Systematically Dissecting the Global Mechanism of MiRNA functions in Stem Cells

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Supplemental materials

Figure S1, Functional enrichments of all targets that are targeted by all up- and down-regulated miRNAs. A, Up-regulated miRNAs. B, down-regulated miRNAs.

Figure S2, total 17 out of top 20 important miRNAs target developmental genes.

Figure S3, down-regulated miRNAs mediate metabolism in stem cells.

Figure S4, all pluripotent genes targeted by up-regulated miRNAs (A) and down-regulated miRNAs (B) in stem cells.

Figure S5. An activated network targeted by down-regulated miRNAs.

Figure S6. Down-regulated miRNAs targeting DNMT3A.

Table S1, Data sources

Table S2, a list of miRNAs that are frequently and significantly differential expressed between stem cells and somatic cells.

Table S3, a list of genes coding for proteins that are frequently and significantly differential expressed between stem cells and somatic cells.

Table S4, a list of top 20 important miRNAs

Figure S1

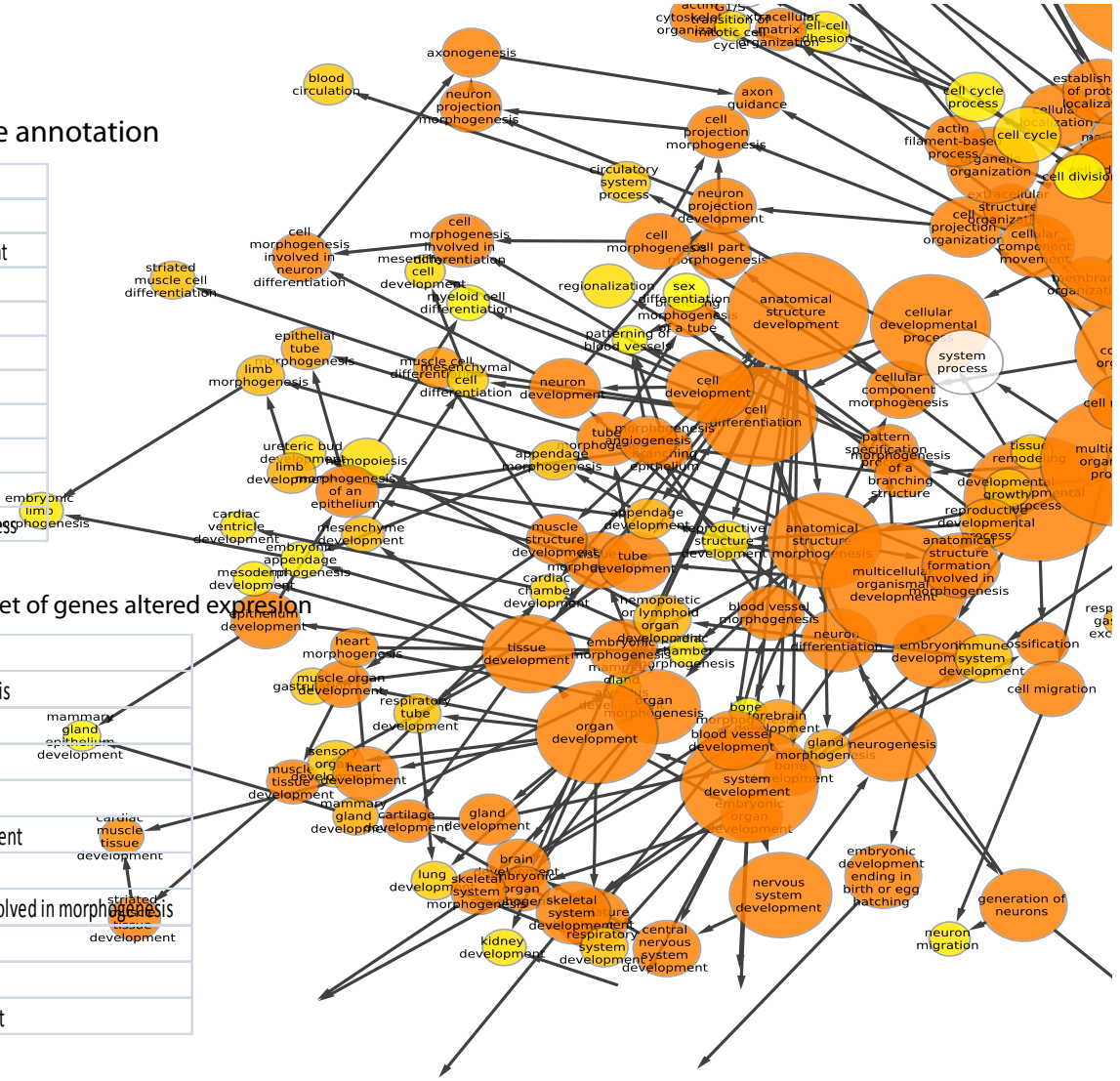
A

Top 10 GO term based on entire annotation

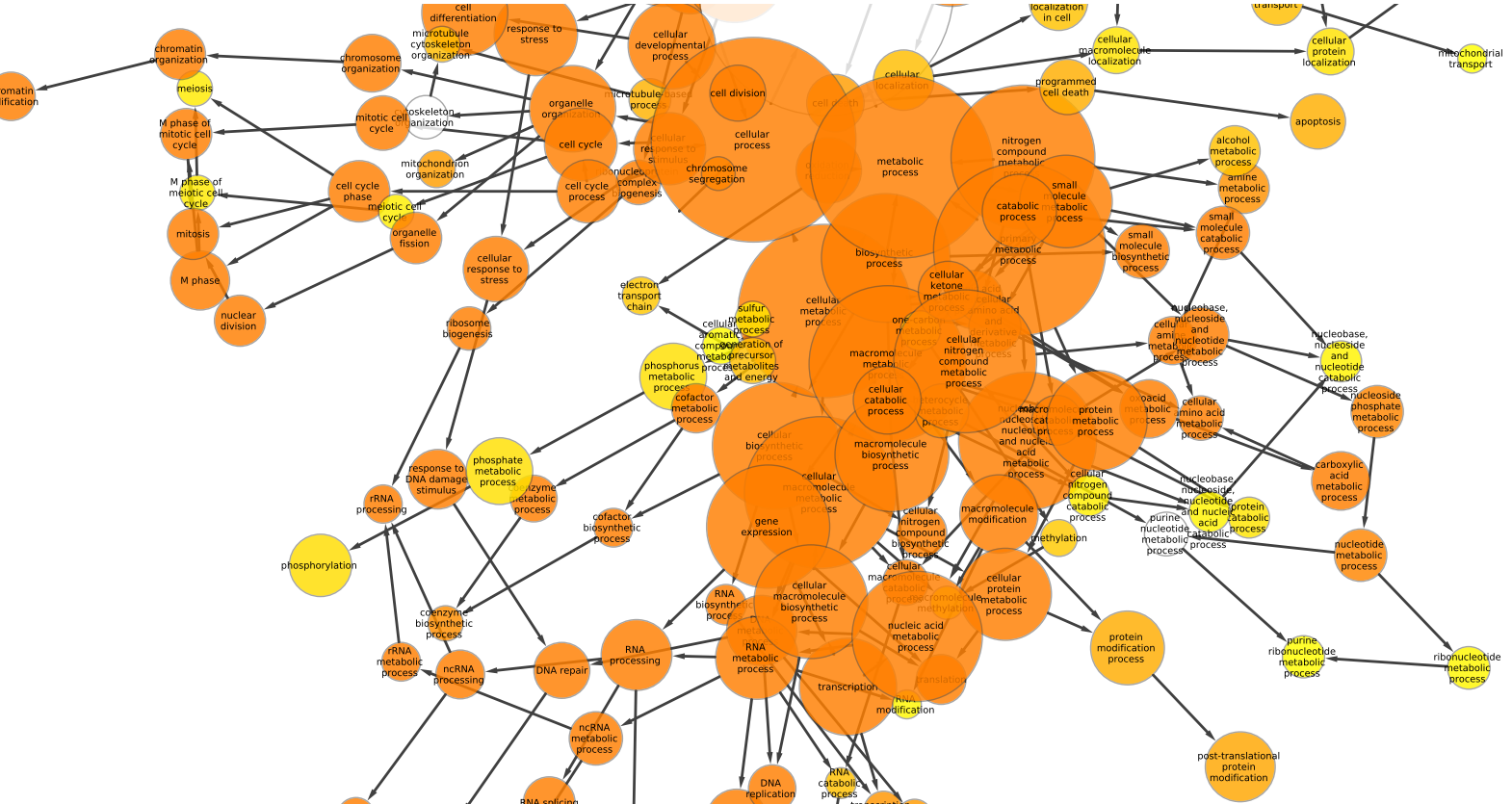
p-value	corr p-valu	Description
3.62E-86	1.11E-82	cellular process
4.26E-65	6.52E-62	multicellular organismal development
1.59E-61	1.62E-58	anatomical structure development
2.27E-61	1.74E-58	developmental process
5.6E-61	3.42E-58	system development
8.15E-53	4.15E-50	anatomical structure morphogenesis
2.18E-48	9.55E-46	biological regulation
1.15E-47	4.38E-45	regulation of biological process
9.41E-47	3.2E-44	organ development
6.01E-44	1.84E-41	positive regulation of biological process

Top 10 GO term using reference of a set of genes altered expresion

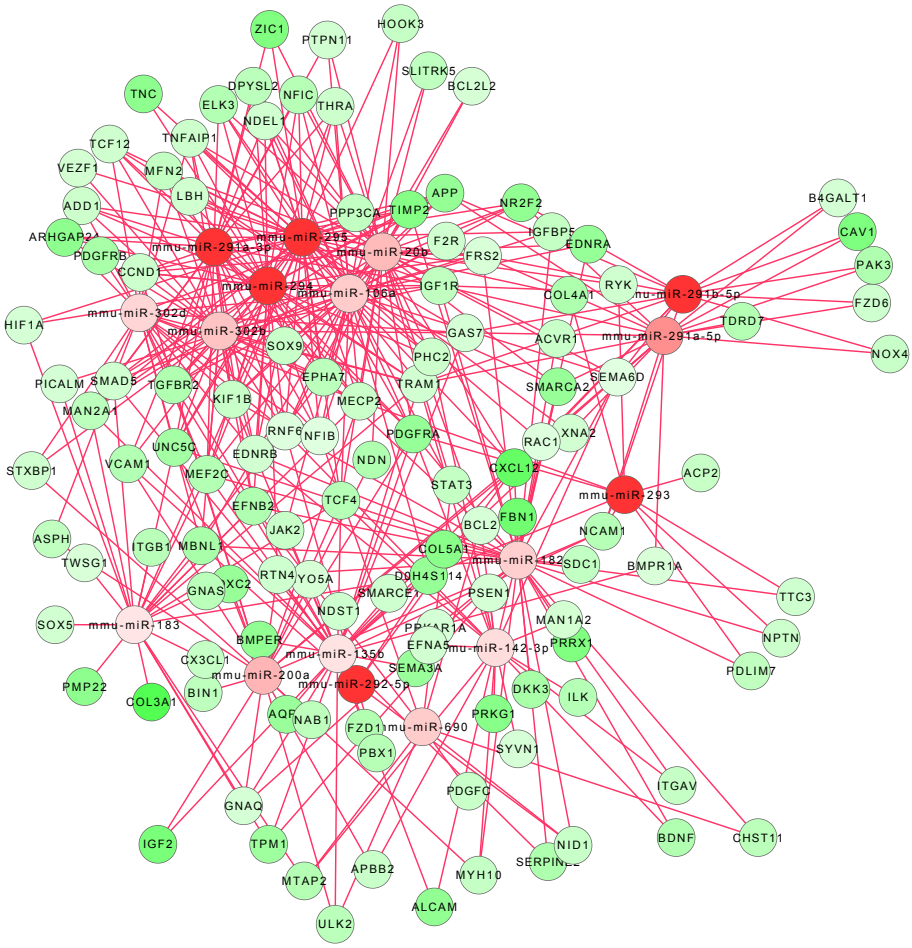
p-value	corr p-valu	Description
1.43E-08	2.10E-05	anatomical structure morphogenesis
1.08E-07	7.95E-05	organ development
2.95E-07	1.45E-04	developmental process
5.06E-07	1.87E-04	anatomical structure development
6.41E-07	1.89E-04	multicellular organismal development
1.57E-06	3.85E-04	system development
3.54E-06	7.45E-04	anatomical structure formation involved in morphogenesis
1.36E-05	2.50E-03	multicellular organismal process
1.95E-05	3.20E-03	cell development
3.33E-05	4.91E-03	striated muscle tissue development



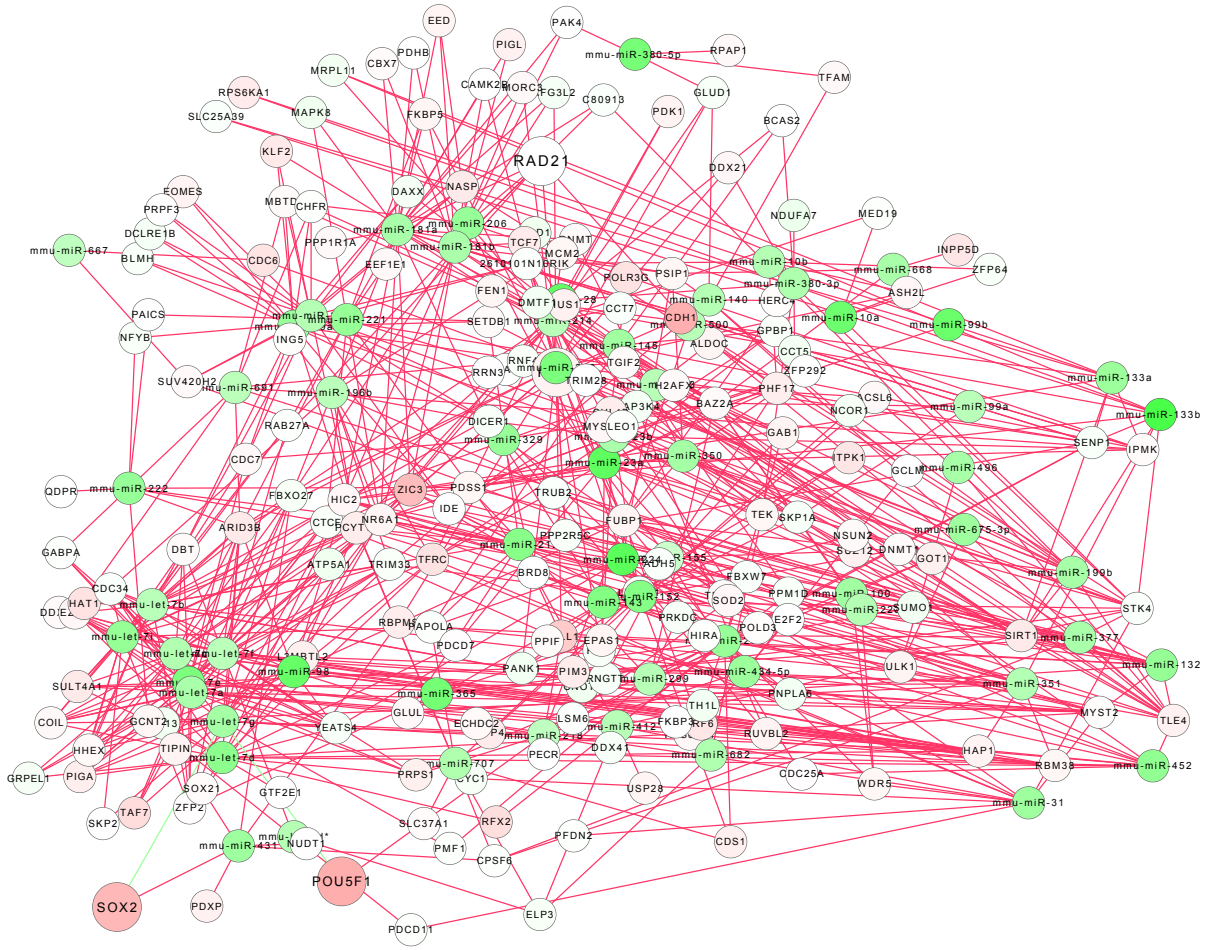
B



Total 17 out of top 20 miRNAs target developmental genes

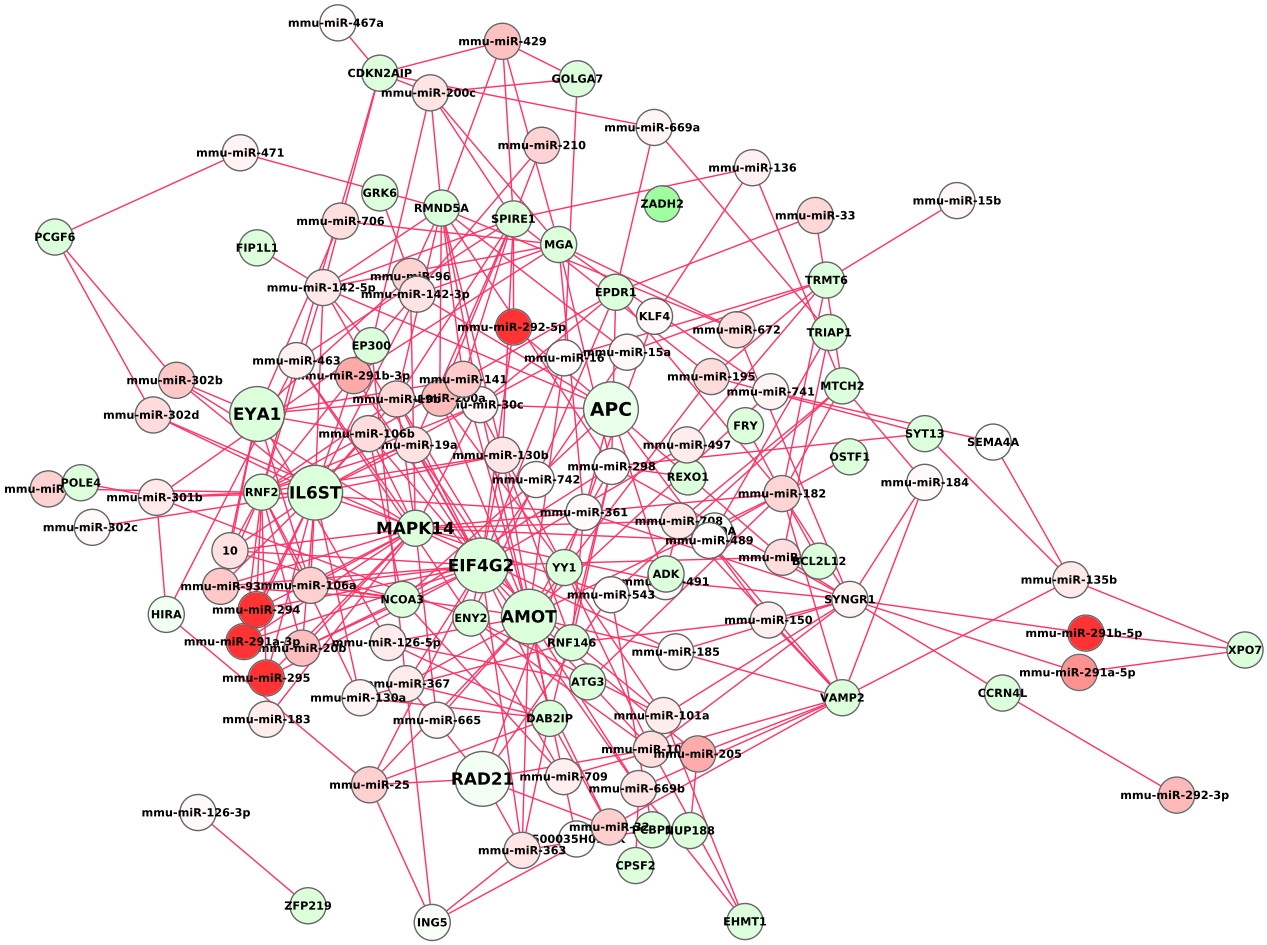


Down-regulated miRNAs mediate metabolism and pluripotency



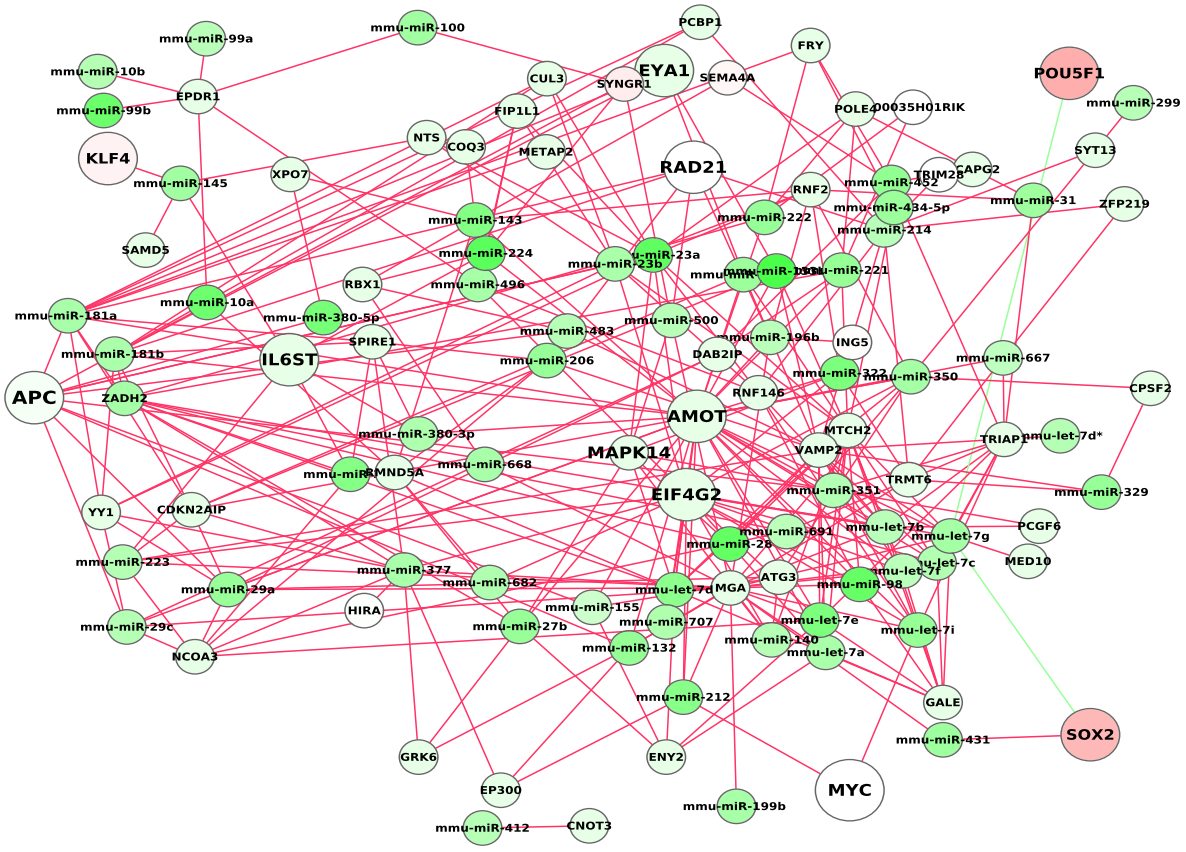
A

Pluripotent genes targeted by up-regulated miRNAs in stem cells



B

Pluripotent genes targeted by down-regulated miRNAs in stem cells



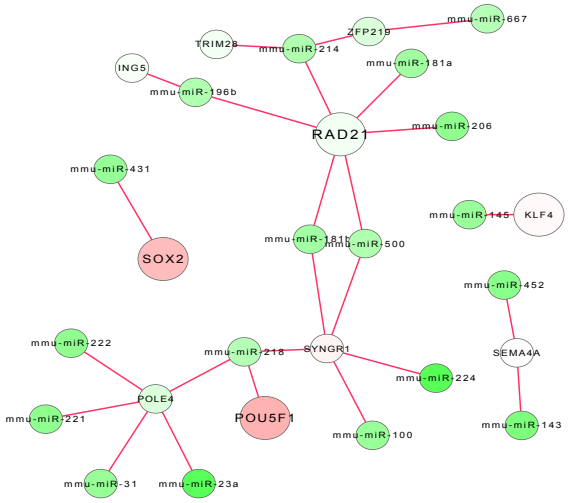

mmu-miR-667
ZFP219
TRIM28
mmu-miR-214
mmu-miR-181a
ING5
mmu-miR-196b
RAD21
mmu-miR-206
mmu-miR-431
mmu-miR-145
KLF4
mmu-miR-181b
mmu-miR-500
SOX2
mmu-miR-452
mmu-miR-222
mmu-miR-218
SYNGR1
SEMA4A
mmu-miR-224
POLE4
mmu-miR-221
POU5F1
mmu-miR-100
mmu-miR-143
mmu-miR-31
mmu-miR-23a

Figure S6

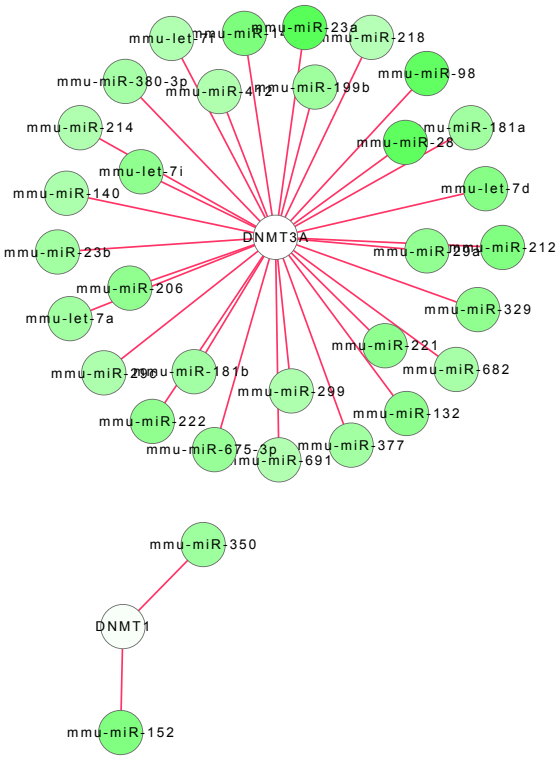

mmu-let-7f
mmu-miR-23a
mmu-miR-218
mmu-miR-98
mmu-miR-380-3p
mmu-miR-199b
mmu-miR-214
mmu-miR-181a
mmu-miR-26
mmu-let-7i
mmu-let-7d
mmu-miR-140
DNMT3A
mmu-miR-23b
mmu-miR-212
mmu-miR-206
mmu-miR-329
mmu-let-7a
mmu-miR-221
mmu-miR-181b
mmu-miR-682
mmu-miR-299
mmu-miR-222
mmu-miR-132
mmu-miR-675-3p
mmu-miR-377
mmu-miR-691
mmu-miR-350
DNMT1
mmu-miR-152

Table S1 data resources

GEO number	Platform	measurement
GSE25310	CLIP-seq	ES miRNA targets
GSE11724	ChIP-seq	TF binding
GSE11431	ChIP-seq	TF binding
GSM278905	RRBS	ES DNA methylation
GSM278902	RRBS	TKO methylation
GSM539867	RNA-Seq	mouse embryonic fibroblast cells [09-002]
GSM539866	RNA-Seq	mouse embryonic stem cells [09-002]
GSE30012	Mouse430_2 array	ES miRNA expression
GSE25310	GPL11410	micrRNA and mRNA expression
GSM231739	Agilent-GPL2872	ES gene expression TKO/WT
GSE15267	AffymetrixGPL1261	Gene expression somatic cells vs stem cells
GSE14012	AffymetrixGPL1261	Gene expression somatic cells vs stem cells
GSE10871	AffymetrixGPL1261	Gene expression somatic cells vs stem cells
GSE14790	AffymetrixGPL1261	Gene expression somatic cells vs stem cells
GSE16062	IlluminaGPL6885	Gene expression somatic cells vs stem cells

Table S2 miRNAs differentially expressed between stem cell vs somatic cells with high frequency >25% of observations

geneID	foldChange.StemcellvsSomaticCells
mmu-miR-291a-3p	23.38772103
mmu-miR-292-5p	20.9773225
mmu-miR-295	18.61514609
mmu-miR-290	16.83638073
mmu-miR-291b-5p	16.74397919
mmu-miR-294	16.33979504
mmu-miR-293	15.71944751
mmu-miR-291a-5p	10.70302558
mmu-miR-291b-3p	8.775662583
mmu-miR-205	8.656636965
mmu-miR-292-3p	7.513040922
mmu-miR-200a	7.476828136
mmu-miR-20b	7.113430578
mmu-miR-429	6.970376253
mmu-miR-93	6.320621674
mmu-miR-302b	6.319533201
mmu-miR-124a	6.210366092
mmu-miR-141	6.112532011
mmu-miR-32	5.892597823
mmu-miR-25	5.664093286
mmu-miR-106a	5.660199796
mmu-miR-96	5.576097803
mmu-miR-690	5.566673137
mmu-miR-210	5.494180249
mmu-miR-182	5.380304319
mmu-miR-339	5.178218031
mmu-miR-33	5.150748639
mmu-miR-19b	5.130661066
mmu-miR-302d	4.786597786
mmu-miR-195	4.773097795
mmu-miR-297b	4.742119218
mmu-miR-499	4.699375408
mmu-miR-106b	4.67924418
mmu-miR-712*	4.616388282
mmu-miR-101b	4.615452785
mmu-miR-706	4.577798951
mmu-miR-672	4.425689091
mmu-miR-20a	4.355849211
mmu-miR-302	4.187271105
mmu-miR-142-3p	4.185529766
mmu-miR-19a	4.154314537
mmu-miR-450b	4.143615059
mmu-miR-200c	4.139625599
mmu-miR-17-5p	4.015734124

mmu-miR-669b	4.005643461
mmu-miR-363	4.004376577
mmu-miR-130b	3.921190227
mmu-miR-142-5p	3.771559152
mmu-miR-708	3.757978939
mmu-miR-301b	3.671137996
mmu-miR-297	3.649760196
mmu-miR-711	3.642487186
mmu-miR-135b	3.61287415
mmu-miR-145	-3.689012325
mmu-miR-125b	-3.750522829
mmu-miR-675-3p	-3.775797104
mmu-miR-31	-3.789955248
mmu-miR-431	-3.827836369
mmu-miR-133a	-3.931634792
mmu-miR-434-5p	-3.95970537
mmu-miR-29a	-4.128390595
mmu-miR-125a	-4.168574915
mmu-miR-27b	-4.181204463
mmu-miR-206	-4.1991836
mmu-miR-222	-4.206742949
mmu-miR-329	-4.226853284
mmu-let-7i	-4.253606445
mmu-miR-221	-4.277690509
mmu-miR-132	-4.327457901
mmu-miR-345	-4.362726416
mmu-miR-452	-4.493999108
mmu-let-7d	-4.733310501
mmu-miR-181a*	-4.890038681
mmu-miR-212	-5.03014549
mmu-miR-152	-5.091913825
mmu-miR-143	-5.251965264
mmu-miR-433-5p	-5.353386842
mmu-let-7e	-5.627257306
mmu-miR-322	-5.627467759
mmu-miR-380-5p	-5.840198038
mmu-miR-666	-5.963478682
mmu-miR-365	-6.053925857
mmu-miR-10a	-6.463178387
mmu-miR-24*	-6.501407687
mmu-miR-99b	-6.54057846
mmu-miR-98	-6.824098585
mmu-miR-28	-6.985496746
mmu-miR-23a	-7.258185943
mmu-miR-675-5p	-7.319121705
mmu-miR-224	-7.383165325
mmu-miR-133b	-8.331863729

mmu-miR-155	-12.36089174

Table S3. Genes differentially expressed between stem cells and somatic cells with high frequency >50% of observations

GB_ACC	ENTREZ_G	Gene.Symbol	logFoldChange.ESvsSC
BC006640	20315	Cxcl12	-7.932773867
BF225802	16011	Igfbp5	-7.7652649
AW550625	12825	Col3a1	-7.7405454
BF227507	12843	Col1a2	-7.50996995
BB542051	18295	Ogn	-7.13772715
U08020	12842	Col1a1	-7.025342217
NM_013655	20315	Cxcl12	-6.8464668
NM_011581	21826	Thbs2	-6.743730283
AV229424	12832	Col5a2	-6.6650371
BB051738	18933	Prrx1	-6.523803517
M65143	16948	Lox	-6.263793183
AF007248	14118	Fbn1	-6.234405867
NM_009933	12833	Col6a1	-6.142877467
NM_007993	14118	Fbn1	-6.087729233
BC019502	12111	Bgn	-6.042548083
AB015978	18414	Osmr	-6.018220117
BE197945	20324	Sdpr	-5.902171217
NM_007729	12814	Col11a1	-5.888984717
AW049660	18032	Nfix	-5.878165733
NM_010514	16002	Igf2	-5.805814817
BB197591	54216	Pcdh7	-5.793524283
AV226618	13837	Epha3	-5.703367667
AF378762	69538	Antxr1	-5.671588117
M68513	13837	Epha3	-5.646988233
BC002064	19242	Ptn	-5.631718783
NM_011340	20317	Serpinf1	-5.561155483
BB795075	18214	Ddr2	-5.5521091
BC023060	216616	Efemp1	-5.541377517
BF144658	21808	Tgfb2	-5.516599417
BB250384	22329	Vcam1	-5.511377133
AB029929	12389	Cav1	-5.478985417
D67076	11504	Adamts1	-5.469247617
BB315728	18032	Nfix	-5.460392167
BI794771	12842	Col1a1	-5.456734267
L06502	18933	Prrx1	-5.448142767
BG793483	21813	Tgfbr2	-5.434682533
BB532202	14264	Fmod	-5.394454433
BB361162	22771	Zic1	-5.383117233
AI931862	12111	Bgn	-5.378983617
BC014690	21809	Tgfb3	-5.302384367
NM_018865	22402	Wisp1	-5.29682725
AV064339	20324	Sdpr	-5.2953667
BG067986	54216	Pcdh7	-5.295023283
NM_030888	81799	C1qtnf3	-5.279631533

BB233297	21826	Thbs2	-5.26170495
BF168458	21858	Timp2	-5.239630733
BB259670	14362	Fzd1	-5.23704885
AA499047	18596	Pdgfrb	-5.226616983
BC026446	219151	Scara3	-5.1983228
NM_010714	16876	Lhx9	-5.18046395
NM_133859	99543	Olfml3	-5.167943083
BB067079	22418	Wnt5a	-5.160633383
AW555664	399558	Flrt2	-5.14692565
BC021484	16651	Sspn	-5.141520367
BC011063	15402	Hoxa5	-5.109899467
M93954	21858	Timp2	-5.0922978
AV310588	12444	Ccnd2	-5.076240083
NM_013589	16997	Ltbp2	-5.07117345
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BQ175880	12444	Ccnd2	-5.031714083
NM_009829	12444	Ccnd2	-5.03108855
BC022107	12558	Cdh2	-5.030543317
NM_011160	19091	Prkg1	-5.010924967
AK007904	12444	Ccnd2	-5.010597567
BB114398	12816	Col12a1	-5.001727783
BB377340	13612	Edil3	-4.984431667
BI455189	12834	Col6a2	-4.981937467
BC018425	22418	Wnt5a	-4.949481167
AF309564	80837	Rhoj	-4.942552217
AW744319	12831	Col5a1	-4.912884333
NM_010284	14600	Ghr	-4.907539267
AK003674	68588	Cthrc1	-4.9040982
NM_009610	11468	Actg2	-4.88703015
BM220945	239217	Kctd12	-4.885967567
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BC019836	16010	Igfbp4	-4.86110935
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AA500897	26362	Axl	-4.824049367
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BQ177170	17112	Tm4sf1	-4.749287983
BM250666	12830	Col4a5	-4.738634083
BC025502	231532	Arhgap24	-4.7154329
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AV246911	12831	Col5a1	-4.70608125
NM_133918	100952	Emilin1	-4.685038
AV260198	83675	Bicc1	-4.676352617
BC021376	225207	Zfp521	-4.6747989
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BI690209	57342	Parva	-4.603038383
AK018128	70717	6330406I15Ri	-4.599817333
AI595932	17260	Mef2c	-4.571089667
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BG075699	399558	Flrt2	-4.550595967
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BM217996	83675	Bicc1	-4.521218667
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AV315205	11658	Alcam	-4.495887367
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BB787243	16010	Igfbp4	-4.408829283
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NM_011150	19039	Lgals3bp	-4.34716645
BB229377	13717	Eln	-4.3469066
BF681826	26360	Angptl2	-4.34243245
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AK012411	20317	Serpinf1	-4.334218667
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NM_007471	11820	App	-4.32309575
BC026153	13841	Epha7	-4.322886683
BE652876	60527	Fads3	-4.31762715
NM_022563	18214	Ddr2	-4.317137833
BC005490	11820	App	-4.311839833

AY083458	235505	Cd109	-4.310650267
AW146109	12505	Cd44	-4.309742383
AF022889	268977	Ltbp1	-4.293317933
BF780807	23972	Papss2	-4.2837158
NM_010222	14231	Fkbp7	-4.283483917
BB765827	74761	Mxra8	-4.28266945
BB369191	27528	D0H4S114	-4.258134683
NM_011658	22160	Twist1	-4.252172233
BC022679	52552	Parp8	-4.249244683
BC024375	14600	Ghr	-4.235411317
AW558570	13617	Ednra	-4.235029783
NM_010151	13865	Nr2f1	-4.23266835
BB053506	207181	Rbms3	-4.227119367
BB464523	12293	Cacna2d1	-4.2176231
AI325255	14230	Fkbp10	-4.2139772
NM_009365	21804	Tgfb1i1	-4.2037574
AW537708	18595	Pdgfra	-4.201673433
BG244279	26360	Angptl2	-4.19122825
AV021105	208647	Creb3l2	-4.189322833
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NM_013519	14234	Foxc2	-4.150217817
BG248060	12153	Bmp1	-4.1456309
AK011935	67155	Smarca2	-4.1424534
BC009660	109042	Prkcdbp	-4.138494033
NM_010730	16952	Anxa1	-4.137948167
NM_017464	18003	Nedd9	-4.125438817
NM_020606	57342	Parva	-4.117250083
NM_054042	70445	Cd248	-4.1162995
AW107196	74480	Samd4	-4.089650683
NM_008520	16998	Ltbp3	-4.088398567
NM_007400	11489	Adam12	-4.087465183
BB138485	70676	Gulp1	-4.06900915
BB041237	17389	Mmp16	-4.0669223
NM_009152	20346	Sema3a	-4.06663545
AK007400	77889	Lbh	-4.065124233
BC027199	233328	Lrrk1	-4.0638856
BC003726	14789	Leprel2	-4.061919033
BM220576	53623	Gria3	-4.059143167
BM570006	20564	Slit3	-4.050010933
NM_007472	11826	Aqp1	-4.049342233
BB329489	12406	Serpinh1	-4.035949167
BC024358	22004	Tpm2	-4.027799067
BB371406	57265	Fzd2	-4.024201683
BI106777	12293	Cacna2d1	-4.016322467
BB484759	224024	Scarf2	-3.995337517

BC025145	19266	Ptprd	-3.96890555
AK004519	56726	Sh3bgrl	-3.915095233
NM_010221	14230	Fkbp10	-3.911402667
BB114067	21345	Tagln	-3.906768233
NM_010517	16010	Igfbp4	-3.895716167
AV164956	22418	Wnt5a	-3.889125017
U71189	13592	Ebf2	-3.883624733
AF339910	18605	Enpp1	-3.88293505
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NM_007802	13038	Ctsk	-3.804638867
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BG963150	20563	Slit2	-3.783541217
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AW551930	83675	Bicc1	-3.698414167
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AK003819	74777	Sepn1	-3.6822946
AW412729	12816	Col12a1	-3.663389833
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Y07687	18028	Nfib	-3.657044833
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BM251152	13003	Vcan	-3.620597833
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AI481026	29817	Igfbp7	-3.56210855
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BG868949	17122	Mxd4	-3.514140767
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NM_009794	12334	Capn2	-3.498667433
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BQ175796	18481	Pak3	-3.4733871
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BC024876	223453	Dap	-3.364419667
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BG066754	67204	Eif2s2	3.0295477
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BE650359	13619	Phc1	3.103443667
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BM935811	16403	Itga6	3.109543333
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U42190	17688	Msh6	3.242437417
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NM_009749	12069	Bex2	4.45785005
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AV095095	17865	Mybl2	5.318561367
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BG064756	99377	Sall4	6.034042167
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NM_013633	18999	Pou5f1	8.090839917
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Table S4 Top 20 important miRNAs in stem cells

mmu-miR-290
mmu-miR-293
mmu-miR-291a-3p
mmu-miR-292-5p
mmu-miR-295
mmu-miR-294
mmu-miR-291a-5p
mmu-miR-291b-5p
mmu-miR-302b
mmu-miR-124a
mmu-miR-182
mmu-miR-200a
mmu-miR-20b
mmu-miR-302d
mmu-miR-106a
mmu-miR-183
mmu-miR-135b
mmu-miR-690
mmu-miR-142-3p
mmu-miR-302