the expression levels of 64 miRNAs were less than 0.5-fold lower in p2-CT neurospheres than in p0-CT neurospheres and were more than 2-fold higher in p2-KD neurospheres than in p2-CT neurospheres (*SI Appendix*, Table S5). Of these candidates, 83 miRNAs were highly expressed and were analyzed further. These 83 miRNAs included miRNA clusters and parts of miRNA clusters (*SI Appendix*, Table S2).

Finally, these miRNAs were functionally screened by performing lentivirus-mediated OE experiments in ESC-derived neurospheres. The miR-17-92 cluster and its paralogs were identified as molecular switches for the neurogenic-to-gliogenic NSPC transition.

Identification of p38.

Quantitative proteomic analyses were performed using the iTRAQ method for miR-LacZ and miR-17 OE p0 and p2 neurospheres using an AB SCIEX TripleTOF 5600 System (AB SCIEX) according to the manufacturer's instructions. A total of 2,185 proteins were detected by iTRAQ. Of these candidates, 172 proteins met the following criteria: 1) had either the same or greater expression in p2-CT neurospheres relative to p0-CT neurospheres; 2) had either the same or lower expression in miR-17 OE p0 neurospheres (p0-OE) relative to p2-CT neurospheres; and 3) had less than 0.75-fold lower expression in p2-OE neurospheres relative to p2-CT neurospheres. The 172 candidate proteins were then further filtered by searching for the sequence GCACUUU, which is complementary to the miR-17/106 seed sequences, with the “HIMAJA” (developed by HIsashi, MAna and JAmes) program. These searches led to the identification of 40 miR-17/106 target candidates (*SI Appendix*, Table S3). These candidates were further narrowed down to ten by bioinformatic evaluation with the Ingenuity Pathway Analysis software. These candidates were then screened by performing lentivirus-mediated OE experiments in ESC-derived neurospheres. Finally, p38 was identified as the direct target of miR-17/106 that was responsible for NSPC competence changes.