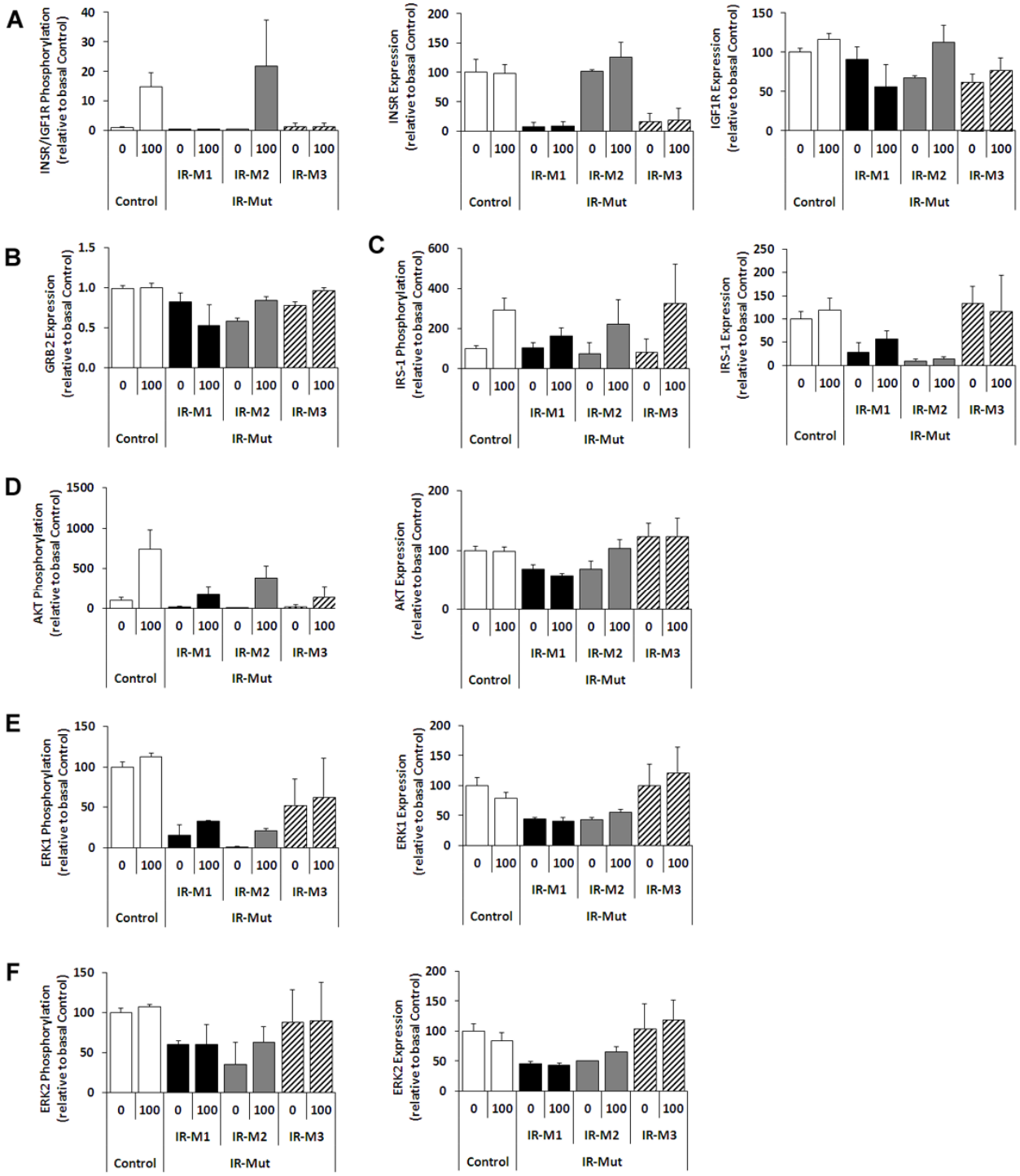
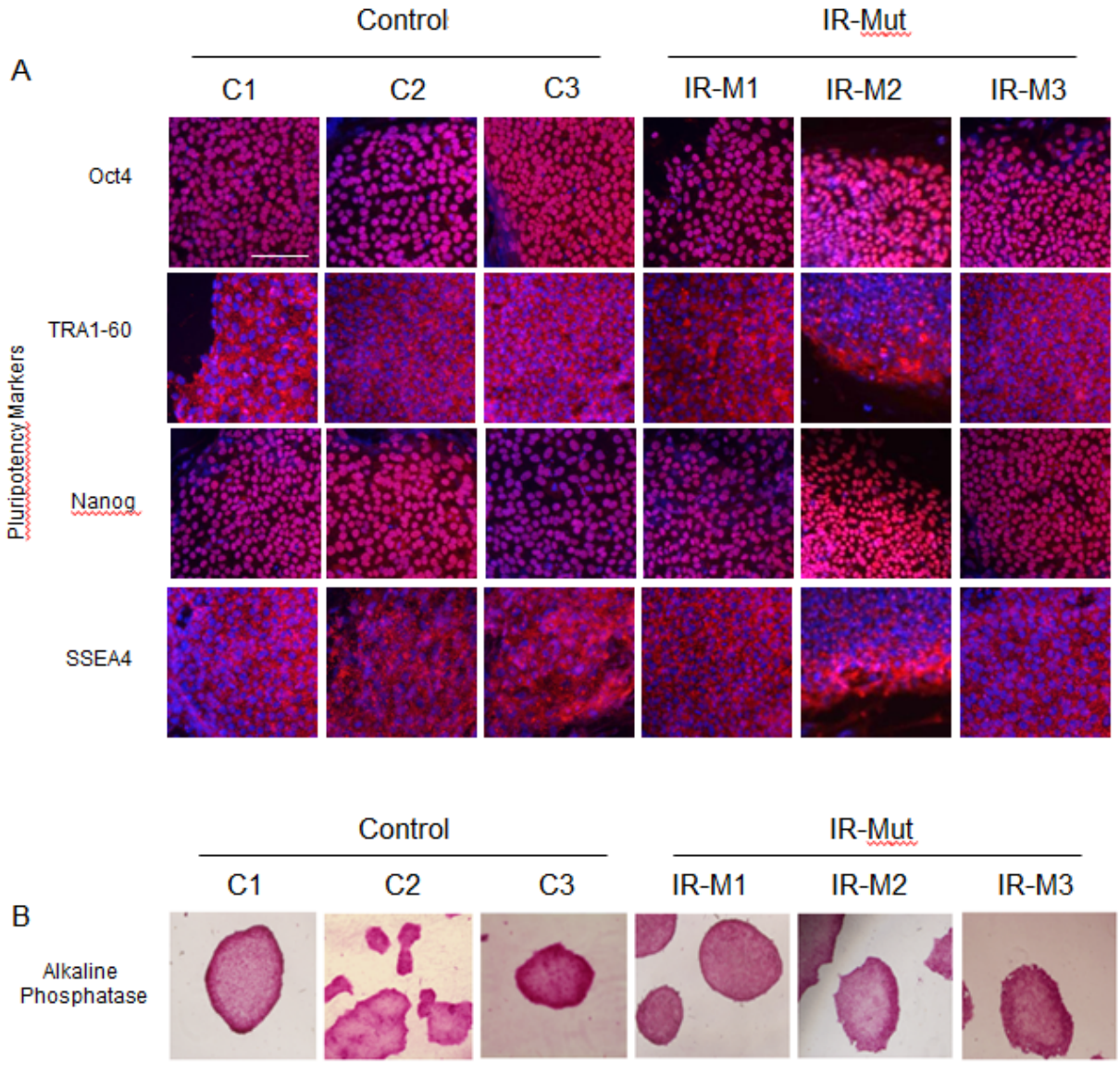
SUPPLEMENTARY DATA

Supplementary Figure 1. Quantification of western blot analysis of fibroblasts (related to Figure 1) (A-F) Quantification of western blot analysis for control and IR-Mut fibroblasts. Data are expressed as mean ± SEM, relative to average of controls (n=2).



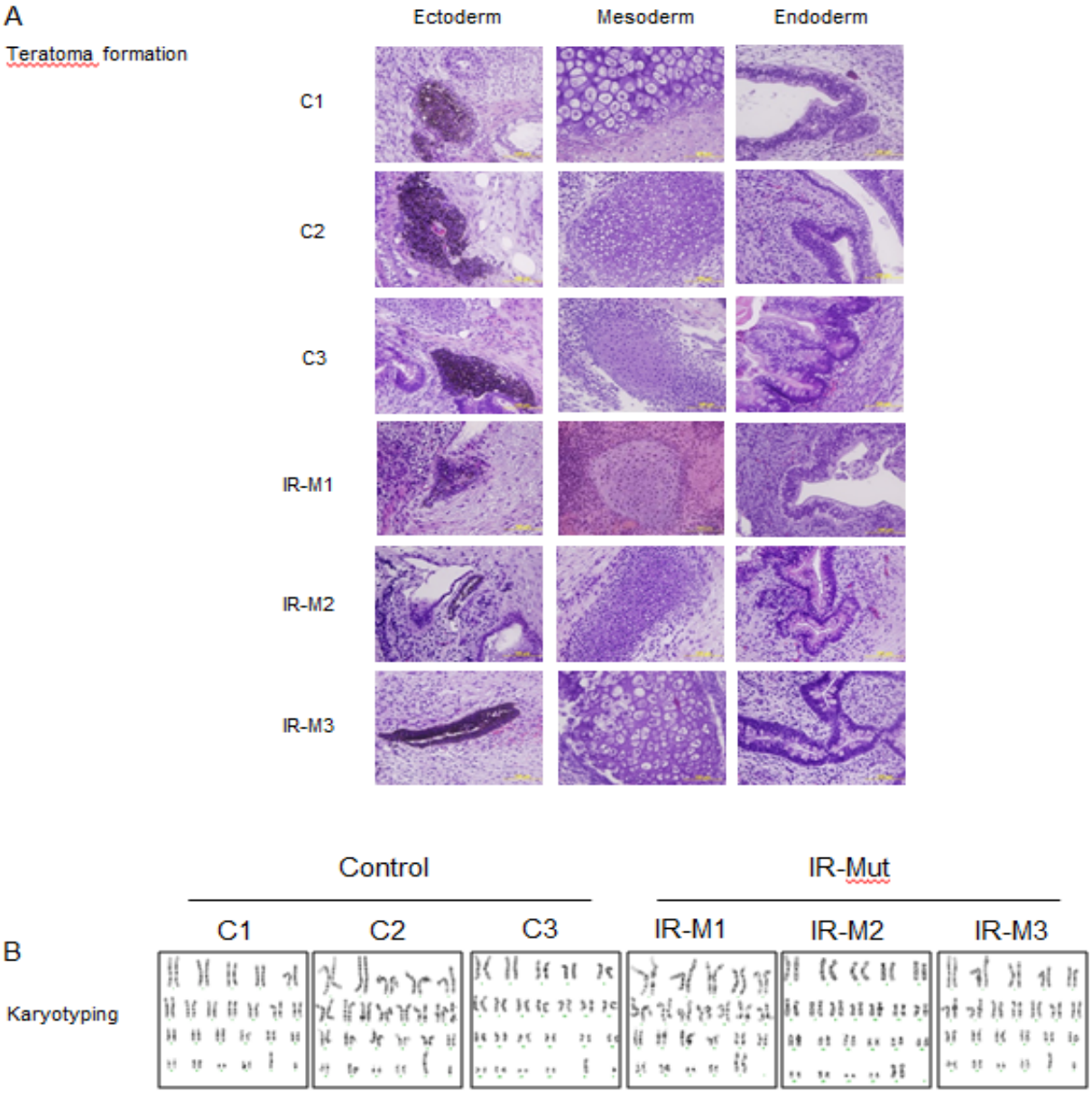
SUPPLEMENTARY DATA

Supplementary Figure 2. Pluripotency markers in control and IR-Mut iPSC (related to Figure 1)
(A) Expression of nuclear NANOG, OCT4 and cytoplasmic SSEA4, TRA1-60 in iPSC . Images show merged colors between blue (Hoechst) and red (indicated protein). Scale bar represents 100 μM.
(B). Alkaline phosphatase activity was measured using a colorimetric kit. Images are representative of 3 wells.



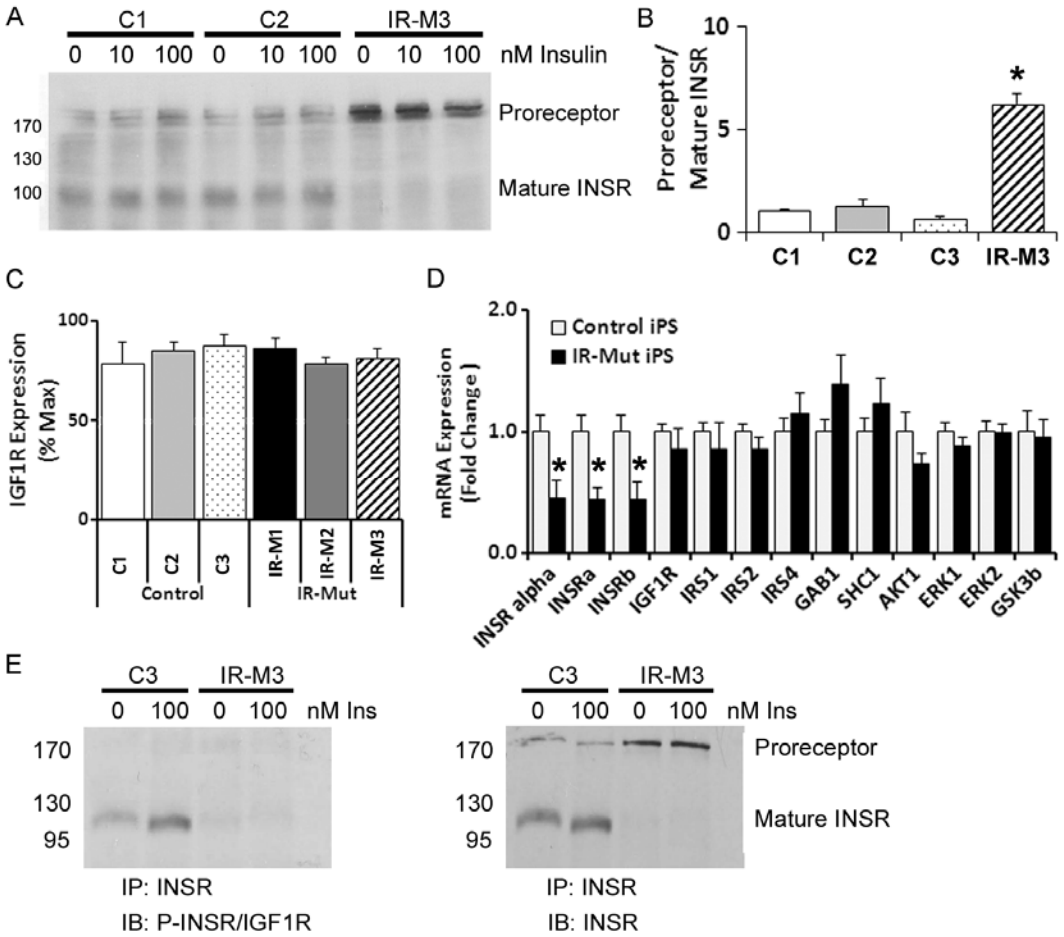
SUPPLEMENTARY DATA

Supplementary Figure 3. Teratoma formation and karyotyping of iPSC (related to Figure 1)
(A) iPSC were injected into SCID mice for in vivo teratoma formation. All three germ layers were observed: ectoderm (pigmented cells and primitive neural tissue), mesoderm (cartilage and smooth muscle), and endoderm (primitive gut and respiratory tissue). Representative images are shown.
(B) Karyotyping analysis revealed normal karyotype for all six iPS lines.



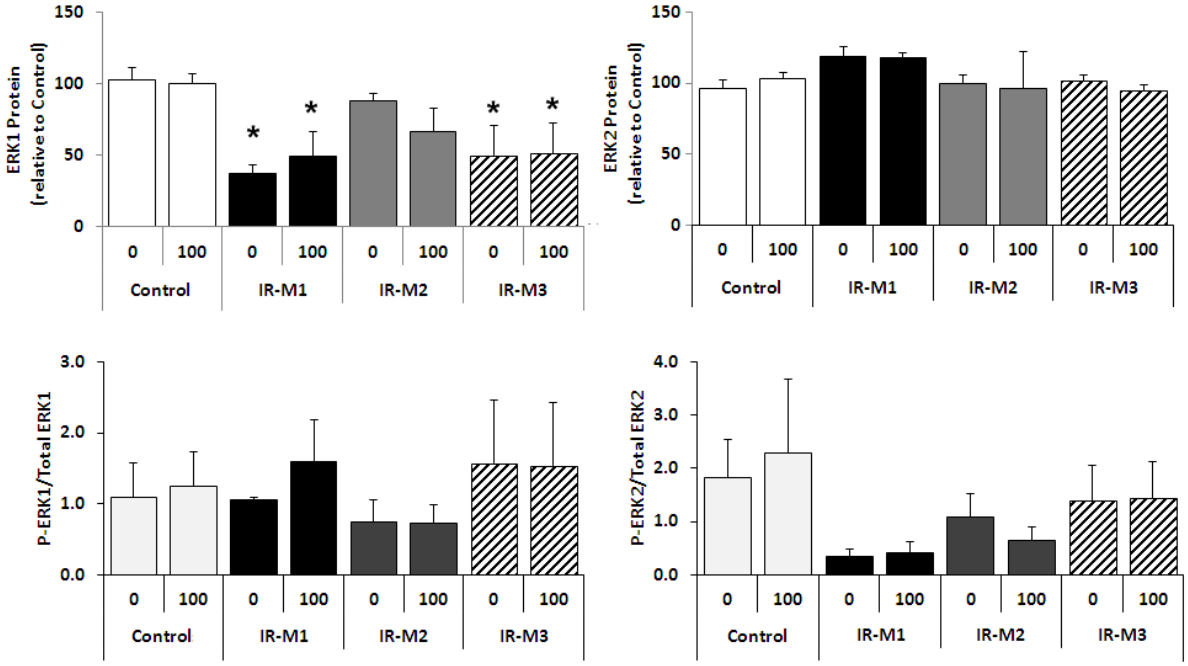
SUPPLEMENTARY DATA

Supplementary Figure 4. mRNA and protein expression key insulin signaling components in iPSC (related to Figure 2)
(A) iPSC were serum starved for 3 hours before 10-minute stimulation with 0, 10, or 100 nm insulin Western blot for mature *INSR* and proreceptor expression, representative of 3 independent experiments.
(B) Quantification of western blot analysis for proreceptor expression. Data are expressed as the ratio of the expression of the proreceptor to the mature receptor (n=3).
(C) Quantification of western blot analysis for IGF1R expression. Data are expressed as percentage of the maximum value (n=3).
(D) mRNA expression for key insulin signaling molecules was analyzed by qRT-PCR using specific primers, as indicated. Data are expressed as fold change relative to the average of the control iPSC (n=3).
(E) iPSC were serum starved for 3 hours before 5-minute stimulation with 0 or 100 nm insulin. Immunoprecipitation of INSR using a β-subunit-specific anti-INSR antibody and immunoblotting with an anti-phospho INSR/IGF1R (left panel) and anti-INSR antibody (right panel) was performed. Representative blots are shown (n=2).
All values represent mean ± SEM. * $p<0.05$.



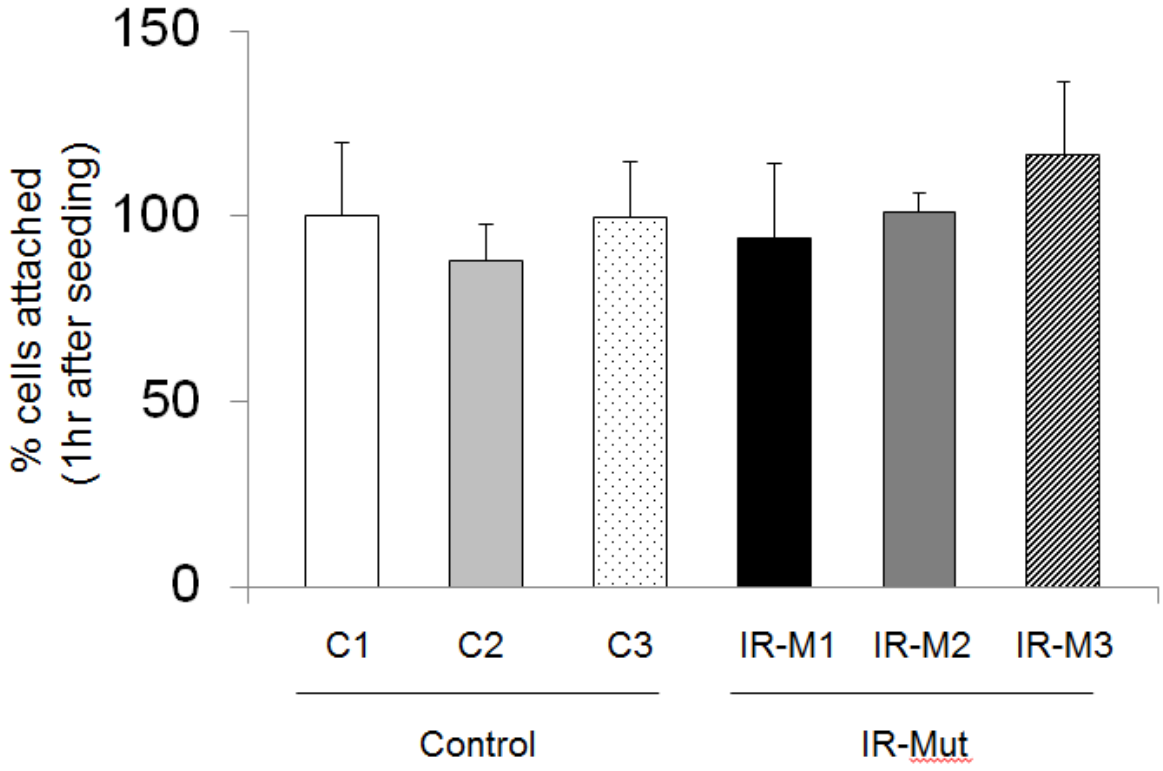
SUPPLEMENTARY DATA

Supplementary Figure 5. Quantification of ERK protein expression and relative phosphorylation (related to Figure 3)
Quantification of western blots for expression and phosphorylation of (A, C) ERK1 , and (B, D) ERK2 protein. Data are expressed as mean ± SEM, relative to average of controls (n=3). * $p<0.05$.



SUPPLEMENTARY DATA

Supplementary Figure 6. Attachment assay of iPSC (related to Figure 4)
Attachment assay of iPSC; cells were plated onto matrigel-coated dishes and counted 1 hour post seeding by Nexcelom automatic cellometer.



SUPPLEMENTARY DATA

Supplementary Table 1. DAVID – pathway analysis of iPS- and fibroblasts-enriched gene groups (related to Figure 5)
DAVID pathway analysis of the top 100 mRNAs of iPS- and fibroblast-enriched groups (log_2 FC > or < 5). The table shows pathways significantly overrepresented ($p<0.001$, $q<0.001$), and indicates example of genes in the pathways and the percentage of differentially expressed genes found in each enriched pathway. Pathways common to the two groups are highlighted in bold.

DAVID pathway analysis

Pathway pattern in gene group	Pathway p<0.001; q<0.1	Example of genes in the pathway	% of genes in the pathway
Fibroblasts-enriched	**Glycoproteins**	IGFBP3-6, FGF5, MMP1, ITGBL1	52%
	Signaling pathways	FGF5-7, PDGFRA, LUM	49%
	Wound healing	FGF7, FN1, COL5A1, TIMP3	26%
	Extracellular matrix deposition	TGFb1, COL3A1, PDGFRA	20%
	Collagen	COL6A3, COL12A1, COL1A1	7%
	Fibronectin	TNC, FN1, COL12A1	7%
iPS-enriched	**Glycoproteins**	IGFBP2, SEMA6A, EPCAM, GABRB3	37%
	Signaling pathways	CXCL5, APOE, IGFBP2, TDGF3, NTS	33%
	Embryonic stem cells	LIN28A-B, POU5F1, NANOG, ZIC2-5	33%
	Development	EPCAM, USP44, TDGF1	13%
	Neurogenesis	APOE, SEMA6A, KIF5C, GABRB3, ANK3	13%

Bold: common pathway

SUPPLEMENTARY DATA

Supplementary Table 2. Transcription factor motif analysis of iPS- and fibroblast-enriched gene groups (related to Figure 5)

We utilized the molecular signatures database (C3, GenePattern) to identify transcription factor binding site motifs over represented in putative 2 kb upstream promoters (enrichment threshold $p<0.001$) for the top 100 iPS- and fibroblast-enriched probes ($\log_2$ FC > or < 5). Examples of genes responsible for the enrichment and the percentage of promoters with these motifs are provided. Putative regulatory transcription factors common to both fibroblast- and iPS–enriched gene groups are highlighted in bold.

Transcription factor motif analysis -2000bpTSS

TF pattern in gene group	TF motif p<0.001	Example of regulated genes	% of genes regulated
Fibroblasts-enriched	**MLLT7 (FOXO4)*+**	TFAP2A, TNFRSF19	26%
	MAZ	MEIS1, SNAP25, PPARG, COL18A1	24%
	LEF1*	SALL1, COL18A1, PPARG	21%
	TAF+	ABCA1, MEIS1, PAX3, SNAP25, PPARG	20%
	NFAT/NFATC*+	SNAP25, ALDH1A1, MEIS1	14%
	FOXA1*+	MEIS1, SNAP25, MAB21L1	13%
	GATA1+	ALDH1A1, ZFPM2	10%
iPS-enriched	**LEF1***	SALL2, ZIC3, SEMA6A	23%
	TCF3*+	SEMA6A, ANK3, ZIC2-3, GPM6B, LRRN1	22%
	MLLT7 (FOXO4)*+	NTS, ZIC2-5, FOXD3	19%
	NFAT/NFATC*+	GPR98, ADCY2, USP44	15%
	PAX4*+	ZIC2-5, SEMA6A, POUF5F1, GPM6B	7%
	PUOF1F1+	ZIC2-5, SEMA6A, OTX2, FOXD3, OTX2	6%
	MEIS1*+	OTX2, ZIC5, GCNT2, SCNN1A	5%

*TF involved in glucose homeostasis/insulin action
+TF involved in ES/iPSC physiology
Bold: shared transcription factor

SUPPLEMENTARY DATA

Supplementary Table 3. Transcription factor motif analysis of gene groups A and B (related to Figure 6)

Transcription factor motif analysis (C3, mSig database) analyzed putative promoter (2000 base pairs upstream the transcription start site) of top 100 statistically significant (nominal $p<0.05$) mRNAs of groups A and B. The table shows significant transcription factor motifs ($p<0.001$), example of regulated genes in the groups and the percentage of genes regulated by the transcription factor. Transcription factors found common between the two gene groups are highlighted in bold.

Transcription factor motif analysis -2000bp TSS

TF pattern in gene group	TF motif p<0.001	Example of regulated genes	% of regulated genes
Group A	LEF1* MYC* E2F1* **FOXF2***	CREB3L1, AP1S2, NEUROG3, PSMF1 NR4A3, ZNF565, ATP5F, ELK1, AP1S2 AP4M1, ZNF565, SLC12A5, KCNH5 AP4M1, KCNH5, NR4A3	13% 12% 10% 9%
Group B	SP1* NFAT/NFATC*+ JUN* **FOXF2*** NF1 CREB1* GABPA/GABPA2* ATF2*	CXCL14, AR, LEPR, EPN1, RASSF2 COL27A1, SLC38A2, HSD17B12 PTPRU, SLC38A1, CXCL14, COL27A1 ACSL1, EPN1, SLC38A2 IRS1, RAI14, CPEB4, C1QTNF1, PALM2 PTPRU, ASPHD1, SLC38A2, LMCD1 EPN1, CPEB4, PLA2G4D, ASPHD1 EPN1, PTPRU, PLA2G4D, ASPHD1	18% 14% 10% 9% 8% 7% 7% 7%

*TF involved in glucose homeostasis/insulin action
+TF involved in ES/iPSC physiology
Bold: shared transcription factor

SUPPLEMENTARY DATA

Supplementary Table 4. DAVID pathway analysis of groups C, D, E, and F (related to Figure 7) Results of DAVID pathway analysis of probes from groups C, D, E, and F (all with $\log_2$ FC > or < 1), including significantly enriched pathways ($p<0.001$, $q<0.001$), example genes, and the percentage of genes in the pathway. The pathways common to fibroblasts and iPS comparisons are highlighted in bold.

DAVID pathway analysis

Pathway pattern in gene group	Pathway p<0.001; q<0.1	Example of genes in the pathway	% of genes in the pathway
Groups C – D (differentially expressed in fibroblasts)	**Glycoproteins**	**BMP2, CDH13, HSD17B12, SERPINE1**, PTPRG, IGF2, BMP6, FGFR2, ITGA7, PODXL, IGFBP3	39%
	Signaling pathways	**RGS5, BMP2, CDH13, SERPINE1**, PTPRG, FGFR2-3, COL15A1, IGF1	31%
	Cell proliferation	**BMP2, CDH13, SERPINE1,** IGF1, IRS1, KIT, VEGFA, IGFBP3	13%
	Development	HOXA5-13, PAX3, MEIS1, WNT7B, BMP6, VEGF	13%
	Extracellular matrix	COLA1, TIMP3, VCAN, MMP3-11	11%
	HOX/Homeobox protein	HOXD8-11, HOXB2-8, MEOX, MEIS1, HOXA1-13, HOXC6-11	10%
	Skeletal system development	IGFBP3, BMP6, HOXD10-11, BMPR1B, BMP2, FGFR2, IGF1-2	9%
	Neuron development	NGF, CXCL12, RUNX3, PAX3, SEMA6A, HOXA1, HOXC10, SNAP25	7%
	EGF signaling pathway	EGF, EGFL6	5%
	Tyrosine kinase receptor signaling	FGFR2, KIT, IGFBP1, IRS1, IGF1-2, INS, IL6	4%
	IGF1R binding/signaling	IGFBP1-3, SOCS2, IRS1	2%
Groups E – F (differentially expressed in iPS)	**Glycoproteins**	**BMP2, CDH13, HSD17B12, SERPINE1,** SEMA6D, ABCG2, CD36	36%
	Signaling pathways	**RGS5, BMP2, CDH13, SERPINE1**, CXCL1, APOA2, GDF15	32%
	Regulation of transcription	ZNF300-503-649, HMX2, NANOG, TFAP2B, TCEAL5	18%
	Cell proliferation	**BMP2, CDH13, SERPINE1**, RUNX2, CAV1-2, CXCL1, EDN1, MYOCD	16%
	DNA binding	HMX2, SIX6, ZNF300-503-649	16%

Bold: common pathway/gene

SUPPLEMENTARY DATA

Supplementary Table 5. Transcription factor binding motif analysis of gene groups C, D and E, F (related to Figure 7)

Transcription factor motif analysis (mSig database) analyzed putative promoter (2000 base pairs upstream the transcription start site) of mRNAs of groups C, D and E, F (all with $\log_2$ FC > or < 1). The table shows significant motifs for transcription factors ($p<0.001$), example of regulated genes and the percentage of putative regulated genes that are recognized by the mSig database algorithm. Transcription factors found common between the two gene groups are highlighted in bold.

Transcription factor motif analysis -2000bp TSS

TF pattern in gene group	TF motif p<0.001	Example of regulated genes	% of regulated genes
Groups C – D (differentially expressed in fibroblasts)	**MLLT7 (FOXO4)*+**	HOXB5, NCAM1, EGR2, MEIS1, IRS1, IGF1	24%
	TCF3*+	GATA3, AP1S2, NCAM1, SNAP25, BMP6, ITGA7, HOXA11, PAX3, PTPRB	21%
	NFAT/NFATC*+	**HSD17B12, BMP2**, GATA3, SOCS2, PDK4	21%
	LEF1*	IL11, RUNX3, PPARG, BMP6, PAX3, FGFR3, IGFBP1	20%
	SP1*	GATA3, AP1S2, NCAM1, HOXA1, SALL1, EGR2, MEIS1, BMP2, SOCS2	18%
	TAF+	**SERPINE1,** SEMA7A, EGR2, IL11, NFIB	17%
	MAZ+	HOXA1, ABCA1, IRS1, PPARG, BMP2	17%
	REPIN1*+	**CDH13, SERPINE1,** AP1S2, SALL1, IL11	15%
	FOXF2*	PPA2B, PDK4, IGF1, HOXC6, HOXA7	13%
	JUN*	IL11, BMP2, COL7A1, WNT7B, IL6	12%
	PAX4*+	SALL1, SEMA6A, HOXC6, IRS1, HOXB2, HOXA5, IGF1	12%
	MYOD1	**CDH13**, CADPS, CCND2, HOXC10, BMP6	10%
	FOXA1*+	IRS1, EGR2, SNAP25, PTPRG, IGF1, IGFBP1	9%
	MEF2A*+	AP1S2, HOXA1, IL11, EGR2, SOCS2, GK, PPAP2B, ITGBL1, KIT, MYO1E, IGF1, FGFR2	8%
Groups E – F (differentially expressed in iPS)	**MLLT7 (FOXO4)*+**	MYOCD, CD36, RUNX2, CAV2,	20%
	TAF+	**SERPINE1**, EDN1, ACTA1, GDF15, ABCG2	19%
	NFAT/NFATC*+	**HSD17B12, BMP2,** TFAP2B, RBMS2, GDA	14%
	REPIN1*+	**CDH13, SERPINE1,** ACTA1, DTNA, ZNF503	14%
	MEF2A*+	MYOCD, EDN1, CTHRC1, RAB20, CXCL1	11%
	MYOD1	**CDH13**, ACTA1, ZNF503, CDH13, SOX15	10%
	PITX2+	MYOCD, SLC12A1, SOX15, NANOG	8%
	POU2F1*+	EDN1, NEDD9	6%
	TEAD1/TEA1*	EDN1, ACTA1, CAV1, TNNT2	6%
	FOXJ1*+	CD36, NAV3, CYR61	5%
	SRF*	ACTA1, MYL7	5%

*TF involved in glucose homeostasis/insulin action
+TF involved in ES/iPSC physiology
Bold: common transcription factor