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Gene Expression in Fetal Murine Keratinocytes and Fibroblasts

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Abstract

Background—Early fetuses heal wounds without the formation of a scar. Many studies have attempted to explain this remarkable phenomenon. However, the exact mechanism remains unknown. Herein, we examine the predominant cell types of the epidermis and dermis—the keratinocyte and fibroblast—during different stages of fetal development to better understand the changes that lead to scarring wound repair versus regeneration.

Materials and Methods—Keratinocytes and fibroblasts were harvested and cultured from the dorsal skin of time-dated BALB/c fetuses. Total RNA was isolated and microarray analysis was

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performed using chips with 42,000 genes. Significance analysis of microarrays (SAM) was utilized to select genes with greater than 2-fold expression differences with a false discovery rate (FDR) of less than 2. Enrichment analysis was performed on significant genes to identify differentially expressed pathways.

Results—By comparing the gene expression profile of keratinocytes from E16 versus E18 fetuses, we identified 24 genes that were downregulated at E16. Analysis of E16 and E18 fibroblasts revealed 522 differentially expressed genes. Enrichment analysis showed the top 20 signaling pathways that were downregulated in E16 keratinocytes and upregulated or downregulated in E16 fibroblasts.

Conclusions—Our data reveal 546 differentially expressed genes in keratinocytes and fibroblasts between the scarless and scarring transition. Additionally, a total of 60 signaling pathways have been identified to be either upregulated or downregulated in these cell types. The genes and pathways recognized by our study may prove to be essential targets that may discriminate between fetal wound regeneration and adult wound repair.

Keywords

Wound healing; Scarless repair; Regeneration; Microarray

Introduction

In 1979 a landmark paper reported that early human fetuses are able to heal wounds without the appearance of a scar (1): whereas scar formation is a physiological process in adult skin and postnatal skin responds to injury with a fibrotic repair process to form scar, embryonic tissue responds with scarless skin regeneration (2). Since then, a number of original articles have attempted to unveil the biological mechanisms underlying this remarkable phenomenon. While the key pathways responsible remain unclear, these studies successfully uncovered a number of important differences between embryonic and adult tissues, all of which may contribute to the observed differences in wound healing. For instance, fetal skin and wounds have been found to differ in terms of both extracellular matrix makeup and response to inflammation (3). In addition, fetal wound research has demonstrated that early to midgestational fetal cutaneous wounds undergo complete scarless regeneration across a number of mammalian species, as well as in ex vivo models (4–6). In mice, wounds up to 1.5 mm in size at a gestational age 16.5 days (E16.5) or younger have been shown to heal scarlessly with normal restitution of the extracellular matrix and demonstrable regeneration of dermal appendages (7). While this ability to heal scarlessly has been attributed to a variety of intrinsic factors within fetal tissue, no specific cytokines, factors, or cells, however, have yet been identified to be the major driving force for this regeneration.

In order to identify the unknown mediators of fetal regeneration, we performed microarray transcriptional profiling on fetal and postnatal keratinocytes and fibroblasts harvested from E16 and E18 murine fetuses to detect transcriptome differences that occur during scarless versus scarring repair. Fibroblasts were chosen due to their role as prominent sources of connective tissue crucial in both the proliferative and remodeling phases of wound healing (8), and keratinocytes for their ability to regulate the development of fibrosis in the skin (9).

Using microarray analysis we found a number of genes with differential transcription in E16 versus E18 cells and mapped them to integrated gene networks via functional genomics. This enabled the identification of relevant pathways that are potential targets for inducing regenerative-type repair with improved collagen architecture and potential epidermal appendage restoration in the postnatal scarring wound.

Materials and Methods

Animals

Six-week-old wild-type BALB/c mice were purchased from Charles River Laboratories (Wilmington, MA). For timed gestations, the mice were bred overnight and the day of vaginal plug was considered E0.5 day of gestation. Animals were maintained in the Stanford Animal Care Laboratory and all procedures were conducted in accordance with university-approved protocols according to National Institutes of Health guidelines.

Primary Cell Culture

Pregnant mice at gestational age E16.5 and E18.5 were euthanized using CO_2 and cervical dislocation. Fetal mice were then removed from uteri. Dorsal skin was collected using a dissecting microscope under sterile conditions. In order to obtain sufficient cells to achieve primary culture, skin from E16.5 (n = 10) and postnatal day E18.5 mice (n = 10) was pooled for subsequent keratinocyte and fibroblast harvest.

For keratinocyte primary cell culture, tissue was incubated in defined keratinocyte-SFM (serum-free media) (Gibco Life Technologies, Carlsbad, CA) with 5 mg/mL dispase (BD Biosciences, San Jose, CA) and 10X antibiotic-antimycotic (Gibco Life Technologies) at 4 degrees for 7 hours. Skin was then cut and treated with 0.25% trypsin for 10 min. The cells were subsequently seeded in keratinocyte-SFM.

For fibroblast primary cell culture, tissue was minced and treated with 0.25% trypsin/EDTA in 37 degrees with gentle agitation for 10 min. Cells were plated with mouse embryonic fibroblast (MEF) culture medium consisting of DMEM (Dulbecco's Modified Eagle Medium), GlutaMAX Supplement (Gibco Life Technologies), 10% fetal bovine serum (Omega Scientific, Tarzana, CA), 0.1 mM 2-mercaptoethanol (Sigma, St. Louis, MO), and 1% penicillin/streptomycin (Gibco Life Technologies).

Keratinocytes and fibroblasts were kept at 37°C in a humid incubator with 5% CO2. Passage one keratinocytes and fibroblasts from both male and female fetuses were used for all experiments.

RNA Extraction and Amplification

RNA from keratinocytes and fibroblasts was extracted using the Trizol protocol (Invitrogen, Carlsbad, CA) per manufacturer's instructions. One microgram of RNA from each experimental sample was amplified using the MessageAmp aRNA kit (Ambion, Austin, TX). At the same time, 1 μg aliquots of universal mouse RNA were amplified in individual reaction mixtures and utilized as an internal amplification control to allow comparisons between different arrays.

Preparation of Fluorescent cDNA Probes

Four micrograms of RNA and 2 μg of random hexamer were heated at 65°C for 10 minutes and reverse transcribed in a 30 μL total reaction volume containing 2 mM of each deoxyribose nucleotide triphosphate, 1X first-strand buffer, 0.5 μL RNAse inhibitor, 200 U superscript II, 10 mM dithiolthretol, and 3 μL Cy3-deoxyribose uridine triphosphate (dUTP) (for experimental samples) or Cy5-dUTP (for universal mouse control samples) at 42°C for 1 hour. An additional 200 U superscript II was added to boost the reaction and incubated for 1 hour at 42°C. Fluorescent Cy3- or Cy5-labeled probes were washed with TE buffer (10 mM tris, 1 mM EDTA) through a microcon mini column (Millipore, Billerica, MA), concentrated with 450 μL TE buffer, and recovered by spinning the inverted mini column into a fresh tube. Probes were immediately hybridized to microarray chips.

Pretreatment of Microarray Chips

Mouse microarray chips were printed in the Stanford Microarray Database Center with 42,000 specific cDNAs printed onto each lysine-coated slide. These cDNAs represent single accession numbers from Genbank. Sequences and accession numbers of the cDNAs can be found on http://genome-www5.stanford.edu//index.shtml. Before hybridization, microarray chips were first rehydrated (held face down briefly over boiling distilled water) and then snap-dried on a 100°C heating block for 5–10 seconds. DNA was then cross-linked using an ultraviolet cross-linker (300 mJ).

Microarray Hybridization

After heating at 100°C for 2 minutes, fluorescent-labeled probes were denatured and subsequently incubated at 37°C for 20 minutes. A hybridization mixture containing 32 μL of the recovered probe, 6.8 μL of 20X saline sodium citrate (SSC), and 1.2 μL of 10% sodium dodecyl sulfate (SDS) was dropped onto prewarmed microarray slides, and a cover slip applied. Slides were then placed in a sealed moisture chamber for 16 hours at 65°C for hybridization. Following this step, slides were immediately washed once with 1X SSC with 0.03% SDS, twice with 0.5% SSC, and twice with 0.06% SSC. After washing, slides were centrifuged at 84 x *g* for 2 minutes and scanned immediately using an Axon microarray scanner (Molecular Devices, Sunnyvale, CA).

Microarray Data Analysis

Scanned images were analyzed using the Genepix Pro 4.0 software (Molecular Devices). The densitometry data was up-loaded into the Stanford Microarray Database for gene identification and analysis. The log (base 2) of red/green normalized ratio (mean) was found and the data filtered based on a regression correlation of 0.6. Individual genes and arrays were centered by median. Genes were included in the analysis if they passed the filter criterion of >80% good data and subsequently clustered using Pearson correlation.

Following gene clustering, significance analysis of microarrays (SAM) was used to select genes with significant expression differences between the E16 and E18 transcriptomes for each time point. SAM identifies statistically significant changes in gene expression through the assimilation of a set of gene-specific *t* tests. Each gene is assigned a score based on its

change in expression relative to the standard deviation of repeated measurements for that gene. SAM uses permutations of the repeated measurements to estimate the false discovery rate (FDR), equivalent to chance, for those genes. Genes that had at least a 2-fold expression difference with FDR less than 2 were selected.

Functional Analysis of Differentially Expressed Genes

To identify functional connections among significantly regulated genes, both network and pathway analyses of the probes filtered by microarray were performed as previously described by Jovov et al., using Ingenuity Pathways Analysis (IPA; www.ingenuity.com, Ingenuity Systems, Redwood City, CA). The significance of networks was calculated by IPA's integrated Ingenuity algorithm, which calculates p-values based on the right-tailed Fisher's exact test for each canonical pathway, evaluating the likelihood that the association between a subset of genes from the whole experimental data set and a related function/pathway is due to random association.

Results

Differential Gene Expression Between Scarless E16 and Scarring E18 Keratinocytes and Fibroblasts

Transcriptomes from E16 keratinocytes and fibroblasts were directly compared to transcriptomes from E18 keratinocytes and fibroblasts. SAM identified 546 genes differentially expressed with greater than 2-fold difference between E16 and E18 keratinocytes and fibroblasts. Of these 546 genes, for keratinocytes, 24 genes were found to be downregulated in E16 as compared to E18 (Table 1). For fibroblasts, 198 genes were found to be downregulated in E16 as compared to E18 (Table 2). Conversely, 324 genes were found to be upregulated in E16 fibroblasts in comparison to E18 fibroblasts (Table 3).

Functional Pathway Analysis

Out of the 24 genes found to be downregulated in E16 keratinocytes (Figure 1A), twenty functional pathways were identified (Figure 1B). The top five pathways were associated with: EIF2 signaling, 1,25-dihydroxyvitamin D3 biosynthesis, regulation of eIF4 and p7056K signaling, Wnt/β-catenin signaling, and RAN signaling.

Of the 198 genes downregulated in E16 fibroblasts compared to E18 fibroblasts (Figure 2A), twenty functional pathways were again identified (Figure 2B). The top five pathways were: endometrial cancer signaling, PDGF signaling, IL-3 signaling, colorectal cancer metastasis signaling and FLT3 signaling in hematopoietic progenitor cells.

From the 324 genes found to be upregulated in E16 fibroblasts in comparison to E18 fibroblasts (Figure 2C), the top five functional pathways were associated with: superoxide radicals degradation, protein ubiquination, melanocyte development and pigment signaling, nNOS signaling, and mitochondrial L-carnitine shuttling.

Discussion

Early gestational skin has the unique ability to regenerate following injury. However, during the later stages of fetal development, this ability gradually diminishes, culminating ultimately with an adult cutaneous wound healing process characterized by scarring. The goal of our study is to identify candidate pathways important to scarless wound healing that might be manipulated in adult wound healing to decrease scarring and promote regenerative healing. In order to achieve this goal, we performed microarray analysis on fetal keratinocytes and fibroblasts from fetal scarless and scarring time points. Furthermore, to better understand individual gene expression changes, we performed signal pathway analysis. This technique allowed us to identify gene cascades that are coordinately regulated during the transition period. In this section we will discuss in greater detail some of the especially relevant pathways found to be differentially activated in E16 versus E18 keratinocytes and fibroblasts.

Beta-Catenin Dependent Wnt Signaling

The Wnt family of glycoproteins is involved in proliferation, differentiation, migration, and carcinogenesis (10) as well as in dermal and epidermal maturation (11). Wnt proteins are expressed following cutaneous injury, and different Wnt signaling in response to injury has been found to occur pre- and post-natally. For instance, a 2010 study by Carre et al. revealed that β-catenin–dependent Wnt signaling expression is different between scarless fetal and scarring postnatal wound repair (7). This finding is corroborated by the results of our study. We demonstrated that Wnt signaling pathways are upregulated in nonwounded scarring fetal keratinocytes at E18 in comparison to nonscarring fetal keratinocytes at E16. While other studies in the past have compared Wnt signaling between fetal and adult skin, our study is the first to compare Wnt activation in early and late gestational age nonwounded skin. The differential activation of Wnt signaling pathways between E16 and E18 keratinocytes suggests that Wnt signaling may play an important role in regulating the different wound healing outcomes in early and late gestational skin. Moreover, Wnt is known to positively regulate TGF-β1, a key mediator of fibrosis implicated in hypertrophic scar formation (12, 13), transcription in postnatal skin cells, suggesting a possible mechanism by which upregulation of Wnt signaling in late gestational keratinocytes might contribute to loss of regenerative ability. Taken together, these data suggest that β-catenin–dependent Wnt pathways may be early and key regulators of embryonic wound healing.

PDGF Signaling

Whereas adult wounds are known to contain large quantities of PDGF, this growth factor is virtually absent in embryonic wounds (14). Similarly, a 2003 study by Song et al. found strong expression of PDGF in adult skin but not in unwounded fetal skin (15). However, no previous study has looked specifically at differential activation of PDGF signaling in early regenerative versus late scarring gestational fetal skin. Our functional pathway analysis data demonstrated for the first time increased activation of PDGF in E18 fibroblasts compared to E16 fibroblasts, suggesting an important role for increased PDGF signaling in loss of regenerative ability in late gestational fibroblasts. This finding is supported by published reports that have established a role for PDGF in regulating the proliferation and

differentiation of keratinocytes and fibroblasts (16), as well as in upregulation of the expression of profibrotic TGF-β1 receptors (17). Furthermore, fetal wounds have been found to have lower concentrations of inflammatory cells such as neutrophils, which are recruited by PDGF, than adult wounds (2). This may provide a key mechanism for scarless fetal regeneration as neutrophils amplify the inflammatory response in wound beds, contributing to the formation of a scar.

Superoxide Radicals Degradation

Conversely, we found that E16 fibroblasts had upregulation of superoxide radicals degradation in comparison to E18 fibroblasts. During the early inflammatory phase following injury, inflammatory cells invade the wound bed. When active, these cells produce large amounts of reactive oxygen species (ROS) as part of their functional role in the wound healing process (18). While essential to debridement of the wound site, excess ROS can inhibit wound healing and lead to tissue damage. For instance, low levels of antioxidants accompanied by raised levels of markers of free radical damage led to decreased wound healing in aged and diabetic mice (19). Taken together, our findings suggest that enhanced detoxification of ROS may contribute to the regenerative ability of fetal skin.

Conclusion

Using functional pathway analysis, for the first time, we demonstrated differential pathway regulation in scarless and scarring fetal skin cells. Due to the large amount of data generated by both microarray and pathway analysis, we focused our discussion on a few pathways known to be particularly relevant to wound healing. However, our study reveals hundreds of genes and tens of pathways novel to the transition from scarless to scarring repair. We believe that identification of these pathways most likely to be proregenerative or profibrotic provides a valuable starting point for further experimental study aimed at elucidating mechanisms underlying the regenerative ability of early embryonic skin, with possible applications to other organ systems.

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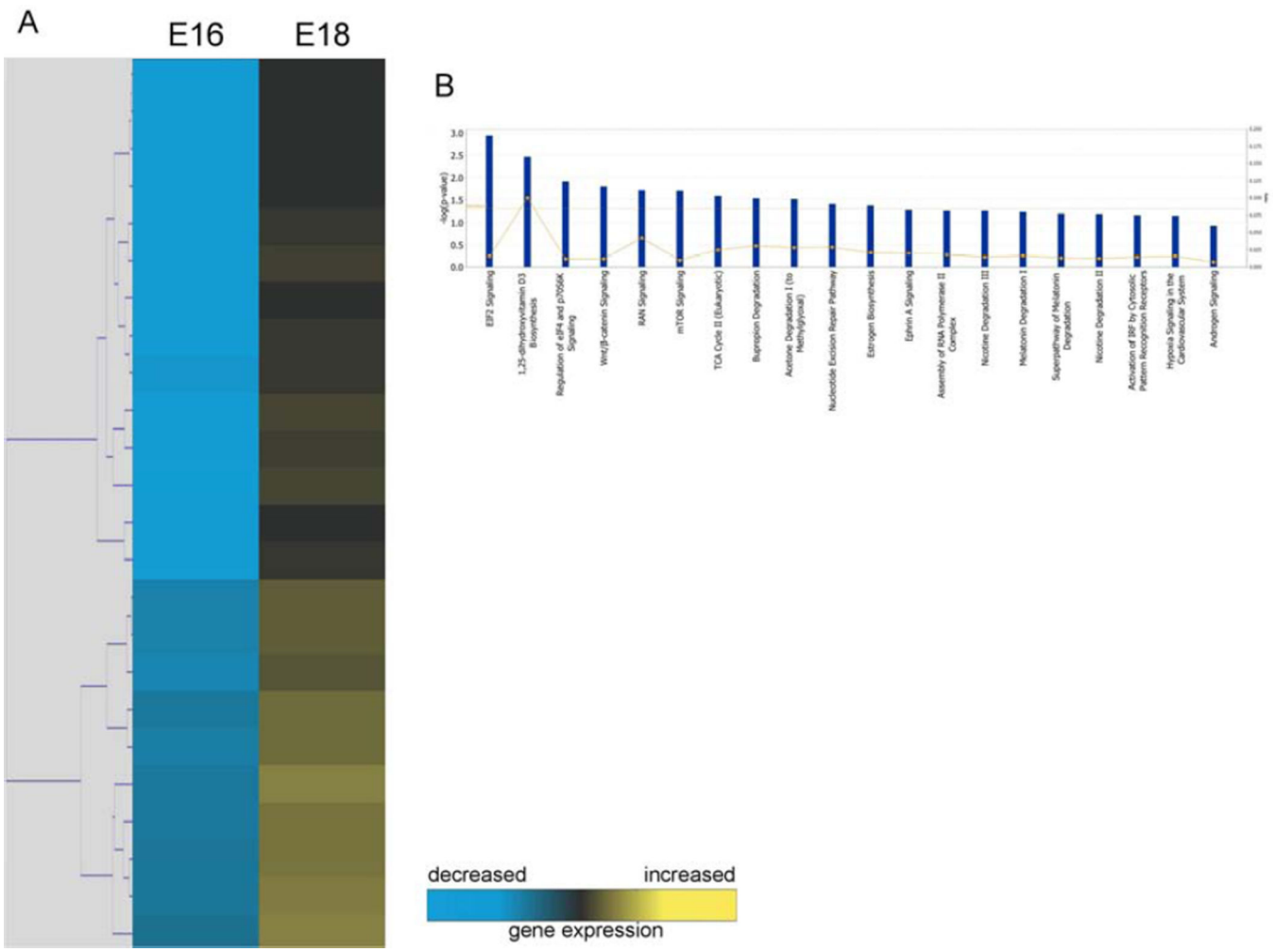

Figure 1. Microarray analysis of E16 and E18 keratinocytes

(**A**) Hierarchical clustering of differentially regulated genes from fetal keratinocytes at E16 vs. E18. Individual genes are clustering according to the dendrogram on the left, and expression levels are represented in the heatmap on the right. Yellow and blue indicate up- and down-regulation, respectively. (**B**) Canonical pathways significantly enriched for among genes whose expression was significantly downregulated in E16 samples compared to E18.

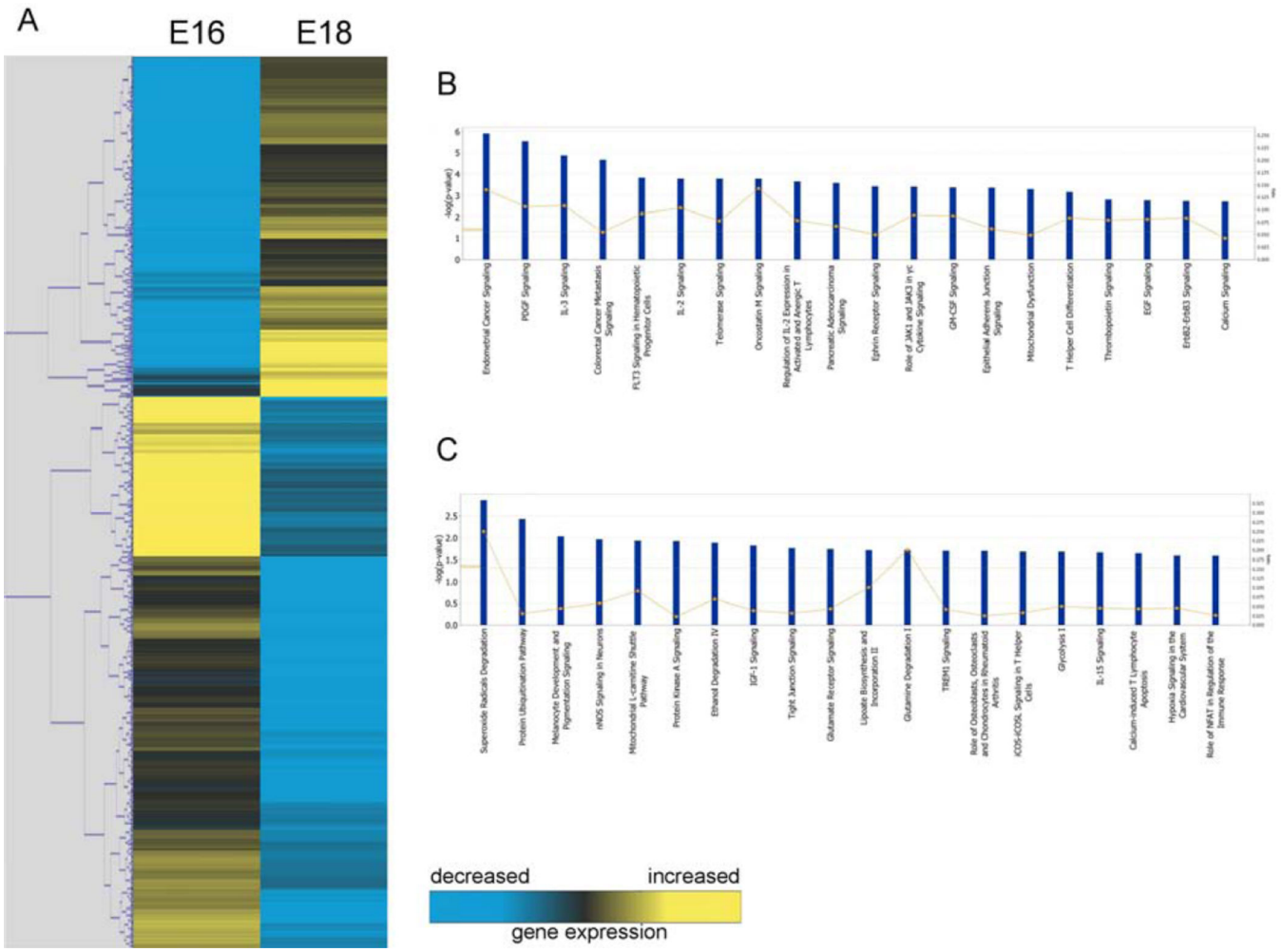

Figure 2. Microarray analysis of E16 and E18 fibroblasts

(**A**) Hierarchical clustering of differentially regulated genes from fetal fibroblasts at E16 vs. E18. Individual genes are clustering according to the dendrogram on the left, and expression levels are represented in the heatmap on the right. Yellow and blue indicate up- and down-regulation, respectively. (**B**) Canonical pathways significantly enriched for among genes whose expression was significantly downregulated in E16 samples compared to E18. (**C**) Canonical pathways significantly enriched for among genes whose expression was significantly upregulated in E16 samples compared to E18.

Table 1

Genes downregulated in E16 keratinocytes.

Symbol	Gene Name
Srp72	signal recognition particle 72
Tpm2	tropomyosin 2, beta
Por	P450 (cytochrome) oxidoreductase
Aco1	aconitase 1
Mrpl35	mitochondrial ribosomal protein L35
Xab2	XPA binding protein 2
Rpl13a	ribosomal protein L13A
Dstn	destrin
Klraq1	KLRAQ motif containing 1
Ube2s	ubiquitin-conjugating enzyme E2S
Gtf2h5	general transcription factor IIH, polypeptide 5
Lphn2	latrophilin 2
Trappc5	trafficking protein particle complex 5
Znrf2	zinc and ring finger 2
Pin1	protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1
Mark2	MAP/microtubule affinity-regulating kinase 2
Fahd2a	fumarylacetoacetate hydrolase domain containing 2A
Cd320	CD320 antigen
Pnrc2	Proline-rich nuclear receptor coactivator 2
Rps15a	ribosomal protein S15A
Kpna6	karyopherin (importin) alpha 6
Eif3d	eukaryotic translation initiation factor 3, subunit D
Snrpg	small nuclear ribonucleoprotein polypeptide G
Efna5	ephrin A5

Table 2

Genes downregulated in E16 fibroblasts.

Symbol	Gene Name	Symbol	Gene Name
Rps29	ribosomal protein S29	Cdk20	cyclin-dependent kinase 20
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	Pcdhg@	protocadherin gamma cluster
Hmgn1	high mobility group nucleosomal binding domain 1	Sun1	Sad1 and UNC84 domain containing 1
Lyrm4	LYR motif containing 4	Ilf3	interleukin enhancer binding factor 3
Dcun1d1	DCN1, defective in cullin neddylation 1, domain containing 1 (S. cerevisiae)	Akr1c19	aldo-keto reductase family 1, member C19
Fkbp1a	FK506 binding protein 1a	Mphosph8	M-phase phosphoprotein 8
Pfkm	phosphofructokinase, muscle	Pop5	processing of precursor 5, ribonuclease P/MRP family (S. cerevisiae)
Adcy7	adenylate cyclase 7	Mpv17	MpV17 mitochondrial inner membrane protein
Krt83	keratin 83	Ulk1	Unc-51 like kinase 1 (C. elegans)
Rrp1	ribosomal RNA processing 1 homolog (S. cerevisiae)	Hspa5	heat shock protein 5
Lrrcc1	leucine rich repeat and coiled-coil domain containing 1	Pax3	paired box gene 3
Ldb3	LIM domain binding 3	Ubr5	ubiquitin protein ligase E3 component n-recognin 5
Hadh	hydroxyacyl-Coenzyme A dehydrogenase	Sorl1	sortilin-related receptor, LDLR class A repeats-containing
Gls	glutaminase	Son	Son DNA binding protein
Msi2	Musashi homolog 2 (Drosophila)	Dnajc19	DnaJ (Hsp40) homolog, subfamily C, member 19
Rbfox2	RNA binding protein, fox-1 homolog (C. elegans) 2	Lyl1	lymphoblastomic leukemia 1
Myo9a	myosin IXa	Csf2	colony stimulating factor 2 (granulocyte-macrophage)
Cdk4	cyclin-dependent kinase 4	Tmem184a	transmembrane protein 184a
Gja1	gap junction protein, alpha 1	Plrg1	pleiotropic regulator 1, PRL1 homolog (Arabidopsis)
Lck	lymphocyte protein tyrosine kinase	Prl8a2	prolactin family 8, subfamily a, member 2
Rpl37a	ribosomal protein L37a	Stim1	stromal interaction molecule 1
Sh2b2	SH2B adaptor protein 2	Klhdc10	kelch domain containing 10
Spnb2	spectrin beta 2	2700097O09Rik	RIKEN cDNA 2700097O09 gene
Arpp19	cAMP-regulated phosphoprotein 19	Tmx2	thioredoxin-related transmembrane protein 2
Rela	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	Nip7	nuclear import 7 homolog (S. cerevisiae)
H2-DMb1	histocompatibility 2, class II,	Xdh	xanthine dehydrogenase

Symbol	Gene Name	Symbol	Gene Name
	locus Mb1		
Wfdc5	WAP four-disulfide core domain 5	Nynrin	NYN domain and retroviral integrase containing
Tyrp1	tyrosinase-related protein 1	Rmnd5a	required for meiotic nuclear division 5 homolog A (S. cerevisiae)
0610031J06Rik	RIKEN cDNA 0610031J06 gene	Ube2b	ubiquitin-conjugating enzyme E2B, RAD6 homology (S. cerevisiae)
	septin 9	Stoml3	stomatin (Epb7.2)-like 3
Grina	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1 (glutamate binding)	S100a9	S100 calcium binding protein A9 (calgranulin B)
Mtch1	mitochondrial carrier homolog (C. elegans)	1 Ing5	inhibitor of growth family, member 5
Cpt2	carnitine palmitoyltransferase 2	B3galnt2	UDP-GalNAc:betaGlcNAc beta 1,3-galactosaminyltransferase, polypeptide 2
Ctnnb1	catenin (cadherin associated protein), beta 1	Rabif	RAB interacting factor
Egfl6	EGF-like-domain, multiple 6	Pex11b	peroxisomal biogenesis factor 11 beta
Golph3	golgi phosphoprotein 3	Abhd16a	abhydrolase domain containing 16A
Tcea1	transcription elongation factor A (SII) 1	Fkbpl	FK506 binding protein-like
Abcb10	ATP-binding cassette, sub-family B (MDR/TAP), member 10	Calm2	calmodulin 2
Mtbp	Mdm2, transformed 3T3 cell double minute p53 binding protein	Foxn3	forkhead box N3
Lias	lipoic acid synthetase	Kdm2b	lysine (K)-specific demethylase 2B
2310011J03Rik	RIKEN cDNA 2310011J03 gene	Gnpnat1	glucosamine-phosphate N-acetyltransferase 1
Cyth2	cytohesin 2	Bik	BCL2-interacting killer
Eif3h	eukaryotic translation initiation factor 3, subunit H	Pde2a	phosphodiesterase 2A, cGMP-stimulated
Bcl2l2	BCL2-like 2	Rcc2	regulator of chromosome condensation 2
Tex2	testis expressed gene 2	Cd151	CD151 antigen
Hnrnpa2b1	heterogeneous nuclear ribonucleoprotein A2/B1	Zfp704	zinc finger protein 704
Tbx15	T-box 15	Sohlh1	spermatogenesis and oogenesis specific basic helix-loop-helix 1
Maoa	monoamine oxidase A	Antxr1	anthrax toxin receptor 1
Psmb9	proteasome (prosome, macropain) subunit, beta type 9 (large multifunctional peptidase 2)	Llph	LLP homolog, long-term synaptic facilitation (Aplysia)
Cdk18	cyclin-dependent kinase 18	Ywhae	tyrosine 3-monooxygenase/tryptophan 5-

Symbol	Gene Name	Symbol	Gene Name
			monooxygenase activation protein, epsilon polypeptide
Cd83	CD83 antigen	Cdk16	cyclin-dependent kinase 16
Tns4	tensin 4	Adss	adenylosuccinate synthetase, non muscle
Slc38a10	solute carrier family 38, member 10	Fam45a	family with sequence similarity 45, member A
Cdc42se1	CDC42 small effector 1	Fastkd2	FAST kinase domains 2
Smurf1	SMAD specific E3 ubiquitin protein ligase 1	Heatr2	HEAT repeat containing 2
1600002H07Rik	RIKEN cDNA 1600002H07 gene	Tpr	translocated promoter region
Cpt1a	carnitine palmitoyltransferase 1a, liver	Lasp1	LIM and SH3 protein 1
Cartpt	CART prepropeptide	Car2	carbonic anhydrase 2
Fam82b	family with sequence similarity 82, member B	Taf10	TAF10 RNA polymerase II, TATA box binding protein (TBP)-associated factor
Tdrd3	tudor domain containing 3	Stx2	syntaxin 2
Galt	galactose-1-phosphate uridyl transferase	Commd10	COMM domain containing 10
Dync1i2	dynein cytoplasmic 1 intermediate chain 2	Lap3	leucine aminopeptidase 3
Ctps2	cytidine 5’-triphosphate synthase 2	Hacl1	2-hydroxyacyl-CoA lyase 1
Naa35	N(alpha)-acetyltransferase 35, NatC auxiliary subunit	Scp2	sterol carrier protein 2, liver
Dcun1d1	DCN1, defective in cullin neddylation 1, domain containing 1 (S. cerevisiae)	Iffo2	intermediate filament family orphan 2
Acd	adrenocortical dysplasia	Upf3b	UPF3 regulator of nonsense transcripts homolog B (yeast)
Cisd1	CDGSH iron sulfur domain 1	Lmbr1l	limb region 1 like
Btf3l4	basic transcription factor 3-like 4	Tmco1	transmembrane and coiled-coil domains 1
Golph3l	golgi phosphoprotein 3-like	Klhl13	kelch-like 13 (Drosophila)
Tbx15	T-box 15	Fbxo15	F-box protein 15
Rprd1a	regulation of nuclear pre-mRNA domain containing 1A	Dnaja1	DnaJ (Hsp40) homolog, subfamily A, member 1
Cat	catalase	Mau2	MAU2 chromatid cohesion factor homolog (C. elegans)
Dclk2	doublecortin-like kinase 2	Ywhah	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide
Alx3	aristaless-like homeobox 3	1110008L16Rik	RIKEN cDNA 1110008L16 gene
Myl6	myosin, light polypeptide 6, alkali, smooth muscle and non-muscle	Rbpms	RNA binding protein gene with multiple splicing
Sra1	steroid receptor RNA activator 1	Tmem38b	transmembrane protein 38B

Symbol	Gene Name	Symbol	Gene Name
Tmc6	transmembrane channel-like gene family 6	Plac1l	placenta-specific 1-like
Brd7	bromodomain containing 7	Dusp26	dual specificity phosphatase 26 (putative)
Cxcl1	chemokine (C-X-C motif) ligand 1	Mmp3	matrix metallopeptidase 3
Ap1g1	adaptor protein complex AP-1, gamma 1 subunit	Cisd2	CDGSH iron sulfur domain 2
St3gal1	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	Son	Son DNA binding protein
Mylk3	myosin light chain kinase 3	2200002K05Rik	RIKEN cDNA 2200002K05 gene
Pdk4	pyruvate dehydrogenase kinase, isoenzyme 4	Krt20	keratin 20
Rtkn	rhotekin	Fam126a	family with sequence similarity 126, member A
Rab11a	RAB11a, member RAS oncogene family	Nynrin	NYN domain and retroviral integrase containing
Epdr1	ependymin related protein 1 (zebrafish)	Smg6	Smg-6 homolog, nonsense mediated mRNA decay factor (C. elegans)
Krt83	keratin 83	1700021C14Rik	RIKEN cDNA 1700021C14 gene
Pax3	paired box gene 3	Cdc34	cell division cycle 34 homolog (S. cerevisiae)
9030624J02Rik	RIKEN cDNA 9030624J02 gene	Rpl17	ribosomal protein L17
Csnk1g2	casein kinase 1, gamma 2	Rpgrip1	retinitis pigmentosa GTPase regulator interacting protein 1
Stk30	serine/threonine kinase 30	Ube2v2	ubiquitin-conjugating enzyme E2 variant 2
Macf1	microtubule-actin crosslinking factor 1	Apbb2	amyloid beta (A4) precursor protein-binding, family B, member 2
Ap3b2	adaptor-related protein complex 3, beta 2 subunit	Crtam	cytotoxic and regulatory T cell molecule
Fubp1	far upstream element (FUSE) binding protein 1	Pon2	paraoxonase 2
Arrdc3	arrestin domain containing 3	Nudt7	nudix (nucleoside diphosphate linked moiety X)-type motif 7
Vim	vimentin	Smg6	Smg-6 homolog, nonsense mediated mRNA decay factor (C. elegans)
Limd1	LIM domains containing 1	Ssr2	signal sequence receptor, beta
Fubp1	far upstream element (FUSE) binding protein 1	Parl	presenilin associated, rhomboid-like
Igfbp5	insulin-like growth factor binding protein 5	Csnk2a1	casein kinase 2, alpha 1 polypeptide
H2-Q8	histocompatibility 2, Q region locus 8	Cdk20	cyclin-dependent kinase 20

Table 3

Genes upregulated in E16 fibroblasts.

Symbol	Gene Name	Symbol	Gene Name
Lpar4	lysophosphatidic acid receptor 4	Bola1	bolA-like 1 (E. coli)
Ankrd17	ankyrin repeat domain 17	Tssk2	testis-specific serine kinase 2
C330019G07Rik	RIKEN cDNA C330019G07 gene	Grin1	glutamate receptor, ionotropic, NMDA1 (zeta 1)
Golt1b	golgi transport 1 homolog B (S. cerevisiae)	Asb12	ankyrin repeat and SOCS box-containing 12
Adprh	ADP-ribosylarginine hydrolase	Mtdh	metadherin
Cstf2t	cleavage stimulation factor, 3' pre-RNA subunit 2, tau	Ankrd1	ankyrin repeat domain 1 (cardiac muscle)
Ifrg15	interferon alpha responsive gene	Slc27a3	solute carrier family 27 (fatty acid transporter), member 3
4632428N05Rik	RIKEN cDNA 4632428N05 gene	Darc	Duffy blood group, chemokine receptor
Gsk3b	glycogen synthase kinase 3 beta	Ezh1	enhancer of zeste homolog 1 (Drosophila)
Slc35a1	solute carrier family 35 (CMP-sialic acid transporter), member 1	AU019823	expressed sequence AU019823
Mepce	methylphosphate capping enzyme	Hist1h2ae	histone cluster 1, H2ae
Ptges	prostaglandin E synthase	Bdh2	3-hydroxybutyrate dehydrogenase, type 2
Slc9a6	solute carrier family 9 (sodium/hydrogen exchanger), member 6	Mphosph10	M-phase phosphoprotein 10 (U3 small nucleolar ribonucleoprotein)
BC016495	cDNA sequence BC016495	Prkag1	protein kinase, AMP-activated, gamma 1 non-catalytic subunit
Mocs1	molybdenum cofactor synthesis 1	Lrat	lecithin-retinol acyltransferase (phosphatidylcholine-retinol-O-acyltransferase)
Pbk	PDZ binding kinase	Gtf3c6	general transcription factor IIIC, polypeptide 6, alpha
Ficd	FIC domain containing	Aasdhppt	aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase
Cdc42ep5	CDC42 effector protein (Rho GTPase binding) 5	Ddx49	DEAD (Asp-Glu-Ala-Asp) box polypeptide 49
4930528F23Rik	RIKEN cDNA 4930528F23 gene	Ilk	integrin linked kinase
Myo10	myosin X	Kcnab3	potassium voltage-gated channel, shaker-related subfamily, beta member 3
Coro1a	coronin, actin binding protein 1A	Krt13	keratin 13
Ppp1r2	protein phosphatase 1, regulatory (inhibitor) subunit 2	Med11	mediator of RNA polymerase II transcription, subunit 11 homolog (S. cerevisiae)
Fank1	fibronectin type 3 and ankyrin repeat domains 1	Appl1	adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1
S100a11	S100 calcium binding protein A11 (calgizzarin)	B4galt1	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 1

Symbol	Gene Name	Symbol	Gene Name
Zcchc3	zinc finger, CCHC domain containing 3	5430437P03Rik	RIKEN cDNA 5430437P03 gene
Rsph9	radial spoke head 9 homolog (Chlamydomonas)	Lysmd4	LysM, putative peptidoglycan-binding, domain containing 4
Tex19.1	testis expressed gene 19.1	Atp4a	ATPase, H+/K+ exchanging, gastric, alpha polypeptide
Ift74	intraflagellar transport 74 homolog (Chlamydomonas)	Il10rb	interleukin 10 receptor, beta
Snap25	synaptosomal-associated protein 25	Dnajc10	DnaJ (Hsp40) homolog, subfamily C, member 10
Tipin	timeless interacting protein	6-Sep	septin 6
Rab3a	RAB3A, member RAS oncogene family	Adal	adenosine deaminase-like
Foxn2	forkhead box N2	Tpm2	tropomyosin 2, beta
Tmsb15l	thymosin beta 15b like	Ppp1r9a	protein phosphatase 1, regulatory (inhibitor) subunit 9A
Ppat	phosphoribosyl pyrophosphate amidotransferase	Hspbp1	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1
Rbm34	RNA binding motif protein 34	Scnm1	sodium channel modifier 1
Mllt3	translocated to, 3	Ctnna2	catenin (cadherin associated protein), alpha 2
Cda	cytidine deaminase	Hao2	hydroxyacid oxidase 2
Plac9	placenta specific 9	Fam20c	family with sequence similarity 20, member C
Zfp821	zinc finger protein 821	Edn2	endothelin 2
Parp16	poly (ADP-ribose) polymerase family, member 16	Rhoc	ras homolog gene family, member C
Uckl1	uridine-cytidine kinase 1-like 1	Cdkn2b	cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)
Cct6a	chaperonin containing Tcp1, subunit 6a (zeta)	Dhfr	dihydrofolate reductase
Acsl6	acyl-CoA synthetase long-chain family member 6	Rabac1	Rab acceptor 1 (prenylated)
Tspan31	tetraspanin 31	Scrn1	secernin 1
Spire1	spire homolog 1 (Drosophila)	Slc33a1	solute carrier family 33 (acetyl-CoA transporter), member 1
Phtf2	putative homeodomain transcription factor 2	Akirin2	akirin 2
Akap13	A kinase (PRKA) anchor protein 13	Wipi2	WD repeat domain, phosphoinositide interacting 2
Mdh2	malate dehydrogenase 2, NAD (mitochondrial)	Isoc1	isochorismatase domain containing 1
Mrpl49	mitochondrial ribosomal protein L49	Plekhf2	pleckstrin homology domain containing, family F (with FYVE domain) member 2
Efna2	ephrin A2	Tspan3	tetraspanin 3
Mbd4	methyl-CpG binding domain protein 4	Ece2	endothelin converting enzyme 2
Vegfc	vascular endothelial growth factor C	Hspb7	heat shock protein family, member 7 (cardiovascular)

Symbol	Gene Name	Symbol	Gene Name
Wrnip1	Werner helicase interacting protein 1	Atf4	activating transcription factor 4
Pikfyve	phosphoinositide kinase, FYVE finger containing	D19Wsu162e	DNA segment, Chr 19, Wayne State University 162, expressed
Cyba	cytochrome b-245, alpha polypeptide	Srp14	signal recognition particle 14
Dstyk	dual serine/threonine and tyrosine protein kinase	Il2	interleukin 2
Stmn3	stathmin-like 3	G3bp2	GTPase activating protein (SH3 domain) binding protein 2
Pepd	peptidase D	Inpp5d	inositol polyphosphate-5-phosphatase D
Chgb	chromogranin B	Slc30a4	solute carrier family 30 (zinc transporter), member 4
Thap7	THAP domain containing 7	Mmp14	matrix metallopeptidase 14 (membrane-inserted)
4833439L19Rik	RIKEN cDNA 4833439L19 gene	Lmbrd1	LMBR1 domain containing 1
Pdgfa	platelet derived growth factor, alpha	D10Wsu102e	DNA segment, Chr 10, Wayne State University 102, expressed
Pja1	praja1, RING-H2 motif containing	Dock7	dedicator of cytokinesis 7
Car10	carbonic anhydrase 10	Camp	cathelicidin antimicrobial peptide
Trmt2a	TRM2 tRNA methyltransferase 2 homolog A (S. cerevisiae)	Usp39	ubiquitin specific peptidase 39
Stat1	signal transducer and activator of transcription 1	Ints4	integrator complex subunit 4
Trappc5	trafficking protein particle complex 5	Senp6	SUMO/sentrin specific peptidase 6
Zmat5	zinc finger, matrin type 5	Csnk2b	casein kinase 2, beta polypeptide
1700012B15Rik	RIKEN cDNA 1700012B15 gene	Hras1	Harvey rat sarcoma virus oncogene 1
Dpep1	dipeptidase 1 (renal)	Med19	mediator of RNA polymerase II transcription, subunit 19 homolog (yeast)
Zyx	zyxin	Pgcp	plasma glutamate carboxypeptidase
Hpcal1	hippocalcin-like 1	Tmem41b	transmembrane protein 41B
Cdk5rap3	CDK5 regulatory subunit associated protein 3	1700014N06Rik	RIKEN cDNA 1700014N06 gene
Ppp3cc	protein phosphatase 3, catalytic subunit, gamma isoform	AI314180	expressed sequence AI314180
Mettl21a	methyltransferase like 21A	Prpsap1	phosphoribosyl pyrophosphate synthetase-associated protein 1
Tpd52l1	tumor protein D52-like 1	Gng13	guanine nucleotide binding protein (G protein), gamma 13
Hoxb2	homeobox B2	Snap23	synaptosomal-associated protein 23
Mobkl2a	MOB1, Mps One Binder kinase activator-like 2A (yeast)	Mpp1	membrane protein, palmitoylated
Txndc16	thioredoxin domain containing 16	Cnot1	CCR4-NOT transcription complex, subunit 1
Galntl5	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 5	Egf	epidermal growth factor
Mcm5	minichromosome maintenance	Myo16	myosin XVI

Symbol	Gene Name	Symbol	Gene Name
	deficient 5, cell division cycle 46 (S. cerevisiae)		
Tinf2	Terf1 (TRF1)-interacting nuclear factor 2	Gatm	glycine amidinotransferase (L-arginine:glycine amidinotransferase)
Krt19	keratin 19	Krt24	keratin 24
Setd3	SET domain containing 3	Gas5	growth arrest specific 5
Bfar	bifunctional apoptosis regulator	Zfp318	zinc finger protein 318
Smarcd2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2	Rapgef4	Rap guanine nucleotide exchange factor (GEF) 4
Il12a	interleukin 12a	Carkd	carbohydrate kinase domain containing
Agpat3	1-acylglycerol-3-phosphate O-acyltransferase 3	2210012G02Rik	RIKEN cDNA 2210012G02 gene
Myc	myelocytomatosis oncogene	1700001J03Rik	RIKEN cDNA 1700001J03 gene
Pon1	paraoxonase 1	Uqcrh	ubiquinol-cytochrome c reductase hinge protein
Slc44a3	solute carrier family 44, member 3	Sult1d1	sulfotransferase family 1D, member 1
Ccr5	chemokine (C-C motif) receptor 5	Paqr5	progestin and adipoQ receptor family member V
Pex19	peroxisomal biogenesis factor 19	Syvn1	synovial apoptosis inhibitor 1, synoviolin
Gadd45g	growth arrest and DNA-damage-inducible 45 gamma	Cox17	cytochrome c oxidase, subunit XVII assembly protein homolog (yeast)
1700028P14Rik	RIKEN cDNA 1700028P14 gene	Crym	crystallin, mu
Cdh3	cadherin 3	Tbl2	transducin (beta)-like 2
Mettl21a	methyltransferase like 21A	Ogdh	oxoglutarate dehydrogenase (lipoamide)
Cenph	centromere protein H	Ypel1	yippee-like 1 (Drosophila)
Khdc1b	KH domain containing 1B	Myl4	myosin, light polypeptide 4
Odz3	odd Oz/ten-m homolog 3 (Drosophila)	D2Ertd750e	DNA segment, Chr 2, ERATO Doi 750, expressed
Stab1	stabilin 1	Nme3	non-metastatic cells 3, protein expressed in
Unkl	unkempt-like (Drosophila)	Sft2d1	SFT2 domain containing 1
Map1lc3b	microtubule-associated protein 1 light chain 3 beta	Wwtr1	WW domain containing transcription regulator 1
Smurf2	SMAD specific E3 ubiquitin protein ligase 2	Asb1	ankyrin repeat and SOCS box-containing 1
Ndufa13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	Serpini2	serine (or cysteine) peptidase inhibitor, clade I, member 2
Rab11fip1	RAB11 family interacting protein 1 (class I)	Elk1	ELK1, member of ETS oncogene family
Atp7a	ATPase, Cu++ transporting, alpha polypeptide	Nubp1	nucleotide binding protein 1
Fcgbp	Fc fragment of IgG binding protein	Scaf11	SR-related CTD-associated factor 11
Josd2	Josephin domain containing 2	Acyp1	acylphosphatase 1, erythrocyte (common) type

Symbol	Gene Name	Symbol	Gene Name
Irx5	Iroquois related homeobox 5 (Drosophila)	Rpl10	ribosomal protein 10
Stra13	stimulated by retinoic acid 13	Herc4	hect domain and RLD 4
Gys1	glycogen synthase 1, muscle	Fam195b	family with sequence similarity 195, member B
Ccs	copper chaperone for superoxide dismutase	Ubash3b	ubiquitin associated and SH3 domain containing, B
Slc1a5	solute carrier family 1 (neutral amino acid transporter), member 5	Slc6a1	solute carrier family 6 (neurotransmitter transporter, GABA), member 1
Ngly1	N-glycanase 1	Angptl1	angiopoietin-like 1
Dcbld1	discoidin, CUB and LCCL domain containing 1	Wdr54	WD repeat domain 54
Mast2	microtubule associated serine/threonine kinase 2	Rbbp6	retinoblastoma binding protein 6
Crlf1	cytokine receptor-like factor 1	1190007F08Rik	RIKEN cDNA 1190007F08 gene
Asnsd1	asparagine synthetase domain containing 1	Dll1	delta-like 1 (Drosophila)
Dcun1d5	DCN1, defective in cullin neddylation 1, domain containing 5 (S. cerevisiae)	Nppb	natriuretic peptide type B
Fam185a	family with sequence similarity 185, member A	Nfatc3	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3
Hdac11	histone deacetylase 11	Lrch2	leucine-rich repeats and calponin homology (CH) domain containing 2
1110034A24Rik	RIKEN cDNA 1110034A24 gene	Atp5b	ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit
Rps4y2	ribosomal protein S4, Y-linked 2	Rrp12	ribosomal RNA processing 12 homolog (S. cerevisiae)
Zfp868	zinc finger protein 868	Dhx16	DEAH (Asp-Glu-Ala-His) box polypeptide 16
Psmc2	proteasome (prosome, macropain) 26S subunit, ATPase 2	Dmap1	DNA methyltransferase 1-associated protein 1
Rbm39	RNA binding motif protein 39	Slc1a4	solute carrier family 1 (glutamate/neutral amino acid transporter), member 4
Ctnna1	catenin (cadherin associated protein), alpha 1	Smc4	structural maintenance of chromosomes 4
Cyth1	cytohesin 1	Camsap1	calmodulin regulated spectrin-associated protein 1
Sco1	SCO cytochrome oxidase deficient homolog 1 (yeast)	Cntln	centlein, centrosomal protein
Calb1	calbindin 1	Ckap2l	cytoskeleton associated protein 2-like
2310001H18Rik	RIKEN cDNA 2310001H18 gene	Katna1	katanin p60 (ATPase-containing) subunit A1
Sh3d19	SH3 domain protein D19	Speg	SPEG complex locus
Acadsb	acyl-Coenzyme A dehydrogenase, short/branched chain	Nsdhl	NAD(P) dependent steroid dehydrogenase-like

Symbol	Gene Name	Symbol	Gene Name
Map2k2	mitogen-activated protein kinase kinase 2	Lsm6	LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae)
Cd3g	CD3 antigen, gamma polypeptide	Tgm1	transglutaminase 1, K polypeptide
Sepn1	selenoprotein N, 1	Notch1	Notch gene homolog 1 (Drosophila)
Ndufa3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3	Ndufa11	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 11
B3gnt7	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7	Srsf3	serine/arginine-rich splicing factor 3
Stat6	signal transducer and activator of transcription 6	Vps26b	vacuolar protein sorting 26 homolog B (yeast)
Nol4	nucleolar protein 4	Cetn3	centrin 3
Rpl37a	ribosomal protein L37a	Tprgl	transformation related protein 63 regulated like
Lhx6	LIM homeobox protein 6	Tgif2	TGFB-induced factor homeobox 2
Myof	myoferlin	BC016423	cDNA sequence BC016423
Cox5a	cytochrome c oxidase, subunit Va	Mycbp2	MYC binding protein 2
Rpl19	ribosomal protein L19	Jak2	Janus kinase 2
Cyth2	cytohesin 2	Metap2	methionine aminopeptidase 2
Chchd3	coiled-coil-helix-coiled-coil-helix domain containing 3	Myh8	myosin, heavy polypeptide 8, skeletal muscle, perinatal
Runx1t1	translocated to, 1 (cyclin D-related)	Ehd3	EH-domain containing 3
Rpl3	ribosomal protein L3	Jak2	Janus kinase 2
Syf2	SYF2 homolog, RNA splicing factor (S. cerevisiae)	Lefty1	left right determination factor 1
Cyp26a1	cytochrome P450, family 26, subfamily a, polypeptide 1	Dynll2	dynein light chain LC8-type 2
Agfg1	ArfGAP with FG repeats 1	Fam57a	family with sequence similarity 57, member A
Pin1	protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1	Srp72	signal recognition particle 72
Tnfrsf12a	tumor necrosis factor receptor superfamily, member 12a	Snhg11	small nucleolar RNA host gene 11
Ttc4	tetratricopeptide repeat domain 4	Celf4	CUGBP, Elav-like family member 4
G3bp2	GTPase activating protein (SH3 domain) binding protein 2	1810043G02Rik	RIKEN cDNA 1810043G02 gene
Tm4sf20	transmembrane 4 L six family member 20	Zrsr1	zinc finger (CCCH type), RNA binding motif and serine/arginine rich 1
Gosr2	golgi SNAP receptor complex member 2	Il2ra	interleukin 2 receptor, alpha chain
Ndufaf1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 1	Wnt4	wingless-related MMTV integration site 4
8030474K03Rik	RIKEN cDNA 8030474K03 gene	Fam187b	family with sequence similarity 187, member B
Stoml2	stomatin (Epb7.2)-like 2	Bola1	bolA-like 1 (E. coli)