Figure S1

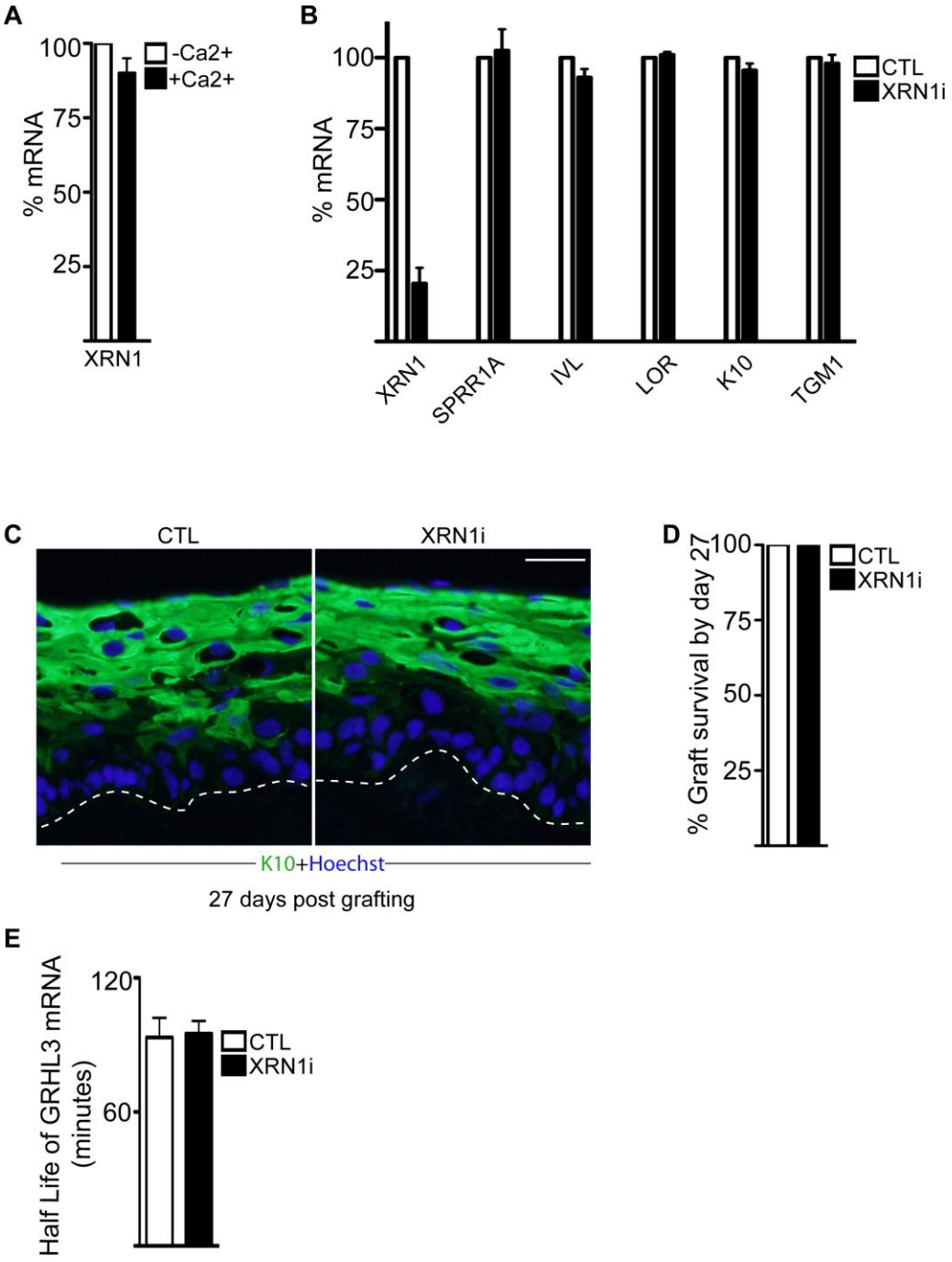

Figure S1. Supports Figure 2. XRN1 transcript levels remain constant during epidermal differentiation and loss of XRN1 has no impact on epidermal tissue differentiation, self-renewal or stability of *GRHL3* mRNA. (A) XRN1 mRNA levels do not change during epidermal differentiation. QRT-PCR was performed on mRNA isolated from undifferentiated (-Ca^{2+}) and differentiated(+Ca^{2+}) epidermal cells for XRN1 expression. Error bars=mean with SEM. **(B)** Knockdown of XRN1 has no impacts on epidermal differentiation gene expression. QRT-PCR was used to determine the levels

of differentiation gene expression in XRN1i tissue. Error bars=mean with SEM. **(C)** Knockdown of XRN1 has no impact on differentiation or self-renewal of epidermal tissue. Keratinocytes expressing shRNAs for XRN1 (XRN1i) or control (CTL) were used to regenerate human epidermis on immune deficient mice. Tissue was harvested 27 days post grafting. Keratin 10 (K10) staining shown in green marks differentiated epidermal layers. Hoechst staining in blue marks the nuclei. The dashed lines denote basement membrane zone (Scale bar=40μm). **(D)** Graft survival (n=4 grafted mice per group). **(E)** The half-life of *GRHL3* mRNA remains constant when XRN1 levels decrease. Control (CTL) and XRN1i cells grown in proliferating conditions were treated with actinomycin D (10ug/ml) for 0, 0.5, 1.5, 2.5, and 4 hours to determine the half-life of *GRHL3* mRNA. RNA was isolated from the samples and QRT-PCR was used to determine the levels of *GRHL3*. Half-life was calculated using the formula $T_{1/2}$= 0.3t/log(D1/D2). D1 and D2 refer to *GRHL3* levels at two different times and t refers to the corresponding time between D1 and D2. Data analyzed using T-test with two tails.

Figure S2

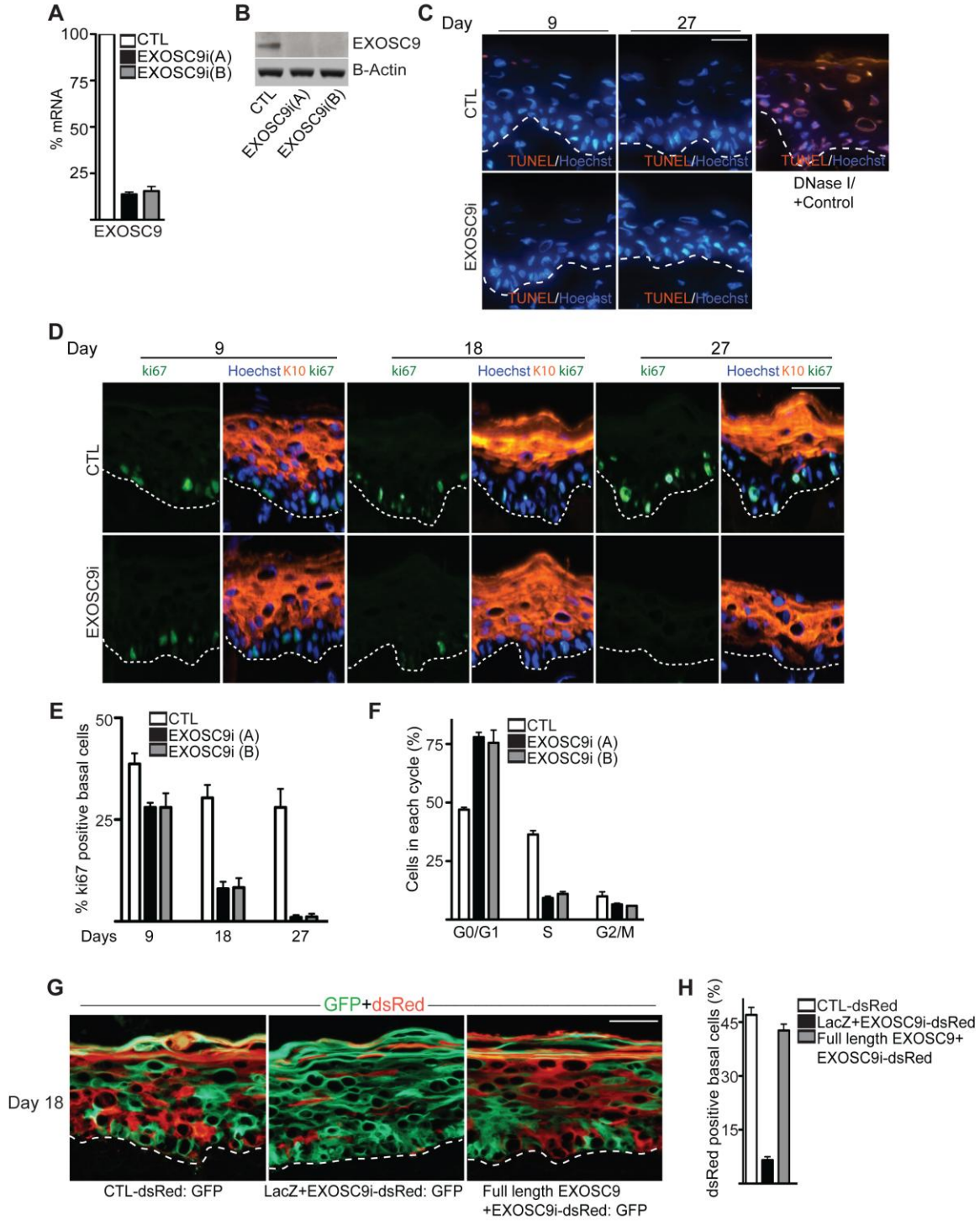

Figure S2. Supports Figure 2. Knockdown of EXOSC9 and impacts on apoptosis and basal cell proliferation in regenerated human epidermis; and expression of full length EXOSC9 rescues loss of progenitor cells from the basal layer in EXOSC9i epidermis. (A) Knockdown of EXOSC9 on the mRNA level. QRT-PCR was used to determine EXOSC9 mRNA levels. Error bars=mean with SEM. **(B)** Knockdown of EXOSC9 on the protein level. Western blot analysis of EXOSC9 expression. B-actin is

used as a loading control. **(C)** EXOSC9 loss does not increase apoptosis in epidermal tissue. TUNEL staining on control (CTL) and EXOSC9i tissue at the indicated timepoints post-regeneration. TUNEL staining for apoptosis is shown in orange and Hoechst staining for nuclei is shown in blue. DNaseI treated epidermal tissue serves as a positive control for TUNEL staining. Scale bar=40μm. **(D)** Loss of proliferative capacity in epidermal tissue lacking EXOSC9. Keratinocytes were knocked down for EXOSC9 or control (CTL) and used to regenerate human epidermis and grafted onto immune compromised mice. Tissue was harvested at 9,18, and 27 days post-regeneration and stained for Ki67 (green) to determine the proliferative capacity of the tissue. Differentiation protein keratin 10 (K10) is shown in orange. Hoechst staining for the nuclei is in blue. Scale bar=40μm. **(E)** Quantification of Ki67 positive cells in the basal layer of the epidermis over a 27 day period. 400 basal cell nuclei were counted for each time point. Error bars=mean with SEM. **(F)** EXOSC9 depleted cells result in G1 cell cycle arrest. Flow cytometry analysis of control (CTL) and EXOSC9 depleted cells (EXOSC9iA and B). N=3. Error bars=mean with SEM. **(G)** Expression of full length EXOSC9 rescues the loss of progenitor cells in EXOSC9 depleted epidermis. Human epidermal progenitor competition assays were performed by first transducing keratinocytes with a retrovirus to constitutively express dsRed. These cells were also transduced to express either a LacZ control or full length EXOSC9. The LacZ-dsRed control cells were then transduced with a control shRNA construct or EXOSC9 shrna construct. The EXOSC9-dsRed cells were transduced with an shRNA to knockdown EXOSC9. Each of these dsRed cells were mixed at a 1:1 ratio with GFP expressing cells and used to regenerate human epidermis. Tissue was harvested 18 days post-regeneration. GFP expressing cells are shown in green while dsRed expressing cells are shown in red. The left panel denotes epidermis regenerated from control shrna-LacZ-dsRed cells mixed with control GFP cells (CTL-dsRed:GFP). The middle panel denotes LacZ-dsRed cells knocked down for EXOSC9 and mixed with GFP cells (LacZ+EXOSC9i-dsRed:GFP). The right panel denotes epidermis regenerated from dsRed cells expressing full length EXOSC9 and knocked down for EXOSC9 mixed with GFP cells (Full length EXOSC9+EXOSC9i-dsRed: GFP). Note that expression of full length EXOSC9 (right panel) rescues the loss of dsRed expressing cells from the basal layer of the epidermis as compared to the middle panel due to knockdown of EXOSC9. The dashed lines denote basement membrane zone (Scale bar=40μm). **(H)** Expression of full length EXOSC9 prevents the loss of dsRed cells from the basal layer in EXOSC9 knockdown epidermis. Quantification of dsRed cells in the basal layer. Basal layer cells expressing dsRed were counted and divided by the total number of basal cells to determine the percentage of dsRed positive basal cells; error bars, mean with SEM.

Figure S3

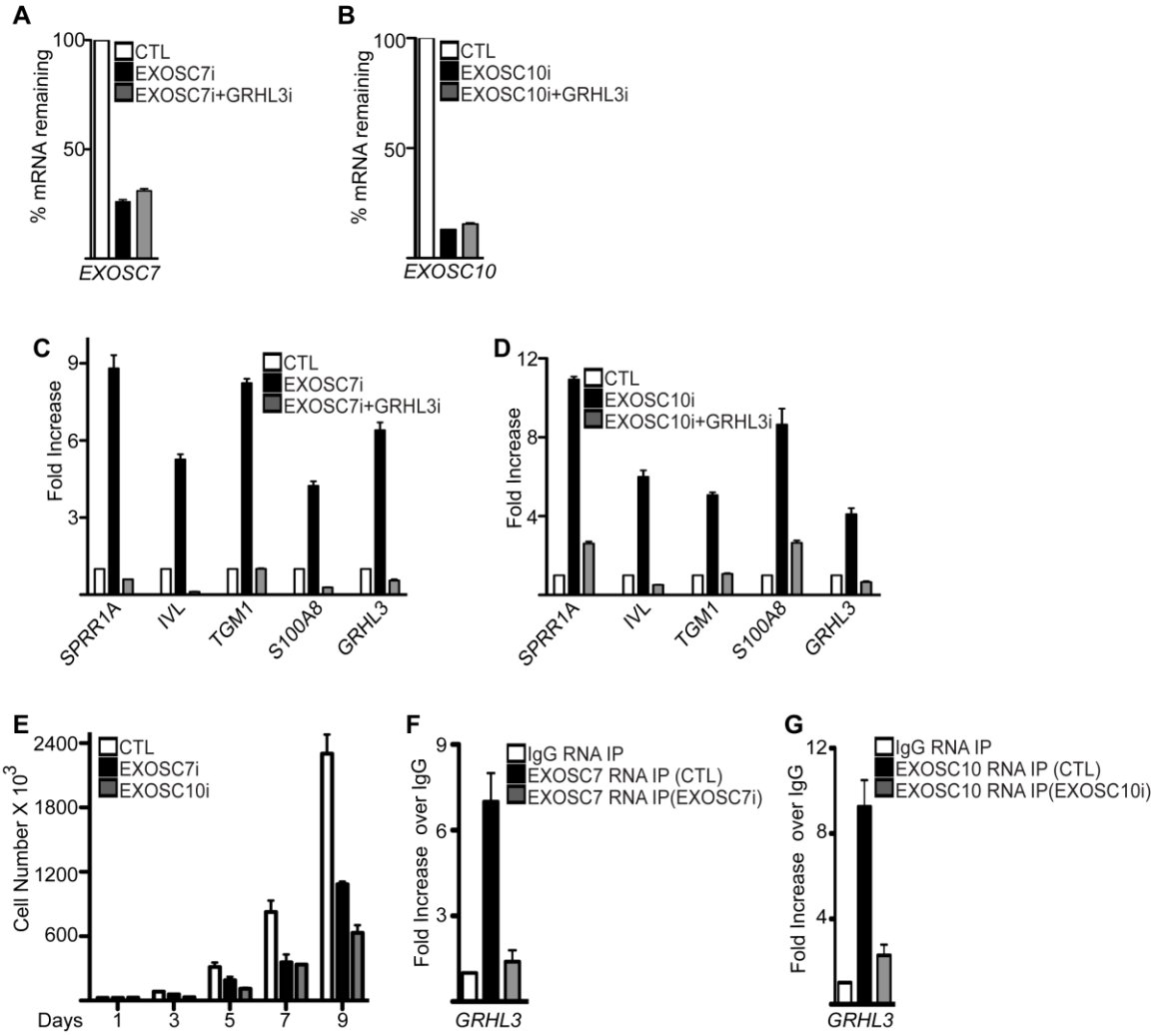

Figure S3. Supports Figure 3. Components of the exosome, EXOSC7 and EXOSC10, bind to *GRHL3* mRNA and are necessary to prevent premature differentiation and sustain proliferation in progenitor cells. (A) Knockdown of EXOSC7. QRT-PCR was used to determine EXOSC7 mRNA levels. Error bars=mean with SEM. **(B)** Knockdown of EXOSC10. QRT-PCR was used to determine EXOSC10 mRNA levels. Error bars=mean with SEM. **(C)** Loss EXOSC7 results in premature expression of differentiation genes which is rescued upon double EXOSC7 and GRHL3 knockdown. Keratinocytes were knocked down for control (CTL), EXOSC7, or EXOSC7 and GRHL3 simultaneously. Knockdown cells were harvested for RNA and QRT-PCR was used to determine differentiation gene expression. Error bars=mean with SEM. **(D)** Loss EXOSC10 results in premature expression of differentiation genes which is rescued upon double EXOSC10 and GRHL3 knockdown. Keratinocytes were knocked down for control (CTL), EXOSC10, or EXOSC10 and GRHL3 simultaneously. Knockdown cells were harvested for RNA and QRT-PCR was used to determine differentiation gene expression. Error bars=mean with SEM. **(E)** EXOSC7 and EXOSC10 are necessary to sustain epidermal proliferation. Cells knocked down for control (CTL), EXOSC7, or EXOSC10 were seeded at 25,000 cells and counted over a period of 9

days. Error bars=mean with SEM. **(F-G)** EXOSC7 and EXOSC10 bind to *GRHL3* transcripts. RNA immunoprecipitations (RIP) were performed using an antibody against EXOSC7, EXOSC10 or IgG on paraformaldehyde crosslinked nuclear extracts isolated from control (CTL), EXOSC7i, or EXOSC10i epidermal progenitor cells. QPCR was used to determine the levels of EXOSC7, EXOSC10 or IgG binding to *GRHL3* mRNA. Error bars=mean with SEM.

Figure S4

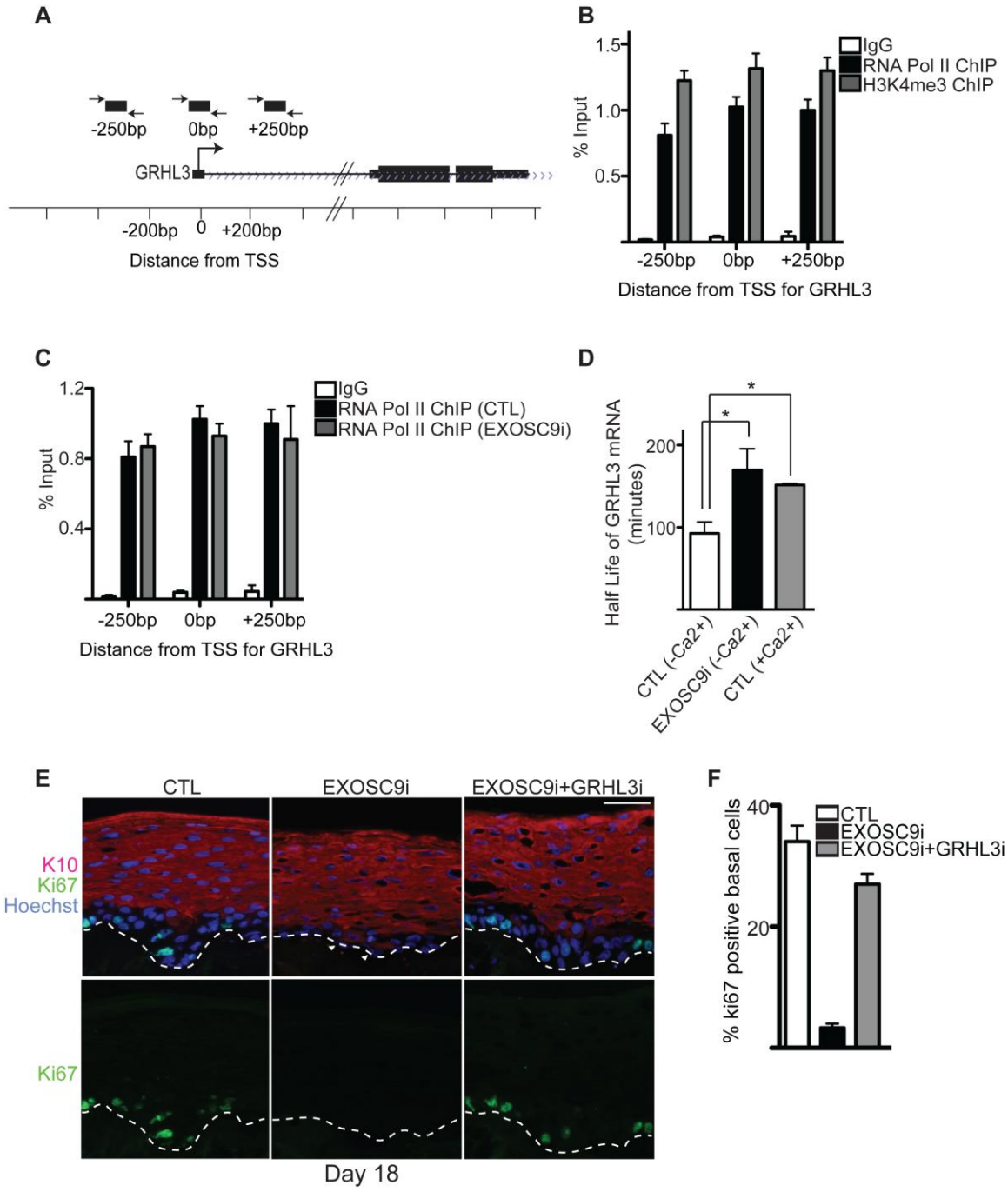

Figure S4. Supports Figure 4. Chromatin marks indicative of active transcription (H3K4me3 and RNA Pol II) are found in the promoter region of *GRHL3* in epidermal progenitor cells; loss of EXOSC9 increases the stability of *GRHL3* transcript; and knockdown of GRHL3 in EXOSC9i epidermis rescues the differentiation and proliferation phenotypes seen in EXOSC9i tissue. (A) Diagram of the promoter region of *GRHL3* in relation to where H3K4me3 and RNA Pol II binding were assayed. **(B)** RNA Pol II and H3K4me3 bind to the promoter region of *GRHL3* in undifferentiated

epidermal cells. Keratinocytes grown in proliferation conditions were used for chromatin immunoprecipitation (ChIP). Antibodies against RNA Pol II, H3K4me3, or IGGs were used to immunoprecipitate chromatin. QPCR was used to assay binding to regions -250bp, 0bp, and 250bp from the transcriptional start site (TSS) of *GRHL3*. Enrichment at each site was normalized as a percent of DNA input. Error bars=mean with SEM. **(C)** The increase in *GRHL3* mRNA levels with EXOSC9 knockdown is not due to increased RNA Polymerase II binding to the promoter of *GRHL3*. ChIP was performed using RNA polymerase II antibodies on chromatin isolated from control or EXOSC9 knockdown cells. QPCR was used to assay binding to regions -250bp, 0bp, and 250bp from the transcriptional start site (TSS) of *GRHL3*. Enrichment at each site was normalized as a percent of DNA input. Error bars=mean with SEM.
(D) The half-life of *GRHL3* mRNA increases when EXOSC9 levels decrease. Control (CTL) and EXOSC9i cells grown in proliferating conditions as well as differentiated control cells (cells were differentiated by growing in high calcium for 3 days) were treated with actinomycin D (10ug/ml) for 0, 0.5,1.5, 2.5, and 4 hours to determine the half-life of *GRHL3* mRNA. RNA was isolated from the samples and QRT-PCR was used to determine the levels of *GRHL3*. Half-life was calculated using the formula $T_{1/2}$= 0.3t/log(D1/D2). D1 and D2 refer to *GRHL3* levels at two different times and t refers to the corresponding time between D1 and D2. Data analyzed using T-test with two tails (* indicates P value $<$0.05). **(E)** Knockdown of GRHL3 in EXOSC9i epidermis prevents premature differentiation and increases the proliferative capacity of EXOSC9i epidermis. Keratinocytes expressing shRNAs for EXOSC9 (EXOSC9i), EXOSC9 and GRHL3 (EXOSC9i+GRHL3i), or control shRNA (CTL) were used to regenerate human epidermis. Tissues were harvested 18 days post regeneration. Keratin 10 (K10) staining shown in red marks differentiated epidermal layers. Ki67 staining shown in green marks proliferative basal layer cells. Hoechst staining in blue marks the nuclei. White arrowheads denote areas of ectopic basal layer differentiation in EXOSC9i tissue. Note the absence of ectopic differentiation in the basal layer of EXOSC9i+GRHL3i epidermis. The dashed lines denote basement membrane zone. Scale bar=40μm. **(F)** Quantification of Ki67 positive cells in the basal layer of the epidermis. 500 basal cell nuclei were counted for each group. Error bars=mean with SEM.

SUPPLEMENTAL EXPERIMENTAL PROCEDURES

Gene knockdown and overexpression

ShRNA retroviral constructs were generated by cloning oligos into the pSuper Retro vector. The oligo sequences targeting EXOSC9, XRN1, EXOSC10, and GRHL3 are as follows: EXOSC9i(A): GAGTCTATAGCAAATCAAA; EXOSC9i (B): GGAGTAGAAGTCTCTGATA; XRN1i: GGGCCTCCAGTATAACTTA; EXOSC10i: GGTGTCGCAGCAACATTAA; GRHL3i: GGAATGCGATCTCTGAGAA. The control shRNA construct was generated as previously described(Sen et al., 2010). shRNA retroviral construct (SMP) for EXOSC7 was purchased from Open Biosystems with the following sequence: EXOSC7i: CAGCAGCATTTGTACATGTAA. SiRNAs used against GRHL3 were synthesized by Dharmacon against the following sequences: CATCAAGTCAGGCGAGTCA, CCACAGGAGTCGATGCTCT, CCAACAAAGTCAAGAGTGT, TTGAGGAGGTGGCCTATAA. Retroviral constructs expressing GFP or dsRed (LZRS-GFP or LZRS-dsRED) were a generous gift from the Khavari laboratory. The full-length open reading frame of GRHL3 was cloned into the LZRS retroviral vector using the restriction enzymes, EcorI and NotI. The primers used to amplify GRHL3 were: GRHL3 for: ACGCAGAATTCGCCACCATGATGAGAGTCAATGGAGATGATGACAGTG and GRHL3 rev: ACGCAGCGGCCGCTTACAGCTCCTTAAGGATGATCTGAATTTTG. The full-length open reading frame of EXOSC9 was cloned into the LZRS retroviral vector using the restriction enzymes, EcorI and NotI. The primers used to amplify EXOSC9 were: EXOSC9 for: ACGCAGAATTCGCCACCATGAAGGAAACGCCACTCTCAAACTGCG and EXOSC9 rev: ACGCAGCGGCCGCTTAATTGGCAGCTCTCTTCTTTTTTCTTCTTTTCAC.

Western blotting and immunofluorescence

50 ug of the cell lysates were used for immunoblotting and resolved on 10% SDS-PAGE and transferred to PVDF membranes. Primary antibodies used include B-actin (Abcam:ab8226) at 1:2000 and EXOSC9 (Abcam:ab54283) at 1:300. Sheep anti mouse or rabbit HRP (Amersham Biosciences) secondary antibodies were used at 1:4000. For immunofluorescence experiments, 7 μm thick epidermal sections from adult human skin or xenografts were fixed in 4% paraformaldehyde for 15 minutes followed by blocking in PBS with 2.5% normal goat serum, 0.3% triton X100, and 2% bovine serum albumin for 30 minutes. Sections were incubated in primary antibodies for 1 hour. Primary antibodies include Keratin 10 (Neomarkers: MS611P/DE-K10) at 1:400, Ki67 (Neomarkers: RM-9106-S) at 1:200, GFP (Abcam:ab6556) at 1:1000 and EXOSC9 (Abcam:ab54283) at 1:300. The secondary antibodies used were Alexa 555 conjugated goat anti-mouse IgG (Molecular Probes) (1:1000), Alexa 488 conjugated goat anti-mouse IgG(Molecular Probes)(1:1000), and Alexa 488 conjugated goat anti-rabbit IgG (Molecular Probes)(1:1000). Nuclear dye, Hoechst 33342, was used at 1:1000(Molecular Probes).

Quantitative reverse transcriptase-PCR analysis

Total RNA from cells was extracted using the RNeasy mini kit (Qiagen) and quantified by Nanodrop. One ug of total RNA was reverse transcribed using the Maxima cDNA synthesis kit from Fermentas. Quantitative PCR was performed using the Roche 480 Light Cycler. Samples were run in triplicate and normalized to GAPDH. Primer sequences for GAPDH, S100A8, and IVL were the same as previously published(Sen et al., 2008). Sequences for LOR, TGM1, KRT10, SPRR1A, GRHL3, EXOSC9, EXOSC7,

and EXOSC10 are as follows: LOR for: CCGGTGGGAGCGTCAAGT, LOR rev: AGGAGCCGCCGCTAGAGAC; TGM1 for: TCAGACGCTGGGGAGTTC, TGM1 rev:GGTCCGCTCACCAATCTG; KRT10 for A: CGCCTGGCTTCCTACTTGG, KRT10 rev: CTGGCGCAGAGCTACCTCA; SPRR1A for: GCCACTGGATACTGAACA, SPRR1A rev: AGGAAGACTAGGGATGGTT; GRHL3 for: GCCAGTTCTACCCCGTCA, GRHL3 rev: GTCAATGACCCGCTGCTT; EXOSC9 for: TGCTGGTGAAAAGGTTTGG, EXOSC9 rev: CAGGATCACGCTCTTCAGG; EXOSC7 for: GATTGGCTATCGGCATGTG, EXOSC7 rev: ACACGCTTGCCAGTCTCC; EXOSC10 for: GGCAGGCACTCACTCGAT, EXOSC10 rev: CCCACATCTCCAGCCTCA.

Chromatin Immunoprecipitation

ChIP was performed as previously described(Sen et al., 2008) using the following antibodies: anti-H3K4me3(Abcam: ab8580), anti-RNA Polymerase II (Covance: MMS-128P), and IgG (Abcam: ab18413). 5 million cells were used for ChIP for each antibody used. 3ug of antibody was used for each pulldown experiment. Experiments were performed in triplicates. Results were represented as a percent of input DNA. QPCR primers for the GRHL3 promoter region are as follows according to distance from transcriptional start site:
-250bp for: GGAAGGGGGAAGCGATAA, -250bp rev: GCCCCCTCCTTCTGTACC; 0bp for: CCCTCCTCCCTCATCTCC, 0bp rev: CTGGCGCTGATTGGCTAC; 250bp for: CTTTCCCGGGCAGAGAAT, 250bp rev: CCTCCAGGAAACCCCATC.

RNA Immunoprecipitation

RNA immunoprecipitation was performed using the following antibodies: anti-EXOSC9 (Abcam:ab54283), anti-EXOSC7 (Abcam: ab89104), anti-EXOSC10(Abcam: ab50558) and IgG control (Abcam: ab18413). 5 million cells were used for RNA IP for each antibody used. 3ug of antibody was used for each pulldown experiment. RNA IP was performed using the RNA IP kit (53024) from Active Motif according to manufacturer's protocol. Immunoprecipitated RNA was converted into cDNA using the Maxima cDNA synthesis kit. QPCR primers for detecting binding to *GRHL3*, *KRT5*, and *GAPDH* mRNA are as follows: GRHL3 for: CAGGGGCAATGAGACGAC, GRHL3 rev: GTGAAGGGCGAGCAGGTA; KRT5 for: CAAATCGACCCCAGCATC, KRT5 rev: GCTCCAGGTTCTGCCTCA; GAPDH for: CTGAGAACGGGAAGCTTGT, GAPDH rev: GGGTGCTAAGCAGTTGGT.

Gene expression profiling

For gene expression profiling, cultured primary human keratinocytes were knocked down for EXOSC9, EXOSC9 and GRHL3, or control. RNA was harvested from the cells 5 days after knockdown. Microarray analysis was performed on duplicate samples. Labeling of cDNA and hybridization to Affymetrix HG-U133 2.0 plus arrays were performed at the UCSD Genechip Microarray Core Facility. For gene expression analysis, arrays were RMA normalized and differential expression was defined using the following filters: Significance Analysis of Microarrays 3.0(Tusher et al., 2001) with a false discovery rate less than 5%, an average fold change ≥ 1.5 at any time point, and an average raw expression intensity ≥ 100 at any time point. Hierarchical clustering and heat map generation were performed as previously described(Sen et al., 2010). For future analyses, Affymetrix probe IDs were converted to unique Unigene IDs. GO term enrichment was performed using DAVID analysis(Huang da et al., 2009) with the total set of genes on the appropriate microarray as the background.

References for supplemental experimental procedures

Huang da, W., Sherman, B.T., and Lempicki, R.A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc *4*, 44-57.
Sen, G.L., Reuter, J.A., Webster, D.E., Zhu, L., and Khavari, P.A. (2010). DNMT1 maintains progenitor function in self-renewing somatic tissue. Nature *463*, 563-567.
Sen, G.L., Webster, D.E., Barragan, D.I., Chang, H.Y., and Khavari, P.A. (2008). Control of differentiation in a self-renewing mammalian tissue by the histone demethylase JMJD3. Genes Dev *22*, 1865-1870.
Tusher, V.G., Tibshirani, R., and Chu, G. (2001). Significance analysis of microarrays applied to the ionizing radiation response. Proc Natl Acad Sci U S A *98*, 5116-5121.

Table S1

Table S1. Global Gene Expression Profiling Comparing Control and EXOSC9i Cells Grown in Self-renewing I

All values are shown in Log2 scale except for the last column which is shown as a fold change between control and
Each sample was performed in biological duplicates. The average value for each sample is shown in Log2 scale.
Significant changes between control (CTL) and EXOSC9i cells were identified by Significance Analysis of Microarray
or equal to 5% and an average fold change of greater than or equal to 1.5 (which is a change of equal to or greater

Gene Symbol	CTL average	EXOSC9i average	Change(EXOSC9i - CTL)	Fold change (EXOSC9i/C
PI3	8.141044415	10.6922808	2.551236382	5.861363789
KRTDAP	8.676046437	11.738218	3.06217156	8.352288583
SLC6A14	3.347759374	6.868716231	3.520956857	11.47925299
LCE3D	8.178654453	10.80936294	2.630708484	6.193300656
IVL	7.942842356	10.57145062	2.628608261	6.184291234
SBSN	6.964533408	9.763500041	2.798966633	6.959417862
CRCT1	7.253753136	10.02833693	2.774583798	6.842785849
SERPINB3	5.479922925	7.837596071	2.357673146	5.12543036
CLIC3	6.873827741	8.330804976	1.456977235	2.745325542
HOPX	7.688027564	10.83406961	3.146042049	8.85223683
SLPI	9.490862612	12.37060646	2.879743848	7.360194277
S100A9	9.212246363	11.57899309	2.366746729	5.157767456
S100A8	9.580402741	12.61103725	3.030634505	8.171690169
WFDC5	5.416404852	7.730979547	2.314574695	4.974579896
CNFN	6.931329018	9.284424053	2.353095036	5.109191587
PRR9	6.981455873	8.130660829	1.149204956	2.217916353
S100A7	6.018496113	7.980996146	1.962500032	3.897367652
SPRR1A	10.65644123	13.03684327	2.380402033	5.206818195
SCEL	5.939895571	7.721337042	1.781441471	3.437694809
RHCG	6.715364774	8.502733234	1.78736846	3.451846856
GRHL3	6.366493238	8.280077747	1.91358451	3.767439932
A2ML1	7.487317275	9.003764988	1.516447713	2.860857648
GJA5	6.734626586	6.112231602	-0.622394984	-1.53942863
SERPINB13	5.797127862	6.979447506	1.182319644	2.269413727
COL4A2	10.86493857	10.21900351	-0.645935067	-1.564753135
HIST2H2BE	7.408467717	8.580534396	1.172066679	2.2533426
UPK1B	6.807296511	8.577485764	1.770189253	3.410986991
NASP	10.56982616	9.855901425	-0.713924736	-1.640260249
CEACAM6	5.348576339	7.338795016	1.990218677	3.972972141
SPRR2G	6.589264482	7.460064257	0.870799775	1.828676367
SPRR3	7.813433011	9.977232502	2.163799491	4.480934042
HMGB3	11.70120021	11.0168975	-0.684302708	-1.606925125
CALB1	5.963787817	7.818594867	1.85480705	3.617033725
LY6D	5.484914628	7.042231929	1.557317301	2.943060707
TAGLN	8.220506366	9.127471684	0.906965318	1.875097115
MTSS1	9.96362122	10.57429143	0.610670211	1.526968405
S100P	6.324570692	8.324513063	1.999942371	3.999840222
GRHL1	6.612145257	8.770537255	2.158391998	4.464170094
hCG_1749898	8.625780841	7.345979165	-1.279801675	-2.428055965
CDC25A	8.88849758	8.055799355	-0.832698225	-1.78101322
AQP3	11.70479306	11.11538538	-0.589407682	-1.504628875

Table S2

Table S2.Genes that overlap between EXOSC9i cells and differentially expressed genes during epidermal differentiation

Genes that change significantly upon EXOSC9 knockdown(595 genes; Table S1) were overlapped with the genes that change significantly upon epidermal differentiation. The genes that change signficantly upon epidermal differentiation were derived by comparing the gene expression profiles of undifferentiated control cells to control cells differentiated in calcium for 3 days. 3,336 genes change significantly (increase or decrease). We previously published this dataset (Sen et al. Nature 2010).

Gene Symbol					
S100P	TGM1	RHCG	CEBPD	TNIK	CDCA7
ZNF750	SPINK5	PTGS2	SPINK6	HMGB2	HSPH1
SBSN	A2ML1	AIFM2	LOC100131564	CP110	CBR3
LCE3D	BAMBI	CDKN2B	EMG1	FRMD4A	LEPREL1
CRCT1	PHACTR3	ZDHHC11	CPM	HSP90B1	SGCB
SPRR3	IL13RA2	EPPK1	HSPB1	IDI1	GAS2L3
LCN2	CEACAM6	IL1F9	C1orf74	PSMC3IP	DLC1
SLC6A14	RRAD	DSG3	LCE1B	DSN1	HMGA2
WFDC5	C9orf150	CALB1	LOC550643	NBN	TIPIN
ABCA12	DUSP1	PNLIPRP3	LOC202781	ANPEP	PDIA4
CDSN	S100A8	HIST3H2A	MIB2	SYNCRIP	CYP24A1
KLK7	TSLP	ID1	KLK10	RIF1	DIS3L
WFDC12	RGS2	MPZL3	C20orf112	C14orf145	IL1R2
KRTDAP	HIST2H2BE	ZNF185	MYLK	SLC7A6	KCNJ15
CLDN1	BMP6	HIST1H1C	TRAF3IP3	LPCAT2	TMEM201
S100A9	SDCBP2	SPINK7	MALAT1	ALDH7A1	GALNT5
PI3	OVOL1	AQP9	FLJ20021	DHX9	CEP135
SCEL	HIST1H2BD	H2AFJ	EXPH5	FLRT2	MATR3
NCF2	LOC100130476	C10orf57	ID3	C10orf93	FAM119A
KLK11	SPRR1A	USP6NL	ZBTB26	C1orf43	BRCA1
HOPX	TXNIP	THAP2	TRIM2	DFFA	TMEM97
CLIC3	KLK6	ALOX15B	PIGL	LOC100132999	POLD1
SPRR2G	GLTP	RPL31	GJB6	AKT2	MRGPRX3
SLPI	VGLL3	INPP5D	CLN8	NT5E	GINS3
GRHL1	DHRS9	LYPD3	LOC100128822	PLA2G7	DUT
SULT2B1	UPK1B	TAGLN	CYP1A1	CTSC	S1PR1
DEFB1	DSC2	COX7A1	CLEC11A	PDE1C	GPX2
IVL	S100A7	LEPR	PPP1R14C	ESM1	RFC2
MAFB	IGFL2	GPSM1	MTSS1	STAMBPL1	CENPL
ABCG1	RNASE7	RPS6KA5	GPR161	EPM2AIP1	SLC8A1
CST6	PRSS23	TP53INP1	KIAA1967	WDR34	FZD10
KRT16	SPRR1B	MMP28	FUBP1	SUPT16H	TRIM59
ATF3	TPPP	ERN1	PM20D2	C11orf75	SMC4
SERPINB3	CEBPA	BTG1	KRT75	CDC25A	EXOSC9
CNFN	PKIB	ANKRD29	MARK1	SLC12A2	MOBKL2B
SERPINB9	TMPRSS11B	MAL2	CCDC8	AQP3	BARD1
IL1RN	SERPINB13	CCL20	USP1	LOC642587	MASTL
GRHL3	CRYAB	USP53	CDH11	DDX11	PLOD2

Table S3

Table S3. Double knockdown of EXOSC9 and GRHL3 restores EXOSC9i regulated genes to control levels

Each sample was performed in biological duplicates. The average value for each sample is shown in Log2 scale. Genes that were rescued to control levels by double knockdown of EXOSC9 and GRHL3 were identified using the f Microarrays with a FDR of less than or equal to 5%. 2) Genes that were restored to control levels were identified as l of EXOSC9 +GRHL3 and control samples of less than 0.58 in log2 scale or a reversal of 0.58 or more in log2 scale i when compared to EXOSC9i samples. All values below are shown in log2 scale.

Gene Symbol	CTL average	EXOSC9i average	EXOSC9i+GRHL3i average	Change (EXOSC9i - CTL)
ZNF750	3.706483811	7.252836477	6.153168488	3.546352667
SLC6A14	3.347759374	6.868716231	3.470246926	3.520956857
HOPX	7.688027564	10.83406961	7.842503458	3.146042049
KRTDAP	8.676046437	11.738218	8.196423335	3.06217156
S100A8	9.580402741	12.61103725	10.07391522	3.030634505
SLPI	9.490862612	12.37060646	9.466524327	2.879743848
SBSN	6.964533408	9.763500041	6.511819868	2.798966633
CRCT1	7.253753136	10.02833693	6.810457004	2.774583798
SPINK6	6.694015816	9.373883261	8.576265322	2.679867446
LCE3D	8.178654453	10.80936294	7.466825083	2.630708484
IVL	7.942842356	10.57145062	7.275949422	2.628608261
PI3	8.141044415	10.6922808	7.123460546	2.551236382
SPRR1A	10.65644123	13.03684327	10.80026816	2.380402033
S100A9	9.212246363	11.57899309	9.025084105	2.366746729
SERPINB3	5.479922925	7.837596071	4.72664849	2.357673146
CNFN	6.931329018	9.284424053	6.831318961	2.353095036
WFDC5	5.416404852	7.730979547	5.236567543	2.314574695
SPRR3	7.813433011	9.977232502	8.350548829	2.163799491
GRHL1	6.612145257	8.770537255	7.277686426	2.158391998
PCF11	7.640606448	9.697319245	8.510683823	2.056712797
S100P	6.324570692	8.324513063	6.82628905	1.999942371
CEACAM6	5.348576339	7.338795016	5.696929956	1.990218677
SPRR1B	11.25681324	13.23259134	11.9560781	1.975778096
S100A7	6.018496113	7.980996146	5.67133638	1.962500032
IGFL2	6.074563865	7.992432936	7.032648888	1.917869071
GRHL3	6.366493238	8.280077747	6.24618203	1.91358451
RRAD	6.247127666	8.139142713	7.11763412	1.892015047
DHRS9	5.853952121	7.742726962	6.879622105	1.888774841
CALB1	5.963787817	7.818594867	6.200898502	1.85480705
RHCG	6.715364774	8.502733234	6.410237864	1.78736846
SCEL	5.939895571	7.721337042	5.607546124	1.781441471
UPK1B	6.807296511	8.577485764	6.857822468	1.770189253
KRT16	10.21222235	11.78361866	11.15704254	1.571396314
LY6D	5.484914628	7.042231929	5.432708708	1.557317301
KLK11	7.116219174	8.659086245	7.967932795	1.542867071
RGS2	7.832684317	9.372154484	8.327756913	1.539470166
IL1F9	5.961532165	7.485530714	6.643331377	1.523998549
SULT2B1	5.787886998	7.305126584	5.900663044	1.517239587
A2ML1	7.487317275	9.003764988	7.059395381	1.516447713
CLDN1	7.877901335	9.393390815	8.67829799	1.515489479