## SUPPLEMENTARY INFORMATION

Supplementary figures, S1-S6

Supplementary table, S1-S4

Supplementary materials and methods

Supplementary reference

**SUPPLEMENTARY FIGURE LEGENDS**

**Figure S1.** ΔNp63 promotes breast cancer cell growth *in vivo*. **A**, Representative immunoblots of ∆Np63 in MCF10DCIS-i-sh∆Np63 cells in the presence of doxycycline (dox). Actin was used as a loading control. **B,** Experimental design to determine the effects of ∆Np63 in primary tumor development. **C**, Tumor volume (mm3) of nude mice injected with MCF10DCIS-i-sh∆Np63 cells and fed with either control diet (-dox) or doxycycline (+dox) diet as described in (B). Asterisk indicates p < 0.05.

**Figure S2.** ΔNp63 expression is essential for breast cancer lung colonization. **A**, Representative immunoblots for ∆Np63 in lysates from primary tumors from Figure 2B. Actin was used as a loading control. **B**, Representative images of immunohistochemistry (IHC) for ∆Np63 and Ki67 in primary tumors and lung metastases from Figure 2B. **C**, Representative images of IHC for ∆Np63 in mammary adenocarcinoma primary tumors and corresponding metastases. **D-E**, Quantification of the percentage of ∆Np63-positive cells in primary tumors (D) and corresponding metastases (E) from immunohistostaining in (C). **F-G**, Representative bright field images of lungs (F) and quantification of visible lung nodules per mouse (G). Data are mean ± SD. n = 4 (group 1 and group 2) or n = 5 (group 3). Asterisk indicates p < 0.0005. **H**, Representative images of IHC for ∆Np63 in mammary adenocarcinoma metastatic colonies in the lungs. Arrows indicate ∆Np63 positive nuclei (brown). Samples were counterstained with hematoxylin.

**Figure S3.** Pathways regulated by ∆Np63-induced and –repressed genes. **A**, Experimental design for ChIP-seq analysis to identify ∆Np63-regulated genes. **B-C**, Pathways enriched in ∆Np63-induced (B) and –repressed (C) gene signatures in MCF10DCIS-control versus MCF10DCIS-sh∆Np63 tumors as described in (A).

**Figure S4.** TGFβ inhibits expression of ΔNp63 via canonical Smad-dependent signaling in breast cancer. **A**, Representative bright field micrographs of MCF10DCIS cells expressing shΔNp63 or treated with TGFβ. **B**, Representative immunoblots for indicated antibodies in MCF-10A, MCF10DCIS and MCFCA1D cells treated with TGFβ. Actin was used as a loading control. **C**, Representative immunoblots for the indicated antibodies in MCF10DCIS cells overexpressing TGFβ1. Actin was used as a loading control. **D**, Representative immunoblots for ΔNp63 in MCF10DCIS cells cultured in the indicated conditioned media. Actin was used as a loading control. **E**, Representative immunoblots for indicated antibodies in MCF10DCIS cells overexpressing ΔNp63α and treated with TGFβ. Actin was used as a loading control. **F**, qRT-PCR of ΔNp63 in MCF10DCIS cells treated with TGFβ alone or TGFβ and TGFBRI inhibitor, LY2157299. Data are mean ± SD. n = 3.

**Figure S5.** TGFβ regulates ΔNp63 expression via miR-22-3p, miR-30a-5p, miR-203a-3p and miR-222-3p. **A,** Representative immunoblots for ΔNp63 expression in MCF-10A, MCFDCIS and MCFCA1D cells transfected with miR-22-3p, miR-30a-5p, miR-203a-3p or miR-222-3p mimics. Actin was used as a loading control. **B-E**, Mutated versions of the 3’UTR of human *TP63* mRNA at binding sites for miR-22-3p (B), miR-30a-5p (C), miR-203a-3p (D) and miR-222-3p (E). **F-I**, qRT-PCR of miR-22-3p (F), miR-30a-5p (G), miR-203a-3p (H) and miR-222-3p (I) in MCF10DCIS cells treated with TGFβ alone or combination of TGFβ (10 ng/mL) and TGFBRI inhibitor, LY2157299 (1μM). Data are mean ± SD. n = 3. Asterisk indicates p < 0.05. **J**, Representative immunoblots for ΔNp63 expression in MCF10DCIS cells treated with TGFβ alone or TGFβ and a combination of inhibitors for miR-22-3p, miR-30a-5p, miR-203a-3p and miR-222-3p. Actin was used as a loading control.

**Figure S6.** Correlation between ΔNp63 and microRNAs expression in cancer cell lines. **A-B**, Representative immunoblots of cutaneous squamous cell carcinoma (cuSCC) line SRB12 (A) and lung squamous cell carcinomas HCC95 (B) treated with TGFβ (10 ng/mL) or with TGFβ plus TGFBRI inhibitor, LY2157299 (1μM). Immunoblots were probed with the indicated antibodies. Actin was used as a loading control. **C**, Immunoblot analysis of ΔNp63 expression in lung squamous cell carcinoma lines, HCC95, H157, H226, H1703 and H2286. Actin was used as a loading control. **D-E**, qRT-PCR of miR-22-3p, miR-30a-5p, miR-203a-3p and miR-222-3p in SRB12 (D) and HCC95 (E) cells treated with or without TGFβ. Data are mean ± SD. n = 3. Asterisk indicates p <0.05. **F-H**, qRT-PCR of miR-22-3p (F), miR-30a-5p (G) and miR-222-3p (H) in HCC95, H157, H226, H1703 and H2286 cells. Data are mean ± SD. n = 3. Asterisk indicates p <0.05. **I**, Representative immunoblots of ΔNp63 in H226, H1703 and H2286 cells treated with or without LY2157299 (1μM). Immunoblots were probed with the indicated antibodies. Actin was used as a loading control. **J-L**, qRT-PCR of miR-22-3p, miR-30a-5p, miR-203a-3p and miR-222-3p in H226 (J), H1703 (K) and H2286 (L) cells treated with or without LY2157299 (1μM). Data are mean ± SD. n = 3. Asterisk indicates p <0.05.

**SUPPLEMENTAL TABLES:**

**Table S1.** List of pathways enriched in ∆Np63-induced and -repressed gene signatures.

**Table S2.** Differential expressed microRNAs in MCF10DCIS cells treated with TGFβ

**Table S3.** List of 64 TGFβ-induced microRNAs that are predicted to have binding sites to 3’UTR of p63 by miRWalk algorithm

**Table S4**. PCA scores for each patient in the four COCA molecular subtypes from TCGA.

**SUPPLEMENTARY MATERIALS AND METHODS**

## Cell lines and culture conditions

Human cutaneous squamous cell carcinoma (cuSCC) cell lines (COLO16, RDEB2, SRB12 and IC1) were provided by Dr. K. Y. Tsai at Moffitt Cancer Center, and were maintained in culture as previously reported (1). Human bladder cancer cell line (BLCA) 5637 was provided by Dr. N. Putluri at Baylor College of Medicine and cultured in RPMI 1640 media supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Human lung cancer cell lines (HCC95, H157, H226, H1703 and H2286) were obtained from the Moffitt Lung Center of Excellence and cultured in RPMI 1640 media supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Head and neck squamous cell carcinoma 22B was maintained as previously reported (2). All the cells lines were regularly authenticated via STR profiling by the Molecular Genomics Core at the H. Lee Moffitt Cancer Center.

## *In vivo* tail vein injection

Cells were trypsinized and washed with HBSS (without Mg2+ and Ca2+), filtered through 70 µM cell strainers and resuspended in HBSS (without Mg2+ and Ca2+). 5x105 cells were injected into nude mice via tail vein. The mice were fed with either control diet or dox diet (200 mg/ kg, Bio-Serv) one day before injection, and continued with the diet for 8 weeks. Then, the mice were euthanized, and the lungs were collected for further analysis.

## Immunohistochemistry

Tissues were fixed in 10% formalin and paraffin embedded tissue sections were prepared as described previously (3). Antigens were unmasked in 10 mM citrate buffer pH 6.0 at 95oC for 30 minutes. Sections were then incubated with anti-ΔNp63 (619002, Biolegend, 1:1000), Twist1 (sc-81417, Santa Cruz, 1:100), and Ki67 (ab15580, Abcam, 1:1000) antibody overnight at 4oC in a humid chamber followed by incubation with horseradish peroxidase conjugated-secondary antibody in the ImmPRESS kit (Vector laboratories) for 45 minutes at room temperature. Visualization was performed using the DAB kit (SK4100, Vector laboratories) and counterstained with hematoxylin (H-3401, Vector Laboratories). The slides were mounted using Histomount (008030, Life Technologies). Human breast cancer tissue microarrays (TMA) included BR480a and BR20837a (US Biomax). Quantification for ΔNp63-positive cells and signal intensity were done using Tissue Studio 4.3 software. Staining score was calculated using the following formula: Score = % positive cells x Average signal intensity. Samples with “low ΔNp63 level” have a score lower than average score of 16. Samples with “high ΔNp63 level” have a score higher than average score of 16.

## qRT-PCR

Total RNA was isolated from cell pellets using miRNeasy kit (Qiagen). Complementary DNA (cDNA) was synthesized from 5 µg total RNA using SuperScript First-Strand Synthesis System (Invitrogen). qRT-PCR reactions were performed with the 7500 Fast real-time PCR, TaqMan PCR master mix (Applied Biosystems), and TaqMan probes (Applied Biosystems) for human ΔNp63 (Hs00978339\_m1) and human RNA Pol2 (Hs00172187\_m1). Each sample was run in triplicate. *C*t values for each gene were calculated and normalized to *C*t values for RNA Pol2.

## miRNA TaqMan assays

Total RNA was isolated from cell pellets using miRNeasy kit (Qiagen). 500 ng of total RNA was used to synthesize cDNA with the Two-Step TaqMan MicroRNA Assay kit (Applied Biosystems) in accordance with the manufacturer’s protocol. qRT-PCR was performed with the 7500 Fast real-time PCR System, TaqMan PCR master mix (Applied Biosystems), and TaqMan probes (Applied Biosystems) for hsa-miR-22-3p (ID:000398), hsa-miR-30a-5p (ID:000417), hsa-miR-203a-3p (ID: 000507) and hsa-miR-222-3p (ID:002276). Each sample was run in triplicate. *C*t values for miRNAs were calculated and normalized to *C*t values for human RNU6B (ID: 001093,Applied Biosystems)*.*

## Western blot analysis

50µg of total protein were electrophoresed on 10% SDS-PAGE gel and transferred to nitrocellulose membrane as previously described (4,5). Blots were then probed with anti-ΔNp63 (619002, Biolegend, 1:500), E-cadherin (3195, Cell Signaling, 1:1000), Vimentin (ab92547, Abcam, 1:1000), Twist1 (sc-81417, Santa Cruz, 1:250), Smad2 (sc-101153, Santa Cruz, 1:500), Smad3 (9523S, Cell Signaling, 1:1000), phospho-Smad2 (ab53100, Abcam, 1:500), and phospho-Smad3 (9520S, Cell Signaling, 1:500) overnight at 4oC. Horseradish peroxidase conjugated-secondary antibodies against either murine or rabbit IgG (Jackson lab) were incubated with the blots for 1 hour at room temperature. Actin (A5060, Sigma, 1:10000) was used as a loading control and was incubated with secondary antibodies conjugated to IRDye® 680LT (1:10,000). Detection was performed using ECL Plus Kit (Amersham) and the Odyssey Fc imaging system (LiCOR).

## Chromatin immunoprecipitation (ChIP) assay

ChIP was performed with nuclear extracts from cell pellets as previously described (5,6). Briefly, cells were grown to 90% confluence. Cells were fixed with 1% formaldehyde and neutralized by glycine. Samples were sonicated on ice to obtain 500-1000bp DNA fragments. 2µg of Smad2/3 antibody (sc-133098 X, Santa Cruz) or control IgG (sc-2027, Santa Cruz) was added to each sample and incubated overnight at 4oC. Then, protein-DNA complex was precipitated using protein A agarose beads/Salmon sperm DNA (Millipore). qRT-PCR was performed with the following primer sequences specific for Smad2/3-binding sites at the promoters of the following human microRNAs:

miR-203a-3p:

CAGATCTGGTGGCTGTGTTCT (FW) and ATACCCTAGAGCCCCCTTCAG (Rev)

miR-30a-5p:

TTGGTTAGGGTTGCTCTTCCC (FW) and AGTCACTGTCAGCAGTTCCC (Rev)

miR-22-3p:

GAAGATTGGCCTCTGCGGTA (FW) and GCCGGCTGTCTGGTTTCTAT (Rev)

miR-222-3p:

GGCTCTTTTCTCACTTGCGG (FW) and GGTCTACAACATGACAGTCTGGA (Rev)

Primer sequences for non-specific binding sites were as follows:

miR-203a-3p:

CTTGTCTGAGGCTAGGGCTGT (FW) and CAGCAACCCAATGACACCCG (Rev)

miR-30a-5p:

CGGCCCATGTGGAAATGTCT (FW) and TAGAGCCCCCTTCAGCACTT (Rev)

miR-22-3p:

CCGTATGTTGTAGATGAGGGG (FW) and CAGATCTGGTGGCTGTGTTCT (Rev)

miR-222-3p:

TTCTTAACGGTGTGGGAGGC (FW) and AGAAGTGAACAAAAACTGCCAC (Rev).

## siRNA transfection

5x105 cells per 60 mm dish were transfected with 40 nM si∆Np63 (Sense: CAGCAGCAUUGAUCAAUCUUA, Antisense: UAAGAUUGAUCAAUGCUGCUG) using Lipofectamine RNAi Max (Invitrogen) according to manufacturer’s protocol. The cells were collected 48 hours after the transfection for further analysis. Transfected cells were analyzed by western blot to determine knockdown efficiency.

**Migration and invasion assay**

MCF10DCIS cells stably expressing mCherry were transfected with si∆Np63 for 48 hours, then treated with mitomycin C (4 μg/ml) for 2 hours followed by trypsinization to collect single cells. 0.3x104 cells were plated into the upper chambers of the Incucyte Clearview 96-well chemotaxis plates coated with growth factor reduced-matrigel (BD Bioscience, 200 μg/ml) in low serum culture media (1% horse serum). 200 µl of complete culture media with 5% horse serum and growth factors were added to the lower chambers. The plates were imaged every 6 hours using the Incucyte Zoom system (Essen Bioscience), and the number of migrating/invading cells were quantified using the Incucyte Zoom software.

## MicroRNA mimics and inhibitors transfection

5x105 cells per 60 mm dish were transfected with 40 nM microRNA inhibitors (ThermoFisher) or 6 nM microRNA mimics (ThermoFisher) using Lipofectamine RNAi Max (Invitrogen) according to manufacturer’s protocol. The cells were collected 48 hours after the transfection for further analysis. The microRNA inhibitors used to target microRNAs are as followed: miR-203a-3p (MH10152), miR-30a-5p (MH11062), miR-22-3p (MH10203), miR-222-3p (MH11376) and negative control (4464077) (ThermoFisher). The microRNA mimics purchased from ThermoFisher are miR-10b-5p (MC11108), miR-21-5p (MC10206), miR-22-3p (MC10203), miR-30a-5p (MC11062), miR-141-3p (MC10860), miR-181a-5p (MC10421), miR-200a-3p (MC10991), miR-203a-3p (MC10152), miR-222-3p (MC11376) and negative control mimics (4464058).

## Luciferase reporter assay

3’UTR of *TP63* gene was cloned into pLightSwitch backbone (pLightSwitch-3’UTR-TP63) (Activemotif). One day before transfection, 1x104 cells per well were plated onto white 96-well plates. Next day, 100 ng empty vector (EV) or pLightSwitch-3’UTR-TP63 vector was transfected together with 20 nM microRNA mimics into the cells using Lipofectamine 2000. 48 hours after the transfection, the plates were kept at -80oC overnight. On the day of the assay, the plates were thawed at RT for at least 45 minutes prior to assaying luciferase activity. Then, 100 µl of LightSwitch assay solution (Activemotif) was added to each well, incubate for 30 minutes at RT in the dark. Each well was read for 2 seconds in a plate luminometer (Promega).

## Site-directed mutagenesis

Mutated versions of the 3’UTR of *TP63* were generated using Q5 Site-directed mutagenesis kit (New England Biolabs) following manufacturer’s protocol. Primers with substitution mutations of the seed sequences of the microRNAs were designed using primer design software NEBaseChanger (New England Biolabs). The following primers were used to generate mutant versions of the 3’UTR of *TP63* for each microRNA tested:

CAACAAGCATcgtcgaTTGCAAACCCATTAAGGGG (miR-22-3p FW)

CAGAAGTTTACAGTGCTTATTAC (miR-22-3p Rev)

atgCTTTCTCTCTCTAAGGTTTACAATAG (miR-30a-5p FW)

ttgtAGCCTCTACATGCAGAGT (miR-30a-5p Rev)

aagTTCTAGTGATGATGGTTC (miR-203a-3p FW)

tacaCAGTAATATAAAATATACCAACAC (miR-203a-3p Rev)

CTTGCAGAACacatcgTGCCATGGCTAGGTAG (miR-222-3p FW)

CTATAGTTTTGAAGGCTTAAAG (miR-222-3p Rev)

## Isolation of RPF-positive cells in the lungs

MCF10DCIS cells stably expressing pLV-i-sh∆Np63 were infected with Firefly luciferase-T2A-RFP-Puro (Biosettia) to make stable cell line expressing RFP, then injected to nude mice via tail vein. The mice were fed with either control diet or dox diet one day before injection. 48 hours post-injection, the mice were euthanized, and the lungs were collected and dissociated as previously described (7,8). Cell pellets were then used for cell sorting to analyze population of RFP-positive cells.

## NanoString human microRNA analysis

Raw array data files (RCC) and miRNA panel file (RLF) were read usingnSolver 3.0 software (NanoString). Data Quality metrics was also generated by this software with the default parameters (Field of view (FOV) < 75, Binding density is between 0.05 and 2.25, Positive control linearity R2 > 0.95, 0.5fM positive control limit of detection < 2 STDEV). Comparison of normalization methods for *NanostringDiff* (9), housekeeping genes and *NanoStringNorm* (10) were made. Raw NanoString counts were normalized using *NanostringDiff* package. Normalized data were log2 transformed. *Limma* package (11) was used for gene differential analysis between two groups. Significant genes were selected as adjusted p value < 0.05 and fold change greater than 2. Heatmaps of the significant genes were generated by *gplots* package of bioconductor.

**ChIP-seq analysis**

2x106 MCF10DCIS-i-sh∆Np63 cells mixed 1:1 ratio with growth factor reduced matrigel (BD Biosciences) were injected into the left and right mammary fat pads of nude mice fed on either control diet or doxycycline diet (200 mg/ kg, Bio-Serv) for 5 weeks. Then, tumors were collected and fixed with 1% formaldehyde for 15 min and quenched with 0.125 M glycine. Chromatin was isolated by the addition of lysis buffer, followed by disruption with a Dounce homogenizer. Lysates were sonicated and the DNA sheared to an average length of 300-500 bp. Genomic DNA (Input) was prepared by treating aliquots of chromatin with RNase, proteinase K and heat for de-crosslinking, followed by ethanol precipitation. An aliquot of chromatin (30 ug) was precleared with protein A (or protein G for ∆Np63) agarose beads (Invitrogen). Genomic DNA regions of interest were isolated using 4 μg of antibody against ∆Np63 or RNA Polymerase II (Pol2). Complexes were washed, eluted from the beads with SDS buffer, and subjected to RNase and proteinase K treatment. Crosslinks were reversed by incubation overnight at 65oC, and ChIP DNA was purified by phenol-chloroform extraction and ethanol precipitation.

Illumina sequencing libraries were prepared from the ChIP-ed and Input DNAs by the standard consecutive enzymatic steps of end-polishing, dA-addition, and adaptor ligation. An automated system (Apollo 342, Wafergen Biosystems/Takara) was used. After a final PCR amplification step, the resulting DNA libraries were quantified and sequenced on Illumina’s NextSeq 500 (75 nt reads, single end). Reads were aligned to the human genome (hg38) using the BWA algorithm (default settings). Duplicate reads were removed and only uniquely mapped reads (mapping quality >= 25) were used for further analysis. Alignments were extended in silico at their 3’-ends to a length of 200 bp, which is the average genomic fragment length in the size-selected library, and assigned to 32-nt bins along the genome. The resulting histograms (genomic “signal maps”) were stored in bigWig files. Peak locations were determined using the MACS algorithm (v2.1.0) with a cutoff of p-value = 1e-7. (In some analyses, RNA Pol2-enriched regions were identified using the SICER algorithm at a cutoff of FDR 1E-10 and a max gap parameter of 600 bp). Peaks that were on the ENCODE blacklist of known false ChIP-Seq peaks were removed.

The ChIP-seq data was deposited to NCBI Gene Expression Omnibus (GEO) repository: GSE144995.

**Pathway analysis**

ΔNp63-repressed genes were selected based on criteria that the fold enrichment of the ΔNp63 peaks within 5,000 bp of the low-profile peak regions of these genes in the ΔNp63-knocked down tumors is no more than half of that in the control tumors, and the fold enrichment of the Pol2 peaks within 5,000 bp of the high-profile peak regions of these genes in the ΔNp63-knocked down tumors is at least two times of that in the control tumors. This gene list is called up\_Pol2\_dn\_ΔNp63. Similarly, we also selected ΔNp63-induced genes that have both of the fold enrichment of the ΔNp63 peaks and Pol2 peaks in the ΔNp63-knocked down tumors is no more than half of that in the control tumors. This gene list is called dn\_Pol2\_dn\_ΔNp63. Then, the selected gene lists were submitted to MetaCore Pathway Analysis Software (<https://portal.genego.com/>). In MetaCore, FDR is controlled by Benjamini-Hochberg Procedure. Only top 50 significant pathways were selected for further analysis.

**PCA analysis**

The TGFβ signature used was from Gordian 2019 (12). The ΔNp63 signature used was from Abbas 2018 (13). The direction of the genes was assigned based on Chakravarti 2014 (14). TCGA data was obtained from the PanCanAtlas [<http://api.gdc.cancer.gov/data/3586c0da-64d0-4b74-a449-5ff4d9136611>]. TCGA data was log2 transformed prior to further analysis. Mouse signature gene symbols were mapped to TCGA human gene symbols using homolog tables from MGI [<http://www.informatics.jax.org/homology.shtml>].

PCA analysis was performed using Evince (Prediktera) [<https://prediktera.com/software/>]. Zero abundances were treated as missing data, rather than left as zeroes or imputed. PCA was performed using the TGFβ and ΔNp63 signatures for each of the C1-C4 cohorts separately (8 PCA models in total). The signs for each first principle component were flipped as appropriate, so that signature-high samples were positive and signature-low samples were negative (signature direction was determined by coloring the PCA loadings by the signs from the original signatures). C2 (r = -0.593, P = 5.55e-20) and C3 (r = -0.612, P = 23.64e-70) exhibited highly significant negative correlation. C1 (r = 0.222, P = 0.0004) and C4 (r = -0.151, P = 0.0842) were poorly correlated.

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