

## **SUPPLEMENTARY INFORMATION**

### **Malfunction of Airway Basal Stem Cells plays a crucial role in Pathophysiology of Tracheobronchopathia Osteoplastica**

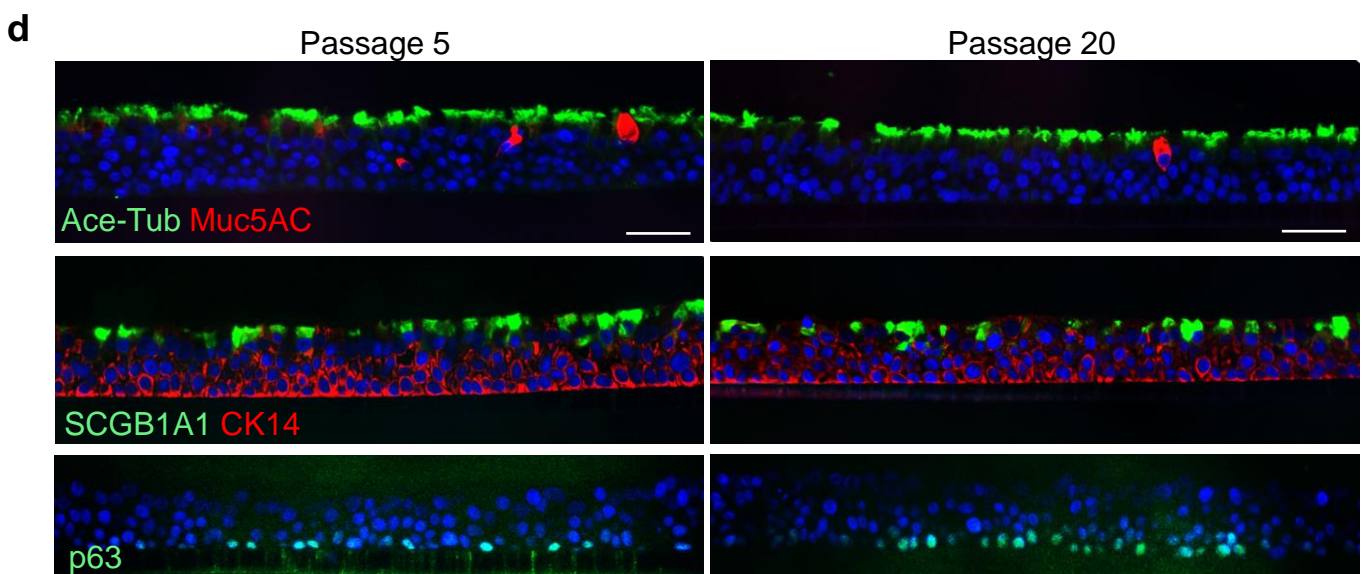
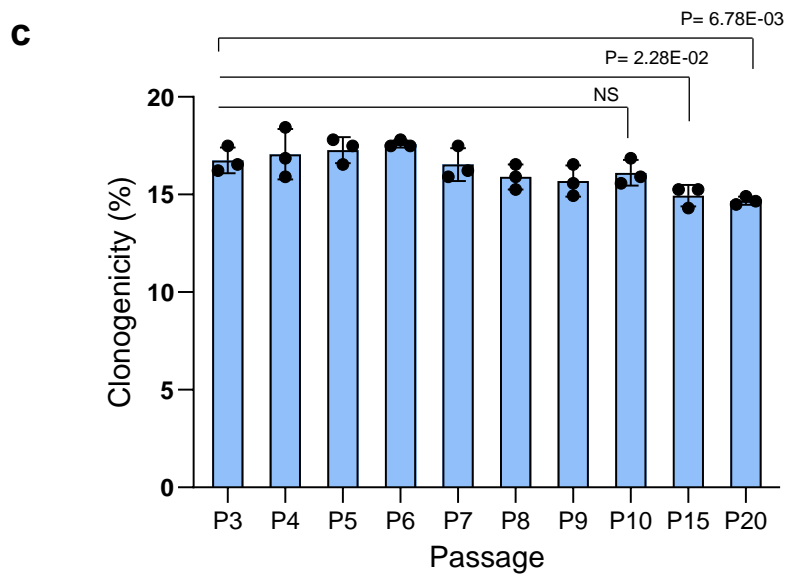
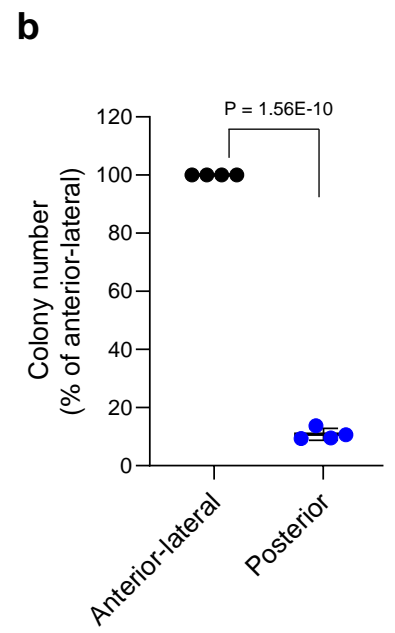
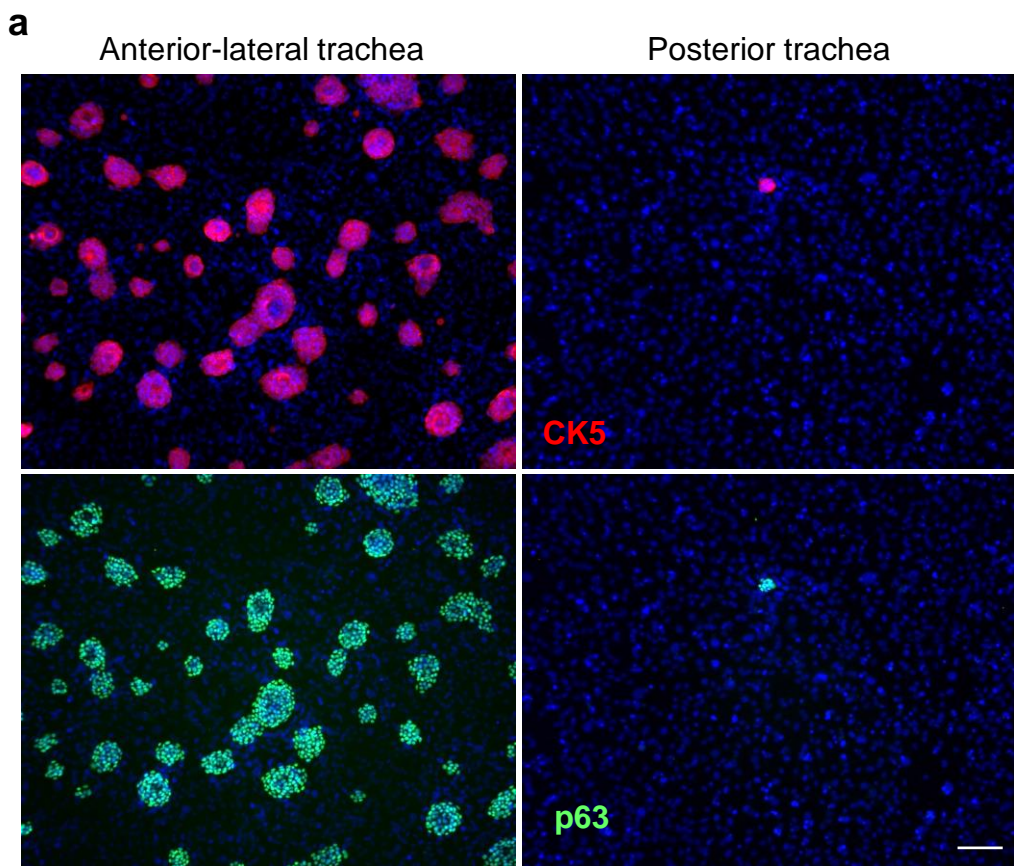
Yue Hong\*, Shan Shan, Ye Gu, Haidong Huang, Quncheng Zhang, Yang Han, Yongpin Dong, Zeyu Liu, Moli Huang, Tao Ren\*

\* Corresponding authors

#### **Content including:**

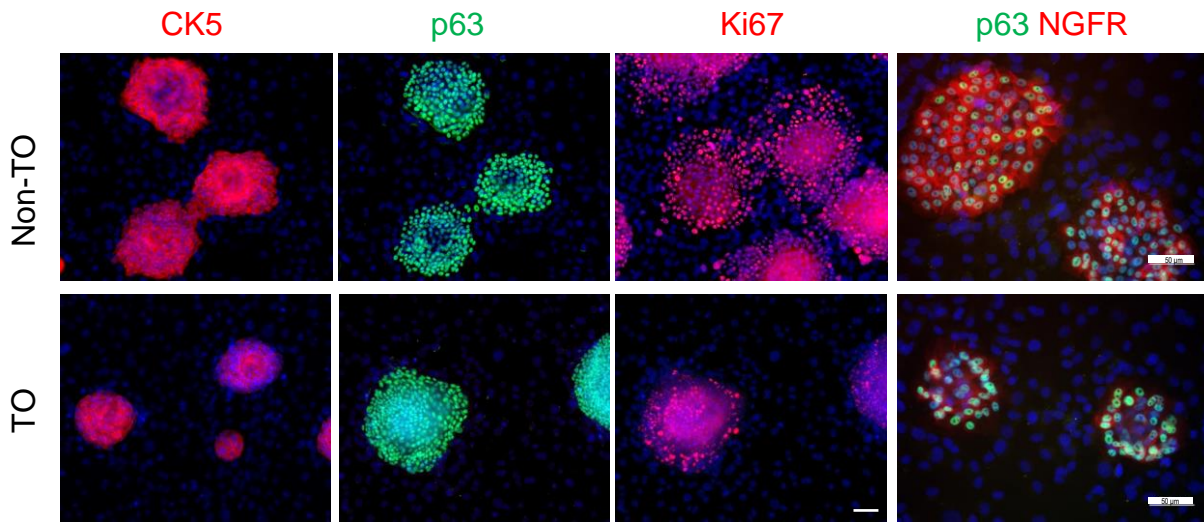
SUPPLEMENTARY FIGURES AND LEGENDS

SUPPLEMENTARY TABLES

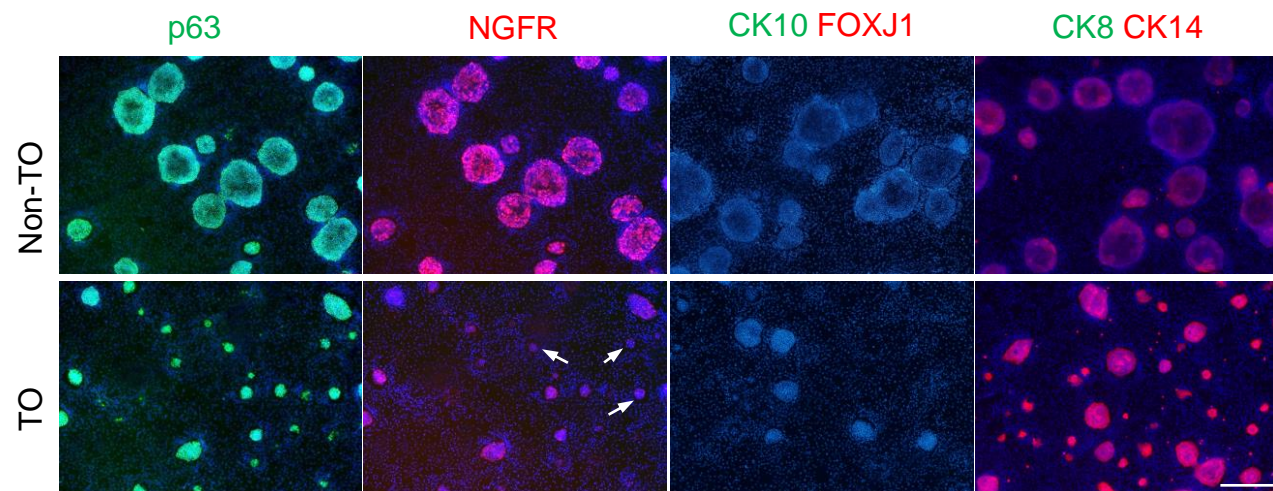
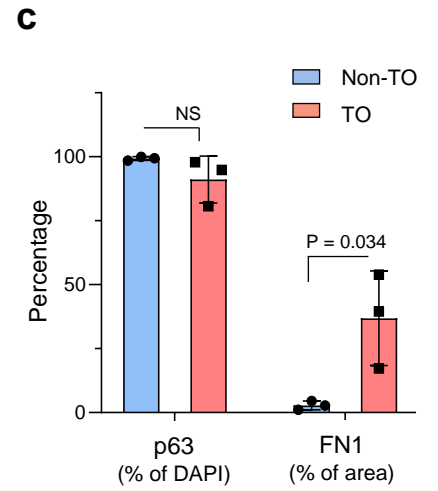
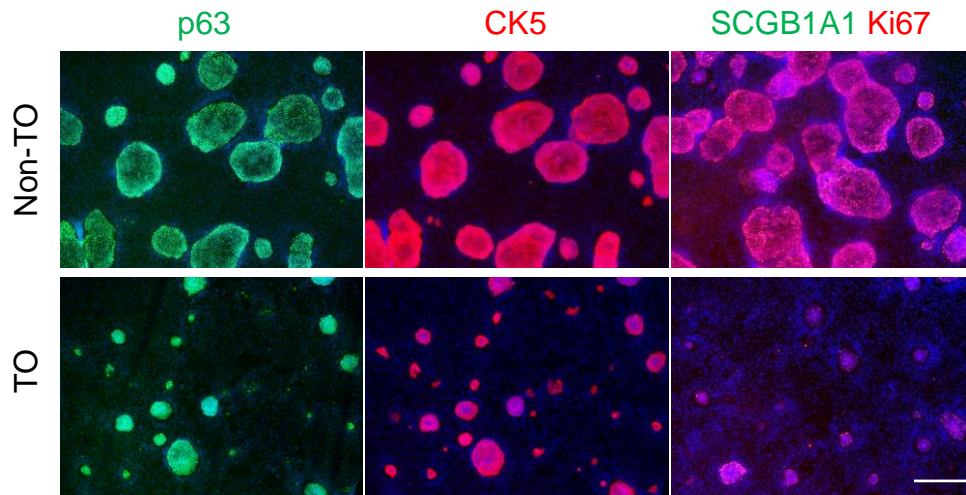


**Supplementary Figure 1. Spatial distribution of proliferative basal stem cells in human tracheas, and stability of cell maintenance in vitro.** (a) Representative images of primary cultures of tracheal stem cells derived from anterior-lateral and posterior portions of normal donors, respectively. Cell character was confirmed by immunofluorescent staining with basal cell markers, CK5 and p63. Scale bar, 200 $\mu$ m. (b) Scatter plot depicting clone numbers counted from sub-regional cultures of 4 independent biological samples, as percentage values of anterior-lateral counterparts. Bars represent mean  $\pm$  SD, and p value is indicated to show statistical significance. (c) Self-renewal ability of isolated normal basal stem cells was assessed by clonogenic assay, shown as percentage of plated cells that formed typical clones on Day 4-5 post-seeding from passage 3 to 20 (n=3 experimental repeats/passage). Results are represented as mean  $\pm$  SD, and p values are indicated to show statistical significance (<sup>NS</sup> p > 0.05). (d) Representative images showing differentiation ability of passaged cells examined by immunofluorescent staining of ALI sections (n=3 experimental repeats) with functional cell markers, acetylated tubulin (ciliated), Muc5AC (goblet), SCGB1A1 (club) and CK14, p63 (basal). Scale bar, 40 $\mu$ m. (b, c) two-tailed Student's t-tests. Source data are provided as a Source Data file.

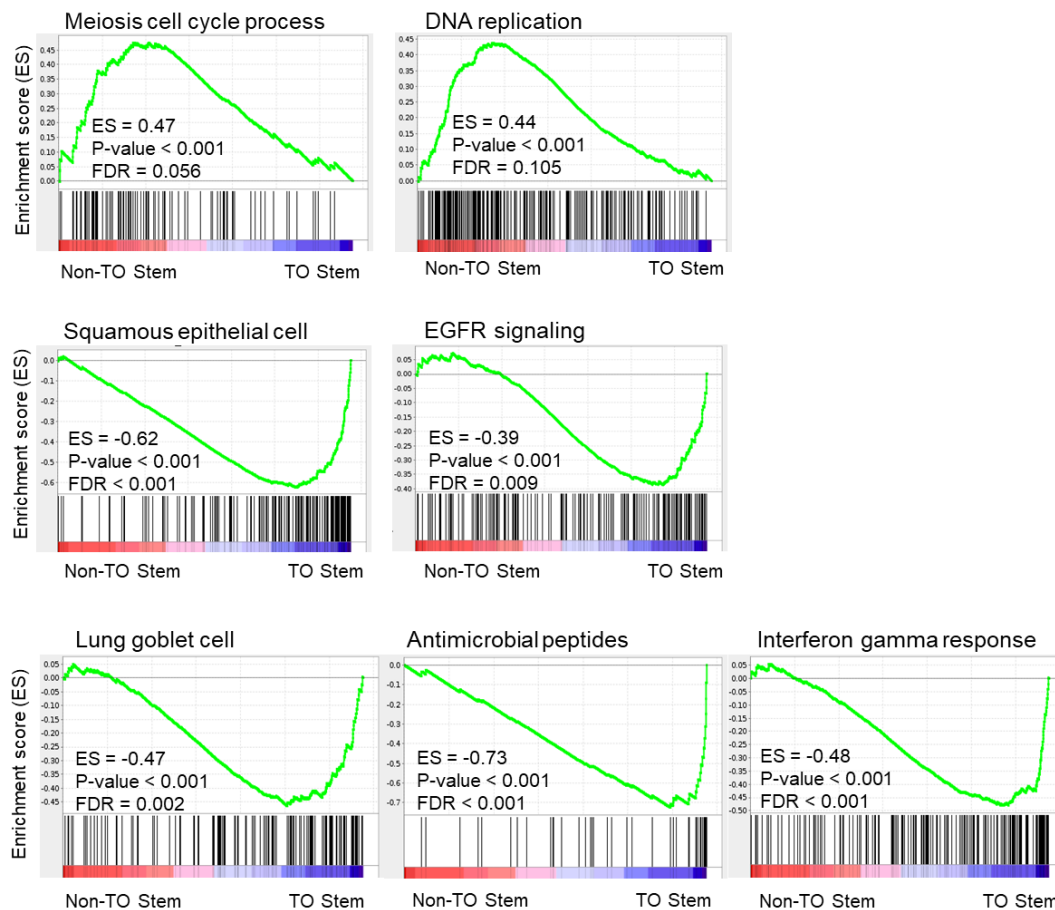
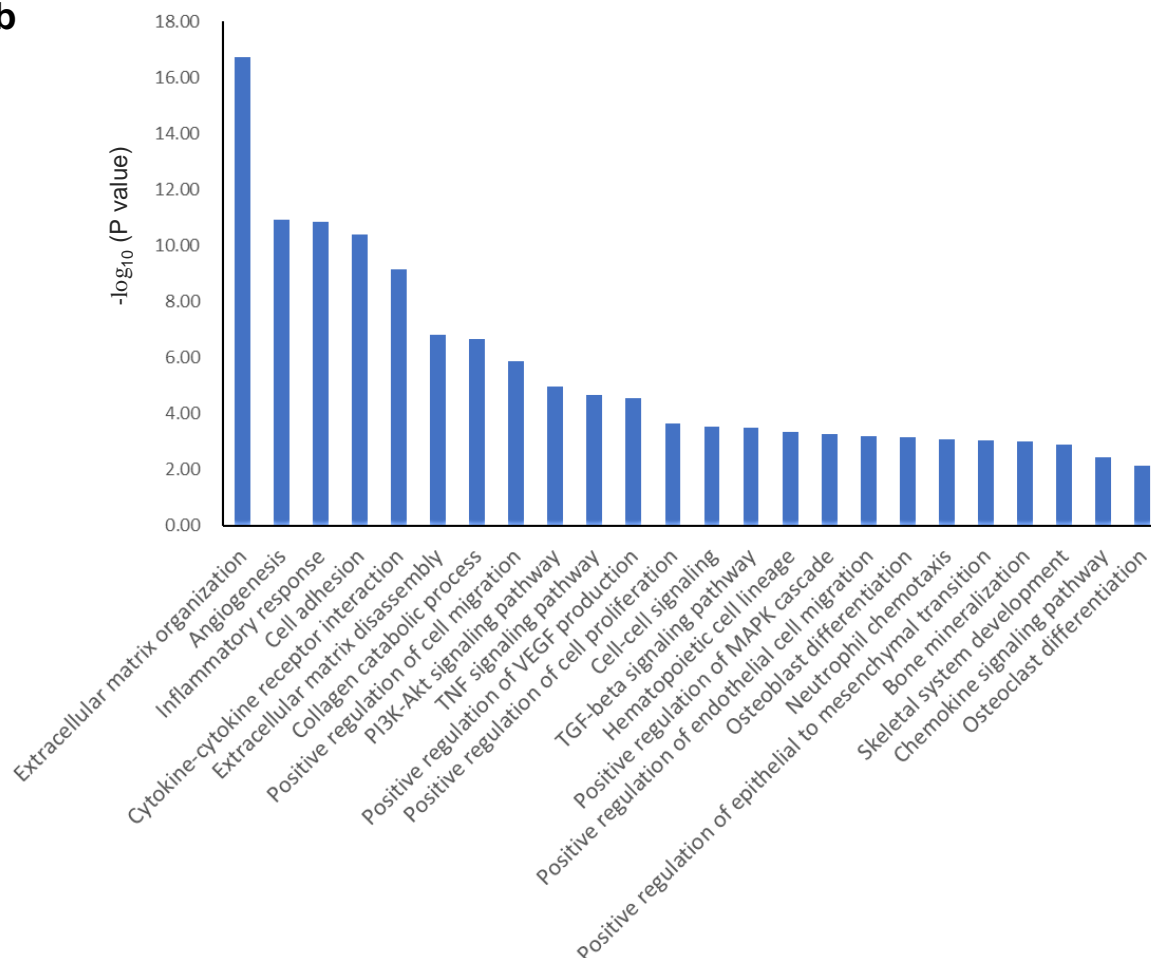
**a** P4 clones



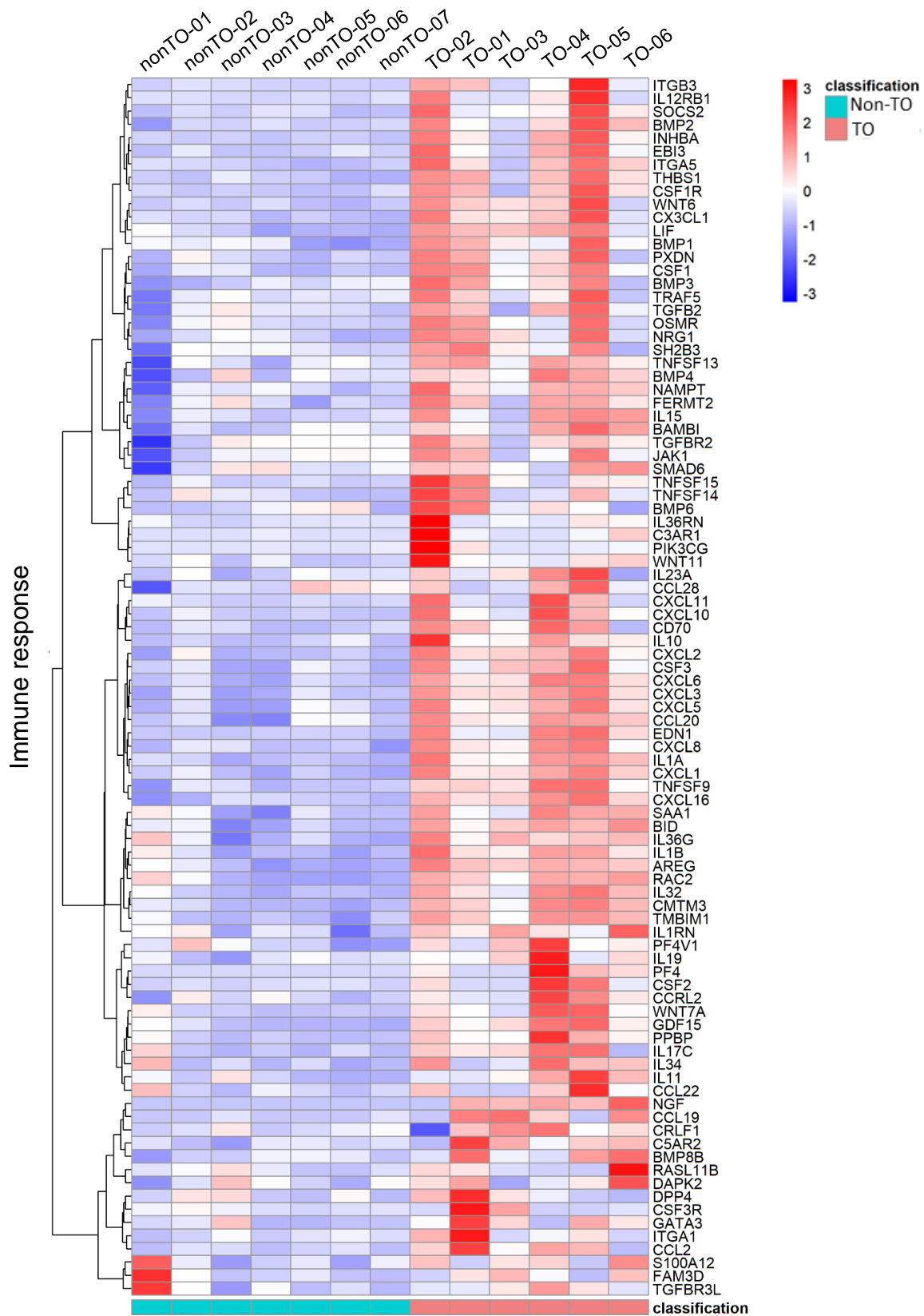
**b** P7 clones



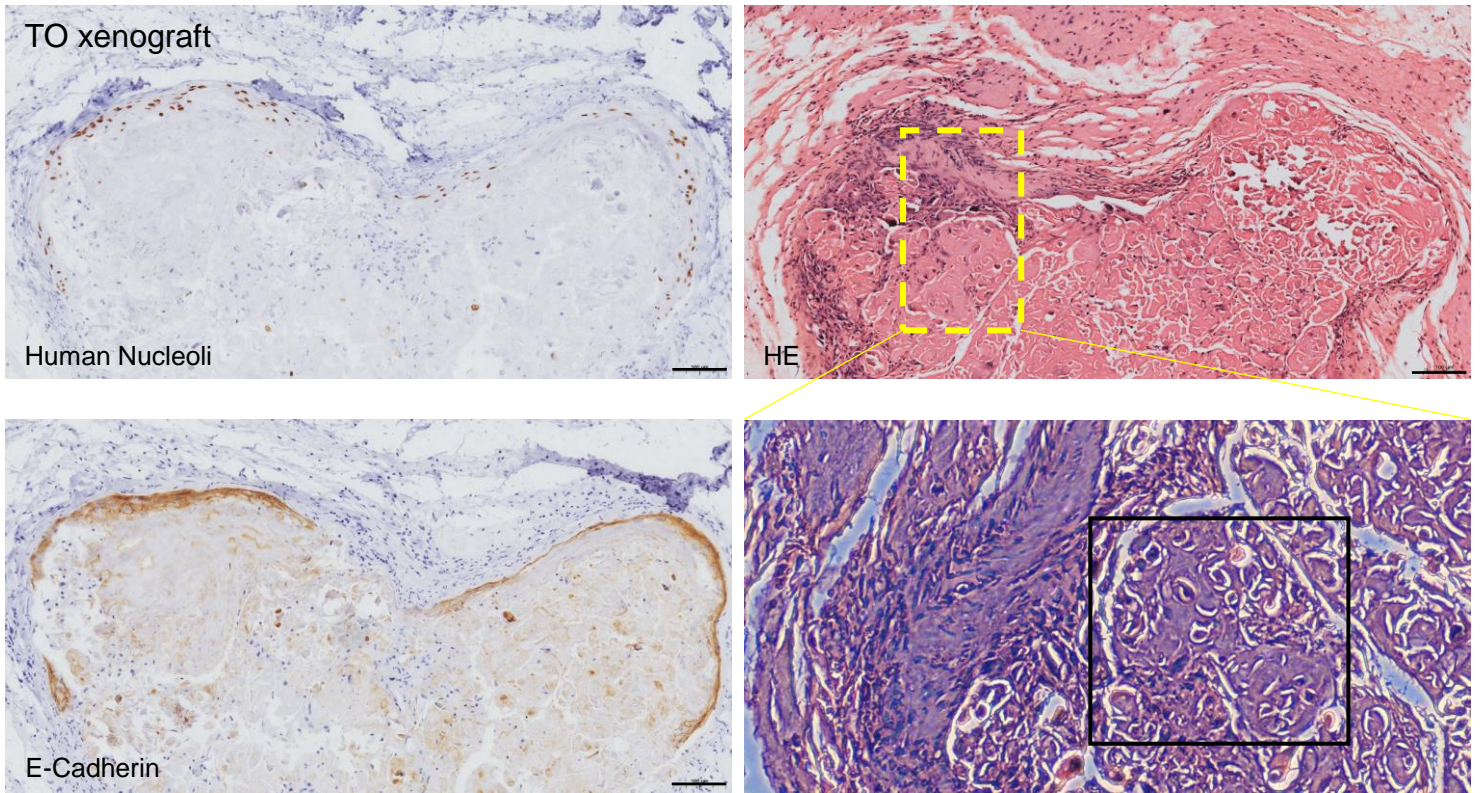
**Supplementary Figure 2. Characterization of isolated TBBCs derived from non-TO controls and TO patients.** (a) Representative immunofluorescent images showing the expression of key basal cell markers CK5, p63, NGFR and Ki67 on clones from P4 culture. Scale bar, 50 $\mu$ m. (b) Representative immunofluorescent images of clones from P7 culture stained with a panel of antibodies against basal cell markers (p63, CK5, NGFR and CK14), proliferation indicator (Ki67), differentiating marker (CK8) and cell-type specific markers (SCGB1A1, CK10, FOXJ1). Scale bar, 500 $\mu$ m. Cells with strong p63 immunoreactivity but almost no NGFR labeling are highlighted by white arrows as examples. (c) Quantification of immunofluorescence results from p63 and FN1 labelled TBBC monolayers using Fiji. For p63, results are presented as mean of percentage of positive cells in total DAPI nuclei via particle analysis; whilst for FN1, due to its diffuse pattern and deposition in extracellular space, results are presented as mean of area fraction. Error bars of  $\pm$ SD and p-values are indicated in the graph (<sup>NS</sup> p > 0.05). (a, b, c) n=3 biologically independent experiments. (c) two-tailed Student's t-tests. Source data are provided as a Source Data file.

**a****b**

**Supplementary Figure 3. Enrichment analyses of RNA-Seq datasets generated from TBBC clones and corresponding ALI differentiated cells. (a)** Gene set enrichment analysis (GSEA) of basal cell RNA-Seq data. **(b)** GO and KEGG enrichment analysis of differentially expressing genes with further increment in severe TO cases (TO-02, 05, 06) compared to moderate cases (TO-01, -03, 04) according to ALI RNA-Seq data.

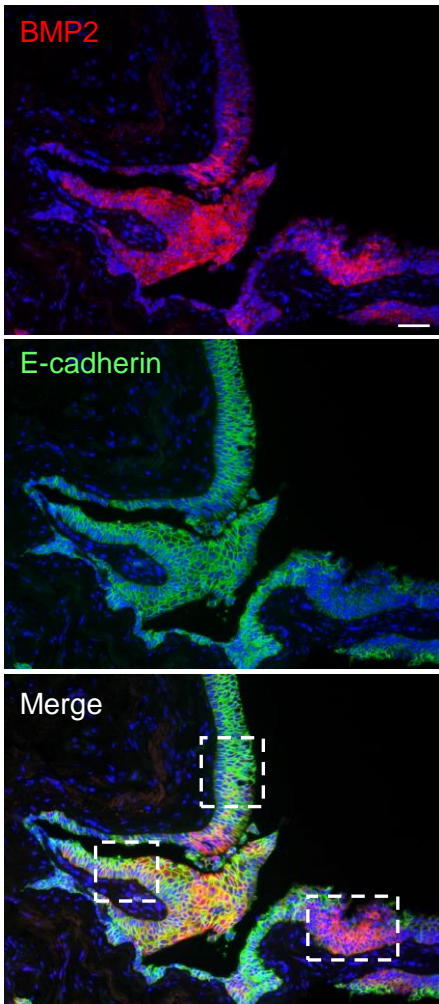


**Supplementary Figure 4. Comparative heatmap showing distinct expression profiles between non-TO and TO groups.** Differentially expressing genes involved in cytokine-cytokine receptor binding and chemotaxis events were selected to show in this heatmap across all non-TO controls and TO cases.

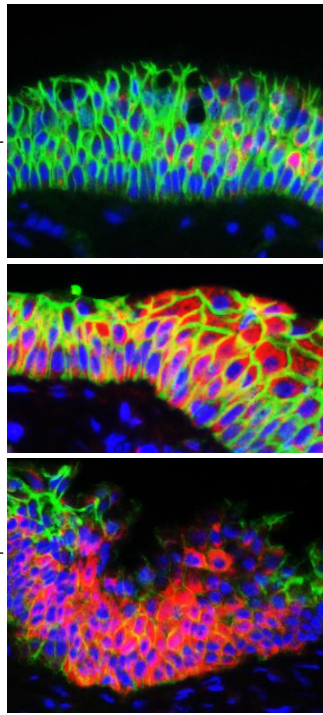
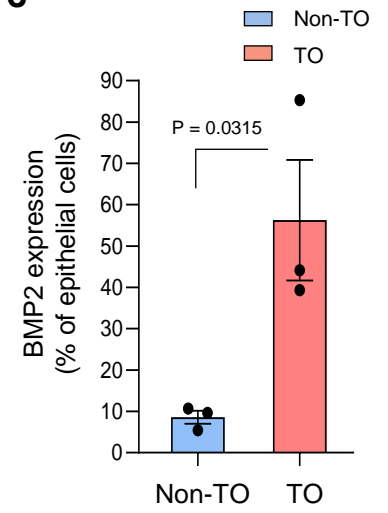
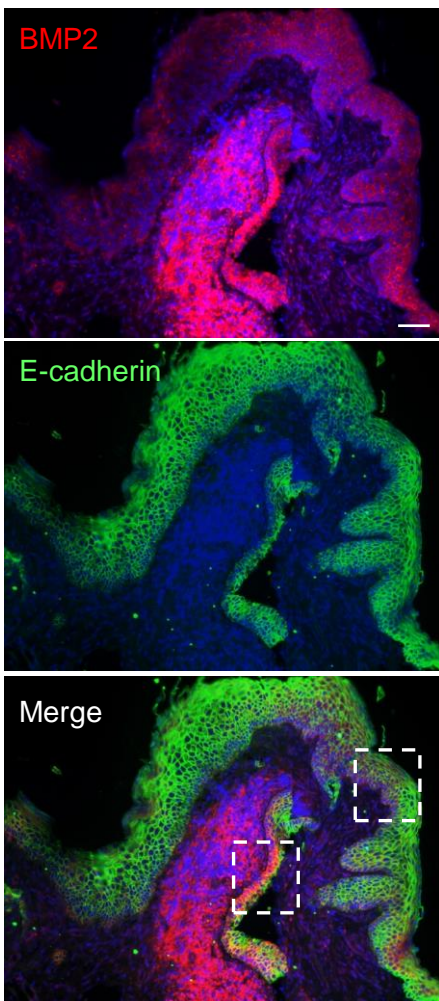


**Supplementary Figure 5. Histological sections showing a representative xenograft sample derived from TO-TBBCs transplantation, which contains a suspectable cartilaginous islet. HE, immunohistochemical staining against anti-human nucleoli and E-Cadherin were performed on serial sections, to identify the transplanted epithelial portion. Yellow dotted box indicates a field that has been magnified into a separate image, and the black box is highlighting a cartilaginous-like islet. n=1 biological sample. Scale bar, 100 $\mu$ m.**

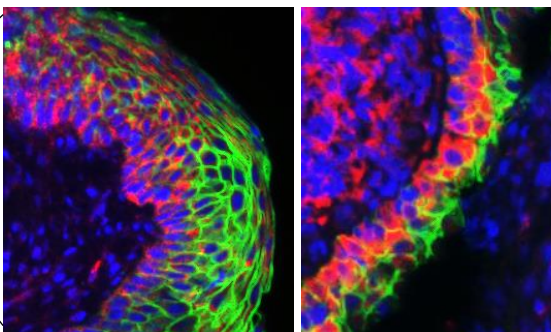


**a**

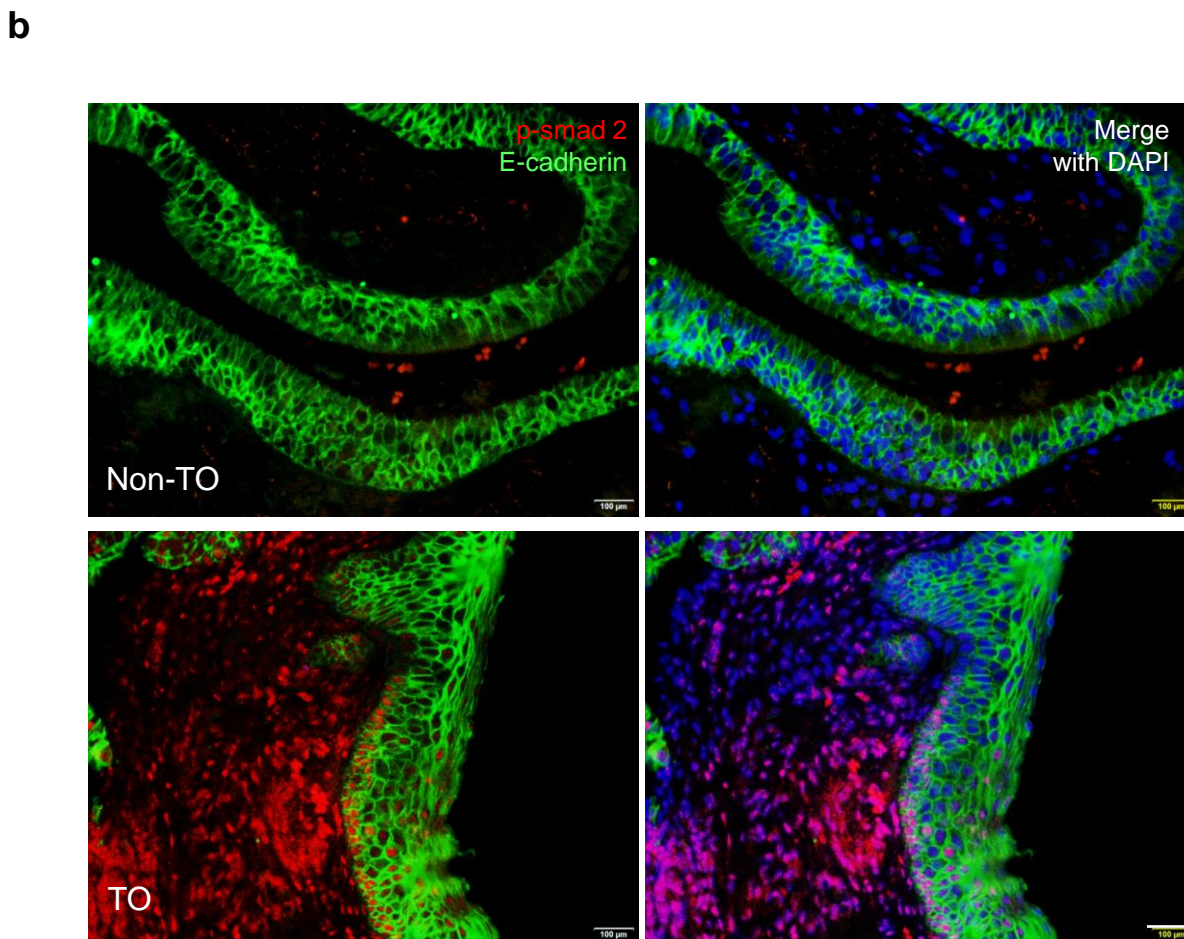
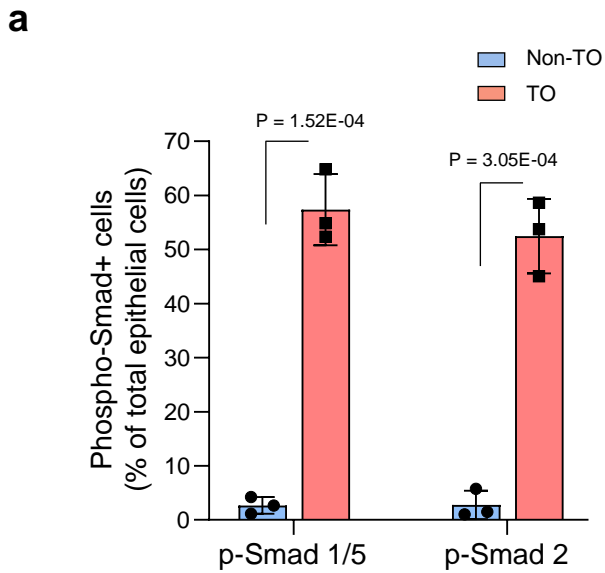
Magnified merge

**c****b**

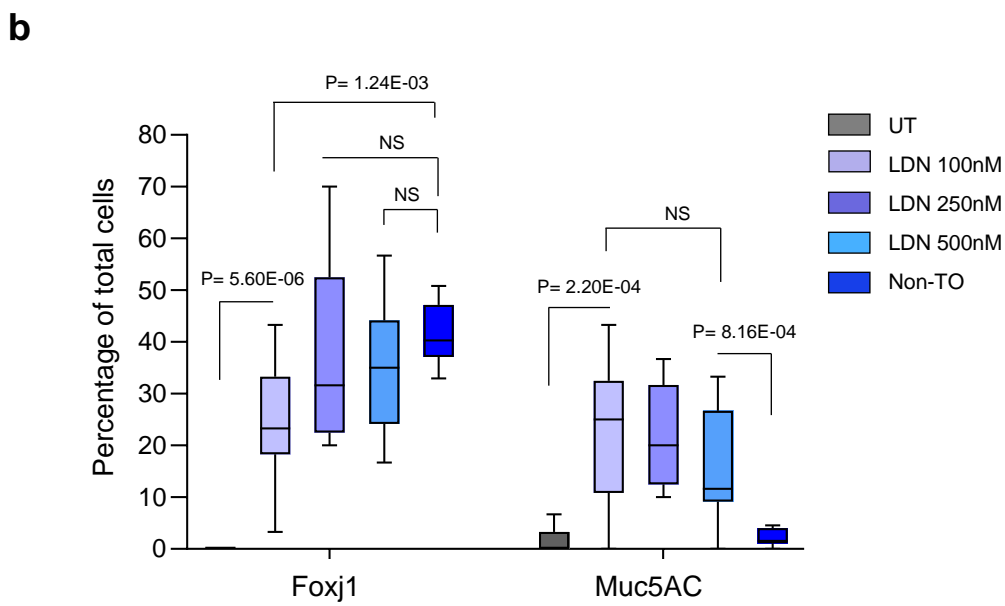
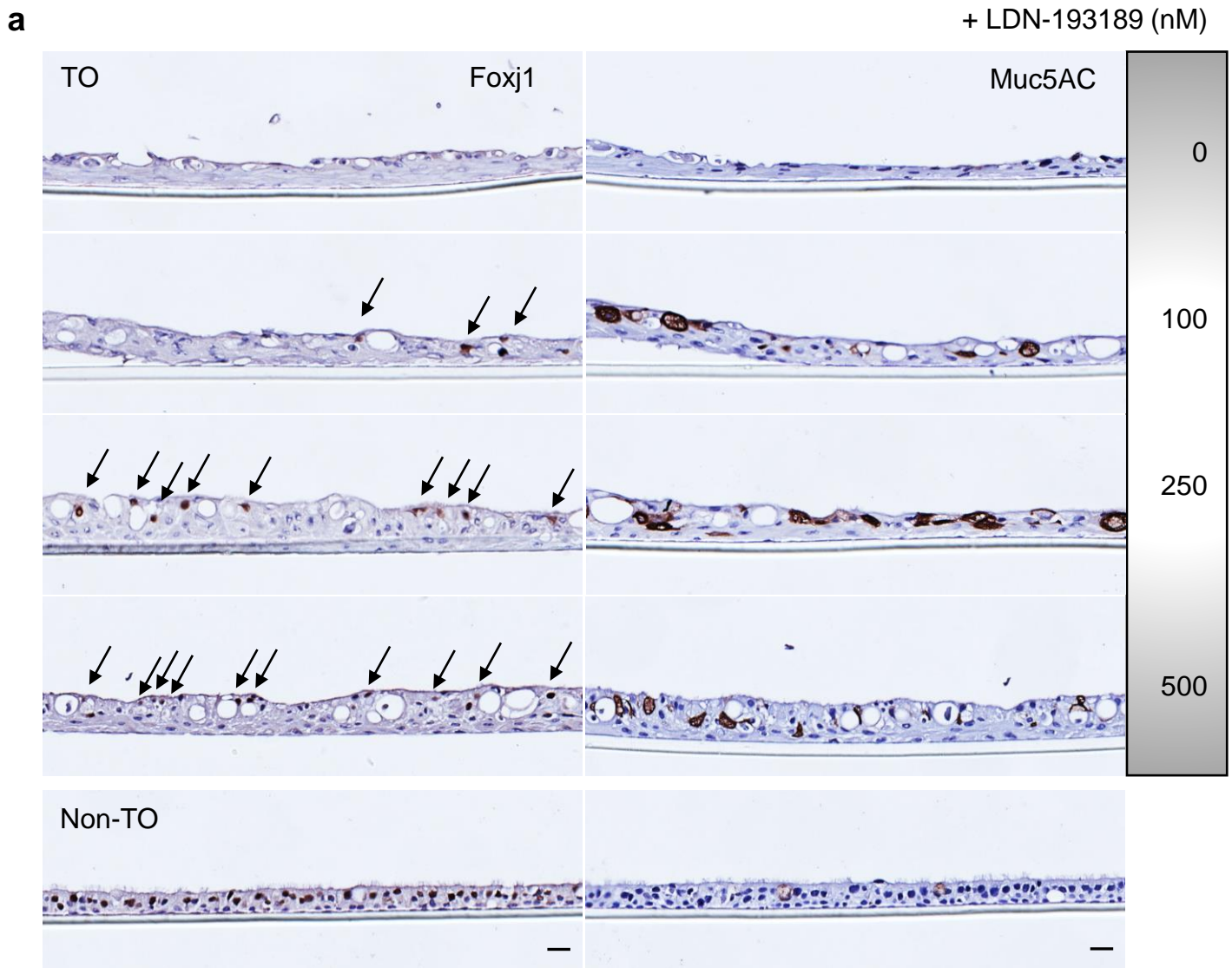
Magnified merge



**Supplementary Figure 6. Detection of BMP2 on patient-derived biopsies. (a-b)** Immunofluorescent images showing BMP2 tissue expression and distribution on paraffin sections from two TO cases. E-Cadherin was stained to locate epithelial compartment in biopsies. Magnified areas were highlighted in white dotted boxes and displayed in separate images. Scale bar, 100 $\mu$ m. **(c)** Quantification of BMP2 expression on tracheobronchial biopsy sections based on immunofluorescence results (non-TO n=3, TO n=3 biologically independent experiments). Results were shown as mean  $\pm$  SD and statistical analysis was performed using two-tailed Student's t-test. P value is indicated to show statistical significance. Source data are provided as a Source Data file.

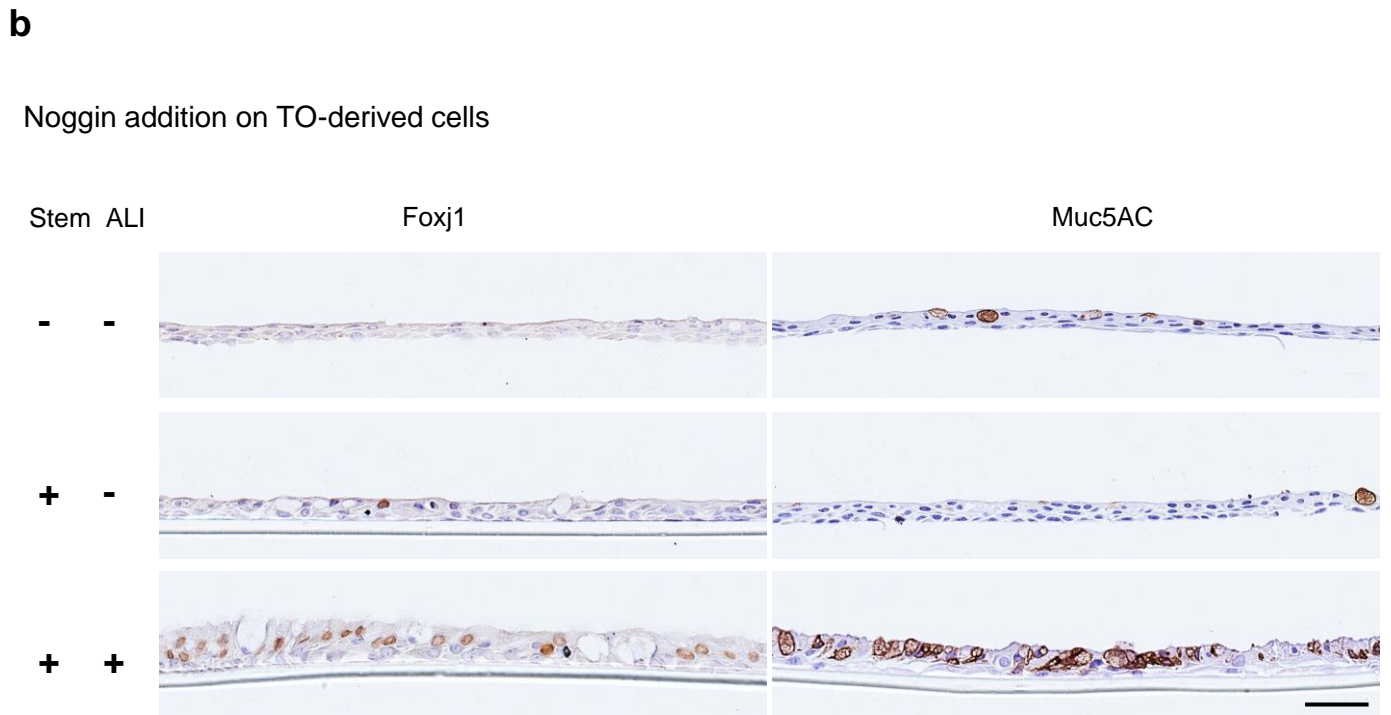
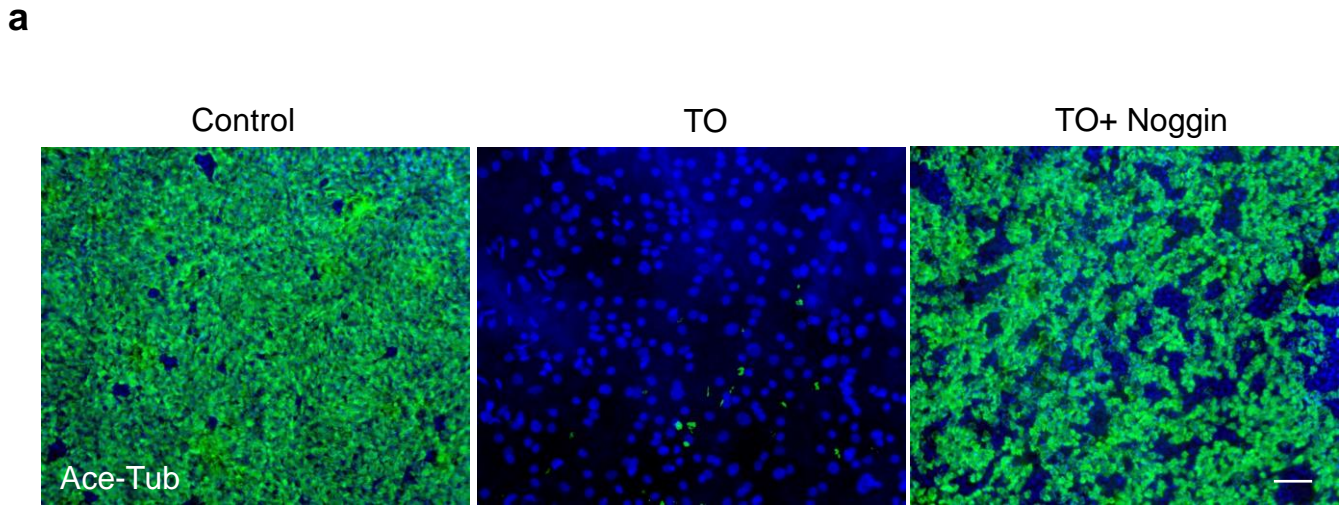


**Supplementary Figure 7. Detection of phosphorylated SMAD on patient-derived biopsies. (a)** Quantification of p-Smad2 and p-Smad1/5 in tissue epithelia based on immunofluorescence results (non-TO n=3, TO n=3 biologically independent experiments). Results were expressed as mean  $\pm$  SD, and p values are indicated to show statistical significance based on two-tailed Student's t-tests. **(b)** Representative co-staining images showing p-Smad2 and E-Cadherin expression on patient biopsies that were proceeded with quantification analysis in (a). Scale bar, 50 $\mu$ m. Source data are provided as a Source Data file.

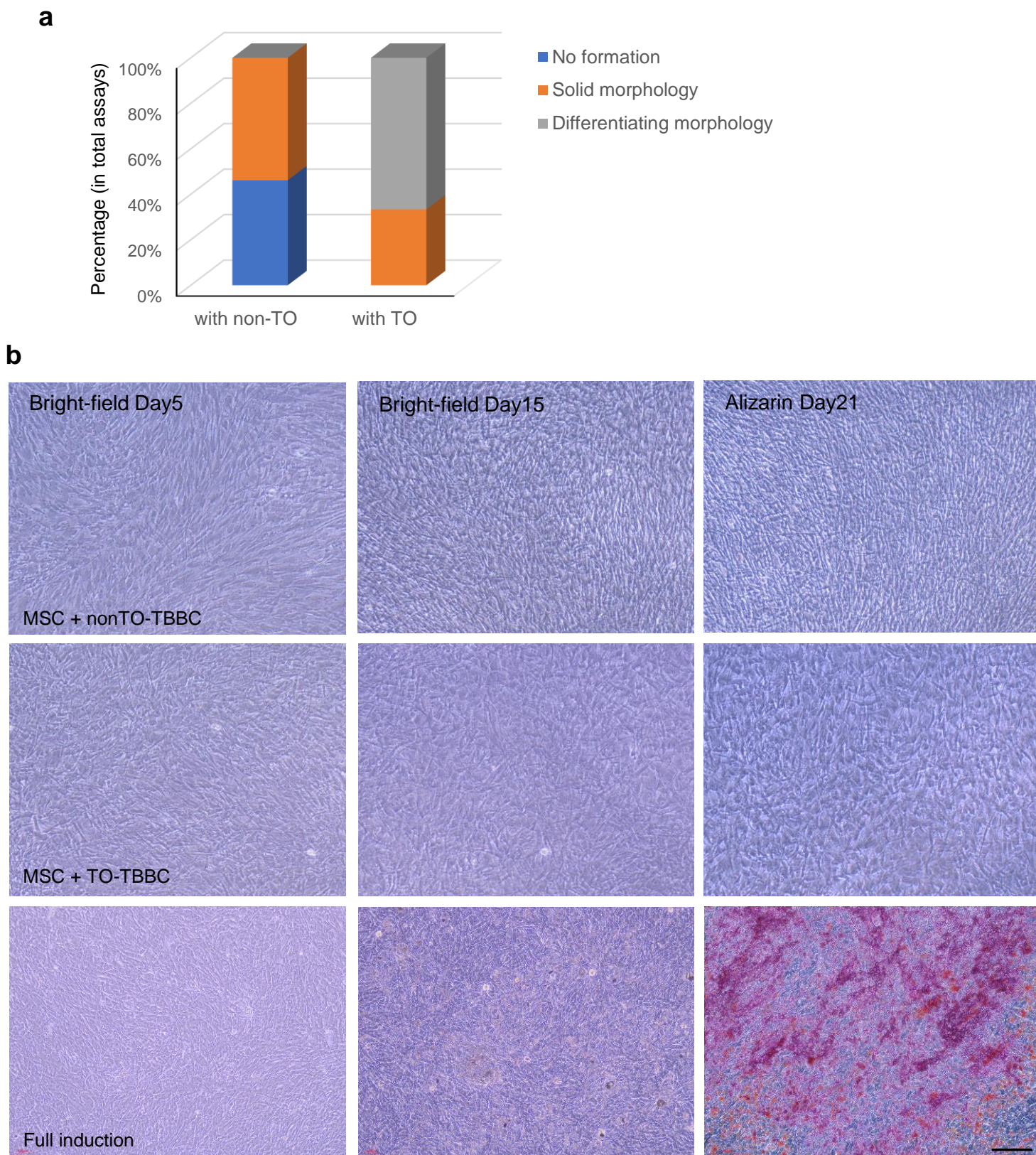


**Supplementary Figure 8. Effect of BMP inhibitor LDN-193189 on TO-basal cell differentiation.**

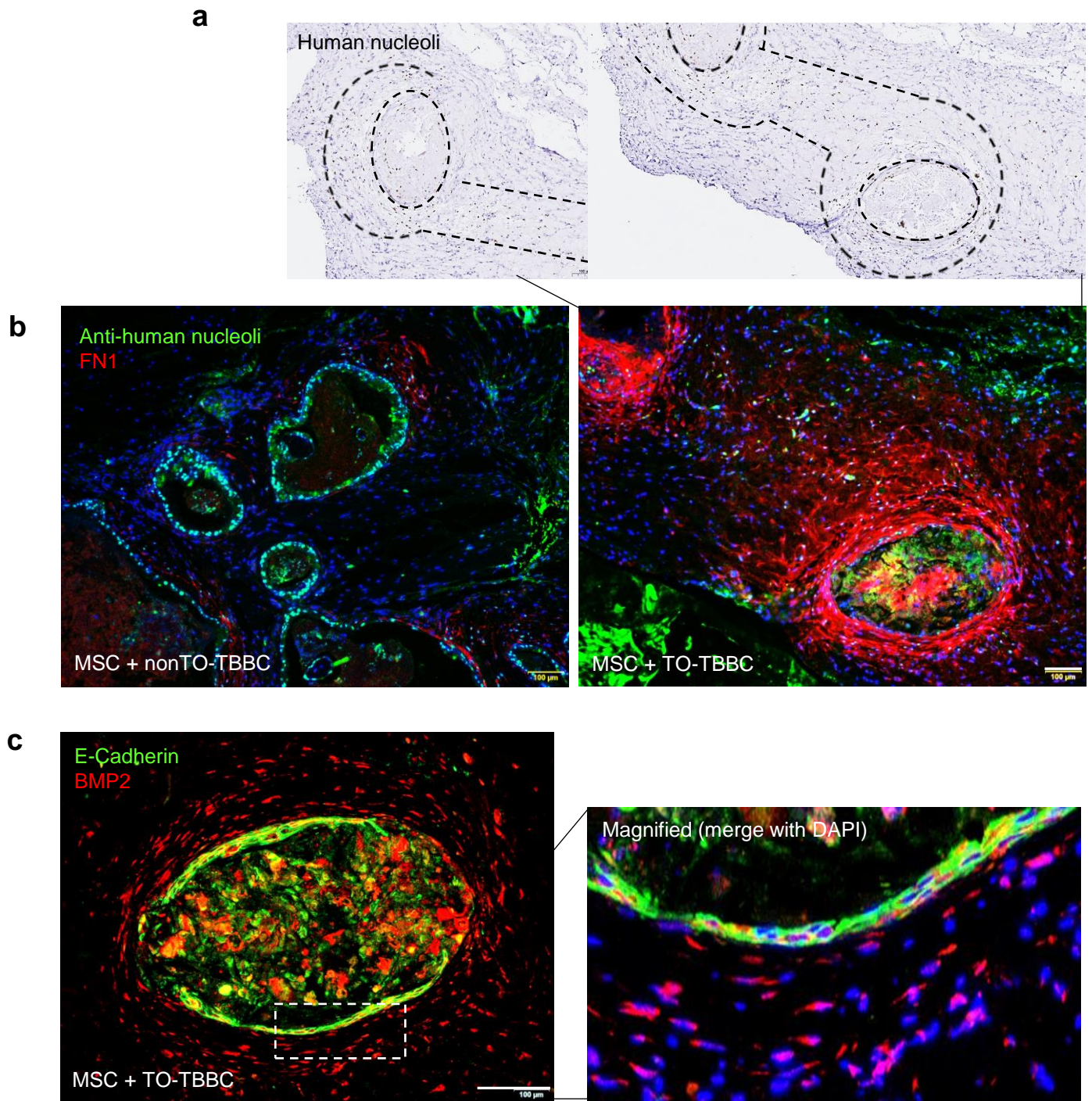
**(a)** TO-derived basal cells were treated with LDN-193189 at concentrations ranging between 100-500nM since Day 0 of ALI differentiation. Day20 structures were fixed to proceed with paraffin sectioning and immunohistochemical staining for mucociliary markers Foxj1 and Muc5AC. ALIs of TO-derived and non-TO basal cells without inhibitor treatment were examined as controls. Foxj1+ cells were highlighted by black arrows on TO-ALI sections. Scale bar, 20 $\mu$ m. **(b)** Quantification of ciliated (Foxj1+) and goblet (Muc5AC+) cell frequencies on TO basal cell-derived ALIs. UT (untreated TO-ALI) and non-TO basal cell-derived ALI were examined as controls. Ten sections from 3 independent experiments were counted per group. Boxes denote 25th and 75th percentile, lines denote median and whiskers min-max. P values are indicated to show statistical significance (<sup>NS</sup> p > 0.05) based on two-tailed Student's t-tests. Source data are provided as a Source Data file.



**Supplementary Figure 9. Effect of BMP antagonist Noggin on TO-basal cell differentiation. (a)** Representative ALI top-view images showing mucociliary differentiation of TO-derived basal cells under Noggin (200ng/ml) treatment since Day 0. TO-ALI without Noggin treatment and non-TO control ALI were examined in parallel. Day 20 structures were fixed to proceed with immunofluorescent staining (n=3 biologically independent experiments). Scale bar, 50 $\mu$ m. **(b)** An immunohistochemical comparison of Noggin on TO-TBBCs throughout ALI differentiation and Noggin withdrawal (n=2 biologically independent experiments). Differentiation efficiency was examined by Foxj1 and Muc5AC staining. Scale bar, 50 $\mu$ m.



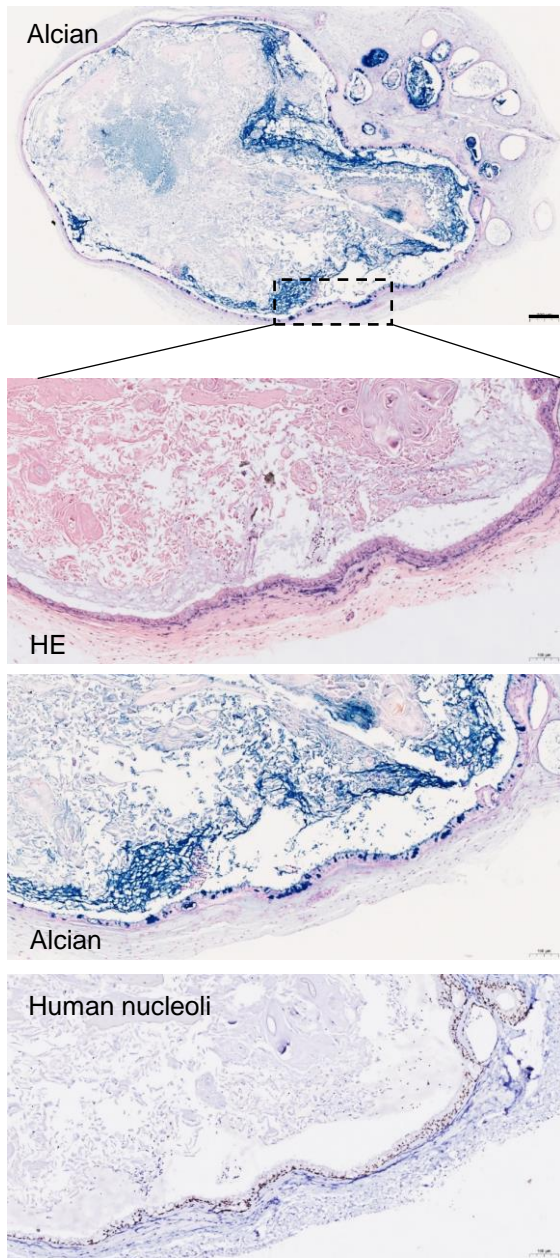
**Supplementary Figure 10. TBBC-MSc in vitro co-culture assays.** (a) A quantitative summary of MSC spheroid formation and differentiation based on observations from chondrogenic-lineage co-culture assays. Y-axis, percentage of total MSC pellets set for co-culture (non-TO n=13, TO n=7). Results were reached from two independent experiments involving a use of 3 non-TO cases and 2 TO-severe cases in examination. (b) A comparison of MSC osteogenic differentiation under co-culture conditions with non-TO controls and with TO-TBBCs derived ALI epithelia. MSCs undergone standard differentiation via full induction was examined in parallel. Calcium deposit was examined by Alizarin Red S Staining. Scale bar, 200 $\mu$ m. Independent experiments n=2 were performed for examination. Source data are provided as a Source Data file.



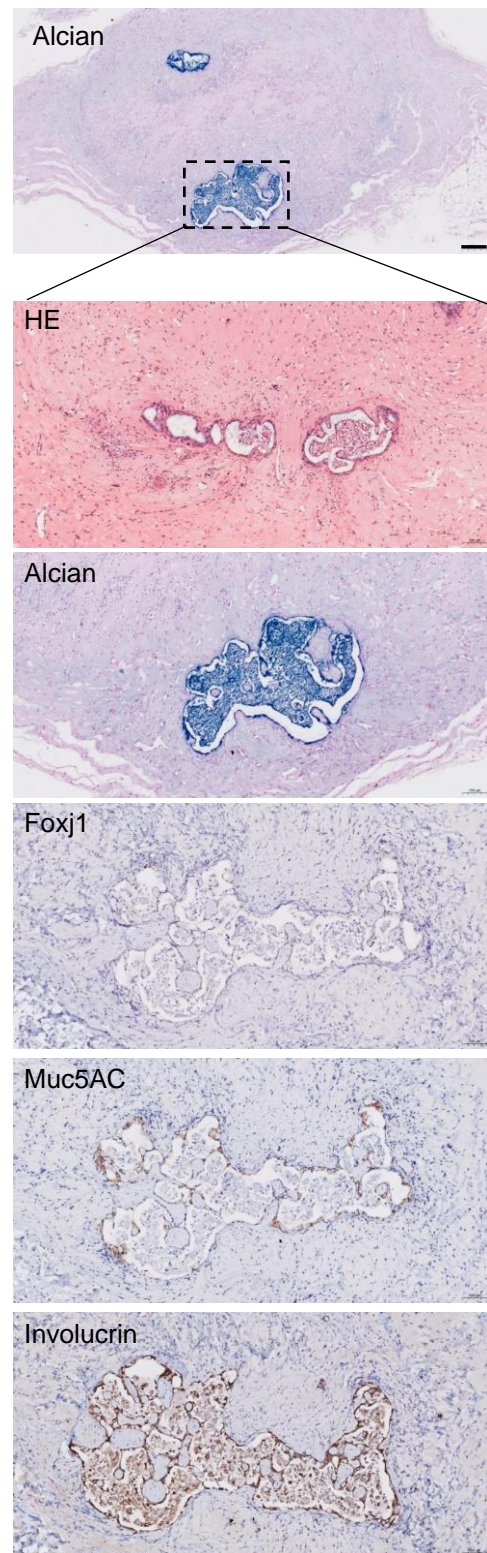
**Supplementary Figure 11. TBBC-MSc in vivo co-culture assays.** (a) Distribution of transplanted cells in xenografts was illustrated by human nucleoli staining, and circled in the pictures. (b) Immunofluorescent images showing FN1 expression in xenografts resulted from MSC growths when co-cultured with non-TO control cells or with TO-TBBCs. Scale bar, 100 $\mu$ m. (c) The serial sections of the same sets of xenografts were proceeded with BMP2 and E-Cadherin co-staining. Representative magnified image showing the area highlighted in white box. Scale bar, 100 $\mu$ m. Independent experiments n=2 were performed for examination. Source data are provided as a Source Data file.



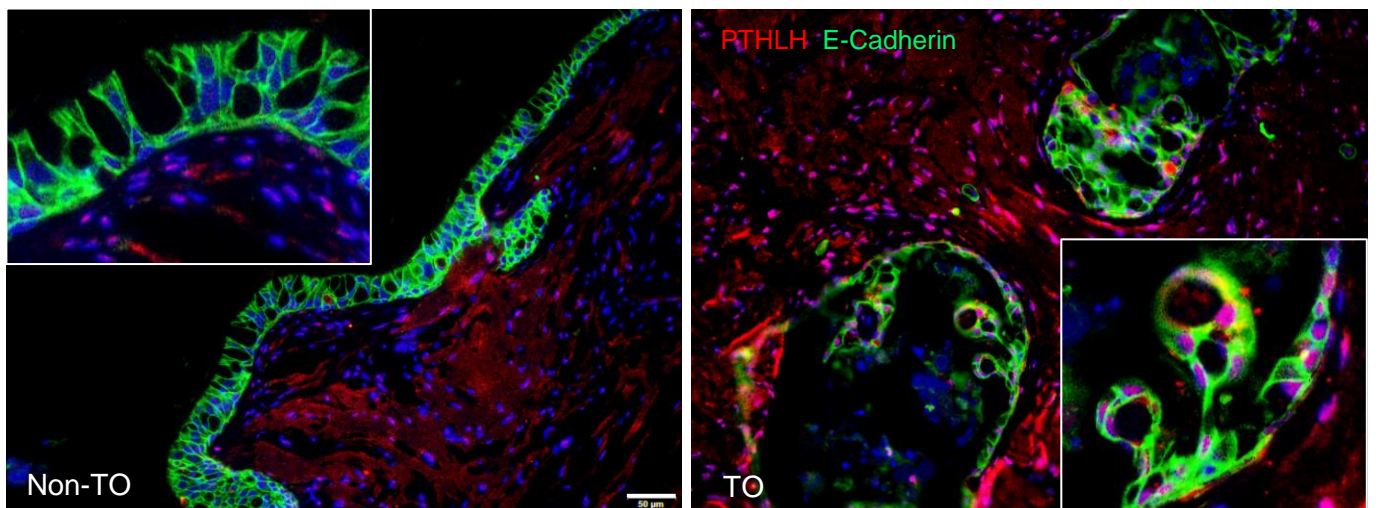
**a** Aggregated MSC + nonTO-TBBC



**b** TO-TBBC transplanted w/o MSC

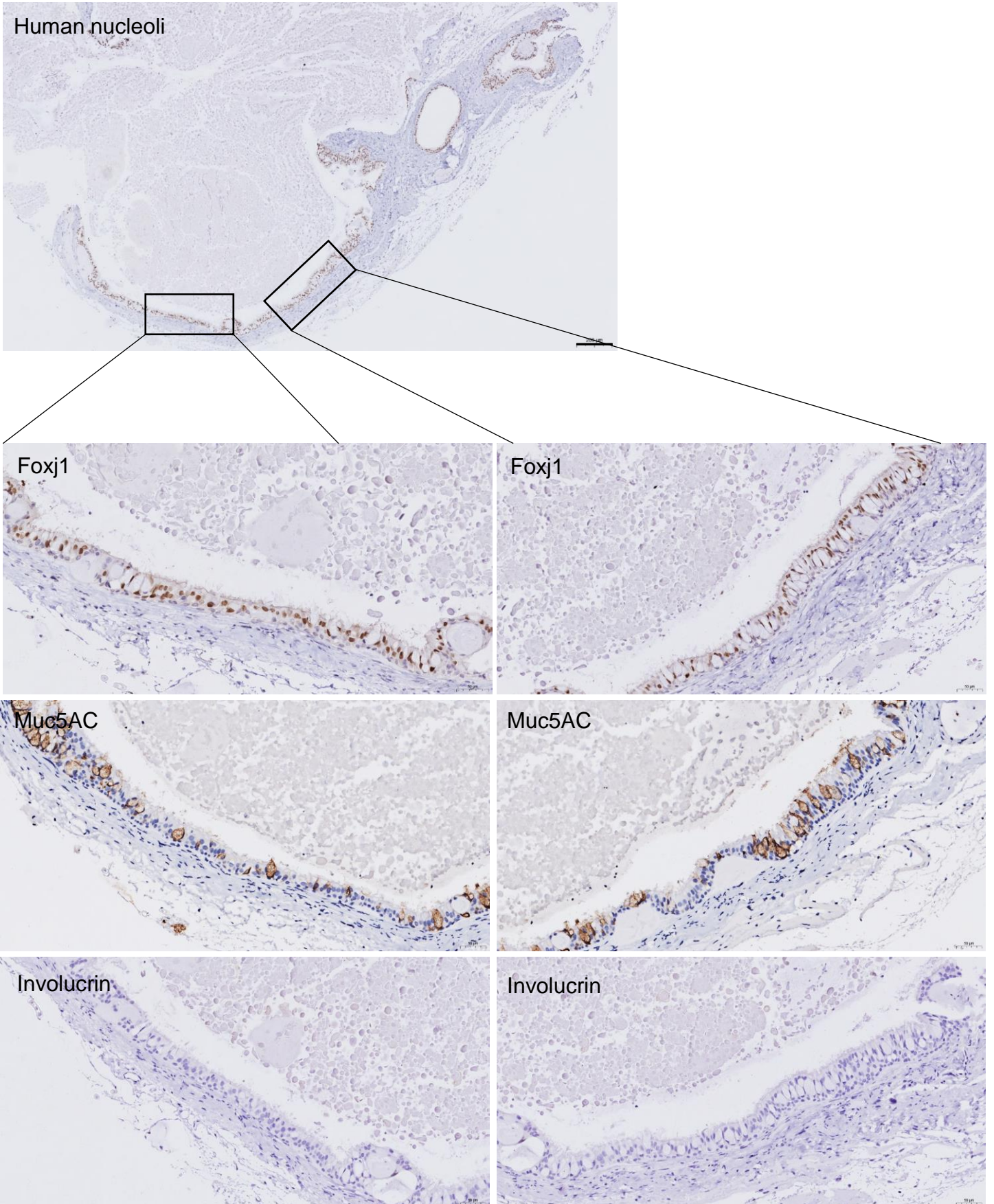


**c**



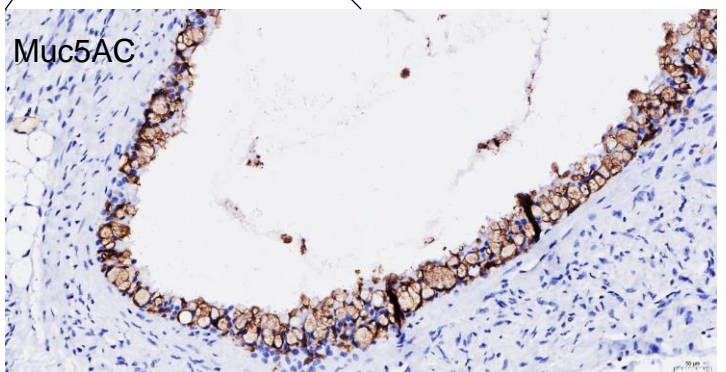
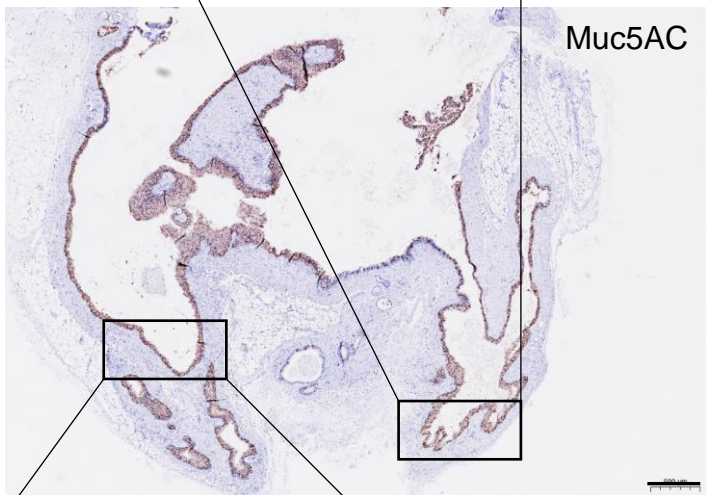
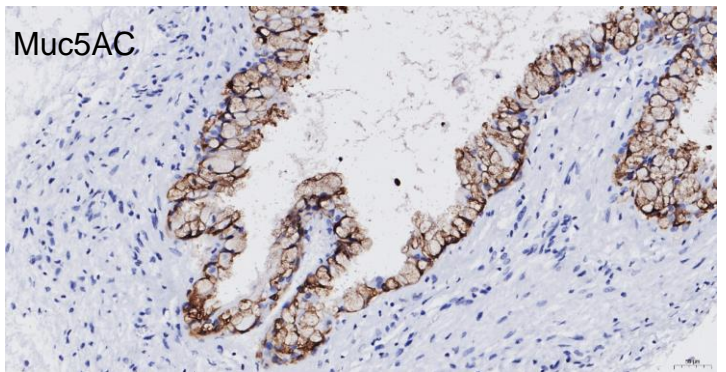
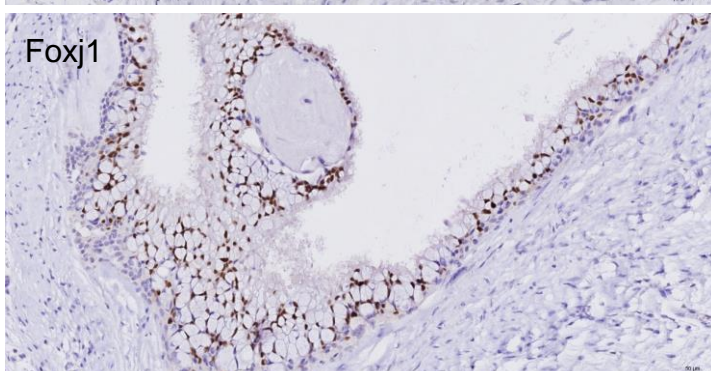
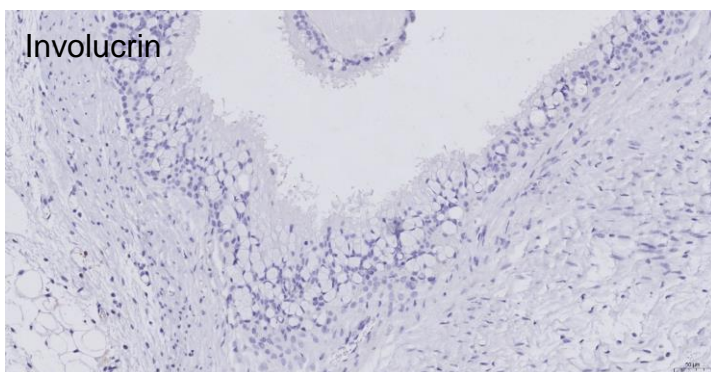
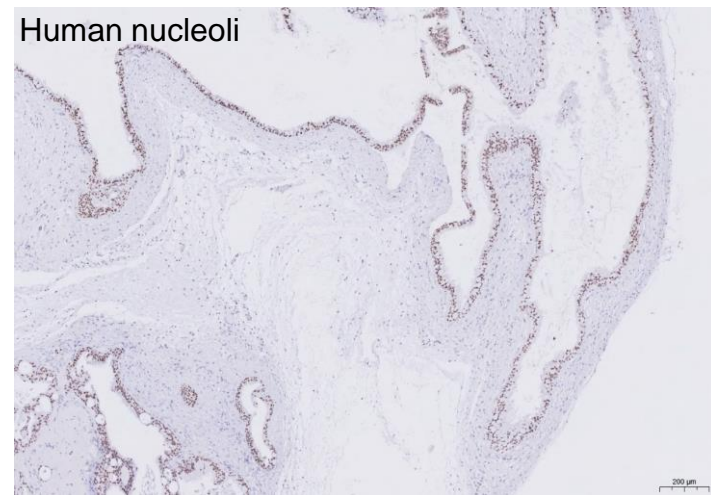
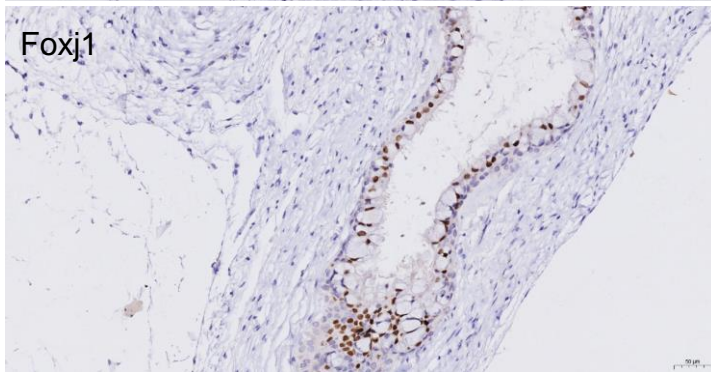
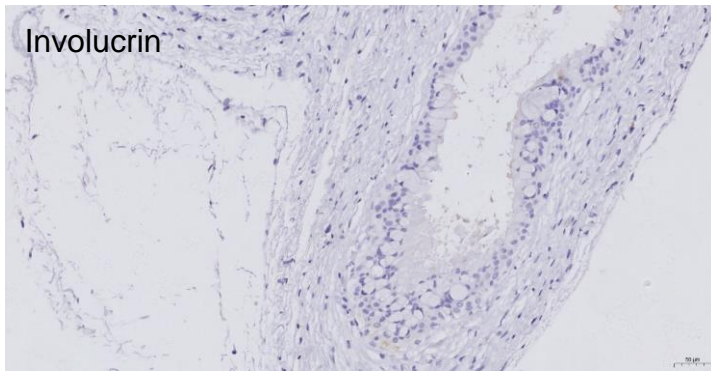
**Supplementary Figure 12. Controls for co-culture assay in vivo and PTHLH expression in non-TO and TO xenografts.** (a) Paraffin sections of 4-week xenografts formed by aggregated MSC spheroid + non-TO TBBC co-transplantation assay were examined by HE and Alcian blue staining. Human nucleoli distribution was confirmed by immunohistochemistry. Scale bar, 200 $\mu$ m. (b) Four-week xenografts formed by TO-TBBCs in the absence of co-transplanted MSC were examined by HE, Alcian blue and immunohistochemical staining for cell-type specific markers. Scale bar, 200 $\mu$ m. (c) Representative immunofluorescent images showing E-Cadherin and PTHLH co-staining on xeno-sections acquired from nonTO-TBBC and TO-TBBC transplantations. Independent experiments n= 2 were performed for examination. Scale bar, 50 $\mu$ m.

PM phenotype: Normal-like

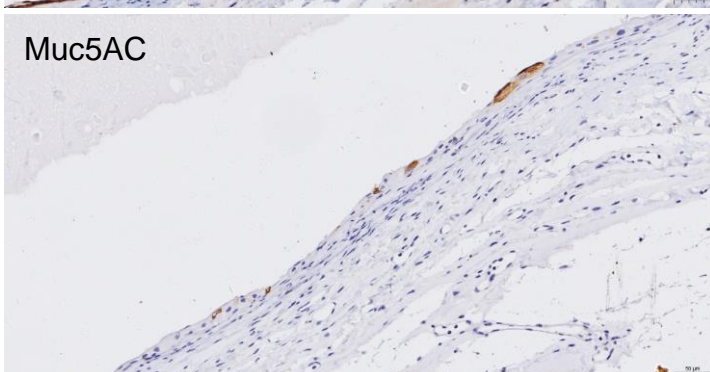
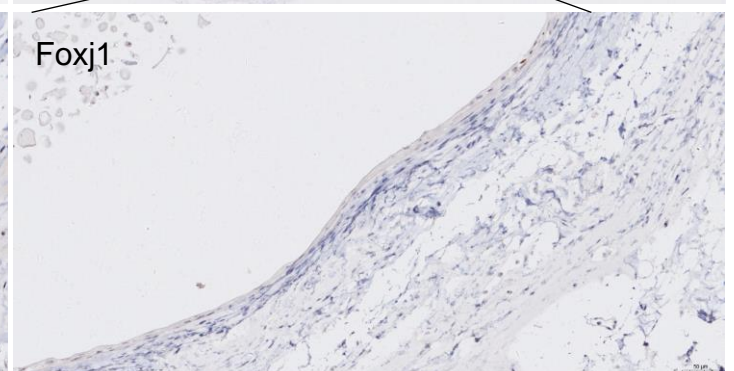
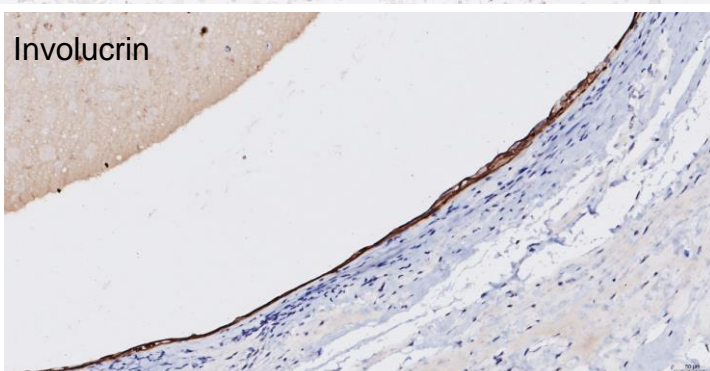
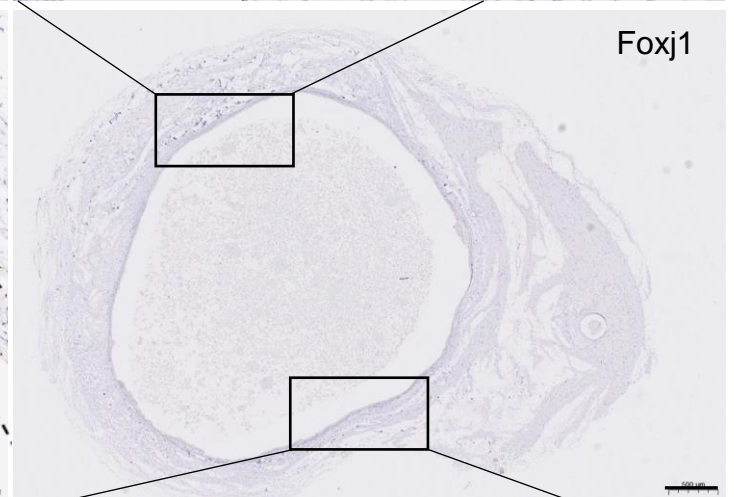
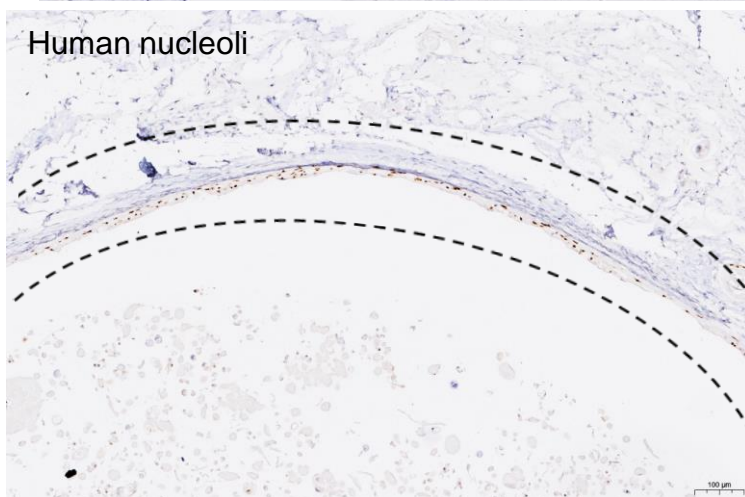
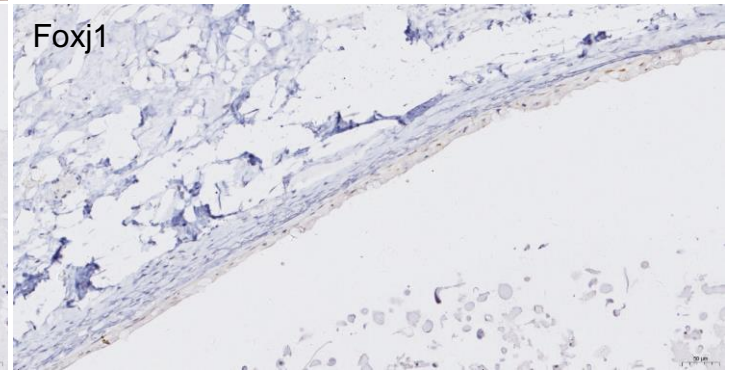
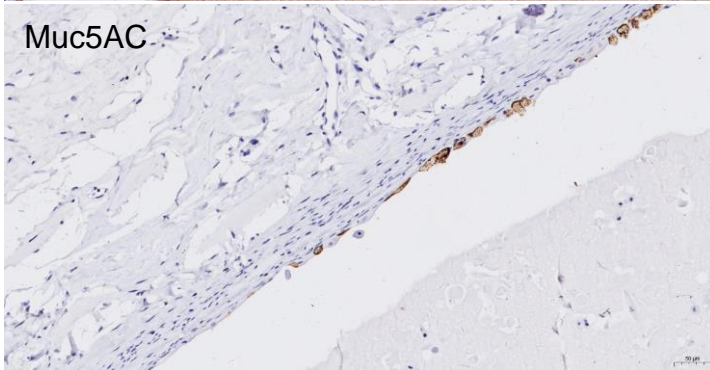
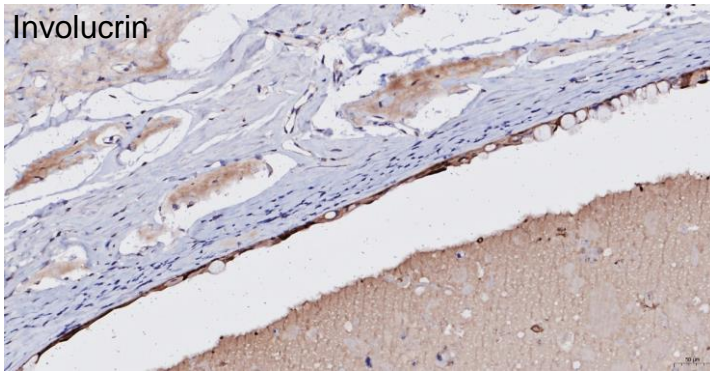


Supplementary Figure 14.

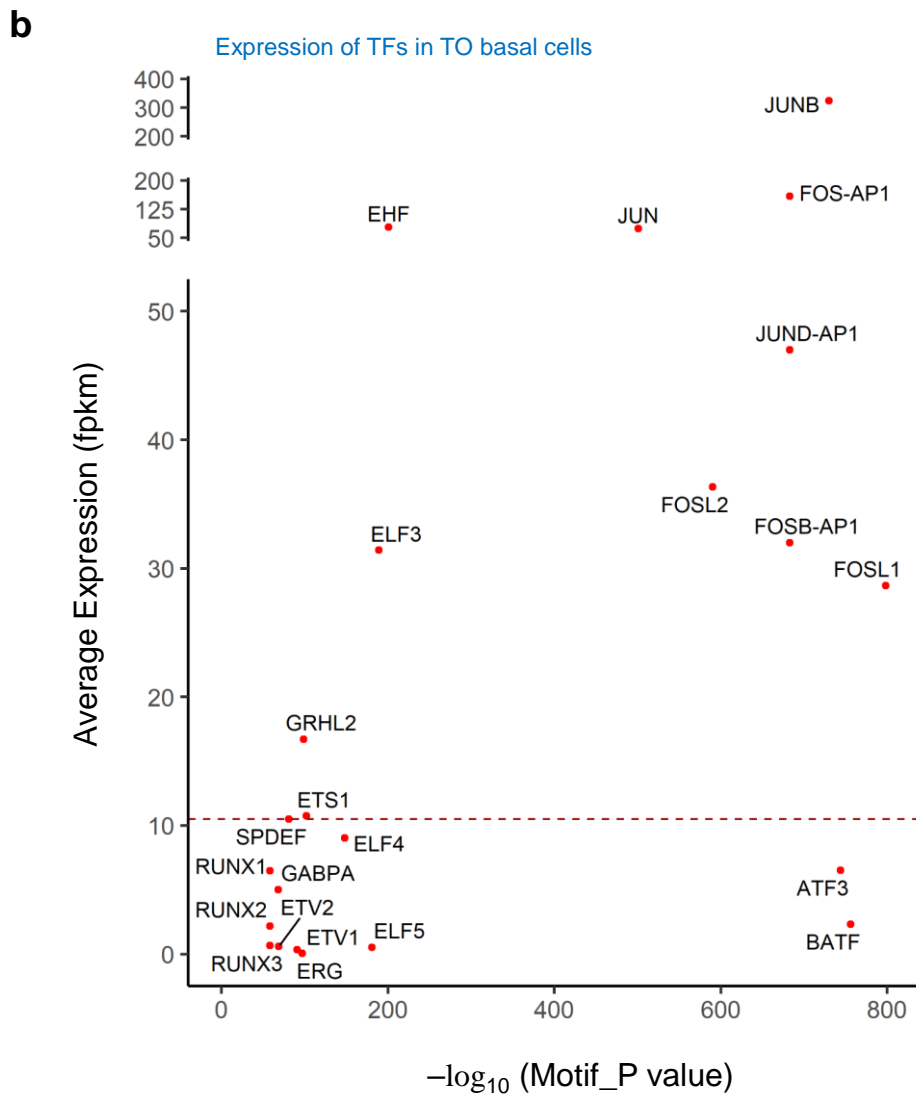
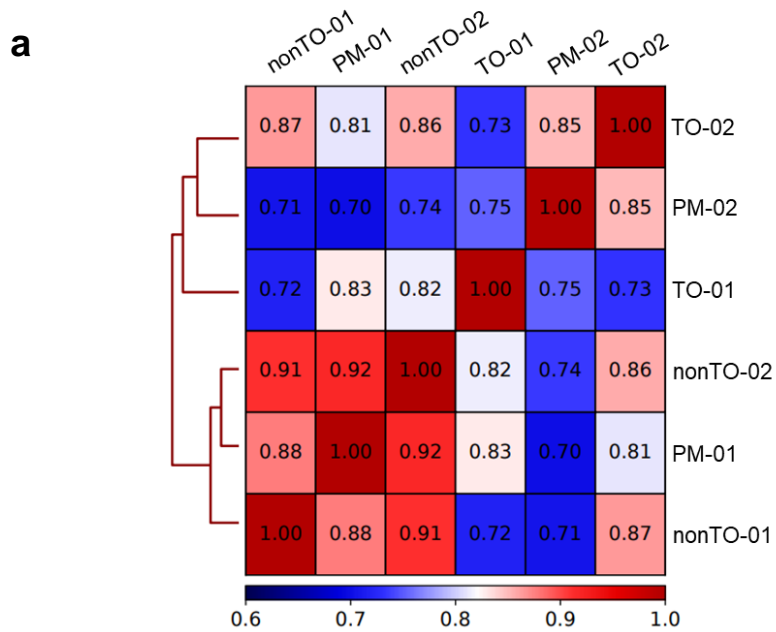
**PM phenotype: Goblet metaplasia**



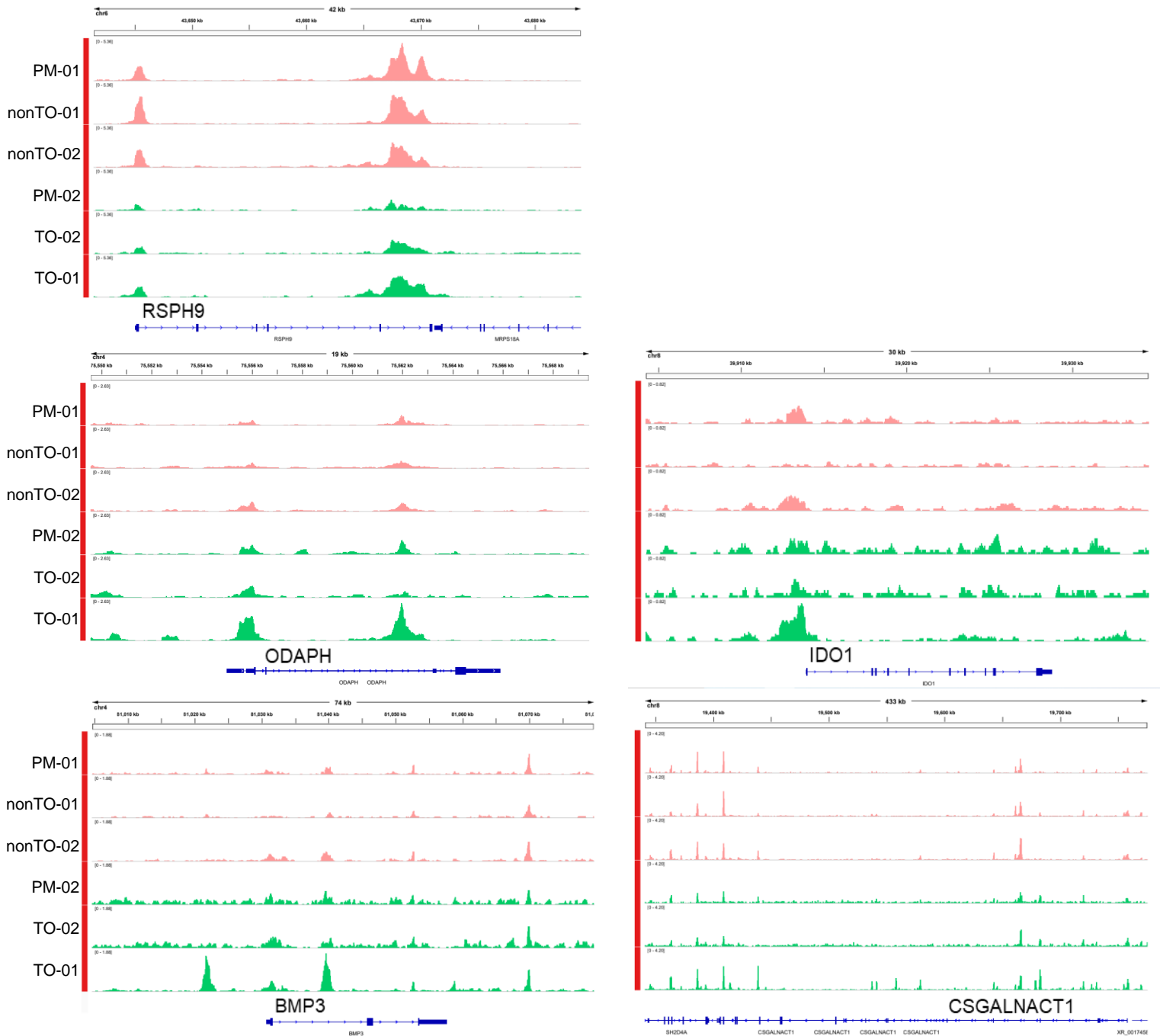
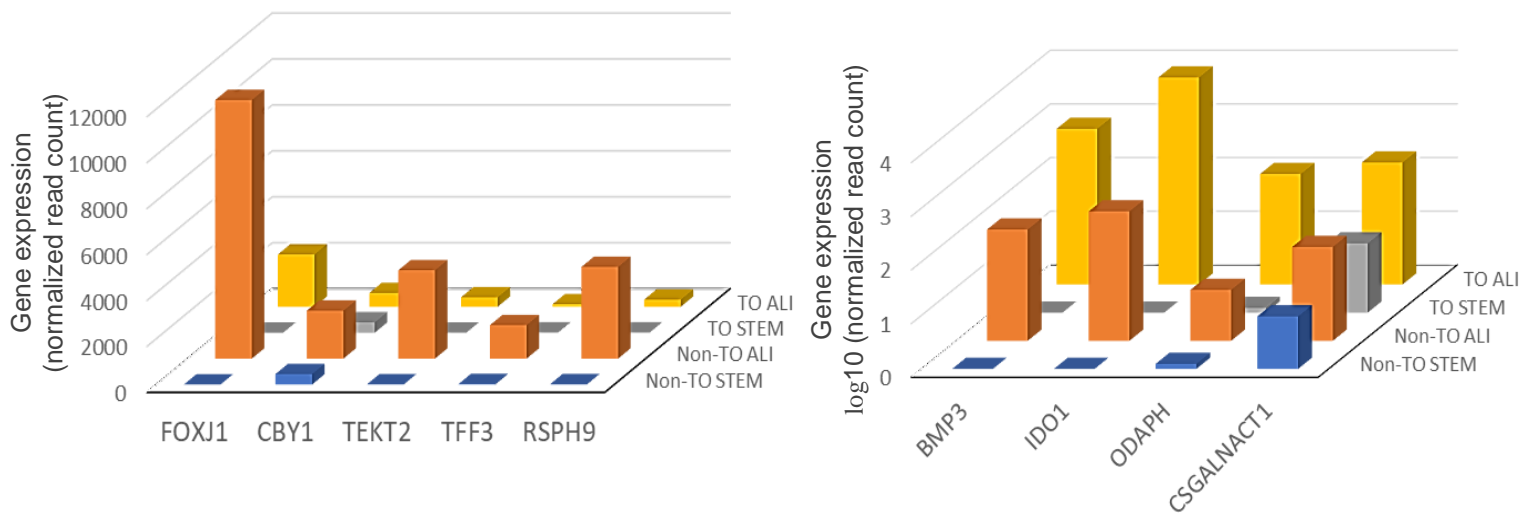
**PM phenotype: Cilium dysplasia**



**Supplementary Figure 13-15. In vivo differentiation of patient-matched TBBCs isolated from the normal-looking regions of patients' trachea-bronchi.** Patient-matched (PM) TBBCs showed distinct differentiation potentials, referring to normal-like, goblet metaplasia and cilium dysplasia phenotypes observed on xenografts, which were collected at Week 4 post subcutaneous transplantation. Representative full-scale immunohistochemical images showing cell type frequencies using antibodies against Foxj1, Muc5AC and Involucrin (n=2 independent experiments). Human nucleoli antibody was used to confirm the location and distribution of transplanted cells. Scale bar, 500µm.



**Supplementary Figure 16. ATAC-Seq of patient-derived TBBCs and joint-analysis with RNA-Seq data. (a)** Pearson correlation result of ATAC-Seq data. **(b)** Correlation of motif enrichment with expression of corresponding transcription factors in TO-TBBCs. Red dotted line indicates the median value according to RNA-Seq data.

**a****b**



**Supplementary Figure 17. Status of chromatin accessibility and gene expression at key loci.**

**(a)** IGV graphs visualizing chromatin accessibility at key loci related to cartilage development, inflammation and ciliogenesis. Peak height is positively correlated to accessibility. Genome scale is included and Y-axis is consistent for all loci. **(b)** Histogram showing transcriptional levels of selected genes between control and TO groups before and after differentiation, corresponding to IGV results shown in this figure and Fig. 7e.











**Supplementary Table 2.** List of genes with increased chromatin accessibility at promoter region and their expressions at stem state and differentiated state

Gene expression linked to peaks up in TO	Gene ID	Peak Annotation	Distance to TSS	p-value	Fold Change (log2)	TO vs. Non-TO
<b>Stem state</b>	FGF10	promoter-TSS (ENST00000264664.4)	-279	0.006825	6.49	up
	ITGAX	promoter-TSS (ENST00000562522.2)	-291	0.011157	4.35	up
	KLK12	promoter-TSS (ENST00000250351.4)	-53	0.001547	2.26	up
	RUNX1T1	promoter-TSS (ENST00000614812.4)	-12	0.019282	5.10	up
	ARHGAP24	promoter-TSS (ENST00000264343.4)	-906	0.005496	-1.52	down
	GRAMD1B	promoter-TSS (ENST00000646146.1)	-346	0.009418	-3.50	down
	IPCEF1	promoter-TSS (ENST00000367220.8)	-25	0.027998	-1.88	down
	RARB	promoter-TSS (ENST00000458646.1)	-76	0.020646	-3.20	down
	SEC16B	promoter-TSS (ENST00000308284.10)	-60	0.03691	-1.12	down
<b>Differentiated state</b>	ADAMTS5	promoter-TSS (ENST00000284987.5)	-899	0.000927	6.34	up
	AGMO	promoter-TSS (ENST00000342526.7)	11	0.015141	3.33	up
	ATP6V0D2	promoter-TSS (ENST00000285393.3)	49	0.000745	5.49	up
	C4orf19	promoter-TSS (ENST00000284437.6)	59	0.023027	1.28	up
	CD69	promoter-TSS (ENST00000228434.7)	-302	0.006832	5.20	up
	COL5A2	promoter-TSS (ENST00000374866.8)	-612	5.35E-07	3.35	up
	CSGALNACT1	promoter-TSS (ENST00000332246.10)	66	0.006357	1.75	up
	GABRP	promoter-TSS (ENST00000518525.5)	-55	1.28E-11	1.41	up
	GNG4	promoter-TSS (ENST00000484517.2)	-505	0.02777	2.29	up
	IDO1	promoter-TSS (ENST00000518237.5)	-201	1.34E-05	4.80	up
	MICAL2	promoter-TSS (ENST00000527546.5)	-478	6.05E-05	1.65	up
	ODAPH	promoter-TSS (ENST00000616557.1)	-209	0.000544	3.74	up
	PITPNM2	promoter-TSS (ENST00000542749.5)	-284	0.000982	1.18	up
	PTPN22	promoter-TSS (ENST00000525799.1)	-159	0.03057	2.51	up
	SATB2	promoter-TSS (ENST00000457245.5)	-242	0.026141	1.53	up
	SH2D1B	promoter-TSS (ENST00000367929.2)	23	0.007382	3.07	up
	TENM2	promoter-TSS (ENST00000518659.5)	-385	1.3E-07	1.99	up
	TNFSF11	promoter-TSS (ENST00000358545.6)	-383	0.006503	2.01	up
	BTNL8	promoter-TSS (ENST00000410920.1)	112	0.026586	-3.69	down
	CFAP58	promoter-TSS (ENST00000369703.1)	50	0.002	-2.39	down
	FABP6	promoter-TSS (ENST00000402432.3)	-590	2.12E-06	-4.35	down
	KLK14	promoter-TSS (ENST00000650543.1)	-348	0.016259	-2.31	down
	LYZ	promoter-TSS (ENST00000549690.1)	56	0.005913	-1.48	down
	MS4A8	promoter-TSS (ENST00000300226.6)	100	0.00853	-2.70	down
	NEK10	promoter-TSS (ENST00000383770.4)	-458, -640	0.041795	-1.76	down
	PACRG	promoter-TSS (ENST00000611387.1)	-900	0.003251	-2.72	down
	PPCDC	promoter-TSS (ENST00000563393.1)	98	0.039533	-1.66	down
	RP1	promoter-TSS (ENST00000637698.1)	94	0.036107	-1.83	down
	SMIM6	promoter-TSS (ENST00000579469.1)	-232	3.73E-06	-4.29	down
	TEKT4	promoter-TSS (ENST00000295201.4)	-443	0.001103	-3.05	down

**Supplementary Table 3.** List of genes with decreased chromatin accessibility at promoter region and their expressions at stem state and differentiation state

Gene expression linked to peaks down in TO	Gene ID	Peak Annotation	Distance to TSS	p-value	Fold Change (log2)	TO vs. Non-TO
Stem state	TNS1	promoter-TSS (ENST00000646520.1)	-33	0.004181	-1.62	down
	BAIAP3	promoter-TSS (ENST00000628027.2)	-18	0.015623	-2.97	down
	PAMR1	promoter-TSS (ENST00000621476.4)	-191	1.23E-05	-4.34	down
	NFIX	promoter-TSS (ENST00000587760.5)	-921	0.007613	-1.47	down
	APCDD1	promoter-TSS (ENST00000578882.1)	-9	0.001803	-2.70	down
	ZFP3	promoter-TSS (ENST00000574352.1)	147	0.008388	-1.77	down
	ALOX15	promoter-TSS (ENST00000570836.5)	-513	0.006552	-5.64	down
	ATP2A1	promoter-TSS (ENST00000561547.5)	55	0.021148	-1.47	down
	BMP4	promoter-TSS (ENST00000558984.1)	-365	0.000296	-2.90	down
	NR4A1	promoter-TSS (ENST00000545748.5)	-610	0.000262	-2.67	down
	SFTA3	promoter-TSS (ENST00000518529.6)	-348	9.49E-05	-4.93	down
	NGFR	promoter-TSS (ENST00000504201.1)	-780	1.81E-07	-1.64	down
	NKX2-1	promoter-TSS (ENST00000498187.6)	69	0.0355	-5.39	down
	FRMD5	promoter-TSS (ENST00000484674.5)	317	0.000449	-3.37	down
	MNX1	promoter-TSS (ENST00000480284.1)	120	0.003431	-6.58	down
	COL6A2	promoter-TSS (ENST00000454245.1)	-82	0.044091	-7.49	down
	HCAR1	promoter-TSS (ENST00000432564.2)	5	0.001076	-4.79	down
	WNK2	promoter-TSS (ENST00000427277.6)	-483	0.014241	-2.31	down
	PHYHD1	promoter-TSS (ENST00000421063.6)	24	0.042853	-1.11	down
	C2orf74	promoter-TSS (ENST00000420918.3)	-53	8.55E-06	-2.38	down
	PGGHG	promoter-TSS (ENST00000409479.5)	-406	8.04E-05	-2.09	down
	IFITM1	promoter-TSS (ENST00000408968.3)	56	9.8E-05	-2.97	down
	ITGB2	promoter-TSS (ENST00000397857.5)	-139	0.000977	-4.47	down
	NRP1	promoter-TSS (ENST00000395995.5)	-281	0.001018	-1.15	down
	PANX2	promoter-TSS (ENST00000395842.2)	-710	0.043984	-1.44	down
	IGF2	promoter-TSS (ENST00000381406.8)	-190	0.006076	-1.78	down
	PAQR7	promoter-TSS (ENST00000374296.3)	-527	0.017417	-1.02	down
	WNT2B	promoter-TSS (ENST00000369684.4)	-42	0.037642	-1.07	down
	SV2A	promoter-TSS (ENST00000369146.7)	-145	0.010278	-2.63	down
	CIART	promoter-TSS (ENST00000369095.5)	-346	0.015809	-1.48	down
	LGR6	promoter-TSS (ENST00000367278.7)	-514	0.012292	-4.43	down
	CCDC88B	promoter-TSS (ENST00000359902.2)	-745	0.011935	-1.63	down
	WNK3	promoter-TSS (ENST00000354646.6)	-256	0.026961	-3.72	down
	PAK5	promoter-TSS (ENST00000353224.9)	-91	0.040812	-5.12	down
	EFS	promoter-TSS (ENST00000351354.3)	-435	0.023909	-1.10	down
	TRPC6	promoter-TSS (ENST00000348423.8)	-13	3.01E-05	-7.75	down
	NRG2	promoter-TSS (ENST00000340391.7)	-160	0.000327	-3.31	down
	VWA1	promoter-TSS (ENST00000338660.5)	-49	0.000741	-1.54	down
	B4GALNT4	promoter-TSS (ENST00000329962.10)	-214	1.05E-05	-1.88	down
	FAIM2	promoter-TSS (ENST00000320634.7)	-71	0.019572	-4.18	down
	HEG1	promoter-TSS (ENST00000311127.8)	-646	0.004292	-1.51	down
	AMOT	promoter-TSS (ENST00000304758.5)	-309	0.01086	-4.81	down
	SIX2	promoter-TSS (ENST00000303077.6)	-265	0.009051	-2.41	down
	KRT8	promoter-TSS (ENST00000293308.11)	-720	2.17E-17	-3.28	down
	PLEKHH2	promoter-TSS (ENST00000282406.8)	95	0.00657	-1.02	down
	NTRK2	promoter-TSS (ENST00000277120.7)	-537	0.018174	-4.82	down
	PSD2	promoter-TSS (ENST00000274710.3)	-75	0.024297	-6.13	down
	CABLES1	promoter-TSS (ENST00000256925.11)	-5	0.02386	-2.02	down
	ALDH3A1	promoter-TSS (ENST00000225740.10)	4, 14	1.51E-07	-2.12	down
	PPP2R2C	promoter-TSS (ENST00000506140.5)	68	0.032996	1.26	up
TNFSF18	promoter-TSS (ENST00000404377.3)	-143	0.000986	2.53	up	
PRSS3	promoter-TSS (ENST00000379405.3)	-173	0.003301	1.63	up	

Continue on the next page...



Differentiated state	AC074143.1	promoter-TSS (ENST00000518227.1)	62	0.023879	-1.60	down
	ADGRB2	promoter-TSS (ENST00000373658.7)	-136	0.019904	-1.53	down
	ALDH3A1	promoter-TSS (ENST00000225740.10)	4, 14	0.000446	-3.45	down
	ALPL	promoter-TSS (ENST00000540617.5)	-93	0.011294	-2.23	down
	ANKRD24	promoter-TSS (ENST00000262970.9)	40	0.021459	-1.28	down
	ANKUB1	promoter-TSS (ENST00000446160.6)	13	0.000173	-2.39	down
	APCDD1	promoter-TSS (ENST00000578882.1)	-9	0.001778	-2.84	down
	BAIAP3	promoter-TSS (ENST00000628027.2)	-18	0.023153	-1.91	down
	BMP8A	promoter-TSS (ENST00000331593.5)	-319	0.018854	-1.70	down
	C2orf74	promoter-TSS (ENST00000420918.3)	-53	0.004271	-2.28	down
	CBY1	promoter-TSS (ENST00000355830.10)	95	8.97E-05	-1.79	down
	CCR10	promoter-TSS (ENST00000591765.1)	-120	0.001471	-2.98	down
	COA3	promoter-TSS (ENST00000588408.5)	573	0.005453	-1.63	down
	EFS	promoter-TSS (ENST00000351354.3)	-435	0.011481	-1.25	down
	FAIM2	promoter-TSS (ENST00000320634.7)	-71	2.78E-05	-4.25	down
	FAM183A	promoter-TSS (ENST00000335282.4)	-272	1.09E-05	-3.55	down
	FOXJ1	promoter-TSS (ENST00000322957.6)	-125	0.003167	-2.29	down
	FRMPD2	promoter-TSS (ENST00000305531.3)	-16	0.033067	-1.93	down
	GLB1L	promoter-TSS (ENST00000409640.5)	72	0.000195	-2.32	down
	GPR162	promoter-TSS (ENST00000428545.6)	-24	0.002601	-3.20	down
	GSTM4	promoter-TSS (ENST00000369833.5)	-16	0.002384	-1.97	down
	HHEX	promoter-TSS (ENST00000282728.9)	-103	0.042015	-1.91	down
	ICAM4	promoter-TSS (ENST00000393717.2)	-424	0.023663	-1.20	down
	IGFBP6	promoter-TSS (ENST00000549628.1)	-414	0.016203	-2.67	down
	ITPKA	promoter-TSS (ENST00000260386.6)	11	0.00934	-1.62	down
	KCNB1	promoter-TSS (ENST00000371741.5)	-283	0.037904	-1.51	down
	KCNH3	promoter-TSS (ENST00000257981.6)	-690	0.005005	-2.28	down
	KCNJ16	promoter-TSS (ENST00000615244.4)	-167	0.033686	-3.92	down
	KIF18B	promoter-TSS (ENST00000587309.5)	12	3.94E-10	-4.30	down
	KRT8	promoter-TSS (ENST00000293308.11)	-720	0.010438	-1.46	down
	LGR6	promoter-TSS (ENST00000367278.7)	-514	0.012392	-3.85	down
	LMNA	promoter-TSS (ENST00000532414.2)	125	0.028175	-1.58	down
	MPPED1	promoter-TSS (ENST00000443721.1)	-31	1.1E-05	-5.53	down
	NPAS1	promoter-TSS (ENST00000449844.6)	466	0.003975	-1.94	down
	NTRK2	promoter-TSS (ENST00000277120.7)	-537	0.011582	-2.62	down
	NUPR1	promoter-TSS (ENST00000395641.2)	-45	0.008744	-1.99	down
	PAQR5	promoter-TSS (ENST00000563004.2)	458	0.003522	-1.70	down
	PLEKHO1	promoter-TSS (ENST00000369124.4)	-12	0.014104	-1.83	down
	PLIN4	promoter-TSS (ENST00000633942.1)	-828	0.033122	-1.19	down
	POLR2J	promoter-TSS (ENST00000393794.4)	-121	0.013957	-1.89	down
	PPM1N	promoter-TSS (ENST00000401593.5)	-451	0.031517	-1.45	down
	PPP1R1B	promoter-TSS (ENST00000579000.5)	-127	0.000441	-3.36	down
	RBM24	promoter-TSS (ENST00000425446.6)	131	0.03824	-1.65	down
	RBP7	promoter-TSS (ENST00000294435.7)	53	0.003665	-3.42	down
	REC8	promoter-TSS (ENST00000611366.4)	56	0.035379	-4.05	down
	RND2	promoter-TSS (ENST00000587250.3)	-379	8.98E-05	-2.55	down
	RNF157	promoter-TSS (ENST00000319945.10)	-401	0.004983	-2.61	down
	SEMA4A	promoter-TSS (ENST00000368286.6)	74	0.013837	-1.09	down
SHISA8	promoter-TSS (ENST00000621082.1)	-355	0.000244	-3.49	down	
SIX2	promoter-TSS (ENST00000303077.6)	-265	0.000579	-2.25	down	
SMKR1	promoter-TSS (ENST00000462322.2)	60	1E-05	-3.84	down	
SOX5	promoter-TSS (ENST00000546136.5)	-2	0.002097	-3.29	down	
STMN1	promoter-TSS (ENST00000399728.5)	9	0.001221	-1.51	down	
SV2A	promoter-TSS (ENST00000369146.7)	-145	0.015212	-3.39	down	
TEKT2	promoter-TSS (ENST00000446354.2)	150	0.000143	-3.22	down	
TFF3	promoter-TSS (ENST00000291525.11)	-20	1.89E-07	-3.70	down	
TRPC6	promoter-TSS (ENST00000348423.8)	-13	0.000826	-4.68	down	
TLL6	promoter-TSS (ENST00000393382.7)	100	0.022268	-2.15	down	

**Supplementary Table 4.** List of genes with increased chromatin accessibility at exon region and their expressions at stem state and differentiated state

Gene expression linked to peaks up in TO	Gene ID	Peak Annotation	Distance to TSS	p-value	Fold Change (log2)	TO vs. Non-TO
<b>Stem state</b>	SDCBP2	exon (ENST00000614659.1, exon 4 of 4)	6912	0.001338	1.73	up
	TNFSF14	exon (ENST00000599359.1, exon 2 of 5)	161	0.017341	5.37	up
	ADGRE2	exon (ENST00000596991.6, exon 19 of 20)	33237	0.029884	2.05	up
	VNN2	exon (ENST00000525270.5, exon 2 of 8)	130	0.007287	6.87	up
	CWH43	exon (ENST00000513409.1, exon 6 of 16)	11877	0.000112	2.52	up
	FAM3D	exon (ENST00000482387.6, exon 17 of 17)	-75644	0.004619	4.43	up
	MUC4	exon (ENST00000463781.7, exon 2 of 25)	21603	0.015398	5.23	up
	SPINK5	exon (ENST00000398454.5, exon 4 of 28)	8213	0.000721	1.10	up
	GCNT3	exon (ENST00000396065.2, exon 3 of 3)	6744	0.02974	3.72	up
	PIK3AP1	exon (ENST00000371109.3, exon 1 of 10)	115	0.020077	1.79	up
	ESR1	exon (ENST00000338799.9, exon 1 of 9)	901	0.011128	2.55	up
	STX3	exon (ENST00000307552.3, exon 1 of 1)	111	0.009271	1.21	up
	ACER1	exon (ENST00000301452.4, exon 1 of 6)	169	0.016538	4.46	up
	GPRIN1	exon (ENST00000261944.9, exon 27 of 32)	19688	0.045576	1.04	up
	HLF	exon (ENST00000376352.6, exon 18 of 18)	-98065	0.003667	-2.67	down
	LOX	exon (ENST00000339397.4, exon 8 of 8)	50017	8.60E-05	-3.09	down
	CAVIN2	exon (ENST00000304141.4, exon 2 of 2)	11535	3.48E-05	-1.69	down
<b>Differentiated state</b>	ADGRE2	exon (ENST00000596991.6, exon 19 of 20)	33237	0.011349	1.86	up
	BMP3	exon (ENST00000282701.2, exon 1 of 3)	625	6.42E-08	2.77	up
	EMP1	exon (ENST00000256951.9, exon 5 of 5)	7210	0.004608	1.10	up
	ESR1	exon (ENST00000338799.9, exon 1 of 9)	901	0.008816	2.68	up
	FKBP14	exon (ENST00000222803.9, exon 4 of 4)	13614	0.000662	1.44	up
	IRAK3	exon (ENST00000457197.2, exon 4 of 11)	22300	0.000296	1.84	up
	ISM2	exon (ENST00000216484.6, exon 12 of 12)	-9928	0.00078	2.42	up
	LAMA3	exon (ENST00000399516.7, exon 33 of 74)	-14929	5.21E-09	2.94	up
	MGAM	exon (ENST00000549489.6, exon 11 of 48)	34593	0.033523	2.63	up
	NRG1	exon (ENST00000356819.7, exon 12 of 12)	44474	0.014837	1.26	up
	NTM	exon (ENST00000374791.7, exon 1 of 8)	360	0.038128	3.22	up
	PCDHA13	exon (ENST00000625195.1, exon 1 of 2)	127	0.030017	3.86	up
	PPARG	exon (ENST00000643888.1, exon 7 of 9)	54510	0.007546	1.32	up
	SATB2	exon (ENST00000428695.5, exon 1 of 7)	207	0.026141	1.53	up
	SEC24D	exon (ENST00000511481.5, exon 13 of 16)	37072	0.048046	1.16	up
	STX3	exon (ENST00000307552.3, exon 1 of 1)	111	0.003332	1.04	up
	TNFSF14	exon (ENST00000599359.1, exon 2 of 5)	161	0.002289	3.62	up
	DEGS2	exon (ENST00000544450.6, exon 11 of 11)	21019	0.003834	-2.36	down
	EFHC1	exon (ENST00000360726.3, exon 3 of 3)	-16338	0.005452	-1.86	down
	ERIC3	exon (ENST00000612390.4, exon 3 of 3)	10371	0.040271	-2.40	down
	FANK1	exon (ENST00000368676.8, exon 19 of 19), (ENST00000368679.8, exon 23 of 23)	66975, 39130	1.78E-06	-2.53	down
	FBF1	exon (ENST00000592193.6, exon 3 of 28)	4524	0.004857	-1.49	down
	IL22RA1	exon (ENST00000327535.5, exon 4 of 7)	-18526	0.003463	-1.83	down
	LCASL	exon (ENST00000485895.6, exon 5 of 5)	5677	0.011146	-1.79	down
	MYLK3	exon (ENST00000394809.8, exon 1 of 13)	387	0.006472	-2.60	down
	NCAPH	exon (ENST00000427946.5, exon 7 of 17)	17568	0.011858	-2.33	down
	NTRK2	exon (ENST00000376208.5, exon 14 of 14)	203993	0.011582	-2.62	down
SYNE3	exon (ENST00000557275.5, exon 17 of 17)	41904	0.04791	-1.67	down	
TCTEX1D1	exon (ENST00000371037.8, exon 22 of 25)	-13116	0.030144	-2.20	down	

**Supplementary Table 5.** List of genes with decreased chromatin accessibility at exon region and their expressions at stem state and differentiated state

Gene expression linked to peaks down in TO	Gene ID	Peak Annotation	Distance to TSS	p-value	Fold Change (log2)	TO vs. Non-TO
Stem state	GNAT1	exon (ENST00000232461.7, exon 8 of 9)	3172	0.04349328	-4.27	down
	BMP4	exon (ENST00000245451.8, exon 1 of 4)	257	2.75708E-05	-2.72	down
	PRPH	exon (ENST00000257860.8, exon 6 of 9)	3849	0.013755449	-4.61	down
	WNT10A	exon (ENST00000258411.7, exon 1 of 4)	118	0.017549088	-1.05	down
	PHYHD1	exon (ENST00000259324.5, exon 4 of 4)	-3444	0.002430617	-1.15	down
	IGFBP4	exon (ENST00000269593.4, exon 1 of 4)	343	0.013647231	-1.53	down
	WNT3A	exon (ENST00000284523.1, exon 1 of 4)	144	0.000203853	-2.11	down
	SOSTDC1	exon (ENST00000307068.4, exon 1 of 2)	128	0.002798447	-4.11	down
	CCDC8	exon (ENST00000307522.4, exon 1 of 1)	254	0.000165404	-3.15	down
	GGT5	exon (ENST00000327365.8, exon 1 of 12)	498	1.70261E-12	-4.43	down
	METTL7A	exon (ENST00000332160.4, exon 1 of 2)	162	0.000470109	-1.68	down
	CKB	exon (ENST00000348956.6, exon 1 of 8)	148	0.003734738	-1.60	down
	SUSD2	exon (ENST00000358321.3, exon 1 of 15)	181	1.98678E-07	-3.35	down
	NRG2	exon (ENST00000361474.5, exon 1 of 10)	332	0.00075442	-2.72	down
	TREX2	exon (ENST00000370211.8, exon 8 of 10)	-7882	0.025254889	-1.24	down
	LDOC1	exon (ENST00000370526.3, exon 1 of 1)	266	1.04493E-06	-4.72	down
	SMOC1	exon (ENST00000381280.4, exon 1 of 12)	231	2.2141E-06	-1.69	down
	RUNX3	exon (ENST00000399916.5, exon 2 of 6)	138	0.028468019	-2.66	down
	RBM38	exon (ENST00000417346.1, exon 1 of 2)	386	0.000912418	-1.17	down
	HCAR1	exon (ENST00000432564.2, exon 1 of 1)	4545	0.003119762	-2.92	down
	PROB1	exon (ENST00000434752.3, exon 1 of 1)	1529	0.004149771	-1.09	down
	RNF165	exon (ENST00000588679.1, exon 1 of 1)	271	3.08181E-10	-2.52	down
	MYO15B	exon (ENST00000610510.4, exon 1 of 63)	1077	0.026822784	-1.20	down
	TPRG1	exon (ENST00000617246.4, exon 11 of 11)	-65461	0.000119316	-1.21	down
	PRODH	exon (ENST00000638240.1, exon 6 of 6)	-10702	0.035269387	-2.84	down

Continue on the next page...

Differentiated state	DOK7	exon (ENST00000340083.5, exon 3 of 7)	10172	0.000405461	-1.37	down
	DOK7	exon (ENST00000340083.5, exon 7 of 7)	9813	0.000405461	-1.37	down
	ESPN	exon (ENST00000636330.1, exon 11 of 11)	7221	0.001509439	-1.52	down
	ESPN	exon (ENST00000636330.1, exon 8 of 11)	689	0.001509439	-1.52	down
	DMRT3	exon (ENST00000190165.2, exon 1 of 2)	114	0.008928564	-3.33	down
	MAMSTR	exon (ENST00000222145.8, exon 5 of 12)	-9517	0.014971701	-1.87	down
	LGR6	exon (ENST00000255432.11, exon 1 of 18)	117	0.012391622	-3.85	down
	PRPH	exon (ENST00000257860.8, exon 6 of 9)	3849	0.038094502	-2.18	down
	PIMREG	exon (ENST00000262483.12, exon 20 of 20)	10881	8.54161E-09	-4.52	down
	UBE2S	exon (ENST00000264552.13, exon 4 of 4)	7192	0.000996521	-2.64	down
	RCN3	exon (ENST00000270645.7, exon 1 of 7)	267	0.015963982	-1.93	down
	WNT3A	exon (ENST00000284523.1, exon 1 of 4)	144	0.007349871	-2.47	down
	HRASLS5	exon (ENST00000301790.4, exon 1 of 6)	186	0.008114229	-2.35	down
	CCDC8	exon (ENST00000307522.4, exon 1 of 1)	254	0.021311823	-2.13	down
	DEF6	exon (ENST00000316637.6, exon 7 of 11)	20520	0.002836985	-1.19	down
	PSAPL1	exon (ENST00000319098.6, exon 1 of 1)	4304	0.000181007	-3.11	down
	GPR62	exon (ENST00000322241.5, exon 1 of 1)	1023	0.015472082	-4.30	down
	C11orf65	exon (ENST00000323468.9, exon 8 of 8)	-5329	0.027419126	-1.30	down
	HMG20B	exon (ENST00000333651.10, exon 8 of 10)	-4002	0.047601065	-1.00	down
	CAPS	exon (ENST00000339485.3, exon 2 of 2)	-1510	1.26422E-05	-4.04	down
	IFT27	exon (ENST00000340630.9, exon 5 of 7)	12156	0.000165931	-2.66	down
	CKB	exon (ENST00000348956.6, exon 1 of 8)	148	1.79983E-05	-2.56	down
	PLEKHA4	exon (ENST00000355496.9, exon 8 of 17)	9515	0.004077529	-1.35	down
	ITPR1PL1	exon (ENST00000361124.5, exon 1 of 1)	4084	2.18949E-05	-2.68	down
	ABCA4	exon (ENST00000370225.3, exon 33 of 50)	41336	0.037652708	-1.21	down
	LDOC1	exon (ENST00000370526.3, exon 1 of 1)	266	0.00679574	-2.83	down
	CFP	exon (ENST00000376983.7, exon 5 of 7)	-7695	0.006550587	-2.66	down
	ZBTB48	exon (ENST00000377674.8, exon 8 of 11)	8052	0.013524327	-1.59	down
	SERP2	exon (ENST00000379179.7, exon 1 of 3)	106	0.03630176	-1.72	down
	SPEF1	exon (ENST00000379756.3, exon 7 of 7)	3460	0.000514229	-3.48	down
	SLC47A1	exon (ENST00000395585.5, exon 1 of 19)	116	0.048438318	-3.72	down
	RBM38	exon (ENST00000417346.1, exon 1 of 2)	386	0.002178803	-1.53	down
	ISOC2	exon (ENST00000438389.6, exon 5 of 5)	8401	0.002990006	-2.68	down
	MMP23B	exon (ENST00000505820.6, exon 20 of 20)	-1643	0.02507483	-4.87	down
	NDUFA9	exon (ENST00000527518.1, exon 4 of 4)	16196	0.035511362	-1.61	down
	MYO15B	exon (ENST00000610510.4, exon 1 of 63)	1077	0.010998191	-1.93	down
	PRR5	exon (ENST00000617066.4, exon 1 of 8)	128	0.048949757	-1.49	down
	TPRG1	exon (ENST00000617246.4, exon 11 of 11)	-65461	0.02411273	-1.53	down
	PRODH	exon (ENST00000638240.1, exon 6 of 6)	-10702	0.040648883	-2.72	down
	BMP4	exon (ENST00000245451.8, exon 1 of 4)	257	0.004487366	1.89	up
	EFHD1	exon (ENST00000264059.7, exon 1 of 4)	614	0.022659204	3.07	up
	GAL	exon (ENST00000265643.3, exon 1 of 6)	225	0.039827589	4.59	up
	MYOM3	exon (ENST00000270800.1, exon 7 of 7)	-8239	7.24585E-05	2.42	up
	CXCL8	exon (ENST00000307407.7, exon 1 of 4)	131	0.001728359	3.12	up
	SPOCK2	exon (ENST00000317376.8, exon 2 of 12)	228	1.51222E-15	5.48	up
	SLC39A14	exon (ENST00000356766.10, exon 23 of 23)	-11881	0.000272043	1.87	up
	DKK3	exon (ENST00000396505.6, exon 2 of 8)	625	3.17259E-07	2.19	up
NAT8L	exon (ENST00000423729.2, exon 3 of 3)	4783	0.002674438	5.83	up	
CPAMD8	exon (ENST00000443236.5, exon 1 of 42)	242	0.000416259	1.96	up	
BIRC3	exon (ENST00000615299.4, exon 3 of 10)	7144	0.000404694	2.52	up	

**Supplementary Table 6.** List of genes with decreased chromatin accessibility at intron region and their expressions at differentiated state

Gene expression linked to peaks down in TO	Gene ID	Peak Annotation	Distance to TSS	p-value	Fold Change (log2)	TO vs. Non-TO
Differentiated state	FOXP1	intron (ENST00000475937.5, intron 10 of 19)	31578	0.039143	-1.61	down
	FOXP1	intron (ENST00000475937.5, intron 11 of 19)	57529			down
	FOXP1	intron (ENST00000475937.5, intron 2 of 19)	55389			down
	FOXP1	intron (ENST00000475937.5, intron 2 of 19)	59619			down
	FOXP1	intron (ENST00000475937.5, intron 5 of 19)	2804			down
	FOXP1	intron (ENST00000475937.5, intron 5 of 19)	9227			down
	FOXP1	intron (ENST00000647725.1, intron 6 of 25)	-13861			down
	ZBTB7C	intron (ENST00000590800.5, intron 1 of 4)	25014	0.045913	-1.28	down
	ZBTB7C	intron (ENST00000590800.5, intron 3 of 4)	63961			down
	ZBTB7C	intron (ENST00000590800.5, intron 3 of 4)	3689			down
	ZBTB7C	intron (ENST00000590800.5, intron 3 of 4)	-2207			down
	ZBTB7C	intron (ENST00000590800.5, intron 3 of 4)	17744			down
	LGR6	intron (ENST00000367278.7, intron 1 of 17)	-3719	0.0123916	-3.85	down
	LGR6	intron (ENST00000367278.7, intron 3 of 17)	15253			down
	LGR6	intron (ENST00000439764.2, intron 1 of 15)	8298			down
	LGR6	intron (ENST00000439764.2, intron 1 of 15)	399			down
	IL2RB	intron (ENST00000216223.9, intron 1 of 9)	4082	0.0232101	-3.29	down
	IL2RB	intron (ENST00000216223.9, intron 2 of 9)	6112			down
	IL2RB	intron (ENST00000216223.9, intron 9 of 9)	18308			down
	PRODH	intron (ENST00000334029.6, intron 1 of 13)	1866	0.0406489	-2.72	down
	PRODH	intron (ENST00000334029.6, intron 2 of 13)	6505			down
	PRODH	intron (ENST00000640084.1, intron 2 of 3)	-2236			down
	GRM4	intron (ENST00000374177.7, intron 1 of 8)	760	0.0106985	-2.27	down
	GRM4	intron (ENST00000374177.7, intron 1 of 8)	-4412			down
	GRM4	intron (ENST00000538487.6, intron 1 of 10)	643			down
	RPL37A	intron (ENST00000446558.5, intron 3 of 3)	41227	0.0014269	-2.25	down
	RPL37A	intron (ENST00000446558.5, intron 3 of 3)	52776			down
	RPL37A	intron (ENST00000446558.5, intron 3 of 3)	34741			down
	SERPINF1	intron (ENST00000254722.8, intron 3 of 7)	8366	0.0032762	-1.65	down
	SERPINF1	intron (ENST00000305513.11, intron 5 of 10)	31351			down
	TRPV4	intron (ENST00000261740.6, intron 1 of 15)	-6104	0.022084	-1.12	down
	TRPV4	intron (ENST00000261740.6, intron 1 of 15)	-4403			down
	KRT8	intron (ENST00000293308.11, intron 1 of 8)	1519	0.010438	-1.46	down
	KRT8	intron (ENST00000552551.5, intron 2 of 8)	2845			down
	CYP251	intron (ENST00000310054.8, intron 1 of 8)	495	0.0072782	-1.34	down
	CYP251	intron (ENST00000310054.8, intron 2 of 8)	2754			down
	ELN	intron (ENST00000320492.11, intron 4 of 28)	11549	0.0008747	-3.69	down
	ELN	intron (ENST00000414324.5, intron 1 of 30)	4279			down
	NTRK2	intron (ENST00000323115.8, intron 11 of 16)	181509	0.0115815	-2.62	down
	NTRK2	intron (ENST00000395882.5, intron 6 of 12)	41203			down
	PLA2G4E	intron (ENST00000399518.3, intron 1 of 19)	15962	0.0028415	-2.39	down
	PLA2G4E	intron (ENST00000399518.3, intron 1 of 19)	19624			down
	UMODL1	intron (ENST00000400424.6, intron 1 of 22)	1292	0.0143468	-2.40	down
	UMODL1	intron (ENST00000400424.6, intron 2 of 22)	7841			down
	MRV1	intron (ENST00000541483.5, intron 1 of 19)	-2547	0.0013676	-2.29	down
	MRV1	intron (ENST00000541483.5, intron 1 of 19)	-7299			down
	FAIM2	intron (ENST00000550890.5, intron 4 of 10)	5835	2.782E-05	-4.25	down
	FAIM2	intron (ENST00000550890.5, intron 9 of 10)	13946			down
	DMRT3	intron (ENST00000569227.1, intron 3 of 4)	-63286	0.0089286	-3.33	down
	DMRT3	intron (ENST00000569227.1, intron 4 of 4)	-16794			down
ELFN2	intron (ENST00000613079.4, intron 1 of 2)	7579	0.0341975	-1.00	down	
ELFN2	intron (ENST00000613079.4, intron 1 of 2)	660			down	
STPG1	intron (ENST00000003583.12, intron 3 of 7)	33895	0.0009024	-1.14	down	
GALK1	intron (ENST00000200181.7, intron 26 of 39)	17176	0.0351854	-1.82	down	
SLC22A4	intron (ENST00000200652.3, intron 4 of 9)	28033	0.0237632	-1.31	down	
FOXN1	intron (ENST00000226247.2, intron 3 of 7)	4134	1.679E-05	-3.37	down	
RPL10A	intron (ENST00000229769.2, intron 8 of 9)	-6987	7.965E-05	-1.42	down	

Continue on the next page...

	MAPRE3	intron (ENST00000233121.6, intron 1 of 6)	699	0.0030833	-1.12	down
	QTRT1	intron (ENST00000250237.9, intron 3 of 9)	5310	0.0270079	-1.25	down
	EEF1AKMT1	intron (ENST00000255305.10, intron 9 of 22)	-40441	0.0086936	-1.32	down
	HRASLS2	intron (ENST00000255695.1, intron 1 of 3)	2568	1.667E-06	-3.08	down
	KCNH3	intron (ENST00000257981.6, intron 7 of 14)	8919	0.0050047	-2.28	down
	PSMB7	intron (ENST00000259457.7, intron 5 of 7)	15632	0.0419781	-1.39	down
	GMPR	intron (ENST00000259727.4, intron 1 of 8)	4771	0.0227813	-1.04	down
	CYSTM1	intron (ENST00000261811.5, intron 1 of 2)	7274	0.0008925	-1.30	down
	TRMU	intron (ENST00000262738.7, intron 15 of 34)	55388	0.0371333	-1.63	down
	RAB36	intron (ENST00000263116.6, intron 2 of 10)	2464	0.0017616	-2.26	down
	CLDN5	intron (ENST00000263201.5, intron 13 of 18)	13385	0.0012544	-3.74	down
	CALR3	intron (ENST00000269881.7, intron 3 of 8)	7301	0.0486552	-4.91	down
	WDR66	intron (ENST00000288912.8, intron 8 of 21)	31493	2.801E-06	-1.57	down
	PPP1R16A	intron (ENST00000292539.8, intron 1 of 10)	-2063	0.0003827	-2.08	down
	POC1A	intron (ENST00000296484.6, intron 9 of 10)	47230	0.0002618	-2.62	down
	MAP1A	intron (ENST00000300231.5, intron 1 of 5)	770	0.0182915	-2.34	down
	TKFC	intron (ENST00000301764.11, intron 5 of 26)	-6962	0.0004774	-1.30	down
	SPATA24	intron (ENST00000302060.9, intron 7 of 7)	-11275	0.0045507	-1.79	down
	ABR	intron (ENST00000302538.9, intron 2 of 22)	-2175	0.0099194	-2.78	down
	ASPSCR1	intron (ENST00000306739.8, intron 4 of 15)	14172	0.0305452	-1.66	down
	SCNN1B	intron (ENST00000307331.9, intron 2 of 13)	20841	0.010799	-1.48	down
	LKAAEAR1	intron (ENST00000308906.6, intron 1 of 1)	604	6.696E-06	-4.77	down
	SOBP	intron (ENST00000317357.9, intron 1 of 6)	2860	0.024268	-1.88	down
	HYAL1	intron (ENST00000320295.12, intron 1 of 5)	2096	0.028551	-1.74	down
Differentiated state	CCDC34	intron (ENST00000328697.10, intron 1 of 5)	5598	5.178E-05	-1.68	down
	BMP8A	intron (ENST00000331593.5, intron 1 of 6)	9538	0.0188536	-1.70	down
	BRAT1	intron (ENST00000340611.8, intron 6 of 13)	13465	0.0249898	-1.27	down
	CCDC30	intron (ENST00000340612.5, intron 1 of 20)	4072	0.0492074	-1.47	down
	SERPINB4	intron (ENST00000341074.9, intron 4 of 7)	2800	0.0088926	-1.18	down
	SSBP4	intron (ENST00000348495.10, intron 4 of 16)	-4182	0.0004209	-2.04	down
	SLC47A2	intron (ENST00000350657.9, intron 8 of 17)	9434	0.0218463	-1.22	down
	SPTBN4	intron (ENST00000352632.7, intron 3 of 35)	20826	0.0025147	-2.55	down
	NR2E3	intron (ENST00000355327.7, intron 8 of 17)	-115506	0.0140028	-2.69	down
	BOC	intron (ENST00000355385.7, intron 4 of 19)	47646	0.001236	-1.28	down
	DTNBP1	intron (ENST00000355917.7, intron 6 of 8)	8179	0.034845	-1.42	down
	OSCP1	intron (ENST00000356637.9, intron 1 of 10)	1616	3.272E-05	-2.65	down
	ASTN2	intron (ENST00000361209.6, intron 16 of 21)	45326	0.0115199	-1.17	down
	UBE2T	intron (ENST00000367278.7, intron 6 of 17)	49495	1.795E-05	-1.46	down
	MYB	intron (ENST00000367814.8, intron 1 of 14)	4036	0.0162834	-1.89	down
	SEMA4A	intron (ENST00000368284.5, intron 6 of 12)	6945	0.0138373	-1.09	down
	PMVK	intron (ENST00000368467.3, intron 2 of 4)	4697	0.0062004	-1.86	down
	PSMD4	intron (ENST00000368884.7, intron 1 of 9)	4778	0.0171525	-1.47	down
	BEND5	intron (ENST00000371833.3, intron 4 of 5)	35188	0.042724	-2.14	down
	CEL	intron (ENST00000372080.6, intron 7 of 10)	5709	2.152E-05	-1.49	down
	RSPH9	intron (ENST00000372165.8, intron 1 of 5)	352	4.689E-05	-3.68	down
	CCDC24	intron (ENST00000372318.7, intron 5 of 8)	2645	0.0007492	-2.10	down
	ANGPTL2	intron (ENST00000373425.7, intron 1 of 4)	10000	0.0006579	-4.14	down
	ADGRB2	intron (ENST00000373655.6, intron 1 of 32)	975	0.019904	-1.53	down
	PIGU	intron (ENST00000374820.6, intron 5 of 10)	52376	0.0239794	-1.62	down
	CROCC	intron (ENST00000375541.9, intron 3 of 36)	3667	0.0005887	-2.04	down

Continue on the next page...

Differentiated state	AQP7	intron (ENST00000377425.8, intron 2 of 6)	2743	0.0079073	-2.17	down
	FOLR1	intron (ENST00000378140.3, intron 2 of 2)	-8258	0.0279488	-1.69	down
	NWD1	intron (ENST00000379808.7, intron 1 of 16)	2986	0.0212596	-2.32	down
	CCDC57	intron (ENST00000392347.5, intron 14 of 16)	18421	0.000774	-1.81	down
	ANKRD39	intron (ENST00000393537.4, intron 1 of 3)	2914	0.0448068	-1.52	down
	RAB17	intron (ENST00000409822.1, intron 1 of 4)	8317	0.0391141	-1.23	down
	CDCA7	intron (ENST00000410019.3, intron 1 of 7)	597	0.0108253	-3.76	down
	FBXO15	intron (ENST00000419743.6, intron 1 of 9)	5908	0.000598	-2.90	down
	PIMREG	intron (ENST00000421306.7, intron 10 of 18)	26985	8.542E-09	-4.52	down
	NT5C3B	intron (ENST00000435506.6, intron 1 of 8)	162	0.0273074	-1.60	down
	ZNF487	intron (ENST00000437590.2, intron 1 of 3)	8320	1.418E-05	-1.72	down
	CYHR1	intron (ENST00000438911.6, intron 2 of 4)	6464	0.0452385	-1.15	down
	MPPED1	intron (ENST00000443721.1, intron 1 of 6)	12718	1.097E-05	-5.53	down
	IGFBP5	intron (ENST00000447289.1, intron 1 of 3)	-15507	0.0188297	-2.64	down
	ATP5MF	intron (ENST00000449683.5, intron 1 of 3)	5310	0.0073866	-2.13	down
	FAM166B	intron (ENST00000455600.1, intron 2 of 11)	9869	0.0006031	-2.90	down
	FAM178B	intron (ENST00000490605.2, intron 12 of 16)	-19015	0.0033887	-2.95	down
	TXNRD2	intron (ENST00000491939.6, intron 7 of 11)	20186	0.0295864	-1.48	down
	EFNA3	intron (ENST00000505139.1, intron 1 of 4)	-5374	0.0227855	-1.89	down
	TOP1MT	intron (ENST00000519148.5, intron 1 of 13)	4700	0.0276524	-1.06	down
	NAALADL1	intron (ENST00000526799.5, intron 2 of 7)	549	5.671E-05	-2.91	down
	NR1H3	intron (ENST00000529444.5, intron 5 of 8)	-4854	0.0012189	-2.04	down
	NPIP86	intron (ENST00000532254.1, intron 1 of 6)	860	0.0059014	-2.88	down
	ANKRD65	intron (ENST00000537107.5, intron 2 of 3)	379	9.626E-05	-2.45	down
	KIF6	intron (ENST00000538893.5, intron 12 of 21)	-23482	0.0011879	-2.48	down
	CNBD2	intron (ENST00000538900.1, intron 7 of 10)	24426	0.0138565	-3.70	down
	PTMS	intron (ENST00000539187.5, intron 1 of 7)	-2091	0.0014826	-2.12	down
	FAM186A	intron (ENST00000543111.5, intron 4 of 7)	1621	0.0488133	-2.15	down
	SLC27A2	intron (ENST00000544960.1, intron 1 of 10)	2299	0.0456375	-1.71	down
	MESP1	intron (ENST00000560294.5, intron 13 of 16)	15970	0.0211654	-3.07	down
	LRRC49	intron (ENST00000560369.5, intron 6 of 15)	16913	0.0001149	-1.74	down
	LRRC36	intron (ENST00000563189.5, intron 2 of 10)	11863	0.0005613	-3.32	down
	SCX	intron (ENST00000569669.5, intron 3 of 15)	6560	0.0073543	-2.30	down
	PKMYT1	intron (ENST00000573944.5, intron 2 of 8)	2557	4.303E-17	-4.61	down
	ZNF232	intron (ENST00000574788.5, intron 4 of 37)	164	0.0001396	-1.41	down
	CLUAP1	intron (ENST00000576634.5, intron 5 of 11)	4541	2.443E-05	-1.83	down
	MBD3	intron (ENST00000585937.1, intron 2 of 6)	2798	0.0107518	-2.23	down
	KCNJ16	intron (ENST00000586462.1, intron 1 of 1)	953	0.033686	-3.92	down
	TMEM161A	intron (ENST00000587583.6, intron 11 of 11)	17815	0.0475359	-1.21	down
	FOXJ1	intron (ENST00000590137.1, intron 6 of 7)	-6687	0.0031671	-2.29	down
	PRKCSH	intron (ENST00000591462.5, intron 10 of 18)	10795	0.0499495	-1.34	down
	SPC24	intron (ENST00000592540.5, intron 1 of 4)	2678	1.877E-08	-4.10	down
	RFX2	intron (ENST00000592546.5, intron 5 of 16)	26743	0.0018349	-1.92	down
	KIF18B	intron (ENST00000593135.5, intron 1 of 15)	-4261	3.942E-10	-4.30	down
	PEX11G	intron (ENST00000593942.5, intron 1 of 6)	2646	0.0005022	-2.78	down
	BCAT2	intron (ENST00000599157.5, intron 4 of 7)	-8763	0.0007964	-1.18	down
	IL24	intron (ENST00000611909.4, intron 2 of 4)	1290	0.0081832	-2.34	down
RAB44	intron (ENST00000612677.5, intron 4 of 13)	18839	0.0027756	-2.84	down	
SCARF2	intron (ENST00000622235.4, intron 1 of 10)	409	0.0004136	-2.43	down	
EFHC1	intron (ENST00000636379.1, intron 2 of 9)	3036	0.0054518	-1.86	down	
GAMT	intron (ENST00000640762.1, intron 1 of 5)	493	0.0420347	-1.58	down	
TPRG1	intron (ENST00000640853.1, intron 8 of 10)	-92361	0.0241127	-1.53	down	
DOK7	intron (ENST00000643608.1, intron 2 of 7)	7339	0.0004055	-1.37	down	

Supplementary table 2-6, Fisher's exact tests were applied to identify the significance.